STENT PLACEMENT FOR RENAL ARTERY STENOSIS

Functional aspects and morphologic intravascular ultrasound parameters that define clinical success

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STENT-PLAATSING VOOR NIERARTERIE-STENOSE

Functionele aspecten en morfologische intravasculaire echografische parameters die het klinisch succes bepalen

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Leer mij, o HEER,
een goeden zin verstaan,
En wetenschap, der dwazen waan
ontvloden;
Psalm 119:33 (ber.)

Aan mijn vader en moeder

Stent placement for renal artery stenosis is reported to benefit some – but not all – patients. This thesis aimed to investigate the parameters that determine vessel patency and clinical outcome of stent placement for renal artery stenosis.

Chapter 1

INTRODUCTION

Obstruction of the renal arteries (renal artery stenosis, RAS) is a frequent entity with reported incidence of up to 53% in autopsy studies in unselected subjects.[1] RAS most often occurs in the context of systemic atherosclerosis and is then associated with plaque accumulation in the intimal layer of the renal artery wall. Less frequently, RAS may be associated with other diseases such as fibromuscular dysplasia, Takayasu's arteritis and neurofibromatosis, or with aortic coarctation.[2-4]

In many vascular territories without abundant collateral circulation, interruption of the supply of oxygen to the target tissue because of arterial stenosis causes symptoms of ischemic pain. In RAS, however, ischemic pain is not a prominent feature. RAS may present clinically with systemic hypertension, renal functional impairment but more often, RAS remains asymptomatic. In asymptomatic patients RAS is often found incidentally whenever angiograms are made for other purposes. It is open to debate whether patients with asymptomatic RAS should undergo revascularization of the renal artery. It has been argued, e.g., that the disease is progressive in severity over time[5,6] and that revascularization is indicated to prevent the future development of end-stage renal failure.[7] On the other hand, it is at present unknown whether RAS, if left untreated in these asymptomatic patients, will truly lead to clinical symptoms that make prophylactic revascularization worthwhile.

Patients with symptomatic RAS are nowadays commonly treated by revascularization of the obstructed artery. Aside from surgical revascularization, RAS may be managed percutaneously by means of balloon angioplasty or stent placement. Although promising results especially of stent placement have been claimed with regard to renal artery patency and clinical outcome, some topics require further clarification. First, long-term vessel patency after renal artery stent placement is not always sustained, with reported restenosis in up to 39% of the patients at 8 months of follow-up.[8] Second, even in the presence of successful revascularization, clinical benefit of stent placement is obtained in only part of the patient population that is treated. For the treatment of hypertension, reported benefit rates range from 39-78% of the patients after stent placement.[9-12] Likewise, renal functional improvement after stent placement has been reported in 20-76% of the patients who were treated with this aim.[13-16]

It is clear, therefore, that additional data are required on the parameters that determine vessel patency and the clinical outcome after stent placement of RAS. Potential causes of restenosis after stent placement in coronary and femoropopliteal arteries may include inadequate stent deployment at the time of stent placement, neointimal tissue proliferation in the stent or at the stent edges, and stent recoil during follow-up.[17,18] To study vessel patency in greater detail, we propose the use of intravascular ultrasound (IVUS). IVUS provides high spatial-resolution tomographic information of the vessel wall (instead of the more limited information on the lumen diameter provided by

angiography), and can thus be used to accurately document the changes in the treated vessel segment that occur over time.

Assessment of the clinical effect of stent placement for RAS is hampered by the absence of uniform definitions of 'clinical success'. Furthermore, it is generally difficult to study the effect of stent placement on the function of the treated kidney in isolation, because the conventional measures to assess renal function (i.e., serum creatinine, Cockroft clearance) reflect the combined functions of the treated and contralateral kidneys together. To obtain information on the effect of stent placement on the treated kidney per se one needs to measure single-kidney function over time.

Finally, it is currently insufficiently known which parameters are predictive for a long-term favorable clinical outcome. Such predictors, if available, would be useful to help select those patients who would clinically benefit from stent placement.

AIM AND OUTLINE OF THIS THESIS

The aim of this work was to provide more insight in some of the questions raised above. In **Chapter 2**, the natural history of incidentally found RAS in patients with peripheral vascular disease is assessed, particularly with regard to the development of end-stage renal failure. This information may answer the question whether prophylactic revascularization in asymptomatic patients is a worthwhile procedure. **Chapter 3** presents a review and meta-analysis of the literature on stent placement and balloon angioplasty for RAS. The two treatment modalities are compared with regard to the vessel patency and clinical outcome. **Chapter 4** describes the IVUS findings that characterize normal and diseased renal arteries in an in vitro set-up as a prelude to the in vivo use of IVUS in patients. **Chapter 5** addresses the morphology of RAS as seen with IVUS in symptomatic patients. This information may be helpful to understand the mechanisms responsible for vessel behavior after stent placement and at follow-up. **Chapter 6** reports on the additional information that may be provided by IVUS at the time of renal artery stent placement, which may optimize the technical aspects of stent deployment. **Chapter 7** describes the differences in the behavior of stents in the renal and femoropopliteal artery at follow-up. The changes in the stented renal artery that are responsible for late lumen loss one year following stent placement are presented in **Chapter 8.** In **Chapter 9** we studied the effect of stent placement on the function of the treated kidney. We performed serial single-kidney function measurements of the treated and contralateral kidneys separately. To identify those patients who will respond favorably to renal artery stent placement, **Chapter 10** describes a regression analysis to identify pre-intervention parameters predictive for one-year clinical outcome of renal artery stent placement. Finally, **Chapter 11 and 12** present the summary and conclusions of this thesis, together with recommendations for the clinical management of asymptomatic and symptomatic RAS and suggestions for further studies.

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Renal artery stenosis (RAS) is frequently encountered as an incidental finding in peripheral vascular disease. To decide whether revascularization is necessary to prevent end-stage renal failure, patients with asymptomatic RAS were studied during 8-10 years of follow-up. None of the 126 patients with asymptomatic RAS developed end-stage renal failure or needed dialysis. Therefore, it seems that there is no clear indication for revascularization of RAS in these patients.

Chapter 2

TEN-YEAR FOLLOW-UP OF UNTREATED INCIDENTAL RENAL ARTERY STENOSIS IN PERIPHERAL VASCULAR DISEASE: A CASE FOR TREATMENT?

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Should incidentally found atherosclerotic renal artery stenosis (RAS) be treated? This question frequently arises whenever RAS is unexpectedly encountered during examinations made for other purposes, e.g. during pre-operative angiography performed for peripheral artery disease.

There are arguments that favor treatment. Atherosclerotic RAS is a recognized cause of ischemic nephropathy[1,2] and has been shown to progress over time,[3-5] with a reported progression rate of the stenotic lesion of 7% per year.[3] RAS is associated with loss of renal function[6] and may cause end-stage renal failure with subsequent need for renal replacement therapy also in patients who initially not present with clear symptoms of renal artery stenosis. Observations in patients with end-stage renal failure showed that ischemic nephropathy was the cause of end-stage renal failure in 14% of patients >50 years of age.[1] The main rationale for revascularizing incidentally found RAS seems therefore the prevention of end-stage renal failure.[7] Other reasons to treat include the prevention of the RAS-induced increase of cardiovascular morbidity and mortality.[8]

On the other hand, there are also arguments not to treat: Why should one expose patients with incidentally found RAS to the potential complications, inconvenience and costs of revascularization treatment whenever there is no immediate need to do so? Furthermore, the true clinical significance of incidentally found RAS remains unclear. A reason not to treat may exist if patients die of other causes before the sequelae of RAS become clinically manifest.

To decide whether or not there is a case for treatment of incidentally found RAS, objective data on the natural history of untreated incidental RAS are needed. There are, however, few such data available. Therefore we studied the 10-year natural history of patients with untreated incidentally found RAS and established whether these patients indeed developed end-stage renal failure and increased incidence of cardiovascular events compared to matched patients without RAS.

METHODS

In a retrospective study a cohort of consecutive patients who underwent digital subtraction angiography because of chronic ischemic peripheral artery disease from January 1989 to December 1991 was followed. This cohort was the oldest one available, given the fact that under Dutch law, hospitals are required to keep archives of all roentgenograms and medical records for a 10-year period. In our university hospital, angiograms made for peripheral artery disease include views of the abdominal aorta and the renal arteries. Patients in whom the angiogram did not allow proper assessment of the renal arteries were excluded from the analysis. Also excluded were patients who had received prior treatment for symptomatic RAS at the time of the angiographic examination. The study was approved by the local ethical review board.

The angiograms were read by two independent observers blinded to the clinical information. The presence and severity of RAS was expressed in 10%-incremental steps starting at RAS of ≥50% lumen diameter stenosis. Differences between the two observers were solved by consensus. Accessory renal arteries with a stenosis were considered

significant whenever more than one-third of the renal mass was estimated to be supplied by the vessel. The stenoses were classified as atherosclerotic if they did not demonstrate the typical string-of-beads appearance. We then grouped the patients with significant RAS for comparison with the patients without RAS as controls. It soon became clear that patients with RAS had a different distribution of age and gender than patients without RAS (see Results). Because both these parameters are known to affect the relevant outcome parameters in this study, we formed the control group by obtaining a random selection of patients without RAS who were matched for age and gender (instead of taking the entire group without RAS).

Baseline characteristics

Six clinical variables were recorded at baseline (i.e., the time of angiography): the Cockroft serum creatinine clearance as a measure of renal function; history of coronary artery disease (myocardial infarction or angina); history of cerebrovascular disease (stroke or transient ischemic attack); diabetes mellitus (present or absent); smoking history (ever or never); obesity (present or absent; defined as a body mass index $\geq$ 25 kg/m^2).

Follow-up data

Follow-up data were collected on patient survival and, where applicable, the cause of death. The occurrence of severe renal insufficiency with need for renal replacement therapy was recorded and, in addition, the incidence of cardiac and cerebrovascular (together, cardiovascular) events. Cardiac events included myocardial infarction, coronary angioplasty or coronary bypass surgery; cerebrovascular events included stroke and transient ischemic attack. It was recorded whenever renal artery revascularization was performed during follow-up. The follow-up data were retrieved by searching medical records and the electronic medical information system of the hospital; in case of insufficient follow-up data the patient's general practitioner was contacted for additional data.

Statistical analysis

Comparisons between groups on ordinate and qualitative variables were done with a Student's *t*-test or chi-squared test where appropriate. Survival curves for the two groups were constructed using Kaplan-Meier analysis and were tested for significant different survival with log-rank tests. Univariate and stepwise multivariate logistic regression analysis of survival was performed using the Cox proportional hazards model. Univariate regression analysis was performed using the clinical variables obtained at baseline, age, gender, and the angiographically scored severity of RAS. The variables that reached significance level in the univariate regression analysis were subsequently entered in the multivariate model. The variables were tested for significant covariant interaction with RAS. Model selection was performed by a backward selection procedure. All statistical tests were performed at the p=0.05 significance level using the SPSS software package, version 8.0.

RESULTS

During the inclusion period angiograms were made in 593 consecutive patients with ischemic peripheral artery disease (Fig. 1). The renal arteries could be assessed in their entirety for possible RAS in 397 of these 593 angiograms. Of the 397 evaluable patients, 11 were excluded because they had symptomatic RAS at the time of the angiographic examination with prior treatment.

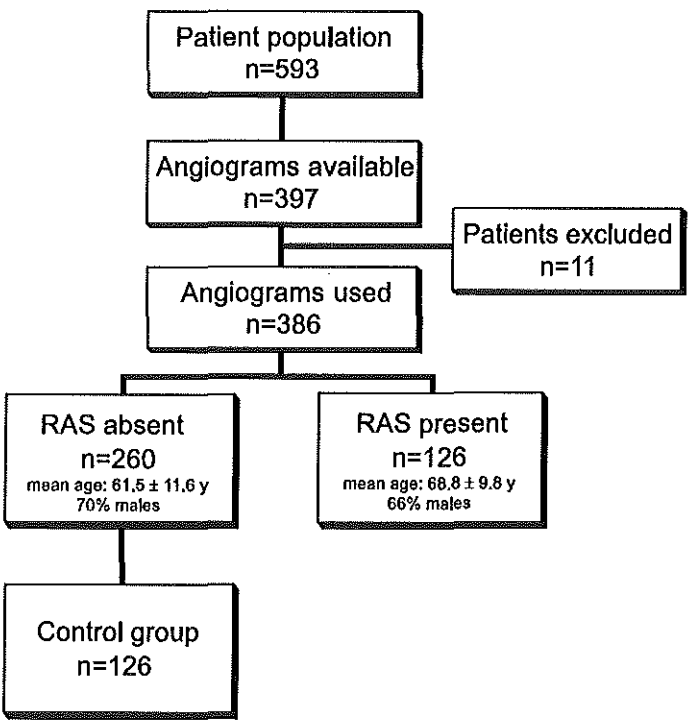

Figure 1. Overview of the study population.

The remaining 386 eligible patients were included in the analysis. RAS was present in 126/386 patients (33%), which was unilateral in 88 patients (Fig. 2), bilateral in 32 patients. Six patients had RAS and a single functioning kidney. Patients with RAS were, on average, older than those without RAS, with mean age ± standard deviation of 68.8 years ± 9.8, versus patients without RAS, 61.5 years ± 11.6. Slightly less patients with RAS were male: 66% versus 70% males in patients without RAS. Accessory renal arteries were present in 84/386 patients (22%).

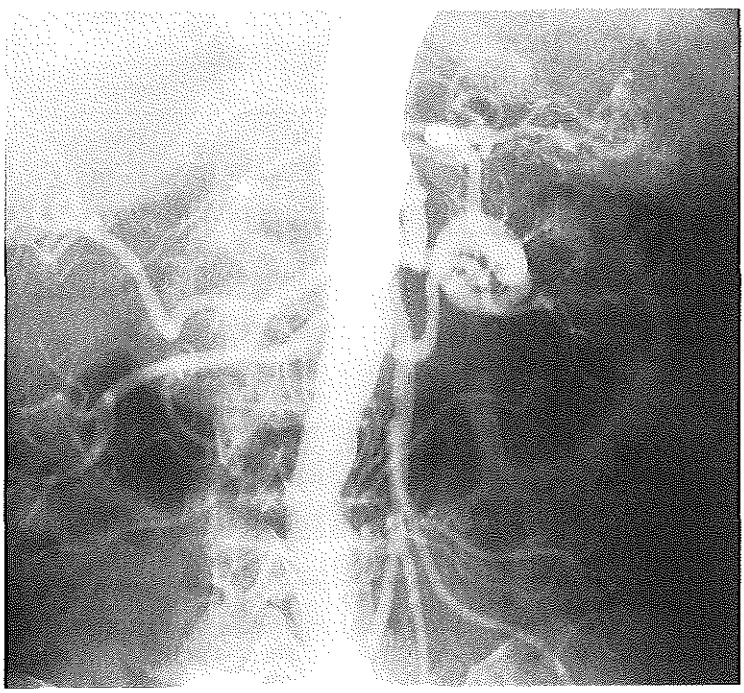

Figure 2. Angiogram showing left-sided renal artery stenosis.

Control group and baseline parameters

The control group consisted of 126 randomly selected patients without RAS who were matched for age and gender. At baseline, patients with RAS differed from controls on two parameters: significantly more patients with RAS had a history of coronary artery disease, p=0.001. Also, patients with RAS had a significantly lower Cockroft clearance, p=0.014 (Table 1).

Morbidity and survival during long-term follow-up

Data on morbidity and long-term survival are given in Table 2. We found that none of the 126 patients with RAS required renal replacement therapy during follow-up. One control patient without RAS developed end-stage renal failure necessitating hemodialysis. Five patients with RAS returned during follow-up because of symptomatic RAS and were treated with revascularization of the renal artery. None of these patients subsequently required renal replacement therapy. These results strongly indicate that incidentally found RAS does not lead to end-stage renal failure if left untreated.

The incidence of cardiovascular events during follow-up did not differ between patients with RAS and the control group. Cardiac events occurred in 29% of patients with RAS versus in 22% of control patients. The incidence of cerebrovascular accidents was 18% for RAS and 11% for controls.

Table 1. Baseline parameters of the study population.

	RAS ≥50%	Controls
n	126	126
Age (years)	68.8 ± 9.8	68.3 ± 9.5
Males (%)	66	66
History of CAD (%)	52*	31
History of CVA (%)	20	15
Diabetes mellitus (%)	22	21
Ever smoked (%)	73	79
Obesity (%)	32	40
Cockroft Clearance (ml/min)	58.2 ± 22.3*	65.4 ± 23.7

n = Number of patients; CAD = Coronary artery disease;
CVA = Cerebrovascular accident;
* = statistically significant different from the control group, $p<0.05$;
mean ± standard deviation indicated.

Table 2. Follow-up data comparing patients with RAS ≥50% and the control group.

		RAS≥50%	Controls
Renal replacement therapy (%)		0	1
Renal revascularizations (%)		4	-
Cardiac events (%)		29	22
	Time to event (months)	54.8 ± 40.9	64.7 ± 40.6
Cerebrovascular events (%)		18	11
	Time to event (months)	56.2 ± 40.7	66.2 ± 40.6
Survival	2 years (%)	77	84
	6 years (%)	55	61
	10 years (%)	40	49

Mean ± standard deviation indicated.

The Kaplan-Meier survival curves for 10-year follow-up showed a difference in survival between patients with RAS and controls, although not significant (p=0.06; Fig. 3). Survival at 2, 6, and 10 years was 77%, 55%, 40% for RAS≥50% and 84%, 61%, 49% for the control group (Table 2).

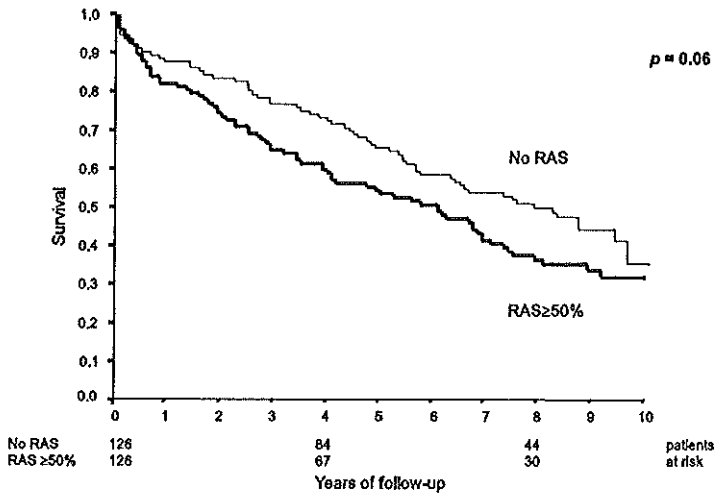

Figure 3. Ten-year survival of patients with RAS ≥50% versus controls.

Table 3. Known causes of death in the patient group with and without RAS.

Cause	RAS (n=52)		Controls (n=49)	
Cardiovascular events, n (%)	19	(37)	18	(37)
General poor physical condition*, n (%)	23	(44)	16	(33)
Neoplasms, n (%)	9	(17)	13	(27)
Following surgery done for unrelated reason, n (%)	1	(2)	2	(4)

n = Number of patients;
* including severe cardiac or pulmonary dysfunction, poorly controlled diabetes, gastro-intestinal bleeding.

Analysis of the causes of death showed no significant difference between patients with RAS and controls (Table 3). The cause of death could be retrieved in 52/88 deceased patients with RAS and in 49/77 deceased control patients. Cardiovascular events were implicated as the direct cause of death in 19/52 patients with RAS (37%) and in 18/49 control patients (37%). A major cause of death in both groups was "general poor physical condition".

Table 4. Variables included in the multivariate regression analysis and their impact on long-term survival.

Variable	Risk ratio	(95% CI)	*p*-value
Male gender	1.4	(1.00-2.13)	0.05
Age > 70 y	1.8	(1.20-2.56)	0.004
RAS ≥ 60%	1.5	(1.04-2.10)	0.03
History of CAD	1.1	(0.70-1.80)	NS
History of CVA	1.5	(1.02-2.43)	0.04
Diabetes mellitus	1.5	(1.01-2.20)	0.05
Obesity	0.9	(0.58-1.29)	NS
Cockroft Clearance < 50 ml/min	2.0	(1.36-2.95)	<0.001

CAD = Coronary artery disease; CVA = Cerebrovascular accident;
CI = Confidence interval; NS = Not significant.

Cox proportional hazards analysis showed that RAS of ≥50% luminal diameter stenosis was not associated with increased mortality. However, more severe RAS of ≥60% stenosis proved to be a significant albeit weak predictor of increased mortality, p=0.03, with a relative risk of 1.5 (95%-confidence interval 1.04-2.10). Other statistically significant independent parameters of decreased survival in the multivariate model were: history of stroke, diabetes mellitus, age >70 years, Cockroft clearance <50 ml/min and male gender (Table 4). No significant covariant interactions between these parameters and RAS≥60% were found.

DISCUSSION

The clinical importance of incidentally found RAS is at present uncertain. The question whether the disease leads to end-stage renal failure and increased cardiovascular morbidity and preventive intervention is indicated, was addressed in the present study.

As a first finding, the present study confirmed the high prevalence of incidental RAS of ≥50% stenosis in patients with peripheral vascular disease: 33% of 386 patients compared with 31% and 38% in two earlier series of 100 and 189 patients, respectively.[9,10] RAS is more commonly present in peripheral artery disease than in coronary artery disease: the prevalence of incidental RAS was reported to be only 15% in 1235 patients undergoing cardiac catheterization.[11]

In our study, incidental RAS was not associated with the development of end-stage renal failure. None of the 126 patients with untreated incidental RAS needed renal replacement therapy during up to 10 years of follow-up, despite the fact that at baseline these patients had, on average, a lower Cockroft clearance than controls (Table 1). Similar observations have been reported by Conlon et al. who found that only 1 of 188

patients with RAS (associated with coronary artery disease) developed end stage renal failure during 4 years of follow-up.[8] Conlon's study and ours strongly indicate that it is not necessary to revascularize incidental RAS to prevent future renal failure. This seems to contradict previous experience because angiographic and duplex ultrasound studies have shown that RAS, if left untreated, is a progressive disease that causes ischemic renal insufficiency and end-stage renal failure.[1,6] However, patients who develop end-stage renal failure due to incidental RAS reported in those studies are probably a different population than patients who present with symptomatic peripheral atherosclerosis such as in the current patient group.

At this point we wish to emphasize that we used the need for renal replacement therapy as the clinical endpoint, instead of the loss of renal mass that is more frequently used as a (substitute) endpoint. We believe, however, that 'need for renal replacement therapy' is the more relevant parameter, as for the individual this makes the difference between being 'a healthy person' or 'a patient'.

Patients with RAS did not experience more cardiovascular events during follow-up than the control group. The cardiovascular mortality was also not increased. Considering these findings, there seems to be no rationale to revascularize incidental RAS with the aim to prevent cardiovascular morbidity and mortality.

An additional finding in our study was that incidental RAS in peripheral artery disease was not associated with a significantly decreased 10-year survival. This was in contrast with the previously mentioned study of Conlon et al.[8], in which incidental RAS in coronary artery disease was associated with decreased 4-year survival compared to controls (65% vs. 89%, respectively). The 10-year survival in our study (40% for patients with RAS versus 49% for controls) was in accordance with the previously reported data of Hertzer. In the latter study the 10-year survival rate in 871 patients with peripheral vascular disease ranged from 30-50%.[12] These data indicate that patients with peripheral vascular disease, in general, have a limited 10-year survival.

In our study RAS ≥60% proved to be a weak predictor for decreased survival. Subanalysis showed, that RAS ≥60% was not associated with increased cardiovascular mortality but that such events occurred earlier during follow-up (52 ± 39.6 months versus 65 ± 40.6 months for controls). This data suggest that incidental RAS is an expression of advanced atherosclerosis rather than a causal factor for cardiovascular morbidity. This might be illustrated by the borderline statistically significant difference in 10-year survival between the two groups. An additional argument to support this view is that at baseline, patients with RAS had more clinical symptoms of atherosclerosis, in particular, a history of coronary artery disease.

Some limitations of our study should be considered. First, not all renal arteries were evaluable in the patients of the cohort. This may have introduced a selection bias in the (unlikely) event that non-visualization of the renal arteries was associated with the presence of RAS. However, we believe that in nearly all cases, non-visualization of the renal arteries was related to technical imaging factors. Second, many angiograms were in

the anterior-posterior projection view only. As a result, RAS may have been missed in some patients, who may then have been erroneously assigned to the control group.
This bias would not interfere with the finding that RAS does not cause end-stage renal failure, but may have led to underestimation of the true prevalence of incidental RAS and have obscured potential differences between patients with RAS and controls. However, the prevalence of RAS in our study was similar to that found in earlier studies.[9,10] Third, in retrospective study like this, it was impossible to obtain reliable blood pressure data. In this way, the effect of hypertension on the major events in this study could not be determined. However, the incidences of cardiac and cerebrovascular events, which are directly related to hypertension, were not statistically significant different for patients with and without RAS. Therefore, we believe that renovascular hypertension did not play a significant role in the present study. Fourth, despite extensive efforts some follow-up data remained missing. Yet, overall we believe that our data are sufficiently complete and do not suffer from systematic bias.
In conclusion, our observations showed that untreated incidental RAS does not cause end-stage renal failure and is unlikely to cause increased cardiovascular morbidity and mortality. The current trend towards aggressive interventional treatment of incidentally found RAS needs careful re-appraisal.

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A meta-analysis of renal artery stent placement in patients with renal artery stenosis in comparison with percutaneous transluminal renal angioplasty (PTRA) was performed. Renal artery stent placement appeared to be technically superior to PTRA alone with higher initial technical success and lower restenosis rates. The clinical effect on blood pressure and renal function was not significantly different for the two treatment modalities, although this analysis was hampered by the wide range of definitions for clinical success used.

Chapter 3

STENT PLACEMENT FOR RENAL ARTERY STENOSIS: WHERE DO WE STAND? A META-ANALYSIS

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In 1978 percutaneous transluminal renal angioplasty (PTRA) was introduced by Grüntzig et al.[1] as an alternative for surgical treatment for renal artery stenosis. In subsequent years numerous studies reported the beneficial effect of PTRA on the management of renovascular hypertension and renal function.[2] Studies showed that PTRA is an attractive alternative with lower complication rates than surgical intervention. Since then PTRA has become widely accepted for treating renal artery stenosis, although a restenosis rate of 27-100% at 6-12 months follow-up has been acknowledged as a major limitation of the procedure.[3,4] Besides, in patients treated for atherosclerotic renal artery stenosis the effects on blood pressure were disappointing, but in patients suffering from renal artery stenosis due to fibromuscular dysplasia, PTRA proved to be successful with cure rates for hypertension of 22% versus 83%, respectively.[5]

With the introduction of self-expanding and balloon-expandable metallic stents a new treatment modality became available to treat atherosclerotic renal artery stenosis that might overcome poor angioplasty results, immediate post-angioplasty complications and restenosis. Since the first studies on renal artery stenting in 1991,[6-8] several case series established the successful placement of stents in renal artery stenosis. This overview presents the findings of these series with regard to the safety and efficacy of the procedure and compared the findings with PTRA.

METHODS

A literature review was performed of studies dealing with renal artery stenting identified by a Medline search of the English-language medical literature up to August 1998. To avoid double counting, data from the most recently published articles from a particular institution were included, thereby ignoring the possible additional information in previously published work. From the 14 series identified,[6-19] when available, the following data were extracted:

1. Patient selection criteria
2. Lesion characteristics
3. Procedure
4. Anti-thrombotic therapy
5. Initial technical success
6. Complications
7. Duration of follow-up
8. Clinical results
9. Restenosis rate.

Data extraction was performed by the first author (TCL) and verified by the co-author (EJG). Discrepancies in the extracted data were solved by these authors examining the articles simultaneously.

The variables initial technical success rate, complication rate, clinical results and restenosis rate across the studies were tested for homogeneity using the chi-squared test (two-sided, $\alpha = 0.05$). As these variables were not uniformly defined or measured under identical conditions a random-effects model, as described by Laird and Mosteller[20] in

1990, was used to combine the data. Mean age of patients, mean number of stents per artery and mean period of clinical and angiographic follow-up across studies were combined with use of weighted means.
Relationship between categorical variables was demonstrated in contingency tables using the chi-squared test; for continuous variables Pearson's correlation coefficient was calculated using SPSS for Windows (version 7.0). Correlation coefficients were determined between 'age' and the following variables: lesion characteristics, stents per artery, initial technical success, complication rate, percentage cured or improved for hypertension or renal function, and restenosis rates. Correlation coefficients were considered worth mentioning in case of r values >0.50. A p value ≤ 0.05 was considered statistically significant (two-sided).
Finally, the results of stent placement in patients with renal artery stenosis were compared with the results of PTRA in a similar patient group. Because the majority of stent studies was published from January 1995 to August 1998, studies dealing with PTRA for renal artery stenosis published in the same period were included to obtain contemporary controls.[3,21-29] The following parameters were compared between the stent studies and the PTRA studies: indication for intervention, initial technical success, complication rate, percentage cured or improved for hypertension or renal function, and restenosis rate. Comparison was performed in contingency tables using the chi-squared test (two-sided, $\alpha = 0.05$) to test for statistical significance.

RESULTS

Pooled data of all patients undergoing renal artery stent placement (n=678) are listed in Tables 1 and 2.

Patient selection criteria

Patients included in the survey had a mean age of 66 years ranging from 55[9] to 70 years.[12,17] The criteria used for selecting patients for stent placement varied widely. Clinical indication for intervention was a combination of hypertension and renal failure in all but four reports.[10,15,17,18] The number of patients treated for hypertension was higher than for renal function impairment (536 vs. 344, respectively). In 10 of the studies stent placement was performed after initial or late PTRA failure.[6-9,11,13-17] In two studies stent placement was the primary intervention[12,19] and the remaining two studies used stent placement as primary or secondary intervention.[10,18] The angiographic definition of a significant stenosis ranged from ≥40% to >70% lumen diameter reduction.

Lesion characteristics

On angiography a distinction was made between ostial and truncal lesions, and lesions due to atherosclerosis or fibromuscular dysplasia. Ostial lesions were defined as stenoses of the renal artery within 2 mm[18], 4 mm[17] or 5 mm[10,13] of the aortic lumen. In one study an ostial lesion was defined as a stenosis without a nondiseased renal artery segment between the lesion and the aorta.[11] More ostial lesions were treated than truncal lesions (371/139). In seven reports either ostial or truncal lesions were treated. In three studies only ostial lesions were treated[8,10,13] and in one study only truncal lesions were involved.[7]

In the remaining three studies the location of the lesion was not mentioned.[15,17,19] Renal artery stenoses were atherosclerotic in origin in the majority of cases. Incidentally, patients were included with renal artery stenosis due to fibromuscular dysplasia (n=6), Takayasu arteritis (n=2) and/or post-transplant stenosis (n=4).[6,7,9,11,14]

Table 1. Patient's characteristics, type of stents used and initial angiographic success following renal artery stent placement.

	Patients					Stent		Initial angiographic success		
Author	Patients n	Age Years	Arteries n	Indication HT/RF	Location Ost/Trunc	Stents per artery n	Stent type	Criterion % DS	Success % arteries	Compli-cations* n arteries (%)
Wilms[6]	11	60	12	10/1	6/6	1.25	Wallstent	<20	83	3 (25)
Kuhn[7]	10	56	10	9/10	0/10	1.40	Strecker	<20	80	4 (40)
Rees[8]	28	66	28	28/14	28/0	1.11	Palmaz	<30	96	5 (18)
Hennequin[9]	21	55	21	21/6	7/14	1.19	Wallstent	<30	100	4 (19)
van de Ven[10]	24	67	28	24/0	28/0	1.14	Palmaz	<10	100	3 (11)
Henry[11]	59	65	64	59/10	34/30	1.00	Palmaz	<20	100	2 (3)
Iannone[12]	63	70	83	63/29	51/32	1.00	Palmaz	<30	99	11 (13)
Blum[13]	68	60	74	68/20	74/0	1.03	Palmaz	<50	100	0 (0)
Boisclair[14]	33	63	35	33/17	19/16	1.00	Palmaz	<30	100	6 (17)
Harden[15]	32	67	32	0/32	NM	1.03	Palmaz	<10	100	1 (3)
White[16]	100	67	133	100/44	107/26	1.12	Palmaz	<30	99	2 (2)
Rundback[17]	45	70	54	0/45	NM	NM	Palmaz	<30	94	5 (9)
Shannon[18]	21	63	23	0/21	17/5	1.09	Palmaz	NM	100	2 (9)
Dorros[19]	163	67	202	121/95	NM	NM	Palmaz	<50	100	23 (11)
Mean†	678‡	66§	799‡	536/344	371/139‡	1.07§			98	11
95% CI									95-100	6-16

n= number; Ost = Ostial; Trunc = Truncal; HT = Hypertension; RF = Renal failure; %DS = Percentage diameter stenosis; NM = Not mentioned; CI=Confidence interval.

* Hematomas and puncture traumas excluded.

† Mean based on Random-Effects Model, except where indicated as weighted mean or as totals.

‡ Totals.

§ Weighted mean.

Table 2. Clinical and angiographic follow-up of patients undergoing renal artery stent placement.

	Clinical follow-up						Angiographic follow-up			
			Hypertension		Renal function				Restenosis	
Author	Patients for follow-up %	Follow-up months	Cured %	Improved %	Improved %	Stabilized %	Arteries for follow-up %	Follow-up months	Criterion % DS	%
Wilms[6]	100	7	30	40	0	0	58	7	NM	29
Kuhn[7]	80	11	29	43	50	NM	100	7	>50	25
Rees[8]	100	7	11	54	36	36	64	8	>50	39
Hennequin[9]	100	32	14	86	17	50	95	29	>70	20
van de Ven[10*]	92	6	68	5	36	64	82	6	>50	13
Henry[11]	92	14	19	57	20	NM	NM	6	>50	9
Iannone[12†]	86	10	4	35	36	45	83	11	>60	14‡
Blum[13]	100	27	16	62	NM	NM	100	27	>50	11
Boisclair[14]	100	13	6	61	41	35	23	NP	>50	NP
Harden[15]	100	6	NM	NM	34	34	75	6	>50	13
White[16]	100	6	NM	NM	20	NM	60	9	>50	19
Rundback[17]	NM	17	NM	NM	NM	NM	52	13	>50	25
Shannon[18*]	100	9	NM	NM	43	29	NM	9	>50	0
Dorros[19†]	28	48	3	51	NM	NM	NP	NM	NM	NP
Mean§	91‖	16¶#	20	49	30	38	72‖	17¶#		17
95% CI			4-37	16-83	22-39	25-51				12-23

n = number; % DS = Percentage diameter stenosis; NM = Not mentioned; Np = Not routinely performed; CI=Confidence interval.

*Primary and secondary stent placement.

† Primary stent placement.

‡ Duplex restenosis.

§ Mean based on Random-Effects Model, except where indicated as weighted mean.

‖ Mean.

¶ Weighted mean.

If number of patients for follow-up not reported, estimated from number of arteries for follow-up and vice versa. If angiographic follow-up not reported, estimated from clinical follow-up.

Procedure

In 11 studies the femoral approach was used for access; the brachial approach was used in the remainder.[15,16,19] Stent placement was preceded by predilatation or balloon angioplasty in all but one study.[19] The reason for predilatation was given in two studies: in one study to decrease the inflation pressure required for stent expansion,[8] and in the second to ensure that full expansion of the lesion was possible.[16] In one study the lesion was overdilated up to 120% of the original vessel size before stent placement.[7] The majority of studies (n=11) did not describe the method used for vessel sizing (probably they used visual estimation). In the remaining three studies digital angiographic analysis was used.[11,12,16] In 11 studies the Palmaz stent was used; two studies reported the use of Wallstents[6,9] and in one study the Strecker stent was used.[7] Overdilatation of the stent was performed in four studies up to 110%[8,16] or 120%[13] of the original vessel size or 0.5-1.0 mm larger than the original vessel.[7] The reason for this overdilation was reported as "to compensate for neointimal growth and to prevent the stent from migrating".[7] For ostial lesions a slight protrusion of the stent into the aorta was recommended in five studies.[10,11,13,14,18] In addition, in one study the part of the stent protruding into the aorta was reshaped with the use of a larger balloon.[11]

Anti-thrombotic therapy

Prophylaxis against thrombosis during the procedure was used in all series, but the regimens varied. These included a bolus 2.000-10.000 IU of heparin,[6,7,9-11,13,16] a bolus of heparin (1,000-5,000 IU) and nitroglycerine (100-400 μg),[8,14,17,18] or a combination of 75 mg dipyridamole, 325 mg aspirin and mannitol (10% i.v.).[19]

Six studies used intravenous heparin for anticoagulation the first days after renal artery stent placement[6,7,9-11,13,14] titrated to obtain a normal partial thromboplastin time two to three times normal. The anticoagulation regimen at patients' discharge was changed to aspirin 100-300 mg/d,[6,9-11] aspirin 660 mg/d and dipyridamole 150 mg/d,[7] aspirin 100 mg/d or ticlopidine 250 mg/d,[13] or warfarin.[14] Other studies used aspirin 75-300 mg/d[18] or warfarin (INR 2.0-2.5, 1-3 months)[16] only, or used a combination of aspirin, dipyridamole and warfarin.[19] Two studies did not routinely use anticoagulation after renal artery stent placement[8,17] and two other studies did not report their anticoagulation regimen.[12,15]

Initial technical success

The initial technical success of the procedure reported was not significantly different among the studies. In the first two studies successful stent placement was achieved in 83% and 80%, respectively,[6,7] followed by success rates ranging from 94% to 100% in subsequent studies (Table 1). It should be noted, however, that the definitions for technical success ranged from <10% residual stenosis[10,15] to <50% residual stenosis.[13,19]

Complications

Of the complications encountered the most frequently reported were hematoma formation and puncture trauma (n=40). More severe complications in 71 of the 799 treated arteries (9%) included renal failure (n=34; three fatal), segmental renal infarction (n=9), perinephric hematoma (n=9; two fatal), renal artery thrombosis or occlusion

(n=6), stent misplacement (n=5), proteinuria (n=2), sepsis (n=1), brachial artery occlusion (n=1), stent/vessel mismatch (n=1), cholesterol embolism to the lower extremities (n=1), dissection of the iliac artery (n=1) and brachial artery bleeding (n=1; fatal). The mean mortality rate related to the procedure was 1.2% (95% CI: 0-2.5). The mortality rate usually included deaths directly or indirectly related to the procedure within the first month after stent placement.[8,12,15,18] In one study the mortality rate included a patient who died six months after stent placement due to rupture of a pseudoaneurysm caused by the intervention.[18] One study did not mention the post-procedural period in which the mortality rate was calculated;[19] therefore this study was not included in the mortality rate. In addition, six other patients died, described as due to a cause not related to the procedure. The complication rate varied significantly across the studies ($p<0.001$) and was significantly lower in studies using Palmaz stents than those using other stent types (8% vs 25%; $p<0.001$); the combined complication rate was 11% (95% CI: 6-16; Table 1).

Follow-up

The clinical follow-up period ranged from six months[10,15,16] to 48 months;[19] for angiographic follow-up six months was the shortest interval,[10,11,15] whilst the longest follow-up period was 29 months.[9]

Clinical results

The clinical effect of renal artery stent placement on blood pressure was expressed in terms of 'cure' and 'improvement', although both classifications were not uniformly defined. In most studies 'cure' was defined as a diastolic blood pressure of 90 mmHg or less without medication.[6,8,9,11-14] Other definitions of 'cure' included blood pressure less than 160/95 mmHg,[10] blood pressure less than 160/95 mmHg without medication[7] and systolic blood pressure less than 160 mmHg and/or diastolic blood pressure less than 90 mmHg without medication.[19] In addition, one study reported 'clinical success' as systolic blood pressure less than 160 mmHg and diastolic blood pressure less than 90 mmHg with the same or less medication.[16] Definitions used for improvement of hypertension varied widely and are summarized in Table 3. More uniform criteria were used to define the effect of renal artery stenting on renal function in terms of 'improvement', 'stabilization' and 'deterioration'. Renal function was considered improved when the serum creatinine values decreased more than 20%,[10,11,15,17,18] more than 15%[8,12,14] or more than 18 μmol/l.[19] Renal function was considered stabilized when the change in serum creatinine values was less than the above-mentioned values and deteriorated when serum creatinine values increased with the above-mentioned values. In five studies no criteria for change in renal function were provided.[6,7,9,13,16]

The percentage of patients cured from hypertension (20%; 95% CI: 4-37) was not uniform between the different studies ($p<0.001$; Table 2). The percentage of patients in whom hypertension improved as result of renal artery stenting was higher (49%; 95% CI: 16-83) and differed significantly between the studies ($p<0.001$). No report found a significant decrease in overall serum creatinine values after stent placement. Renal function in patients with renal failure was improved in 30% (95% CI: 22-39), and stabilized in 38%

(95% CI: 25-51). These results did not vary significantly across the studies (p=0.13 and 0.11, respectively; Table 2).

Table 3. Definitions used to describe improvement of blood pressure following renal artery stent placement.

Author	Definition
Wilms[6]	Diastolic blood pressure ≥15% decreased and > 90 mmHg but < 110 mmHg
Kuhn[7]	Decrease in systolic and diastolic blood pressure ≥10 mmHg, the same or fewer medication
Rees[8]	Diastolic blood pressure ≥15 mmHg decreased with the same or fewer medication or fewer medication or diastolic blood pressure ≥15% decreased and > 90 mmHg but < 110 mmHg and the same or fewer medication
Hennequin[9]	Diastolic blood pressure <90 mmHg with the same or fewer medication or diastolic blood pressure ≥15% decreased and > 90 mmHg but < 110 mmHg and the same or fewer medication
van de Ven[10]	Decrease of mean arterial pressure ≥20%
Henry[11]	Diastolic blood pressure ≥15% decreased with the same or fewer medication
Iannone[12]	Diastolic blood pressure <90 mmHg and fewer medication or diastolic blood pressure >90 mmHg and >10 mmHg decrease with fewer medication
Blum[13]	Diastolic blood pressure of 91 to 110 mmHg and a ≥15% decrease or diastolic blood pressure of 91 to 110 mmHg, a ≥10% decrease and ≥1 drug less medication
Boisclair[14]	Diastolic blood pressure <90 mmHg or 90-110 mmHg, a ≥15% decrease with the same or fewer medication
Harden[15]	NM
White[16]	Clinical success: systolic blood pressure <150 mmHg and diastolic blood pressure <90 mmHg with the same or fewer medication
Rundback[17]	NM
Shannon[18]	NM
Dorros[19]	Systolic or diastolic blood pressure ≥10% or ≥15% decreased with the same medication or systolic or diastolic blood pressure remained the same or decreased <10% or <15% with fewer medication

NM = Not mentioned.

Restenosis rate

Angiographic follow-up was performed in all but three studies: in two studies follow-up angiography was not routinely performed[14,19] and one study used duplex ultrasound for detection of restenosis.[12] The definitions used for restenosis were not uniform among the studies. The criterion of ≥50% diameter stenosis was used for restenosis in most studies. Incidentally, >60% stenosis[12] and >70% stenosis[9] were criteria for restenosis. Unclear, however, was whether the percentages were calculated at the stent site (local stenosis)

Table 4. Patient's characteristics and initial angiographic success following percutaneous transluminal renal angioplasty.

	Patients					Initial angiographic success		
Author	Patients n	Age Years	Arteries n	Indication HT/RF	Location Ost/Trunc	Criterion % DS	Success % arteries	Complications* n arteries (%)
Karagiannis [21]	62	65	76	62/27	NM	<50	72	3 (4)
Jensen [22]	107	63	147	NM	NM	NM	82	8 (5)
Eldrup-Jorgensen [23]	52	68	60	10/42	NM	NM	92	3 (5)
Bonelli [24]	190	64	252	NM	53/189	<30	82	56 (23)
Von Knorring [25]	38†	60	38	38/0	9/29	NM	NM	NM
Tullis [26]	41	65	52	41/0	29/23	<60‡	75	NM
Baumgartner [27]	56	60	63	25/25	NM	<60‡	NM	NM
Hoffman [3]	50	66	52	46/36	52/0	<30	58	9 (18)
Plouin [28]	23	59	23	23/0	7/16	NM	NM	6 (26)
Webster [29]	25	60	25	25/0	13/12	NM	NM	3 (12)
Mean§	644‖	64¶	778‖	270/130‖	163/269‖		77	13
95% CI							68-86	6-19

n= Number; Ost = Ostial; Trunc = Truncal; HT = Hypertension; RF = Renal failure; %DS = Percentage diameter stenosis; NM = Not mentioned; CI=Confidence interval.

* Hematomas and puncture traumas excluded.

† Only patients with atherosclerotic renal artery stenosis analyzed.

‡ Based on Duplex Ultrasound.

§ Mean based on Random-Effects Model, except where indicated as weighted mean or as totals.

‖ Totals.

¶ Weighted mean.

or compared to the reference site (relative stenosis). This may cause considerable variation between the reviewed studies. The overall restenosis rate after renal artery stent placement, depending on the angiographic definition, was 17% (95% CI: 12-23) and ranged from 0%[18] to 39%[8] (p=0.04).

Table 5. Clinical and angiographic follow-up of patients undergoing percutaneous transluminal renal angioplasty.

	Clinical follow-up						Angiographic follow-up			
			Hypertension		Renal function				Restenosis	
Author	Patients for follow-up %	Follow-up months	Cured %	Improved %	Improved %	Stabilized %	Arteries for follow-up %	Follow-up months	Criterion % DS	%
Karagiannis[21]	48	40	19	52	22	50	NM	NM	NM	NP
Jensen[22]	78	12	12	40	NM	NM	77	12	>75	9
Eldrup-Jorgensen[23]	NM	28	NM	NM	NM	NM	NM	NM	NM	NP
Bonelli[24]	NM	33	8	62	NM	NM	NM	22	>70	NP
Von Knorring[25]	71	48	11	74	NM	NM	NM	48	NM	NM
Tullis[26]	35	28	11	33	50	40	35	24	>60	55
Baumgartner[27]	70	13	9	46	48	36	NM	13	>60¶	28
Hoffman[3]	49	21	2	64	32	36	50	11	>50	27
Plouin[28]	23	6	NM	NM	NM	NM	100	6	>50	13
Webster[29]	25	NM	NM	NM	NM	NM	35	12	NM	NM
Mean†	50‡	22‡	10	53	38	41	59‡	19‡‖		26
95% CI			7-14	42-63	25-51	35-48				11-42

n = Number; % DS = Percentage diameter stenosis; NM = Not mentioned; NP = Not standardly performed;
CI = Confidence interval.
† Mean based on Random-Effects Model, except were indicated as mean or weighted mean.
‡ Mean.
§ Weighted mean.
‖ If number of patients for follow-up not reported, estimated from number of arteries for follow-up and vice versa. If clinical follow-up not reported, estimated from angiographic follow-up.
¶ Based on Duplex Ultrasound.

Relationship between variables

Calculation of correlation between variables showed that older patients had more ostial lesions (r=0.61; p=0.05), significantly less stents per artery (r=-0.65; p=0.02), and a significantly lower complication rate than younger patients (r=-0.56; p=0.04). Finally,

patients' age was significantly related with success rate for hypertension: the older the patient, the smaller the effect on blood pressure (r= -0.77; p=0.009).

Comparison with PTRA

Data on PTRA are given in Tables 4 and 5. The patient groups for stent placement and PTRA showed significant differences in indication for intervention and the location of the lesion involved. In the stent studies more patients with renal failure and more ostial lesions were included than in the PTRA studies (p<0.02 and p<0.001, respectively). The technical success rate was significantly higher after stent placement compared with PTRA alone (98% and 77%, respectively; p<0.001). The complication rate was not significantly different between stent and PTRA alone (11% and 13%, respectively; 0.2<p<0.3). The proportion of patients in whom hypertension was cured was significantly different (20% after stent placement and 10% after PTRA; p<0.001); the proportion of patients with improvement of hypertension was very similar for both treatment strategies (49% and 53%, respectively; 0.1<p<0.2). The percentage of patients with improved renal function was significantly lower for stent placement than for PTRA (30% vs 38%, respectively; p<0.001). Restenosis rates, however, were significantly lower after stent placement than after PTRA alone (17% and 26%, respectively; p<0.001).

DISCUSSION

Review of 14 studies dealing with patients with hypertension and/or renal failure indicated that renal artery stent placement is an attractive treatment modality showing a high initial success rate (98%) with an average restenosis rate of 17% at 17 months follow-up. At six to 48 months follow-up hypertension was cured in 20% of the patients and improved in 49%. Renal function in the patients with impaired renal function was improved in 30% and stabilized in 38%.

In the early studies the majority of patients studied was included in order to assess the effects on blood pressure. Later studies assessed the effect on renal function in patients with renal failure regardless of the presence of hypertension.[15,17,18] It is acknowledged that although the minority of patients with chronic renal failure has renovascular disease, intervention by PTRA or stenting in renal failure associated with renovascular disease seems worthwhile since a stenosis of the renal artery is one of the few correctable causes of renal failure. In most of the reviewed studies secondary renal artery stent placement was performed i.e. after initial or late failure of PTRA. In some studies, however, primary stent placement or combined primary or secondary stent placement was performed. Patients undergoing secondary stent placement after unsuccessful PTRA may have more severe renal artery disease and are therefore perhaps more difficult to treat with stent placement than patients undergoing primary stent placement. This phenomenon could have caused a selection bias and makes comparison between studies of technical and clinical results difficult.

The majority of patients selected had atherosclerotic renal artery stenosis. According to the literature the outcome of PTRA for renal artery stenoses due to fibromuscular dysplasia appears to be much better than for atherosclerotic stenoses.[2] No conclusions

could be drawn about the value of stenting for fibromuscular dysplasia because these patients were much underrepresented in this review.

Most investigators used the Palmaz stent; only three studies used other stent types.[6,7,9] Clinical success and restenosis rates in these series did not substantially differ from those reported with Palmaz stents. Complication rates, however, were higher in the studies, which did not use Palmaz stents, but these results have to be interpreted with caution since only three studies used other stent types. In the studies using Wallstents[6,9] problems were encountered with the stent visibility on fluoroscopy. This is of utmost importance for correct stent placement, especially when the selected stent is short. The femoral approach for access into the renal artery was commonly used in the reviewed studies and seems to be safer than the brachial approach which is illustrated by the case of the patient who died due to uncontrolled bleeding from a brachial puncture site.[15]

In the reviewed studies no specific relation could be found between the anti-thrombotic therapy used and the outcome and complications of the intervention. Anti-thrombotic therapy is warranted to prevent thrombosis, but at the same time significant bleeding complications should be avoided.

Initial technical success of renal artery stenting was high, and concurred with success rates of stent placement in coronary arteries.[30,31] However, the difference in angiographic definitions used for technical success made adequate comparison difficult. We ourselves used intravascular ultrasound following angiographically successful renal artery stent placement and found that intravascular ultrasound data warranted further increase of vessel dimensions in 33% of the patients studied.[32] Future studies will learn whether renal artery stent placement guided by intravascular ultrasound is beneficial for the long-term outcome.

The initial technical success rate of stent placement was consistently high (>80%). The complication rate encountered (11%) varied among the studies reviewed. The cause of the difference in complication rates between the studies (0% to 40%) remains speculative. The mortality rate due to renal artery stent placement was the same as previously reported following coronary artery stenting (1.2%).[33]

Reviewing the results of renal artery stent placement for renovascular disease, it appears that there is no universally accepted reporting standard. Although all reports describe a decrease in systolic and diastolic blood pressure after stent placement, there is much variation between definitions for 'cure' and 'improvement' of hypertension. This aspect hampered adequate comparison between the different studies included and may explain the difference in clinical results achieved. In addition, the adjustment of anti-hypertensive drugs after stent placement was not sufficiently described and quantified. The actual effect of stent placement on blood pressure in these uncontrolled studies, therefore, remains elusive, especially when one bears in mind that blood pressure lowering can also be obtained by medication alone.[28] Reporting all actual data on blood pressure, as well as the amount and type of antihypertensive drugs used, may provide a more accurate comparison between results of the various studies. The best way to express the amount of antihypertensive drugs is, to our knowledge, the calculation of

Defined Daily Doses (DDDs) according to the World Health Organization to reflect both the number and dosage of the prescribed drugs.[34] In concurrence with results after PTRA, a beneficial effect of renal artery stent placement on renal function has not been convincingly established. Nevertheless, 30% of the patients with renal failure was regarded as improved and 38% as stabilized, which may indicate that the effect of stent placement on renal function may be stabilization rather than statistically significant improvement. It is noteworthy that the most recent studies focused on the effect of renal artery stent placement on the management of renal function,[15,17,18] while the effects on hypertension seem to be of less importance. This shift-of-focus from hypertension to renal function seems not be justified regarding the data on blood pressure and renal function among the studies reviewed. It should be noted, however, that hypertension has been the subject of numerous previous studies, and renal function has been somewhat ignored, which may be corrected in the later studies.

The averaged restenosis rate following renal artery stenting of 17% (range 0% to 39%) after six to 29 months follow-up concurred with restenosis rates in coronary arteries.[35] Restenosis rates were significantly lower than after PTRA alone, although again a randomized trial would be warranted to investigate this topic in more detail. The cause of the different restenosis rates between the different studies was not clearly established, nor were the mechanisms related to restenosis.

Calculation of correlations between the different variables revealed that older patients had less benefit from stent placement with regard to hypertension than younger patients. This may reflect the coexistence of essential hypertension and irreversible arteriolosclerosis in older patients. A serious limitation associated with the calculation of correlations between the different variables across the studies is the absence of raw data. The fact that, for example, one patient may have undergone two stent placement procedures could not be taken into account in an analysis as presented in this study. Therefore, conclusions must be interpreted carefully. For the same reason, we were unable to perform a multivariate regression analysis, which may establish the prediction of outcome of intervention based on patient or lesion characteristics. The results of our study, however, demonstrate that such an analysis would be interesting to perform.

Comparison between stent placement and PTRA showed higher initial success rates and lower restenosis rates after stent placement. The percentage of patients cured from hypertension tended to be higher after stent placement than after PTRA. The results as presented here were in accordance with the results of the randomized trial comparing renal artery stent placement with PTRA.[36] In the latter study renal artery stent placement was a better technique than PTRA to achieve vessel patency with higher technical success and lower restenosis rates (88% vs 57% and 14% vs 48%, respectively).[36] The clinical outcome, however, was not significantly different between stent and PTRA. In the meta-analysis presented here, stent placement was associated with a lower percentage of patients with improved renal function. This may be due to the fact that the stent studies included more patients with impaired renal function

instead of hypertension, which may affect the clinical outcome in terms of renal function. It should be stressed that the major limitation of the present study is that it is not a randomized controlled clinical trial. Although randomized controlled clinical trials are the superior mode for evaluating and comparing therapeutic interventions, they also have limitations.[37] First, a randomized trial, performed in an ideal setting with a selected, usually small, patient population may hamper generalization of the results. Second, these trials are costly and often have a short follow-up period for both practical and ethical reasons. Meta-analysis of cohort studies, on the other hand, may reflect the general clinical practice, is cheaper and supplies additional data on a larger number of patients and may be a reasonable alternative for a randomized controlled clinical trial. However, it should be acknowledged that a meta-analysis as presented here has well-known deficits including unequal number of patients and different end-points between the studies. A multi-center trial with uniform patient entry criteria and outcome measures would provide valuable results.

NEED FOR FUTURE STUDIES

The following issues need to be addressed in future studies:

- The assessment of the outcome of PTRA, stent placement and optimal medical therapy in a randomized controlled setting.
- The long-term effects of the treatment modalities on blood pressure, renal function and restenosis rates. Accurate monitoring of the amount of antihypertensive medication in Defined Daily Doses is of critical importance, since inaccuracies blur the outcome of intervention.
- Optimal visualization of the effect of endovascular renovascular intervention. Possible modalities are the use of intravascular ultrasound[32] and magnetic resonance angiography.[38]

CONCLUSIONS

Renal artery stent placement appears to be superior, regarding initial success and restenosis rates and clinically comparable to PTRA alone. Future studies are needed to focus on the prevention of complications and on the assessment of long-term benefit, as well as on the factors determining success or clinical failure of the intervention.

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To investigate the feasibility of using intravascular ultrasound to characterize normal and diseased renal arteries, renal artery specimens removed at autopsy were studied in vitro. Intravascular ultrasound images were qualitatively and quantitatively analyzed and compared to the histologic findings as gold standard. This study showed intravascular ultrasound to be a reliable technique for distinguishing renal arteries with or without a lesion. Also, it appeared that both plaque development and local vessel narrowing may result in renal artery stenosis.

Chapter 4

IN VITRO VALIDATION, WITH HISTOLOGY, OF INTRAVASCULAR ULTRASOUND IN RENAL ARTERIES

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Renal artery stenosis may cause renovascular hypertension and may lead to renal dysfunction. [1-3] Stenosing plaques are most common at the proximal part of the renal artery and are usually bilateral.[4,5] Atherosclerotic lesions account for 70-75% of the renal artery stenoses, the remainder being due to fibromuscular dysplasia.[6,7]
Percutaneous transluminal renal angioplasty (PTRA) has been advocated as the treatment of choice for renal artery stenosis. Long-term results of PTRA show that cure rates are mainly dependent on the type of lesion involved: cure rates for hypertension arising from fibromuscular dysplasia are better than for atherosclerotic renal artery stenosis.[6,7]
Intravascular ultrasound (IVUS) is a unique way of obtaining cross-sectional morphologic and quantitative data of the normal and diseased arterial wall *in vivo*.[8,9] Previous studies in coronary arteries have established that adaptive remodeling of the vessel can compensate for the accumulation of atherosclerotic plaque.[10,11] Furthermore, arterial shrinkage is now recognized as an important factor in peripheral arterial stenosis.[12]
In the present in vitro study, we compared qualitative IVUS findings in renal arteries with histology as gold standard, and determined the quantitative characteristics of renal artery stenosis.

METHODS

Human specimens

Renal arteries attached to the abdominal aorta (n=44) were removed from 21 consecutive humans over 40 years of age (14 males, seven females; median age 66 years, range 42-88) at autopsy. Twelve of these patients had coronary artery disease, three had peripheral vascular disease, five had cerebrovascular disease, nine had hypertension, and three had end-stage renal failure. The specimens were stored frozen at -20°C. For the in vitro study, the specimens were thawed, and side-branches and the proximal and distal ends of the aorta were tied off with sutures. The distal ends of the renal arteries were connected with sheaths and fixed in a waterbath at room temperature (Fig. 1). During the study, the arteries were pressurized at 100 mmHg by means of a fluid reservoir containing water connected to the side arm of the sheath.

Intravascular ultrasound

A mechanical 30 MHz imaging system, designed for clinical use, was used with a Princeps 30 MHz 4.3F catheter (Endosonics, Rijswijk, The Netherlands). Since access to the renal artery from the aorta was impossible due to the acute angle of the renal artery, the IVUS catheter was introduced via the sheath distal in the renal artery and advanced up to the aorta. A displacement sensing device was used to match IVUS images with the corresponding histologic sections.[13] Displacement of the ultrasound catheter tip in steps of 0.1 mm was related to a reference site (the aorta) and mixed automatically with the ultrasound information on a videoscreen. IVUS images were made during pullback of the catheter and stored on S-VHS videotape for further analysis.

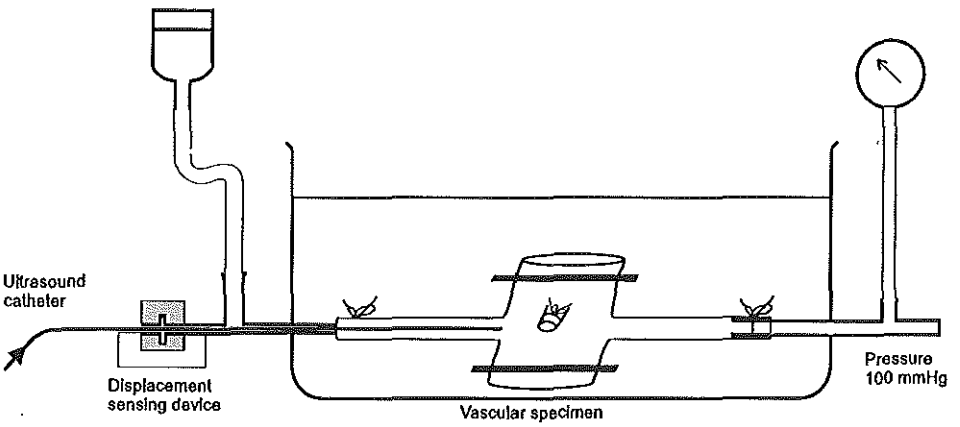

Figure 1. In vitro set-up showing the intravascular ultrasound catheter advanced through the sensing unit of the displacement sensing device and sheath distal into the pressurized renal artery.

Histology

For histologic comparison, the arteries were fixed under pressure (100 mmHg) in 10% buffered formalin for 2 hours, and subsequently decalcified in a standard rapid decalcification solution (Apex Inc., Plainfield, Illinois, USA) for 5 hours. The arteries were processed for routine paraffin embedding. Transverse sections (5 µm thick) were cut perpendicular to the long axis of the vessel at 10 mm intervals. Pathologic sections of the artery, marked with a needle, were cut at 1 mm intervals, and stained with elastic van Gieson and hematoxylin-eosin techniques.

Qualitative analysis

Data from the displacement sensing device and from the aorta as an anatomical marker were used to correlate IVUS images with the corresponding histologic sections. To assess lesion morphology, two to four sets of corresponding IVUS images and histologic sections were selected from each vascular specimen, including the most stenotic site. The renal arterial wall was defined as normal when wall thickness (i.e. intima and media) was 0.5 mm or less. A distinction was made on IVUS between bright lesions superimposed on the arterial wall with or without peripheral shadowing. Lesion morphology identified on histologic sections included fibromuscular lesions with or without calcifications. A fibromuscular lesion was defined as a lesion mainly composed of smooth muscle cells and a disorderly arrangement of elastin fibers. Calcification was defined as calcium crystals within a fibromuscular lesion seen on the sections stained with the hematoxilin-eosin technique. Lesions were classified on IVUS as eccentric and concentric. A concentric lesion was involved when the whole vessel was diseased and an eccentric lesion was present when a part of the vessel wall was disease-free. The location of the most stenotic site (i.e. smallest lumen area) recorded by IVUS was defined as ostial (i.e. within 10 mm from the aorta), or as truncal (i.e. non-ostial).[14]

Quantitative analysis

A multitude of IVUS cross-sections was quantitatively analyzed with an interval of 5 mm. Analysis included assessment of lumen area, vessel area, plaque area, and percentage area obstruction (Table 1). Lumen area was defined as the area encompassed by the inner boundary of the intimal surface. Vessel area was defined as the native vessel area bounded by the medial-adventitial border. Plaque area was obtained by subtraction of lumen area from vessel area. Percentage area obstruction was calculated as plaque area divided by vessel area. From each vascular specimen a target site and a reference site were selected. The target site was the IVUS cross-section with the smallest lumen area. The reference site was the IVUS cross-section with the largest lumen area (before the first major side-branch) proximal or distal to the target site. The vessel area measured at the target site was expressed as a percentage of the vessel area measured at the reference site by dividing the target site vessel area by the reference site vessel area, and multiplying by 100. A relative vessel area of >110% at the target site represented a larger vessel area (group I), 90-110% indicated no change (group II), and a vessel area of <90% indicated a smaller vessel area at the target site with respect to the reference site (group III). A cut-off point of 10% was used to correct for interobserver differences in measurements.

To determine whether vascular tapering was present,[15] a second reference site was chosen from each vascular specimen 10 mm distal to the target site and analyzed for vessel area. A comparison was made between the mean vessel area obtained at the target site, the reference site 10 mm distal to the target site, and the reference site before the first major side-branch distal to the target site.

The relationship between the extent of lesion, the relative vessel area, the location of the target site (ostial or truncal), and the reference site (proximal or distal to the target site) on the one hand, and patient's age and sex on the other hand, was determined.

The reproducibility of IVUS parameters used in this study has been reported previously.[16] For the present study, quantitative analysis of both lumen and vessel area of 40 preselected IVUS cross-sections was repeated after three months in order to determine the intraobserver variability in measurements.

Statistical analysis

Data are expressed as means ± SD. Measurements of the target and reference site and intraobserver differences were analyzed with Student's *t*-test for paired observations. The degree of intraobserver variation was presented as a coefficient of variation, defined as the SD of the paired differences divided by the mean of the absolute values. $p<0.05$ was considered statistically significant.

RESULTS

In 41 of the 44 renal artery specimens IVUS investigation was completed successfully. In three specimens, the IVUS catheter was advanced subintimally; these specimens were not used for further analysis. The mean length of the renal arteries studied up to the first major side-branch was 32 mm (range 12 to 65 mm). As the catheter was pulled back, it became evident that lumen area changed markedly.

Qualitative analysis

From the 41 renal artery specimens, 130 corresponding IVUS images and histologic sections were available for analysis. The renal arterial wall was characterized on IVUS by a three-layered structure specific for muscular arteries: a hypoechoic media with clear definition of the intima and adventitia, showing bright echoes (Fig. 2). In 55 IVUS cross-sections, there was no evidence of a lesion; this was in agreement with the histologic results. Bright lesions seen on IVUS (n=75) corresponded with fibromuscular lesions on the histologic sections. In 31 of the 75 cross-sections, part of the lesion showed peripheral shadowing corresponding with calcium deposits seen histologically. Calcifications observed by IVUS were scored false positive on five cross-sections and false negative on four cross-sections. The sensitivity of IVUS in detecting calcifications was 87% and the specificity was 89%. Of the 75 lesions, 17 were concentric and 58 were eccentric on IVUS imaging. The most stenotic site was located near the ostium in 20 specimens (ostial lesion) and in the truncus in 21 specimens (truncal lesion).

Quantitative analysis

All 20 ostial lesions had a distal reference site. Of the 21 truncal lesions, 13 had a proximal reference site and eight had a distal reference site. Quantitative data on the target and reference site are given in Table 1.

Table 1. Quantitative data of 41 renal arteries studied with intravascular ultrasound *in vitro*

	Group I (n = 8)		Group II (n = 12)		Group III (n = 21)	
	Target	Reference	Target	Reference	Target	Reference
Lumen area (mm^2)	16.9 ± 7.8[†]	25.0 ± 9.5	15.1 ± 8.1[†]	20.7 ± 9.8	15.5 ± 8.9[‡]	23.1 ± 10.5
Vessel area (mm^2)	43.1 ± 10.7[‡]	33.9 ± 10.1	30.2 ± 14.3	30.6 ± 14.0	25.3 ± 12.4[‡]	33.3 ± 14.6
Plaque area (mm^2)	26.2 ± 5.6[‡]	8.9 ± 1.6	15.1 ± 8.1[†]	9.9 ± 5.6	9.8 ± 5.2	10.2 ± 5.4
Area obstructed (%)	62.4 ± 12.0[‡]	28.0 ± 8.0	49.5 ± 14.7[‡]	32.2 ± 11.0	40.3 ± 16.0[*]	30.4 ± 8.3

Values are means ± SD. Specimens were grouped on the basis of whether the target site had a larger (>110%; group I), similar (90-110%; group II) or smaller vessel area (<90%; group III) than that of the reference site.
[*]p <0.05, [†]p <0.01, [‡]p <0.001, versus reference site.

In group I (n=8 of which six were ostial) the lumen area decrease was mainly due to the extent of plaque, and was associated with a large vessel area (Fig. 3). In group II (n=12 of which five were ostial) decrease in lumen area at the target site was solely caused by the extent of plaque. In group III (n=21 of which nine were ostial) decrease in lumen area at the target site was associated with a significantly smaller vessel area than at the reference site (p<0.001); the plaque area was as small as that at the reference site. A diagrammatic representation of the three groups is shown in Figure 4. Data on the reference sites showed little variation in vessel area between the groups (30.6±14.0 mm^2 to 33.9±10.1 mm^2).

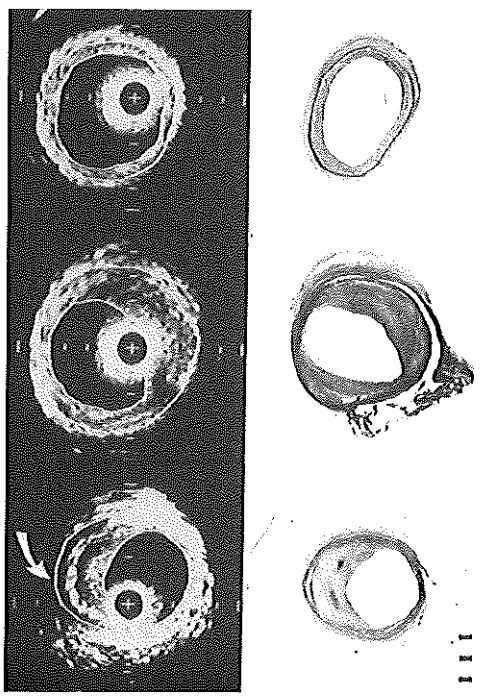

Figure 2. Intravascular ultrasound cross-sections and their histologic counterpart (elastic van Gieson staining). The inner contour presents the lumen area and the outer contour the vessel area. The upper panel shows a normal renal artery with a three-layered structure. The middle panel shows a renal artery with a fibrous lesion (from 11 to 4 o'clock). No calcifications are evident. The lower panel shows a fibrous lesion in the renal artery (from 6 to 12 o'clock) with calcification (arrow). Note the absence of echo reflections behind the calcification. Calibration = 1 mm; + represents the catheter.

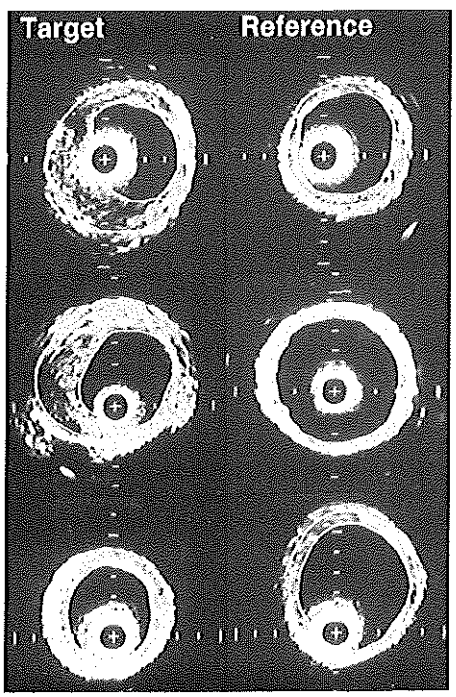

Figure 3. Intravascular ultrasound cross-sections obtained from renal arteries showing the target site (left panel) and the reference site (right panel). The inner contour presents the lumen area and the outer contour the vessel area. The vessel area at the target site is larger (upper panel), in the same order (middle panel), and smaller (lower panel) than at the reference site. Calibration = 1 mm; + represents the catheter.

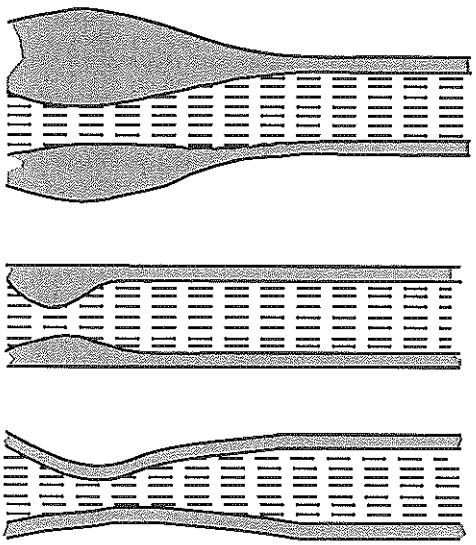

Figure 4. Diagram of three types of renal artery stenosis. In group I, renal artery stenosis was the result of an increase of both vessel and plaque area; in group II, plaque area was the only contributor to renal artery stenosis; and in group III, the renal artery stenosis was caused by a decrease in vessel area with respect to the reference site; the plaque area did not increase.

Comparison between the mean vessel area at the target site (30.2±14.1 mm^2), the reference site 10 mm distal to the target site (31.7±13.8 mm^2), and the reference site before the first major side-branch distal to the target site (mean 15 mm; 33.8±14.0 mm^2) revealed no tapering of the renal artery.

In 15 of the 41 specimens studied, no lesion was scored with qualitative analysis at the target site. This was in agreement with the histologic results. Five of these normal target sites belonged to group II and 10 to group III. The relative vessel area for ostial lesions was significantly larger than for truncal lesions (99.3±24.5 vs. 85.2±19.6, respectively; p=0.05). For ostial lesions significant larger plaque areas were found than for truncal lesions (19.1±9.0 mm^2 vs. 9.7±5.2 mm^2, respectively; p<0.001). The relative vessel area calculated for vessels with a proximal reference site was significantly smaller than for vessels with a distal reference site (78.8±14.7 vs. 98.7±23.8, respectively; p=0.008). In a review of the histologic sections for potential differences in the media, external elastic lamina and adventitia between the target and the reference sites and between the three groups, the only difference found was a marked thickening of the external elastic lamina at the target site of group I compared with a thin, well-defined external elastic lamina seen at the reference site.

No relationship was evident between patient's age, the quantitative IVUS measurements and location of the lesion. Measurements of lumen, vessel, and plaque gave significantly higher values in males than in females. Relative measurements (target values divided by reference values), however, were not significantly different. Intraobserver differences for lumen and vessel area were not significant (p=0.193 and p=0.112, respectively) with a coefficient of variation of 3.4% for the lumen area and 11.4% for the vessel area.

DISCUSSION

With the development of new techniques for the endovascular treatment of renal artery stenosis, there is an increasing need for optimal knowledge and visualization of renal artery pathology. In the present study renal artery pathology revealed by IVUS imaging was compared with histology findings, used as gold standard.

Qualitative analysis

Bright lesions on IVUS corresponded with fibromuscular lesions on histology. The sensitivity and specificity of IVUS in detecting calcifications were good (87% and 89%, respectively). These results concur with those of other studies reporting a sensitivity of 77-97% and a specificity of 98-99%.[17-19] In our study, four of the five false-positive and four false-negative calcifications scored on IVUS can be explained by the difficulty to detect shadow behind a lesion in the absence of surrounding tissue. This problem is inherent to in vitro studies and may not be encountered in clinical studies. In one false-positive scored calcification on IVUS a dense fibrotic cap imitated the ultrasound signal of a calcified lesion. In a previous IVUS study we documented that densely organized fibrous tissue may induce excessive attenuation of the ultrasound signal, suggesting calcification.[20]

Quantitative analysis

In the present study, we compared quantitative IVUS measurements from the target site with those obtained at the reference site. The lumen area at the target site was similar in all groups selected. Percentage area obstruction, however, differed between the groups and was strongly related to plaque load and vessel area. In 20% of the specimens (group I) a relatively large vessel area was seen at the target site, probably in response to plaque area increase, a process also described by Glagov et al.[10] In 29% of the specimens (group II) lumen area reduction was solely caused by the extent of plaque. In 51% of the specimens (group III), however, lumen area reduction was associated with a small vessel area at the target site with respect to the reference site. The plaque burden seen at the target site was as low as at the reference site. Similar local differences in vessel size were described in coronary arteries and in peripheral arteries.[12,21] Pasterkamp et al.[12] regarded the small relative vessel area at the target site as either shrinkage or as failure to enlarge. In the present study small relative vessel areas were encountered without histologic abnormalities; the potential mechanisms related to this phenomenon remain unknown. In 1994 Gibbons and Dzau[22] reported on the alteration of vessel structure (remodeling) in response to increased arterial pressure. Active restructuring of the cellular and noncellular components of the vessel wall resulted in marked changes in luminal dimensions, with relatively small changes in wall thickness. Whether this process may explain the findings of the present study needs to be established in future studies. In order to acquire insight in the cellular mechanisms that may explain the findings of the present study, one could assess the expression of genes for vasoactive factors, such as platelet-derived growth factors and transforming growth factor-β1 at the target and the reference site.

Comparison of mean vessel area measured at the target and distal reference sites showed that tapering did not occur in the selected renal arteries. It is noteworthy that these features can not be evidenced by angiography, a technique unable to provide cross-sectional imaging and wall morphology.

In the present study, ostial lesions had significantly larger relative vessel areas and larger plaque areas than truncal lesions. This finding suggests that ostial lesions are

mainly caused by plaque development and truncal lesions mainly the result of a small vessel area. We found no significant differences in lesion locations between males and females. However, the significant differences in vessel dimensions between males and females have to be taken into consideration in clinical practice (e.g. for balloon size selection).

From a clinical viewpoint, we postulate that absence of a large plaque burden and a small relative vessel area at the target site may have important implications for selecting the optimal treatment of renal artery stenosis. For example, PTRA and stent placement may have a different outcome in renal arteries obstructed by atherosclerotic plaque as opposed to constricted renal arteries. Clinical studies with IVUS are needed to establish whether this assumption is correct.

Study limitations

Some potential limitations of the present study need to be addressed. First, data derived from the specimens used in this study may represent an anatomic substrate different from that in clinical series of patients undergoing renal artery interventions. Second, comparison of a target and a reference site gives a problem concerning the definition of those sites. In the present study lumen area magnitude was considered to be most important in developing hemodynamically significant renal artery stenosis, and therefore target and reference sites were selected as those sites with the smallest and largest lumen area, respectively. Third, the reference site may undergo compensatory dilatation (post-stenotic dilatation) and falsely demonstrate a small vessel area at the target site. However, we believe that compensatory dilatation of the reference site was not an important factor in this study, because vessel area at the reference site did not differ markedly between the groups, and post-stenotic dilatation (by definition distal to the target site) did not occur in 13 proximal reference sites. Finally, it should be remembered that changes in arterial dimensions occur over time. By choosing target and reference site in the same artery, the assumption was made that different sites in one artery are representative for the narrowing process over time. Whether this assumption is correct needs to be established in serial studies.

In conclusion, IVUS proved to be reliable in distinguishing renal arteries with or without a lesion. Apart from atherosclerotic lesions, local differences in renal arterial wall dimensions may be important in the development of renal artery stenosis.

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A recent study of human cadaveric renal arteries revealed that renal artery narrowing could be due not only to atherosclerotic plaque compensated for by adaptive remodeling, but also to hitherto undescribed focal narrowing of an otherwise normal renal arterial wall (i.e. coarctation). The present study showed that vessel coarctation could also be identified in patients with symptomatic renal artery stenosis (RAS).

Chapter 5

INTRAVASCULAR ULTRASOUND EVIDENCE FOR COARCTATION CAUSING SYMPTOMATIC RENAL ARTERY STENOSIS

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It is generally accepted that atherosclerotic plaque accumulation is the principal cause of renal artery stenosis (RAS).[1,2] A recent intravascular ultrasound (IVUS) study in human renal arteries obtained at autopsy, however, suggested an alternative cause of RAS. [3] In that study we observed that in 60% of the specimens plaque accumulation with or without compensatory vessel enlargement (i.e. adaptive remodeling) caused lumen narrowing. This phenomenon was first described by Glagov et al. [4] and, subsequently, by others. [5,6] In the remaining 40% of the specimens, however, focal narrowing of the renal artery wall with little or no plaque was observed. Here, we propose the term "coarctation" to describe the latter condition (Dorland's Medical Dictionary defines "coarctation" as "a condition of stricture or contraction" [7]).
If this condition is present in vivo, it might cause hemodynamically significant RAS. However, to the best of our knowledge, renal artery coarctation has not been described before in vivo, especially not in patients with atherosclerotic renal vascular disease. The first aim of the present study was, therefore, to establish whether renal artery coarctation could be identified as a contributing factor to RAS in symptomatic patients with angiographically proven renal artery stenosis. The second aim was to identify angiographic and/or clinical variables that might be predictive for the distinguishing lesions.

METHODS

Between September 1996 and March 1999, we studied 48 consecutive patients (16 f, 32 m, aged 59±9 years [mean±SD]) with hypertension and/or renal function impairment and atherosclerotic RAS who were referred for percutaneous transluminal stent placement guided by IVUS. Previous angiograms had revealed >50% diameter stenosis in all patients. The Local Committee on Human Research approved the investigation. Patients were included in the study after informed consent was obtained.
Revascularization was performed via the femoral approach. The stenosis was crossed with a 5F selective catheter in combination with a 0.035-in hydrophylic guidewire [Terumo, Tokyo, Japan]. The hydrophylic wire was exchanged for a 0.020-in stiff guidewire with a flexible tip [Boston Scientific, Bülach, Switzerland] for guiding the IVUS catheter, the angioplasty balloon and the balloon-expandable stent. A 30-MHz mechanical IVUS imaging system was used with 4.3F catheters ("Princeps", Endosonics, Rijswijk, The Netherlands).[8] The IVUS catheter was positioned distally from the stenosis in the first major side-branch. Real time cross-sectional images of the renal artery wall obtained during slow pullback of the IVUS catheter were displayed on a monitor and stored on S-VHS videotape for off-line analysis.

Image analysis

From each renal artery, multiple IVUS cross-sections were quantitatively analyzed to select the target site and a reference site for further analysis. The target site was the IVUS cross-section with the smallest lumen area. The reference site was the most distal cross-section in the renal artery truncus with a normal appearance.

Analysis included assessment of lumen area (LA), media-bounded area (MBA), plaque area (PLA) and percentage area stenosis. LA was defined as the area encompassed by the inner boundary of the intimal surface. MBA was defined as the native vessel area bounded by the external elastic lamina. PLA was calculated by subtraction of LA from MBA. Percentage area stenosis was calculated as LA at the target site divided by the LA at the reference site.
The MBA at the target site was expressed as a percentage of the MBA at the reference site. A relative MBA of >85% at the target site indicated a similar or larger MBA ("adaptive remodeling" group) and a relative MBA of ≤85% at the target site indicated a smaller MBA than at the reference site ("coarctation" group). Based on our previous observation that tapering of the renal artery does not occur,[3] we used a 15%-tolerance interval to define a smaller MBA, to be on the conservative side. It was assessed whether the conclusions of the quantitative analysis, which were performed by two independent observers (TCL, JAvE), were consistent for the two observers individually. Mean values of the two observers are given.

Statistical analysis

The two groups were compared with regard to the MBA and PLA at the target and the reference sites, relative MBA and percentage area stenosis. Student's *t*-tests were used at the $p < 0.05$ significance level.
Interobserver variability for quantitative IVUS measurements was quantified by regression analysis and a coefficient of variation, defined as the standard deviation of the paired difference divided by the mean of the absolute value.
Multivariate logistic regression analysis was performed to predict the presence of either of the two lesions. A logistic regression model was fitted including angiographic and clinical parameters as the independent variables. Angiographically, a distinction was made between ostial and truncal lesions.[9] Dependence on the following clinical characteristics was assessed: age, sex, signs and symptoms of atherosclerotic vascular disease (angina pectoris, intermittent claudication, cerebrovascular accident or vascular surgery), duration of hypertension (<1 year, 1-2, 2-5 or >5 years), smoking history (ever or never), obesity (body mass index ≥25 kg/m^2), serum creatinine concentration and hypercholesterolemia (serum cholesterol level >6.5 mmol/L or use of cholesterol-lowering agents). In addition, we assessed whether any differences were found in the initial technical success rate and the three months clinical results (systolic and diastolic blood pressure, number of antihypertensive drugs and serum creatinine level) between the two groups.

RESULTS

IVUS images were obtained in 18 patients before intervention and in 18 other patients after predilatation with an angioplasty balloon 5 or 6 mm in diameter. In the remaining 12 patients, the interventionist did not use IVUS before stent placement.

Quantitative IVUS data for the group studied before intervention are given in Table 1. Nine out of 18 patients showed the coarctation phenomenon with an MBA at the target site of 24.0±5.1 mm^2, which was significantly smaller than in the adaptive remodeling group (33.9±6.8 mm^2, p = 0.003; Figure). PLA in the coarctation group (13.9±4.4 mm^2) was also significantly smaller than in the "adaptive remodeling" group (23.7±6.1 mm^2; p =0.001). Quantitative parameters at the reference site and the degree of area stenosis were not significantly different between the two groups. Similar results were encountered in the 18 patients studied after predilatation Table 1.

The two observers showed good observer agreement with regard to the IVUS measurements, with high correlation coefficient (r=0.98; observer-2 = 0.98 * observer-1 + 0.64 mm^2), and an overall coefficient of variation of 10.7%. The conclusions were consistent for each observer individually. Multivariate regression analysis did not reveal any angiographic or clinical parameter predictive for either adaptive remodeling or coarctation; no differences were encountered in initial technical success and 3-month clinical outcome between the two groups.

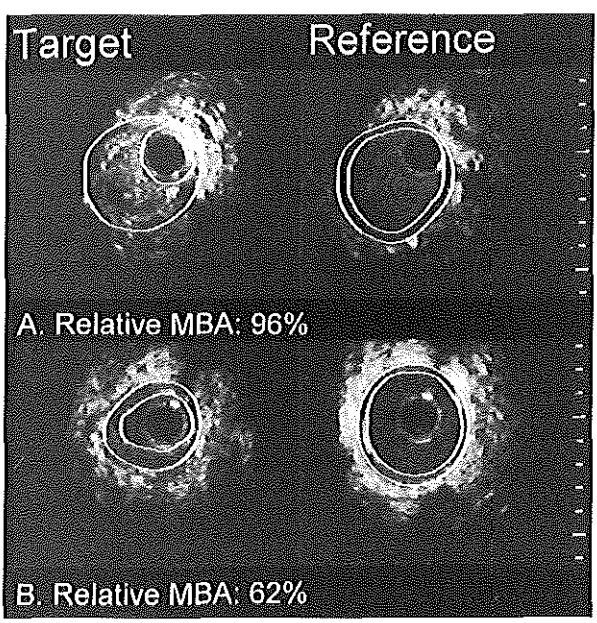

Figure 1. Intravascular ultrasound cross-sections obtained from renal arteries before intervention showing the adaptive remodeling (A) and the coarctation type of renal artery stenosis (B).
The left panel represents the target site and the right panel the reference site. The cross-sections are contour-traced, facilitating the recognition of lumen area (inner contour) and media-bounded area (outer contour).
Note the small relative media-bounded area and little plaque in the coarctation stenosis (B).
Calibration = 1 mm;
black circle = catheter.

Table 1. Quantitative cross-sectional intravascular ultrasound data of renal arteries before intervention (18 patients) and after predilatation (18 patients).

	Adaptive remodeling group	Coarctation group	*p*
Before intervention	n = 9	n = 9	
Target			
MBA, mm^2	33.9 ± 6.8	24.0 ± 5.1	0.003
PLA, mm^2	23.7 ± 6.1	13.9 ± 4.4	0.001
Reference			
MBA, mm^2	33.5 ± 7.6	33.9 ± 3.8	NS
PLA, mm^2	7.9 ± 2.0	7.8 ± 1.4	NS
MBA target/reference, %	103 ± 13	71 ± 11	< 0.001
Area stenosis target/reference, %	61.2 ± 19.7	61.4 ± 19.3	NS
After predilatation	n = 10	n = 8	
Target			
MBA, mm^2	43.0 ± 12.4	24.1 ± 10.6	0.004
PLA, mm^2	28.2 ± 13.0	12.3 ± 8.0	0.008
Reference			
MBA, mm^2	33.2 ± 6.3	35.2 ± 17.1	NS
PLA, mm^2	7.8 ± 1.9	6.9 ± 2.8	NS
MBA target/reference, %	130 ± 31	70 ± 10	< 0.001
Area stenosis target/reference, %	42.5 ± 18.0	52.1 ± 17.3	NS

Renal arteries are divided into the "adaptive remodeling" and "coarctation" groups according to the relative media-bounded area (MBA) at the target site >85% and ≤85%, respectively. Values are mean ± standard deviation and represent the averaged results of the two independent observers. PLA= Plaque area, NS= Not significant.

DISCUSSION

The conventional concept of development and progression of atherosclerotic RAS is the accumulation of plaque with or without compensatory vessel enlargement (i.e., adaptive remodeling). The current findings suggest an alternative substrate of symptomatic RAS, characterized by focal narrowing of the renal artery wall and little plaque (i.e., coarctation). The latter phenomenon was responsible for symptomatic RAS in 50% of patients, a prevalence of coarctation similar to that previously seen in our autopsy study.[3] Coarctation could be identified even after balloon dilatation in 44% of the patients. The present study is the first in which coarctation as cause of RAS was evidenced clinically. It is noteworthy that 32 years ago, McCormack et al. [10] described a proportion of histologic RAS with "arterial spasm fixed by accumulation of collagen", which may reflect the coarctation as seen in the present study. In our previous autopsy study in which we combined IVUS with histologic analysis, however, coarctation was not associated with specific histologic characteristics. Mintz et al.[11] described de novo stenotic lesions in coronary arteries that were characterized by inadequate remodeling and less plaque than expected. One might postulate that these coronary lesions are similar to the coarctation lesions in renal arteries seen in the present study.

The pathogenesis of coarctation RAS obviously remains speculative at this stage. Abdominal aortic coarctation with or without involvement of the renal arteries may be related to renal artery coarctation, but as with fibromuscular dysplasia, Takayasu's arteritis and neurofibromatosis, this is a relatively rare cause of RAS that commonly involves younger patients. In the present study angiographic and clinical data were similar for both the adaptive remodeling and the coarctation groups. In the coronary artery study of Mintz et al,[11] a significant association was found between inadequate remodeling lesions and the extent of lesion calcium. This led the authors to postulate that inadequate remodeling was a manifestation of advanced atherosclerosis. In the present study in renal arteries, however, only small, incidental speckles of calcium were present, both in the adaptive remodeling and in the coarctation groups. This, together with the fact that coarctation was also evidenced in human cadaveric renal arteries without plaque accumulation, suggests that in renal arteries, coarctation is a non-plaque determined phenomenon, possibly related to an early rather than a late stage of atherosclerosis, or perhaps not even related to atherosclerosis at all.

Clinical implications

The heterogeneity of atherosclerotic RAS as shown in the present study may have important clinical implications. Plaque-focused treatment by means of intravascular radiation therapy or plaque-lowering agents could be of minor importance for coarctation RAS. In addition, renal artery revascularization by either balloon angioplasty or stent placement is clinically successful in only part of the patient population treated. [12] Currently, which parameters determine the outcome of revascularization is insufficiently known. Whether the type of RAS determines the outcome of intervention is a question that will be investigated in future studies.

A limitation of our study was that IVUS images were not obtained in all 48 patients. This may have resulted in a selection bias; the prevalence of coarctation RAS as presented here must, therefore, be interpreted with caution.

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To study the impact of intravascular ultrasound (IVUS) during renal artery stenting, patients with atherosclerotic renal artery stenosis were studied with IVUS after predilatation and after angiographic successful stent deployment. After predilatation IVUS warranted the use of larger-sized balloons than suggested by angiography. Even after angiographic successful stent placement IVUS information resulted in additional dilatation or additional stent placement in 33% of the patients.

Chapter 6

STENT PLACEMENT FOR TREATMENT OF RENAL ARTERY STENOSIS GUIDED BY INTRAVASCULAR ULTRASOUND

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Renal artery stenosis may cause renovascular hypertension and is an important cause of renal failure.[1-3] Results of percutaneous transluminal renal angioplasty are more encouraging for stenosis due to fibromuscular dysplasia than for atherosclerotic renal artery disease.[4,5] Stenting of the renal artery may improve the treatment of atherosclerotic renal artery stenosis.[6-8] Adequate stent expansion, however, seems to be an important factor determining success or failure of balloon-expandable stent placement.[9]

It has been shown that intravascular ultrasound (IVUS) can provide accurate data on vessel dimensions, extent of the lesion involved, and the presence of stent underexpansion in patients undergoing renal artery interventions.[10,11] The present observational study was performed:

1. to evaluate the contribution of IVUS-derived parameters to the procedure,
2. to assess the qualitative and quantitative IVUS data obtained after renal artery stent placement, and
3. to determine the short-term clinical outcome.

MATERIALS AND METHODS

Study group

Between September 1996 and December 1997, 22 consecutive patients with symptomatic occlusive disease of the renal artery were referred for primary renal artery stent placement. The study group consisted 16 males and six females with a mean age of 60±10 years. Patients were referred for drug-resistant hypertension (n=9), renal function impairment (n=10), or hypertension associated with renal failure (n=3). In all patients renal digital subtraction angiography revealed a stenosis >50%. Blood pressure was measured with a sphygmomanometer at three consecutive visits at least one to two weeks apart, three times per visit after five minutes of rest, with the patient in the upright position. Hypertension was defined as a diastolic blood pressure >95 mmHg. Patients were regarded as having drug-resistant hypertension if they remained hypertensive on a two-drug regimen. Renal function impairment was defined as a creatinine level >110 µmol/l (normal value range 50-110 µmol/l). The baseline characteristics of the patients are given in Table 1. The Local Committee on Human Research approved the investigation; patients were included in the study after giving written informed consent.

Procedure

Spiral CT of the upper abdomen was performed one or more days before renal artery stent placement in 14 out of 22 patients in order to determine the exact angle between the renal artery and the aorta for optimal stent placement.[12] Procedures were performed by the femoral approach with a 9F introducer system [Cordis Europe, Roden, The Netherlands]. In order to evaluate the technical results of the procedure, a 5F straight flush catheter was introduced through the contralateral femoral artery and placed just proximal to the renal arteries. A 5F catheter was advanced up to the renal artery ostium

and the stenosis was crossed with a 0.035-in Terumo flexible wire. When the catheter had passed the stenosis the Terumo flexible wire was exchanged for a 0.020-in stiff guidewire [Schneider Europe, Bülach, Switzerland]. Digital subtraction angiography was performed followed by predilatation of the stenosis. The balloon size selected was based on visual assessment of the angiographic reference lumen diameter proximal or distal in the renal artery (without interposition of side-branches).

Table 1. Characteristics of the study population undergoing renal artery stent placement monitored by intravascular ultrasound.

Patient characteristics	Value
Sex (male/female)	16 / 6
Age (years)	61.3 ± 10.2
Blood pressure (mm Hg)	
Systolic	178 ± 28
Diastolic	96 ± 15
Mean	123 ± 18
Serum creatinine (µmol/l)	121 (71-427)
Antihypertensive drugs (DDDs)	3.06 ± 1.49
Coexisting risk factors	
Smoking	12
Diabetes mellitus type II	1
Coronary artery disease	12
Peripheral vascular disease	9
Cerebrovascular disease	4

Values are expressed as mean ± standard deviation, except for serum creatinine which is expressed as median (range);
DDDs = defined daily doses.

Palmaz stents [Johnson & Johnson Interventional Systems, New York, USA] were used. Stent length was based on angiography and was the shortest possible that minimally overlapped the stenotic site with one mm. A slight protrusion of the stent into the aortic lumen was applied. The stents were mounted on a 5F balloon catheter and preloaded in a "hockey stick" 8F guiding catheter [Cordis Europe, Roden, The Netherlands]. The guiding catheter-balloon-stent assembly was then passed over the guidewire across the lesion.

A Y-connector [Namic, Tullamore, Ireland] attached to the guiding catheter was used to enable accurate control of stent positioning. The delivery system was then withdrawn into the aorta, leaving balloon and stent in situ. The balloon was inflated to pressures of 10-12 Atm for 30 seconds. After removal of the balloon an angiogram was performed. The post-stent angiogram was considered successful based on a complete stent-vessel wall apposition and lesion covering and a residual diameter stenosis <10%.
Just before stent placement the patients received an intra-arterial bolus of heparin (5,000 IU). For anticoagulation, after the procedure 20,000 to 30,000 IU heparin per day was given intravenously for 48 hours under control of the activated partial thromboplastin time, followed by oral acetylsalicylic acid (100 mg daily) for six months.
Intravascular ultrasound
IVUS studies were performed after predilatation and after angiographic successful stent placement (vide supra). A commercially available mechanical system containing a single rotating ultrasound element [30 MHz; Endosonics, Rijswijk, The Netherlands] was used with a guidewire tipped 4.3F flexible catheter ("Princeps"; 0.035-in). The system is based on a mechanically motor-driven rotating catheter tip element connected to a flexible drive shaft. The element is covered by an acoustically transparent dome. Axial resolution is 75 µm and lateral resolution is better than 225 µm at a depth of one mm. The unit is connected to a prototype instrument that provides continuous real-time cross-sections of the vessel wall (up to 16 images per second).[13] The ultrasound catheter was introduced over the guidewire through the guiding catheter and advanced distally beyond the renal artery lesion. Under fluoroscopic control, IVUS cross-sections of the diseased segment were obtained during slow pullback of the catheter. The resulting images, together with the fluoroscopic data, were displayed on a videoscreen and stored on S-VHS videotape.
Qualitative analysis
The angiographic levels and the corresponding IVUS cross-sections were analyzed for the presence of vascular damage after predilatation and after stent placement. Angiographically, vascular damage included dissection, defined as the presence of irregular contrast filling of the treated part of the renal artery. On IVUS vascular damage included dissection, plaque rupture, and vessel rupture[14]. Dissection was defined as a tear in the intimal surface separating the lesion from the underlying arterial wall; plaque rupture was defined as a radial tear in the intimal surface perpendicular to the arterial wall, and vessel rupture was defined as an interruption in the internal elastic lamina and media that exposed the hyperechoic adventitia to the lumen.

Quantitative analysis

First, during the procedure semiquantitative analysis of the IVUS images was applied in order to test whether the planned intervention required modification based on IVUS criteria. After predilatation, IVUS was used to assess whether the balloon size selected angiographically was correct. When the balloon diameter was more than 20% smaller than the reference lumen diameter, a larger balloon was selected for stent placement. After stent placement the success of the intervention on IVUS imaging was based on:

- Complete stent-vessel wall apposition (absence of flow behind the stent struts). When incomplete apposition was present additional dilatation with or without a larger balloon was performed.
- An intra-stent lumen diameter of at least 80% compared to the lumen diameter of the normal reference site; when the intra-stent diameter was more than 20% smaller than the reference lumen diameter, an additional dilatation with a larger balloon was performed.
- The absence of a residual lesion proximal or distal to the stent; when a more than 20% lumen reduction compared to the smallest intra-stent lumen diameter was encountered, an additional dilatation or additional stent placement was performed.

Second, to determine the ultimate effect of the intervention the IVUS images were quantitatively analyzed off-line, using a digital video analyzer system [International Business Machines, Boca Raton, FL].[15] Analysis included assessment of the smallest intra-stent lumen area (i.e. target site), reference lumen area, balloon area, and percentage residual area stenosis after predilatation, after stent placement and (when performed) after additional intervention. Lumen area was defined as the area encompassed by the inner boundary of the intimal surface or by the stent circumference. Percentage residual area stenosis was defined as the difference between the lumen area at the reference site and the lumen area at the target site divided by the reference lumen area.

In addition, a comparison was made between the smallest intra-stent lumen area and the lumen area measured at both stent edges. The difference between the lumen area at both stent edges and the smallest intra-stent lumen area was calculated and expressed as a percentage of the smallest intra-stent lumen area. A relative difference >10% indicated a larger stent edge. A cut-off point of 10% was used to correct for intra-observer differences in measurements.

Follow-up

Patients returned for regular follow-up at the outpatient clinic. Blood pressure, the amount of antihypertensive drugs prescribed, and serum creatinine concentrations were monitored before stent placement and during follow-up of three months. Blood pressure

data were compared to the blood pressure values during the last three months prior to intervention.

The use of antihypertensive drugs was recorded during the last three months prior to intervention, and during three months of follow-up. The amount of antihypertensive drugs was expressed as the summarized defined daily doses of the individual drugs (DDDs; the DDD is the assumed average maintenance dose per day for a drug used based on its main indication in adults).[16]

The median of all serum creatinine values measured in the year prior to the intervention was compared with the serum creatinine values at follow-up. In addition, using the Cockroft formula, glomerular filtration rates were calculated from each patient before intervention and at follow-up.

Statistical analysis

Quantitative measurements obtained after predilatation and after stent placement, and measurements of blood pressure, amount of antihypertensive drugs, serum creatinine, and glomerular filtration rates were compared using Student's paired *t*-test. Serum creatinine values were transposed in logarithmic values when performing a Student's paired *t*-test. A p-value <0.05 was considered statistically significant. Values are expressed as mean and standard deviation.

RESULTS

In two patients (9%) it was technically impossible to pass the stenosis with a guidewire because of severe calcification of the aorta and the lesion involved and to perform an intervention. Balloon size used for predilatation ranged from four to six mm. In 19 patients a single stent was placed, and in one patient two stents were implanted. In total 10 p154 stents and 11 p204 stents were used. IVUS images were obtained in 18 of the 20 patients who received a stent; in one patient failure of the IVUS system was encountered and in another patient the ultrasound catheter could not be advanced into the renal artery following stent placement. No adverse effects attributable to the use of IVUS were observed. The total time required for the use of IVUS was five to 10 minutes. After predilatation IVUS images were obtained in nine patients; in five patients it was impossible to advance the ultrasound catheter over the guidewire into the renal artery and in four other patients the radiologist refrained to use the ultrasound catheter due to the potential risk for vessel damage. After stent placement IVUS images were obtained in all 18 patients.

Qualitative analysis

In six of nine patients studied with IVUS after predilatation, both angiography and IVUS revealed vascular damage. On IVUS a dissection was seen in four patients, a plaque rupture in one patient, and a vessel rupture in the remaining patient. Following stent placement, vascular damage seen on IVUS in five patients (dissection in four patients; vessel rupture in one patient; Fig. 1) was seen on the angiogram in two patients.

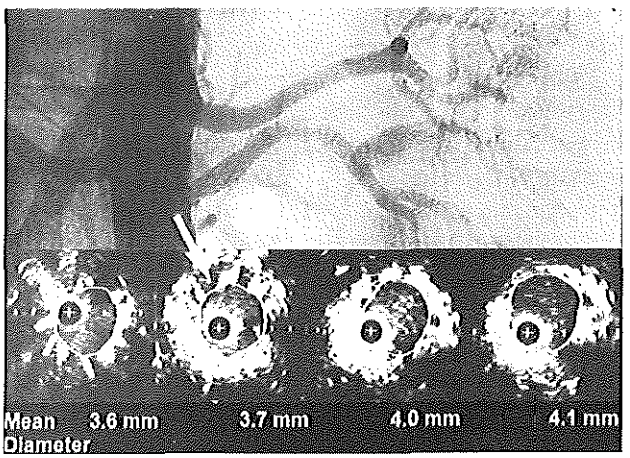

Figure 1a. After stent placement (5 mm balloon)

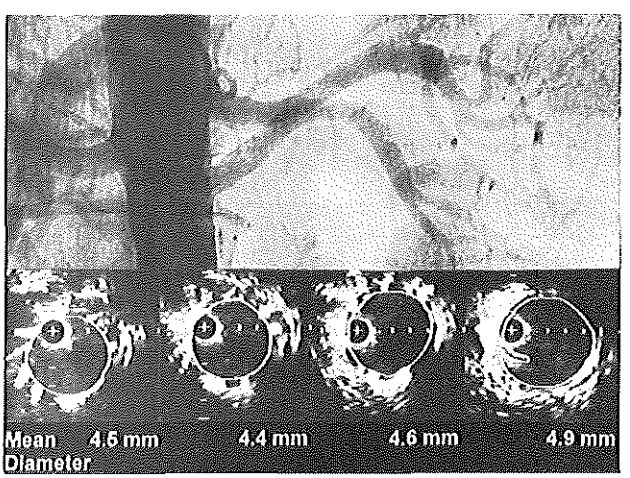

Figure 1b. After additional dilatation (5 mm balloon)

Figure 1. Angiograms and corresponding intravascular ultrasound (IVUS) cross-sections obtained after stent placement (A) and after additional dilatation (B). The contour in the IVUS cross-section represents the lumen or stent area. IVUS images display (from right to left) the reference site, the distal stent edge, in-stent site, and the proximal stent edge in the aorta. After stent placement IVUS showed incomplete stent-vessel wall apposition (arrow), which was not seen on angiography. Note the discrepancy between the balloon size (5 mm) and the smallest intra-stent diameter (3.6 mm), and that the target site is located at the proximal stent edge. Additional dilatation performed because of incomplete stent-vessel wall apposition, resulted in an increase in lumen diameter and complete stent apposition. Note the small dissection (arrowhead) at the reference site, not evidenced angiographically. + = catheter; calibration = 1 mm.

Quantitative analysis

On the basis of semiquantitative analysis of the IVUS images after predilatation in five patients a difference more than 20% was encountered between the balloon diameter selected and the reference lumen diameter. In these patients it was decided to select a larger balloon for stent placement.

After stent placement:

- Incomplete stent-vessel wall apposition evidenced in one patient was treated by additional dilatation (Fig. 1).
- An intra-stent lumen diameter more than 20% smaller than the reference lumen diameter was observed in three patients and treated with additional dilatation using a larger balloon.
- A lesion distal to the stent causing more than 20% obstruction was evidenced in two patients. Additional dilatation was performed in one patient, and additional stent placement in the remaining patient.

On IVUS the final semiquantitative result after stent placement was successful in all patients. Table 2 summarizes the mean data obtained from the off-line quantitative analysis of the IVUS images. In the nine patients studied with IVUS after predilatation, stent placement resulted in a significant increase of lumen area (46%; p=0.001). The mean residual area stenosis decreased from 48% before stent placement to 32% after

Table 2. Mean quantitative intravascular ultrasound data after predilatation, after stent placement and after additional intervention, and balloon size used.

Study Group	n	Target site (mm^2)	Reference site (mm^2)	Balloon (mm^2)	% Area Stenosis
Patients studied after predilatation:					
After predilatation	9	13.1 ± 3.8	26.1 ± 7.5	22.7 ± 5.8	48
After stent placement	9	19.1 ± 4.2	28.4 ± 6.0	27.3 ± 2.9	32
Final result	9	21.6 ± 3.2	29.3 ± 5.3	28.4 ± 4.7	25
Patients studied after stent placement:					
No additional intervention	12	22.3 ± 4.8	31.4 ± 9.8	28.6 ± 6.3	25
Before additional intervention	6	18.2 ± 4.7	28.7 ± 10.8	26.8 ± 3.5	33
After additional intervention	6	22.5 ± 5.9	32.2 ± 12.1	30.2 ± 7.2	28
Final result	18	22.4 ± 5.0	31.7 ± 10.3	29.2 ± 6.5	26

stent placement (p=0.097). In four of these patients an additional stent dilatation was performed. The final result of the nine patients showed a mean residual area stenosis of 25%. Modification of the balloon size after predilatation based on IVUS imaging resulted in a good correlation between balloon size and reference segment (r=0.80; p=0.01). In 12 patients with a successful semiquantitative IVUS result after stent placement,

quantitative analysis revealed a residual area stenosis of 25%. In six patients who underwent additional intervention based on IVUS after stent placement, lumen area increased significantly (24%; p=0.03) and residual area stenosis decreased from 33% to 28%. Final results after stent placement of all patients showed a lumen area of 22.4±5.0 mm^2 (mean lumen diameter 5.3 mm). The balloon size used for stent placement exceeded the resulting intra-stent lumen area (mean difference 22%; p=0.02).
Comparing the smallest intra-stent lumen area and the lumen area measured at both stent edges individually it was found that in three stents the areas were in the same order. In three other stents the smallest intra-stent lumen area was smaller than the lumen area of both stent edges (range 15-51%). In the remaining 12 stents either the lumen area at the proximal stent edge (i.e. in the aorta; n=4; range 23-48%), or at the distal stent edge (n=8; range 11-37%) was larger than both the smallest intra-stent lumen area and opposite stent edge area.

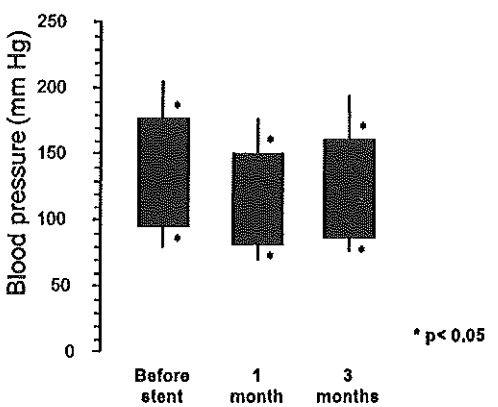

Figure 2.

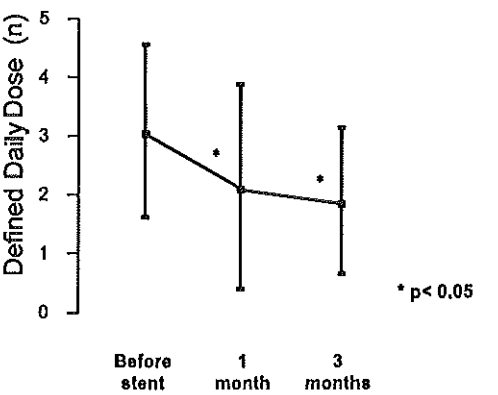

Figure 3.

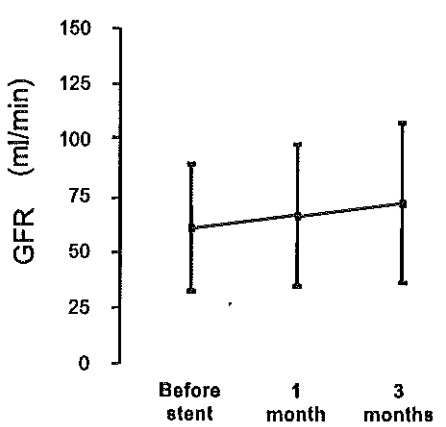

Figure 4.

Figure 2. Changes in systolic and diastolic blood pressure before and after stent placement.

Figure 3. Amount of antihypertensive drugs prescribed before and after stent placement.

Figure 4. Glomerular filtration rates before and after stent placement calculated from the Cockroft formula.

Follow-up

All patients were followed for three months. One patient developed a rise in serum creatinine level after stent placement due to cholesterol crystal embolization, which appeared reversible at follow-up. Two patients known to have a serum creatinine >300 µmol/l prior to intervention, became definitively dependent on hemodialysis after stent placement. The overall mean change in systolic and diastolic blood pressure is shown in Figure 2. The mean systolic blood pressure of 178±28 mm Hg before intervention showed a significant decrease to 150±26 mm Hg at one month (p<0.001) and remained significantly lowered at three months follow-up (162±33 mm Hg; p=0.01). Values for mean diastolic blood pressure before (96±15 mm Hg), at one month (85±14 mm Hg) and at three months follow-up (88±11 mm Hg) showed a similar significant decrease (p<0.001). The amount DDDs of antihypertensive drugs before and after stent placement is shown in Figure 3. Drug use decreased significantly from 3.06±1.46 DDDs before stent placement to 2.08±1.70 DDDs at one month, and to 1.99±1.23 DDDs at three months follow-up (p=0.002).

Median serum creatinine level before stent placement (121 µmol/l; range 71-427) was stable at one month (121 µmol/l; range 52-364), but decreased to 96 µmol/l (range 74-485) at three months follow-up. Student's t test on the logarithmic values of serum creatinine showed a p-value of 0.24. The effect of stent placement on renal function indicated by the mean glomerular filtration rate is shown in Figure 4. Filtration rates showed an increase from 62.10±28.52 ml/min before stent placement to 69.78±35.71 ml/min at three months follow-up (p=0.09), suggesting some renal function improvement.

DISCUSSION

Combined balloon angioplasty and stent placement is rapidly gaining ground as the method of choice in the treatment of atherosclerotic renal artery stenosis. Stent placement is usually guided by angiography. The present study reports our first experience with renal artery stent placement guided by IVUS in a consecutive series of 22 patients.

In five patients IVUS imaging after predilatation was impossible due to the inferior slope of the renal artery, creating an acute angle with the aorta. In such cases it is likely that the left brachial approach described by Dorros et al.[17] gives more direct access into the renal artery; however, hemorrhagic complications with this approach are reported due to left brachial arterial puncture.[18] Whether this counterbalances better access into the renal artery needs to be established. In addition, the learning curve for the radiologist to use IVUS in renal arteries played an important role in their decision to use IVUS in the other four patients. Technical success rate for stent placement in the current study was 91%. This was in accordance with the results of other studies on stent placement,[17-19] but in contrast with the results following balloon angioplasty alone.[4,5]

Qualitative analysis

Comparison between angiography and IVUS after predilatation revealed no difference between the two modalities in detecting vascular damage. After stent placement, however, IVUS detected vascular damage in three patients that was not seen angiographically. A possible reason for this is that the presence of a stent in the renal artery may impair visualization of the adjacent reference segment angiographically. Vessel damage may also be missed on angiography when single-plane imaging is used. It is noteworthy that angiography was not able to distinguish between dissection, plaque rupture and vessel rupture; similar shortcomings were reported by Sheikh et al.[10]

Quantitative analysis

In the present study, semiquantitative analysis of the IVUS images after predilatation showed that in five out of nine patients a larger balloon was selected to place the stent. Despite an angiographic successful result after stent placement, additional intervention was performed in six patients based on IVUS criteria. We assume that the incidence of incomplete stent-vessel wall apposition (one patient) and insufficient stent expansion (three patients) compared to the reference site seen on IVUS, may be reduced when the stent is placed with a high inflation pressure. This was previously described in stents placed in coronary arteries[20] and may also be applied in renal artery stent placement. In two of our patients IVUS revealed a lesion distal to the stent which implicates that the stent used was too short. Previous studies in coronary arteries showed that the plaque burden of the adjacent vessel segment was the predominant predictor of in-stent restenosis at the stent margins.[21] We believe that in order to document the length of the lesion to be stented the use of a displacement sensing device may provide accurate information about the length of the lesion involved.[22]

Quantitative analysis of IVUS data in the present study showed that stent placement resulted in significant lumen gain compared with dilatation alone. Despite angiographic successful stent placement in six patients IVUS revealed a suboptimal result. Additional dilatation, with or without a larger balloon, or stent placement in these patients resulted in vascular damage, significant lumen gain and a reduction of residual area stenosis. Ellis et al.[23] reported that the extent of residual stenosis after stent placement correlated highly with the incidence of restenosis in coronary arteries at follow-up. We postulate that IVUS may be beneficial in reducing restenosis rates by diminishing residual area stenosis. Future studies will show whether this hypothesis is correct.

In the present study we learned that the lumen gain after additional intervention depended on the selection of a larger balloon for dilatation. Comparison between balloon size used and smallest intra-stent lumen area revealed a discrepancy of 22%. These findings concur with the data of Van Sambeek et al.[24] in peripheral arteries, who observed a mean difference of 32-43% between balloon size and final intra-stent lumen area. It is noteworthy that in the present study the discrepancy of 22% remained after additional intervention.

Comparing the smallest intra-stent lumen area and the stent area at both stent edges in all patients, IVUS evidenced that in only three stents the smallest intra-stent lumen area

was in the same order as the stent edge area. Surprisingly, in eight patients the proximal stent edge in the aorta was smaller than the distal stent edge. Compression of the stent by plaque[25] or plaque resistance[26] as a cause of inadequate stent expansion is unlikely in the present study, because these determinants are almost absent at the proximal stent edge in the aorta. A possible solution for this phenomenon is described by Henry et al.[27] who tried to reshape the stent at the origin of the renal artery by dilating the proximal stent edge with a balloon larger than that used for initial stent placement.

Analysis of the clinical benefits for our study group includes a significant decrease in systolic and diastolic blood pressure. After an initial fall, systolic and diastolic blood pressure values increased at one and three months follow-up. Blood pressure values in the present study are comparable with those reported by Taylor et al.[18] after stent placement in renal arteries. Other studies fail to report mean blood pressure values, or express results in terms of cure, improvement or worsening; however, the use of varying definitions for these parameters hampers adequate comparison of the results.[5,28] A significant decrease in drug use was observed after the procedure. We expressed drug use as the number of DDDs to reflect both the number and the dosage of the prescribed drugs. Although the change in serum creatinine was not significant compared to the pre-stent values, median serum creatinine values decreased, suggesting improvement in renal function. Besides, glomerular filtration rates increased slightly at follow-up. In order to determine the effect of renal artery stent placement, Harden et al.[29] analyzed the rate of progression of renal function impairment before and after stent placement to assess the effect of renal artery stent placement on renal function. Follow-up data of the present study are not sufficient to perform the same analysis, but a longer follow-up will determine the effects of renal artery stent placement on the preservation of renal function.

Some potential study limitations need to be addressed. Only nine of the 18 patients were studied with IVUS after predilatation. Whether this problem can in part be solved by extra radiological appliances that give better access into the renal artery, or by the use of a different IVUS system, needs to be examined. Clinical follow-up at three months may be a too short period to allow valid conclusions about the effects of stent placement on the clinical parameters. We expect to solve these problems by a longer follow-up period of our patients in the near future. Finally, it should be acknowledged that considerable costs are associated with the use of IVUS; besides the ultrasound apparatus, IVUS catheters ($ 750) are needed. However, we believe that the use of IVUS for research purposes is definitely warranted to understand the parameters related to the short and long-term outcome of renal artery stenting. These results are not available yet.

CONCLUSIONS

IVUS monitoring of stent placement for the treatment of renal artery stenosis showed favorable technical and clinical results. Compared with standard angiography, IVUS provided additional information on lumen dimension and stent expansion, which influenced the intervention in several patients.

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To allow determination of the processes responsible for lumen loss at follow-up in renal and femoropopliteal Palmaz stents, the first consecutive patients treated with renal artery stents (n=4) and femoropopliteal artery stents (n=3) for occlusive vascular disease were studied with serial intravascular ultrasound. Lumen loss in renal artery stents appeared to be considerably less (17%) than in femoropopliteal artery stents (62%). In the renal location, late lumen loss was due to neointimal tissue whereas stent area remained unchanged. Late lumen loss seen in femoropopliteal artery stents was due to both neointimal tissue and stent area reduction.

Chapter 7

RESPONSE OF RENAL AND FEMOROPOPLITEAL ARTERIES TO PALMAZ STENT IMPLANTATION ASSESSED WITH INTRAVASCULAR ULTRASOUND

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In the ongoing evaluation of endovascular stents, serial intravascular ultrasound (IVUS) imaging has been used to assess vessel wall reaction and late lumen loss in different arterial segments.[1-6] Apparently, the mechanisms for stent restenosis differ according to arterial location. In coronary stents, for example, IVUS imaging has shown that late lumen loss was mainly due to neointimal hyperplasia,[2-4] whereas neointimal hyperplasia and stent recoil have been reported in femoropopliteal stents.[5,6] Insofar as we know, IVUS has not been used to investigate late lumen loss in renal artery stents, so we began a study to preliminarily investigate the processes related to late lumen loss after renal and femoropopliteal stent implantation.

METHODS

The study population comprised the first seven consecutive patients (five men, mean age 59±10.5 years) treated with balloon expandable Palmaz stents (Cordis Endovascular, a Johnson & Johnson Company, Warren, NJ, USA) and studied with IVUS according to a protocol approved by the Local Committee on Human Research. Under this protocol, renal stenosis patients giving informed consent were studied with IVUS intraprocedurally and periodically after stent placement, while consenting patients with femoropopliteal stents were evaluated for recurrent symptoms of disabling claudication or for study purposes. All patients were known to have angiographically documented >50% diameter reduction in the ostial renal artery (n=4) and femoropopliteal segment (n=3). Palmaz stents were implanted routinely after predilatation in the renal arteries, whereas femoropopliteal stents were implanted for suboptimal balloon angioplasty (>50% residual stenosis). Operators were not blinded to the IVUS findings during stent implantation. Compliant and noncompliant balloons (4-7 mm; OPTA or Powerflex, Cordis Europe, Roden, the Netherlands) were used. Anticoagulation was routinely initiated after stent placement using aspirin (80 to 100 mg/d) or warfarin (International Normalized Ratio of 2.0 to 2.5) Angiographically, stent placement was considered successful when a residual diameter stenosis <10% was evidenced. On IVUS stent deployment was considered successful in case of complete apposition of the stent to the vessel wall and when the residual diameter stenosis was <20%.[7]

IVUS imaging was performed using a commercially available mechanical system containing a single rotating ultrasound element (30 MHz; Endosonics, Rijswijk, the Netherlands) with a 0.035-in guidewire tipped, 4.3F flexible catheter (Princeps). Axial resolution is 75 µm and lateral resolution is > 225 µm at a depth of one mm. The unit was connected to a prototype instrument that provided continuous real-time cross-sections of the vessel wall (up to 16 images/s).[8] The same imaging technique was used immediately after angiographic successful stent placement and at follow-up examinations. The IVUS catheter was advanced distally beyond the stented segment and cross-sections were obtained during pullback of the catheter. In the femoropopliteal arteries, the position of the ultrasound catheter was documented with a radiopaque ruler and a displacement sensing device, which consisted of a disposable unit fitted with a small wheel that turns simultaneously with movement of the IVUS catheter.[9]

The resulting images, together with their unique frame number, were displayed on a monitor via a video-scanned memory and stored on an S-VHS video system.
The IVUS images obtained after successful stent placement were compared with the corresponding images at follow-up. For the purpose of this study, the cross-sections showing the smallest lumen area inside the stent, and both stent edges, obtained at follow-up, were matched to the cross-sections derived immediately after successful stent placement. Cross-sectional area measurements of the lumen, stent and lesion were performed off-line using a computer-based analysis system.[10] Lumen area was defined as the area encompassed by the inner boundary of the intimal surface. Stent area was defined as the area encompassed by the stent circumference. Lesion area i.e. neointimal tissue, seen at follow-up was calculated by subtracting lumen area from stent area. Late lumen loss was defined as the difference between the lumen area obtained after stent placement and at follow-up.
The reproducibility of quantitative IVUS parameters has been described previously.[11] To assess the interobserver reproducibility, all matched cross-sections were analyzed by a second independent observer (WvL). Interobserver measurements were compared using Student's paired *t*-test. The degree of interobserver variation was presented as a coefficient of variation, defined as the standard deviation (SD) of the paired difference divided by the mean of the absolute value. All values are given as mean ± SD. A *p*-value <0.05 was considered statistically significant.

RESULTS

Stent placement was angiographically successful in all patients. Renal artery stent placement was successful on IVUS in all four patients; in one of these patients, a distinct lesion distal to the stent seen on IVUS warranted the use of a second overlapping stent in order to obtain complete lesion covering. Stent placement in the femoropopliteal artery was considered successful on IVUS in all three patients; in one of these patients extensive dissection due to balloon angioplasty was solved by placement of overlapping stents.
Six patients were asymptomatic at the time of follow-up angiography and IVUS. In the remaining patient treated with overlapping stents in the femoropopliteal artery, restenosis was suspected at five months follow-up based on recurrent symptoms; repeat angiographic and IVUS examination showed restenosis (diameter stenosis >50%). No adverse effect attributable to the use of IVUS was observed in any patient. Follow-up angiography in the four patients with renal artery stents was performed at 6, 9, 9 and 12 months, respectively, while surveillance examinations for the three patients with femoropopliteal artery stents were performed at 5, 11, and 34 months, respectively.[6]
A total of seven most stenotic sites and 14 stent edges were available for analysis. Quantitative data on renal and femoropopliteal artery stents are summarized in Table 1. Late lumen loss at the most stenotic site of renal artery stents was less than in femoropopliteal artery stents (17% and 62%, respectively). Late lumen loss in renal artery stents was mainly due to lesion area increase (3.0 ± 1.3 mm^2), while the stent area

Table 1. Quantitative intravascular ultrasound data obtained from stents in renal and femoropopliteal arteries immediately after stent placement and at follow-up.

	After stent		At follow-up		Change	
Most stenotic site	**Renal (n=4)**	**Femoro-popliteal (n=3)**	**Renal (n=4)**	**Femoro-popliteal (n=3)**	**Renal (n=4)**	**Femoro-popliteal (n=3)**
Lumen area (mm^2)	21.3 ± 6.5	20.7 ± 7.7	17.6 ± 5.8	7.8 ± 3.5	3.7 ± 3.1 17%↓	12.8 ± 10.0 62%↓
Stent area (mm^2)	21.3 ± 6.5	20.7 ± 7.7	20.6 ± 5.9	15.3 ± 5.1	0.7 ± 1.8 3%↓	5.4 ± 3.6 26%↓
Lesion area (mm^2)	0.0 ± 0.0	0.0 ± 0.0	3.0 ± 1.3	7.4 ± 8.2	13.0 ± 1.3	17.4 ± 8.2
Stent edges	**Renal (n=8)**	**Femoro-popliteal (n=6)**	**Renal (n=8)**	**Femoro-popliteal (n=6)**	**Renal (n=8)**	**Femoro-popliteal (n=6)**
Lumen area (mm^2)	23.3 ± 6.9	20.1 ± 6.3	20.9 ± 5.7	11.0 ± 2.9	2.4 ± 2.7 10%↓	9.2 ± 4.2 46%↓
Stent area (mm^2)	23.3 ± 6.9	20.1 ± 6.3	23.5 ± 6.4	16.8 ± 5.6	0.2 ± 1.7 1%↑	3.4 ± 2.1 17%↓
Lesion area (mm^2)	0.0 ± 0.0	0.0 ± 0.0	2.6 ± 1.5	5.8 ± 2.9	12.6 ± 1.5	15.8 ± 2.9

Values are mean ± SD; ↓ = decrease; ↑= increase

reduced minimally (3%) (Fig. 1). In femoropopliteal artery stents, late lumen loss was due to a combination of lesion area increase (7.4±8.2 mm^2) and stent area reduction (26%) (Fig. 1). Both in renal and femoropopliteal artery stents, lesion area increase and stent area reduction at the most stenotic site were larger than at the stent edges. In addition, in two patients with femoropopliteal artery stents located in the adductor canal, elliptical deformation of the stent was seen at the distal stent edge.

Normal distribution of all analyzed data was evidenced. There was no significant interobserver difference for lumen area after stent placement and at follow-up (+0.43±1.06 mm^2 and -0.01±0.66 mm^2, respectively). The interobserver difference for stent area at follow-up (+0.76±0.96 mm^2) was significant (p=0.002). The coefficient of variation for lumen area after stent placement and at follow-up was 4.9% and 4.3%, respectively. For stent area at follow-up the coefficient of variation was 4.9%.

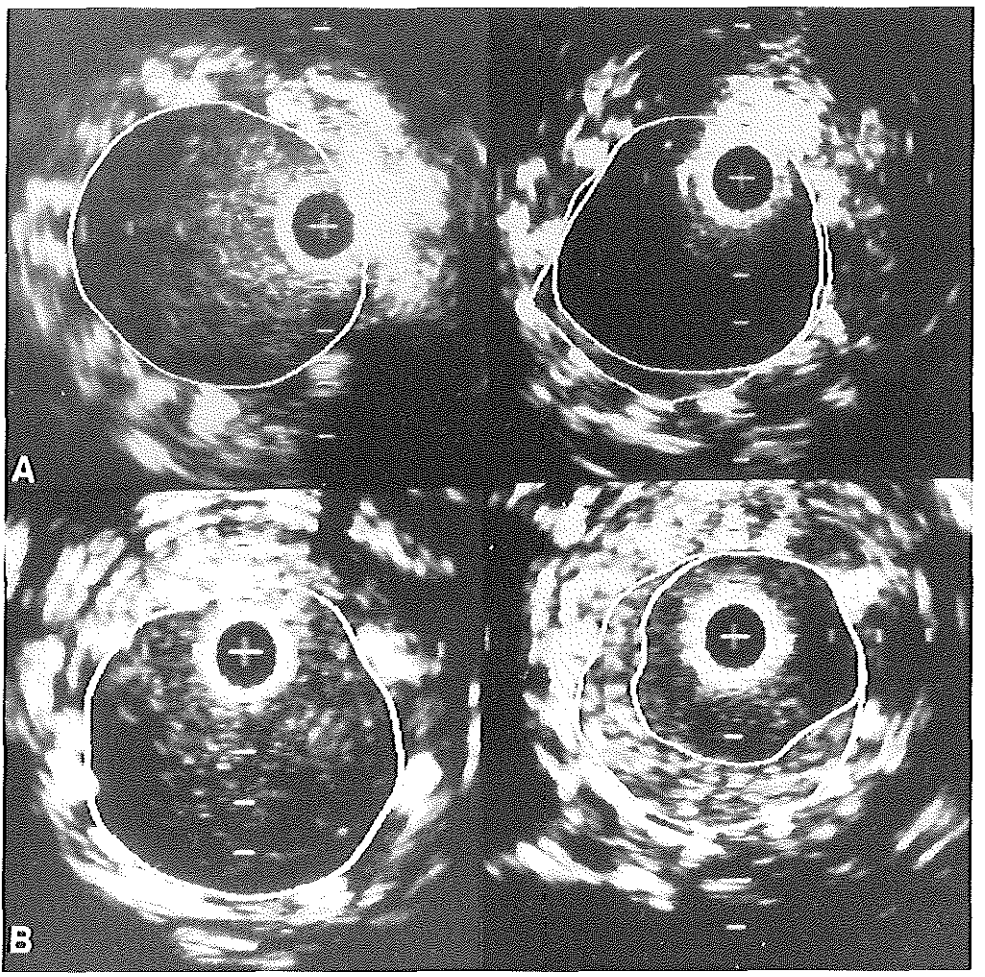

Figure 1. Intravascular ultrasound cross-sections after stent implantation (left panel) and at follow-up (right panel) of the renal artery (A) and femoropopliteal artery (B). Lumen area (inner contour) and stent area (outer contour) display quantitative results. A, late lumen loss is minimal and solely due to neointimal tissue proliferation. B, both neointimal tissue proliferation and stent area reduction contribute to late lumen loss at follow-up.

DISCUSSION

In a similar fashion to previous IVUS investigations in coronary and lower limb arteries,[3,5] our study has shown that the mechanisms for and extent of late lumen loss may differ in renal and femoropopliteal stents. In the renal arteries we interrogated, intimal hyperplasia was minimal at the most stenotic site within the stent and at the stent

edges (an 11% to 14% decrease from the initial stent lumen diameter). However, in femoropopliteal stents, neointimal proliferation was twice as exuberant (29% to 35% late lumen loss), comparable to that reported in coronary arteries (30%).[2,12]

A remarkable observation in the present IVUS study was the stent area reduction encountered in the femoropopliteal artery stents (mean 26% decrease at the most stenotic site, 17% at the stent edges). This loss was due not only to a decrease of stent circumference at the most stenotic site but also to elliptical deformation at the adductor canal in two of three distal stent edges at the adductor canal (contributing for 11% and 45% to the late lumen loss, respectively). Rosenfield et al.[5] reported stent compression and neointimal tissue proliferation as the major causes of restenosis in femoropopliteal stents, but they did not mention elliptical deformation.

In a similar fashion to reports for coronary stents,[3,4] our IVUS study did not document significant stent area reduction in renal stents. However, our observations do not agree with the quantitative angiographic data of Khosla et al.,[13] who reported that tissue ingrowth (15 to 19%) and stent recoil (25-42%) contributed to the late lumen loss six months after renal artery stenting. This discrepancy may be due to a phenomenon, alluded to by Hoffmann et al.,[14] that quantitative coronary angiography significantly overestimates the initial stent lumen diameter compared to IVUS. The authors postulated that contrast flow around the stent struts immediately after stent deployment may increase the stent lumen diameter measurable on the angiogram. Consequently, a falsely elevated stent area reduction might be seen at follow-up with quantitative angiographic measurements, which could explain the stent recoil observed by Khosla et al.

In our admittedly small sample, overlapping stents in the renal artery did not result in restenosis at follow-up, a feature found to be responsible for the restenotic process in femoropopliteal artery stents.[6] However, no reliable comments on or comparisons of restenosis rates between renal and femoropopliteal stents can be made based on these limited observations. At present, we routinely deploy stents when we treat renal atherosclerotic lesions according to protocol in an ongoing trial. Conversely, we do not commonly use stents in the femoropopliteal segment, as recommended by Henry et al.[15]

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Prospectively, 38 patients who underwent stent placement for symptomatic renal artery stenosis were studied with intravascular ultrasound (IVUS) and angiography after stenting and at one-year follow-up. At follow-up, IVUS showed a significant lumen area decrease in the stent solely due to plaque accumulation. At the distal main renal artery, lumen area decreased significantly solely due to vessel area decrease; this was confirmed angiographically. Clinically, blood pressure, and number of antihypertensive medications were significantly decreased and serum creatinine concentrations remained stable. In conclusion, renal artery stent placement is followed by unexplained shrinkage of the distal main renal artery.

Chapter 8

SHRINKAGE OF THE DISTAL RENAL ARTERY ONE YEAR AFTER STENT PLACEMENT AS EVIDENCED WITH SERIAL INTRAVASCULAR ULTRASOUND

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Stent placement is in common use for the revascularization of renal artery stenosis (RAS). However, restenosis after renal artery stent placement continues to be a problem, with reported restenosis rates in up to 39% of patients at eight months follow-up.[1] In order to characterize the restenotic process we used intravascular ultrasound (IVUS), as an adjunct to standard angiography, because IVUS provides accurate data on vessel and plaque dimensions that allow to monitor changes that occur over time in the treated vessel.

The aim of the present study was to determine the quantitative IVUS and angiographic changes in the renal artery seen at one-year follow-up, together with the clinical outcome in a series of consecutive patients who underwent renal artery stenting for atherosclerotic RAS.

METHODS

Patients

Between September 1996 and December 1998, 41 consecutive patients (27 men, 14 women; aged 60 ± 9 years [mean ± SD]) presenting with symptomatic RAS of ≥50% diameter stenosis were treated with stent placement. One patient underwent stenting of both renal arteries on two separate occasions; thus, a total of 42 renal arteries were treated. Patients had renal function impairment (serum creatinine ≥110 µmol/l; n=26) and/or drug resistant hypertension, defined as a diastolic blood pressure ≥95 mmHg while receiving two "defined daily doses" of antihypertensive drug treatment (n=26; DDDs; the DDD is the assumed average maintenance doses of the individual drugs based on its main indication in adults).[2] Patients were studied with IVUS and angiography before any intervention was performed and immediately after stent placement. During follow-up, patients returned to the outpatient clinic. Blood pressure, the amount of antihypertensive drugs prescribed, and serum creatinine concentrations were monitored. If possible, the type of antihypertensive medication was held constant during the follow-up period. At one-year follow-up IVUS and angiographic examinations were repeated. The Local Committee on Human Research approved the investigation. Written informed consent was obtained from all patients.

Procedure

Pre-intervention digital subtraction angiograms were obtained using aortic-flush injections. The stenosis was then crossed with a 5F selective catheter. Pre-intervention IVUS imaging was performed over a 0.020-in flexible tip guide wire (Boston Scientific, Ireland). The lesion was predilated with an angioplasty balloon five or six mm in diameter. A Palmaz stent (Johnson & Johnson Interventional Systems, New York, USA) was then placed (p104, p154 or p204 stents). The stent placement was considered technically successful when post-procedural IVUS and angiography showed complete stent-vessel wall apposition, complete lesion covering, and a <20% residual diameter stenosis.[3] When necessary, additional stent dilatation was performed using a six or seven mm balloon. During the procedure, the patients received 5,000 IU of heparin, after which heparin infusion was continued for 48 hours (20,000-30,000 IU per day).

Oral acetylsalicylic acid (100 mg daily) was started at the day of the procedure and continued during the entire follow-up period.

IVUS analysis

For IVUS examination, a 30 MHz mechanical imaging system ("Princeps", Endosonics, Rijswijk, The Netherlands)[4] with 4.3F catheters was used. The IVUS catheter was positioned distally from the stenosis in a second-order renal artery branch. Real-time cross-sectional images of the entire main renal artery, obtained during slow pullback of the IVUS catheter, were displayed on a monitor and stored on S-VHS videotape. For the purpose of this study quantitative analysis was performed. Before intervention, a reference cross-section of the distal renal artery just proximal to the first major side-branch was analyzed.

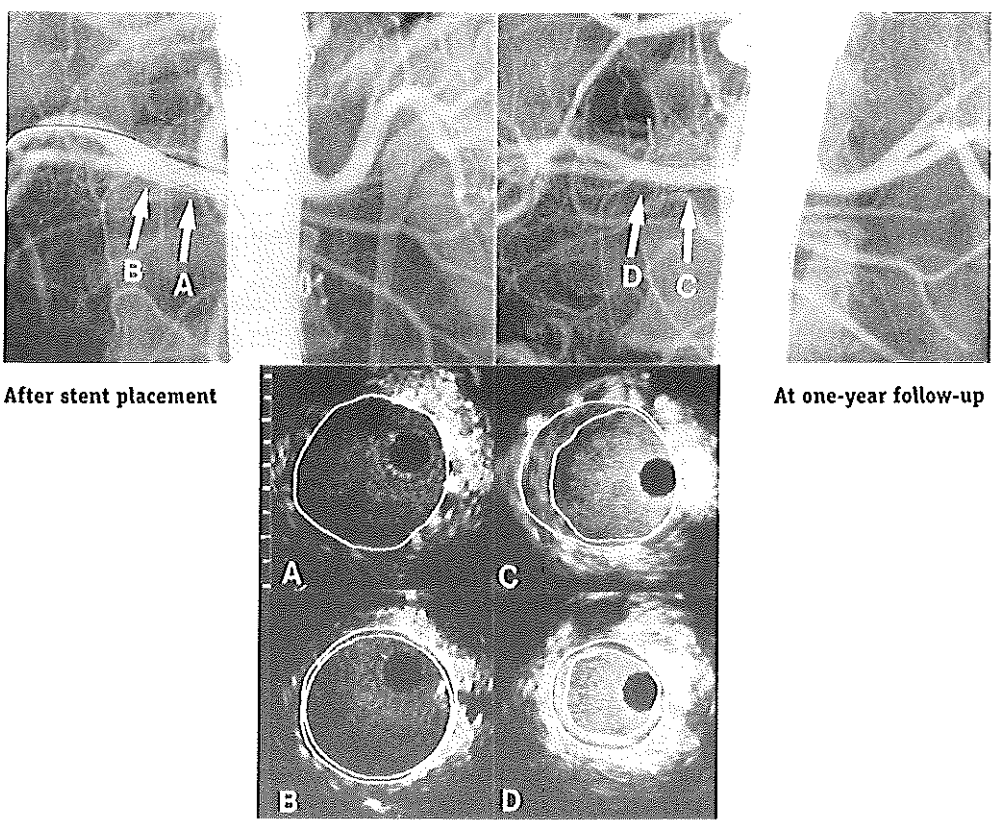

Figure 1. Intravascular ultrasound and angiographic images after stent placement (A and B) and at one-year follow-up (C and D). The inner contour of the intravascular images presents the lumen area; the outer contour the stent or vessel area. At follow-up plaque accumulation was evidenced in the stent (C) whereas the distal reference cross-section (D) showed shrinkage without plaque accumulation.

In addition, after IVUS and angiographic successful stent placement and at one-year follow-up three cross-sections selected from the IVUS examinations were analyzed: one cross-section at the most stenotic site in the stent and two reference cross-sections in the distal renal artery (one just distal to the stent and another just proximal to the first major side-branch). Analysis included assessment of the lumen area (LA; the area encompassed by the inner intimal surface), the native vessel area (VA; the area bounded by the external elastic lamina), the stent area (SA; the area encompassed by the stent struts), and the plaque area (PLA; calculated as VA minus LA, or SA minus LA for the stented and non-stented cross-sections, respectively). All IVUS measurements were performed by two independent observers; mean values of the two observers are given.

Angiographic analysis

Angiographic in-stent restenosis at one-year follow-up was defined as a ≥50% diameter reduction in the stent, compared to the distal distal main renal artery. After stent placement and at follow-up, angiographic lumen diameter of the ipsi- and contralateral main renal arteries (before the first major side-branch) and of major intrarenal branches were quantified in an absolute sense by relating the measurements to the known length of the Palmaz stent. In addition, the angiographic diameter of the affected renal artery distal to the lesion before and immediately after stent placement and at follow-up was expressed as a percentage of the diameter of the contralateral renal artery.

Clinical outcome

Systolic and diastolic blood pressure measurements obtained before and immediately after stent placement and at one-year follow-up were compared. In addition, the amount of antihypertensive drugs and serum creatinine concentrations were compared before intervention and at one-year follow-up. Clinical outcome for blood pressure and renal function was determined for the subgroups of patients with hypertension or renal function impairment.

Statistical analysis

Observer variability for IVUS measurements was analyzed using regression analysis and Bland-Altman's method. Student's *t*-test for paired observations was used to test for significant differences between measurements at baseline, after stent placement and at follow-up. Furthermore, we assessed whether there was a relation between procedural (i.e. stent length), IVUS and angiographic data and the clinical outcome. Relationship between categorical variables was demonstrated in contingency tables using the chi-squared test. Categorical variables included stent length, angiographic lesion location (ostial or truncal[5]), and angiographic stent patency. Relationship between categorical and continuous variables was assessed using Student's *t*-tests. For continuous variables Pearson's correlation coefficient was calculated using SPSS for Windows (version 9.0). Correlation coefficients were determined between the percentage change in vessel area of the distal renal artery and the change in systolic or diastolic blood pressure. Correlation coefficients were considered worth mentioning in case of r values ≥0.50. A p-value <0.05 was considered statistically significant (two-sided).

RESULTS

Stent placement was technically successful in 39 renal arteries of 38 patients. At baseline IVUS was performed in 14 patients and after stent placement in 38 patients. In the remaining patients, the IVUS catheter could not pass the stenosis, or the interventionist refrained from using IVUS before stent placement. Follow-up (12.2 ± 2.8 months [mean ± SD]) IVUS imaging was completed in 30 renal arteries of 29 patients. In one patient the IVUS catheter could not pass the stent. Angiography before and after stent placement was obtained in all 38 patients and in 28 patients at follow-up: in two patients with poor renal function angiography was not performed. Eight patients were lost to follow-up (dialysis n=3; patient refusal n=4; patient death n=1). Stent patency was demonstrated in the latter patients during follow-up with spiral CT or captopril renography. Angiographic in-stent restenosis was encountered in four of 28 patients (14%) and these patients underwent additional balloon angioplasty.

Lumen area in the stent decreased significantly during follow-up from 24 ± 5.6 mm^2 to 17 ± 5.6 mm^2 ($p<0.001$; Table 1), which was entirely due to an increase of plaque area in the stent; the stent area (and the stent diameter) remained unchanged. In the renal artery distal to the stent, the lumen area decreased significantly due to a decrease in vessel area (39 ± 14.0 mm^2 immediately after stent placement to 29 ± 9.3 mm^2 at follow-up; $p<0.001$; Fig. 1) without plaque accumulation. Of all reference cross-sections after stent placement, 42 showed a vessel area decrease, 11 showed a less than 10% change, and seven showed an enlargement. Of 10 patients with matched pre-intervention and follow-up IVUS data, the reference vessel area at follow-up was smaller (>10%) than before any intervention was performed in five patients, had less than 10% change in two patients,

Table 1. Intravascular ultrasound measurements in 30 renal arteries obtained immediately after stent placement and at one-year follow-up. Cross-sections were analyzed at the most stenotic site in the stent and at two reference sites distal to the stent in the main renal artery (n=60).

		After stent placement (mm^2)	Follow-up (mm^2)	*p*-value
Stent	Lumen area	24 ± 5.6	17 ± 5.6	<0.001
	Stent area	24 ± 5.6	25 ± 5.5	NS
	Plaque area	0	7 ± 4.0	<0.001
Main renal artery	Lumen area	29 ± 11.4	20 ± 7.3	<0.001
	Vessel area	39 ± 14.0	29 ± 9.3	<0.001
	Plaque area	10 ± 4.7	10 ± 4.4	NS

Values are mean ± SD; NS = Not significant.

and was larger (>10%) in three patients. There was good observer agreement for IVUS measurements, with a high correlation coefficient (r=0.978; observer-2 = 0.99 * observer-1 - 0.01) and an overall coefficient of variation of 6.3%.
Similar to the IVUS measurements, quantitative angiographic measurements of the distal main renal artery showed a significantly decreased diameter at one-year follow-up when compared to diameters measured immediately after stent placement (p<0.001; Table 2). In contrast, the diameter of the intrarenal branches and the contralateral renal artery diameters remained unchanged. Whereas immediately after stent placement there was no significant difference between the diameter of the ipsi- and contralateral renal arteries, the treated renal artery at follow-up was significantly smaller than the contralateral artery (5.0 ± 1.4 mm vs. 5.8 ± 1.2 mm, respectively; p=0.004). The distal renal artery diameter at follow-up was also significantly smaller than before stent placement (86 ± 5.1% [mean ± SEM] vs. 104 ± 5.3% of the contralateral renal artery diameter; p=0.003; Fig. 2).

Table 2. Angiographic measurements obtained immediately after stent placement and at one-year follow-up (n=28).

		After stent placement (mm)	Follow-up (mm)	p-value
Treated renal artery	Main renal artery	6.5 ± 1.4	5.0 ± 1.4	<0.001
	Intrarenal branch	2.7 ± 1.0	2.8 ± 0.7	NS
Contralateral renal artery	Main renal artery	6.1 ± 1.3	5.8 ± 1.2	NS
	Intrarenal branch	3.0 ± 1.0	2.9 ± 0.8	NS

Values are mean ± SD; NS = Not significant.

In patients treated for hypertension (n=22), systolic blood pressure was decreased immediately after stent placement (180 ± 17.4 to 130 ± 46.5 mmHg; p=0.001) and remained significantly decreased at one-year follow-up (151 ± 22.4 mmHg; p<0.001). The same applies to diastolic blood pressure, which decreased immediately after stent placement (103 ± 6.7 to 74 ± 25.1 mmHg; p=0.002) and at follow-up was significantly decreased compared to pre-intervention values (86 ± 9.5 mmHg; p<0.001). Similar to the decrease of blood pressure, there was a significant decrease in the number of antihypertensive medications used at one-year follow-up (3.8 ± 1.80 to 2.6 ± 2.11 DDDs; p=0.001). In patients treated for renal failure (n=13), serum creatinine values remained stable (150 (134) µmol/l [median (range)] to 131 (334) µmol/l; p=NS).
In the subgroup of patients treated for hypertension, the percentage vessel area decrease in the distal renal artery was significantly associated with the decrease in systolic blood

pressure at follow-up (r=0.50; p=0.032). No relationship was found between procedural and angiographic data and the changes in IVUS and clinical parameters.

DISCUSSION

In the present study we quantified the change in vessel dimensions of the renal arteries during the first year after stent placement for atherosclerotic RAS. At one-year follow-up there was a significant decrease in lumen area in the stent, which was solely due to plaque accumulation. There was no evidence for recoil of the Palmaz stent which agrees with findings reported in coronary stents;[6] however, the typical plaque accumulation at the stent edges, as reported in coronary stents,[7] was not seen in renal stents. The

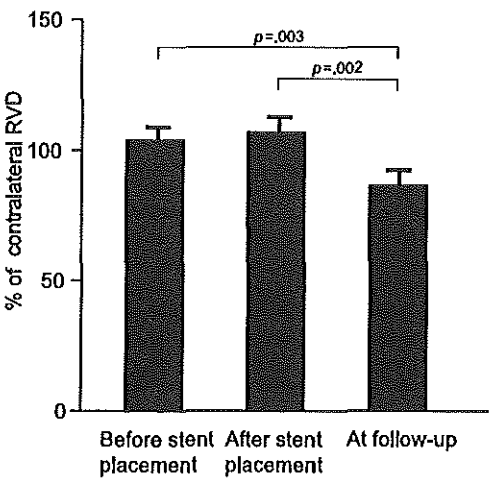

Figure 2. Renal vessel diameter (RVD) of the affected side before and after stent placement and at follow-up expressed as percentage of the contralateral artery diameter. The relative diameter at follow-up was significantly smaller than pre-interventional values. Mean ± SEM are indicated.

in-stent restenosis rate of 14% in the present study was similar to the 19% restenosis rate reported in a series of 100 renal stent patients by White et al.[8] It should be acknowledged that the favorable restenosis rate in the present study may be related to the use of IVUS during the stent placement procedure: in 33% of the patients additional dilatation or stent placement was warranted to achieve accurate stent placement. However, a randomized study is required to assess the true beneficial role of IVUS on the long-term stent patency.

A remarkable finding in the present study was shrinkage of the affected distal main renal artery without plaque accumulation at follow-up. The absolute vessel area as measured with IVUS decreased by 25%. This shrinkage was also evidenced with angiography and was limited to the main renal artery distal to the stent. At angiography the diameter of the affected main renal artery (compared to the contralateral renal artery) at follow-up was significantly smaller

than immediately before and after stent placement. To the best of our knowledge, this shrinkage has not been described before. At present, there is no clear explanation for this phenomenon, and the following discussion is therefore speculative.

A potential explanation for shrinkage may be found in the change of blood flow due to stent placement. Stent placement is reported to cause an increase in blood flow in the distal main renal artery.[9] Increased blood flow will increase the wall shear stress (wall shear stress = 4*blood viscosity*flow/πr^3). Increased wall shear stress will induce an adaptation process of the vessel wall mediated by nitric oxide,[10] which may result in vessel dilatation both immediately after stent placement and at follow-up. After stent placement, this agreed with data presented previously and with our previously presented findings that predilatation and stent placement resulted in enlargement of the distal renal artery.[3,8] At follow-up, however, we experienced shrinkage of the distal renal artery instead of a dilatation.

On the other hand, long-term data on blood flow after stent placement are scarce and it is not clear whether renal artery stenting results in long-standing flow improvement. Since a kidney regulates blood flow by changing vascular resistance, an initial increase of renal vessel dimensions may be explained as a lack of immediate adaptation to increased blood flow. On the long-term, the kidney may have adapted its vascular resistance, which might have resulted in a decrease of renal blood flow, thereby decreasing the renal vessel dimensions.

The decrease in renal vessel diameter may also reflect an active shrinkage process. This may be due to iatrogenic damage to the renal artery segment immediately distal to the stent during stent placement. It has been previously reported that such stretching of the vessel wall in coronary arteries may cause injury with fragmentation of the internal elastic lamina, resulting in neointimal thickening at follow-up.[11] In the present study, however, shrinkage occurred without neointimal thickening; also it occurred in the distal renal artery segment, unlikely to be touched by the dilatation balloon.

Clinical results for blood pressure were favorable and renal function stabilized. The encountered shrinkage seemed to have clinical implications in that the extent of vessel shrinkage was associated with the extent of decrease in systolic blood pressure at follow-up. Possible (patho)physiologic mechanism underlying these findings, however, should be determined in future studies. Aside from measurements of renal blood flow before and immediately after stent placement and at follow-up, it would be of interest to study whether shrinkage is associated with endothelial dysfunction or is a more generalized reflection of vascular pathology. This may be determined by measuring the vasodilative capacity of the distal renal artery after infusion of endothelial-dependent and - independent substances, e.g., by using Doppler flow-wires.

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To study the effect of stent placement for renal artery stenosis on the function of the treated and contralateral kidneys, 18 patients underwent renal vein blood sampling before angiography and stent placement and at one-year follow-up, after constant systemic infusion of ^{131}I-hippuran and ^{125}I-thalamate. This allowed assessment of the single-kidney contributions to the total renin secretion, effective renal plasma flow (^{131}I-hippuran clearance) and glomerular filtration rate (^{125}I-thalamate clearance). Analysis showed that renal artery stenting was capable of causing longstanding improvement of renal blood flow and glomerular filtration rate of the treated kidney, and disappearance of renin suppression of the contralateral kidney.

Chapter 9

EFFECT OF STENT PLACEMENT FOR RENAL ARTERY STENOSIS ON THE FUNCTION OF THE TREATED AND CONTRALATERAL KIDNEYS

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Renal artery stenosis (RAS) due to atherosclerosis is a progressive disease that may ultimately lead to renal artery occlusion and loss of renal function. Revascularization of symptomatic RAS is thought to be beneficial by improving the function of the affected kidney or, at least, halting the progressive loss of renal function. Revascularization by stent placement is now well accepted as part of the treatment of atherosclerotic RAS.
Clinical experience has shown that renal artery stenting may improve overall renal function in some but not all patients.[1] To explain this heterogeneous response, hard data on the physiological effects of stent placement, especially on the treated kidney, are required. Such data, however, are scarce due to the difficulty of evaluating the function of the left and right kidneys separately.
The aim of this study was, therefore, to determine the separate effects of renal artery stent placement on the treated and untreated contralateral kidney rather than on the overall renal function. For this purpose, we determined the single-kidney vein-to-artery ratios of renin and extraction ratios of ^{131}I-hippuran and ^{125}I-thalamate prior to stent placement and at one-year follow-up in conjunction with measurements of the two-kidney clearances of ^{131}I-hippuran (effective renal plasma flow) and ^{125}I-thalamate (glomerular filtration rate).

METHODS

Patients

The study group comprised 18 patients (12 males, 6 females; aged 56 ± 10.7 years [mean ± SD]) who underwent stent placement for angiographically proven symptomatic unilateral atherosclerotic renal artery stenosis of ≥50% luminal diameter reduction and were studied by means of renal vein blood sampling. These patients were selected from a group of 40 consecutive patients undergoing stent placement who were referred to our hospital in the years 1997 and 1998. The length of the treated kidney, as determined by ultrasound, was > 8 cm in all patients. Renal scintigraphy with mercaptoacetyltriglycine (MAG_3) and other single-kidney renal function studies were performed within one month before stent placement. These tests were repeated one year after the procedure, prior to the angiographic follow-up examination. Medication regimen and blood pressure were recorded before intervention and at follow-up. The study protocol was approved by the Local Committee on Human Research and written informed consent was obtained from all patients.

Renal scintigraphy

Scintigraphy was performed with the patient in the supine position and using the posterior view. Patients received 25 or 50 mg of captopril orally at one hour before the examination. After intravenous administration of 74 MBq ^{99m}Tc-MAG_3, data were collected in 10-second frames during a 20-minute period. The number of total counts accumulated in the kidney during the first 60 seconds were quantified and were taken as a measure of the renal plasma flow to the affected and contralateral kidneys. This method is based on the assumption that the early part of the time-activity curve is determined solely by the renal plasma flow.

Renal vein blood sampling

Concentrations of active renin and ^{131}I-hippuran and ^{125}I-thalamate in the left and right renal veins were measured and assayed as described by Wenting et al.[2] The method involves constant infusion of ^{131}I-hippuran and ^{125}I-thalamate through an antecubital vein. After reaching the steady state, a renal venous blood sample was taken at each side simultaneously with a sample from the abdominal aorta. Samples from these sites were also used for renin measurements. Additional blood samples were taken at 15-minute intervals from a peripheral vein to estimate the total (two-kidney) clearances of ^{131}I-hippuran and ^{125}I-thalamate. All blood samples were immediately centrifuged and measurements were made in plasma. Determination of blood oxygen saturation served to assure that blood samples were taken from the renal veins. Single-kidney extraction ratios of ^{131}I-hippuran and ^{125}I-thalamate were defined as (A-V)/A, where A = activity in the abdominal aorta and V = activity in renal vein. The total clearances of ^{131}I-hippuran and ^{125}I-thalamate were taken as a measure of total effective renal plasma flow (ERPF) and glomerular filtration rate (GFR), respectively. The concentration of active renin in plasma was measured by radioimmunoassay.[3] The normal value of the vein-to-artery ratio of renin is 1.24. In case of renal artery stenosis, the vein-to-artery ratio at the treated side is considered elevated with values >1.48. Contralateral suppression of renin secretion is defined as a vein-to-artery renin ratio <1.13.[4]

Stent placement

Pre-intervention digital subtraction angiograms were obtained using aortic-flush injections. The stenosis was then crossed with a 5F selective catheter and the lesion was predilated with an angioplasty balloon. A Palmaz stent (Cordis, Johnson & Johnson Interventional Systems, New York) was placed, and the procedure was considered technically successful when both intravascular ultrasound and angiography showed complete stent-vessel wall apposition, complete lesion-covering, and <20% residual diameter stenosis.[5] If necessary, additional stent dilatation was performed. During the procedure the patients received 5,000 IU of heparin, and heparin infusion was continued for 48 hours (20,000-30,000 IU per day). Oral acetylsalicylic acid (100 mg daily) was started at the day of the procedure and continued during the entire follow-up period.

Calculations

Two-kidney ERPF was calculated by dividing the infusion rates of ^{131}I-hippuran by the peripheral venous plasma concentration of ^{131}I-hippuran. Similarly, two-kidney GFR was calculated by dividing the infusion rate of ^{125}I-thalamate by the peripheral venous plasma concentration of ^{125}I-thalamate. In addition, single-kidney RPF, ERPF and GFR were calculated by using single-kidney data derived from MAG_3-scintigraphy as explained in the Appendix.

Statistical analysis

The effect of intervention on single-kidney function parameters was analyzed using Student's paired *t*-tests at $p<0.05$. Analysis was repeated for the subgroup of patients (n=9) who used the same medication both pre-stenting and after one year, to test whether differences in medication had influenced the results.

RESULTS

Stent placement was angiographically successful in all patients. Angiography at follow-up (12 months in 16 patients and six months in two patients) showed restenosis ≥50% (compared to the distal main renal artery diameter) in four patients.

At follow-up, the renal vein-to-artery renin ratio at the treated side had decreased from 1.65 ± 0.131 to normal, 1.23 ± 0.076 ([mean ± SEM]; p=0.009; Table 1). Contralaterally, the vein-to-artery renin ratio was 1.09 ± 0.042 before stenting and 1.17 ± 0.029 at follow-up (p=NS). Peripheral renin values decreased significantly from 251 ± 114.0 ng Angiotensin I/ml per hour before stenting to 94 ± 55.1 ng Angiotensin I/ml per hour at one-year follow-up (p=0.046).

Table 1. Measured single-kidney function parameters obtained before stent placement and at one-year follow-up in 18 patients.

		Before stent placement	At follow-up	p-value
Vein-to-artery renin ratio	Treated	1.65 ± 0.131	1.23 ± 0.076	0.009
	Contralateral	1.09 ± 0.042	1.17 ± 0.029	NS
Aortic renin concentration, ng Ang I/ml per hour		251 ± 114.0	94 ± 55.1	0.046
Extraction ratio ^{131}I-hippuran	Treated	0.48 ± 0.049	0.62 ± 0.034	0.006
	Contralateral	0.67 ± 0.033	0.73 ± 0.026	NS
Extraction ratio of ^{125}I-thalamate	Treated	0.12 ± 0.014	0.17 ± 0.012	0.002
	Contralateral	0.18 ± 0.013	0.22 ± 0.011	0.015
Two-kidney ERPF, ml/min		323 ± 23.1	333 ± 27.8	NS
Two-kidney GFR, ml/min		76 ± 7.2	77 ± 7.8	NS

Values are mean ± SEM; ERPF = Effective renal plasma flow; GFR = Glomerular filtration rate.

The renal extraction ratios of ^{131}I-hippuran improved at the treated side (0.48 ± 0.049 to 0.62 ± 0.034; p=0.006) and did not change contralaterally (0.67 ± 0.033 to 0.73 ± 0.026; p=NS). The extraction ratio of ^{125}I-thalamate, which equals the filtration fraction, improved at both sides (0.12 ± 0.014 to 0.17 ± 0.012 at the treated side; p=0.002; and 0.18 ± 0.013 to 0.22 ± 0.011 contralaterally, respectively; p=0.015).

Total (two-kidney) ERPF did not change (323 ± 23.1 to 333 ± 27.8 ml/min; p=NS). The same was true for the total effective renal blood flow (575 ± 45.6 to 564 ± 66.7 ml/min; p=NS). Total GFR also did not change (76 ± 7.2 to 77 ± 7.8 ml/min; p=NS).

Table 2. Calculated single-kidney function parameters obtained before stent placement and at one-year follow-up in 18 patients.

		Before stent placement	At follow-up	p-value
Flow ratio treated/contralateral		0.85 ± 0.105	0.89 ± 0.110	NS
RPF, ml/min	Treated side	212 ± 19.8	226 ± 24.5	NS
	Contralateral side	342 ± 33.2	284 ± 22.2	0.023
ERPF, ml/min	Treated side	106 ± 15.6	136 ± 15.4	0.057
	Contralateral side	213 ± 19.4	227 ± 19.2	NS
GFR, ml/min	Treated side	27 ± 4.5	38 ± 4.7	0.022
	Contralateral side	59 ± 7.1	64 ± 6.4	NS

Values are mean ± SEM; RPF = Renal plasma flow; ERPF = Effective renal plasma flow; GFR = Glomerular filtration rate.

Calculated RPF of the treated kidney was 226 ± 24.5 ml/min before stent placement and 212 ± 19.8 ml/min at one-year follow-up (p=NS; Table 2). Calculated RPF of the contralateral kidney decreased significantly from 342 ± 33.2 to 284 ± 22.3 ml/min (p=0.02). Calculated ERPF of the treated kidney was 106 ± 15.6 ml/min before stenting and 136 ± 15.4 ml/min at follow-up (p=0.057). Calculated ERPF of the contralateral kidney was 227 ± 19.2 ml/min before stenting and 213 ± 19.4 ml/min at follow-up (p=NS). The flow improvement of the treated kidney, indicated by these calculations, are in agreement with the normalization of the renal vein-to-artery renin ratio of the treated kidney. Calculated GFR of the treated side rose significantly from 27 ± 4.5 to 38 ± 4.7 ml/min (p=0.022) and did not change contralaterally (59 ± 7.1 to 64 ± 6.4 ml/min; p=NS).

Finally, the conclusions of the analysis in the subgroup of patients (n=9) with unchanged medication regimen were consistent with those of the entire patient group.

DISCUSSION

Evaluation of the effect of renal artery stent placement on renal function is hampered by limited data on the function of the kidneys separately. In the present study single-kidney function was determined before and one year after renal artery stent placement.

We found a decrease in the vein-to-artery renin ratio of the treated kidney and an increase contralaterally. This finding extends previous studies on the effects of balloon angioplasty without stenting, which reported that the lateralization of renin secretion to the stenosed kidney together with contralateral suppression had normalized 6-39 months after the procedure.[6,7] Under steady state conditions, an increased vein-to-artery renin ratio of a kidney perfused by a stenosed renal artery is a reflection of decreased renal blood flow rather than increased renin secretion. Consequently, the normalization of the vein-to-artery renin ratio we observed after one year primarily reflects a lasting increase of blood flow to the treated kidney. We observed a decrease in aortic renin concentration, which indicates a decrease of the two-kidney release of renin. Since, before the intervention, renin release of the contralateral kidney was suppressed, the observed change in arterial renin levels can be considered as evidence indicating a decrease in renin release by the treated kidney.

Data on single-kidney function measurements before and after renal artery stent placement are, to the best of our knowledge, not available in the literature. The present study shows that the extraction ratios of ^{131}I-hippuran and ^{125}I-thalamate of the treated kidney improved at one-year follow-up. Before intervention, the extraction ratio of ^{131}I-hippuran was impaired, which is in accordance with the literature.[2] This may be explained by a redistribution of renal blood flow in the presence of a renal artery stenosis in such a way that the sites where ^{131}I-hippuran is excreted by the tubules are bypassed. An alternative explanation is a reduction in urine flow resulting in some tubular reabsorption of ^{131}I-hippuran. The increase in ^{125}I-thalamate extraction of the treated kidney reflects an increase of filtration fraction and, probably, due to an increase in GFR.

So far, we discussed our data in semiquantitative terms. In order to obtain quantitative information, we made use of calculations of single-kidney RPF, ERPF and GFR on the basis of the court-ratio (treated/contralateral kidney) as derived from the MAG_3 time-activity curve. The implicit assumption was that the extraction ratios of the intravenously infused radiofarmacon were not different between the treated and contralateral kidney. This study, however, shows that the extraction ratio of ^{131}I-hippuran at the treated side was smaller than contralaterally. Therefore, our calculated data underestimated the true renal plasma flow of the treated kidney and, consequently, the GFR of the treated kidney. It should be noted here, that MAG_3-scintigraphy was performed with captopril challenge and this is known to reduce the extraction ratio of ^{131}I-hippuran.[2] However, the direction of changes as shown by our calculations is in agreement with the conclusions derived from the renin measurements.

The two sets of data showed an increase of ERPF and GFR after stenting at the treated side. We found that the total GFR was unchanged, which may be explained by the fact that differences in function of the contralateral kidney counterbalanced the beneficial effect on the treated kidney. Our finding that the filtration fraction of the contralateral kidney was increased after stent placement, suggests a proportionally larger decrease in RPF than in GFR. This was in agreement with the calculated data of the contralateral kidney.

Although renal artery stent placement resulted in improvement of renal function in the patient group as a whole, on individual basis there was a wide range of responses. This may have been caused by restenosis or by progressive renal disease. We found no significant differences in single-kidney function data between the patients with and without restenosis. Our analysis, however, was limited to a small group of patients.

Some other limitations of the present study should also be addressed. First, serial single-kidney measurements were available in only 18 of the 40 patients. This may have caused a selection bias. Second, as explained above, the renal blood flow measurements derived from MAG_3-scintigraphy should be interpreted with caution. Third, the single-kidney measurements may have been influenced by the medication used at the time of renal vein blood sampling. This, however, seems less likely since the conclusions derived from the analysis in patients with unchanged medication were consistent with those derived from the entire patient group.

In conclusion, renal artery stent placement is capable of causing longstanding improvement of blood flow and glomerular filtration rate of the treated kidney and leads to disappearance of renin suppression of the contralateral kidney. These results also illustrate that single-kidney function measurements may provide information on the effects of stent placement that cannot be obtained by conventional renal function measurements.

APPENDIX

The renal plasma flow of the treated side (RPF_{tr}) and contralaterally (RPF_{cl}), the effective renal plasma flow of the treated side ($ERPF_{tr}$) and contralaterally ($ERPF_{cl}$), together with the glomerular filtration rate of the treated side (GFR_{tr}) and contralaterally (GFR_{cl}) were calculated as follows:

Extraction ratio of ^{131}I-hippuran (Ehip) = effective renal plasma flow / renal plasma flow;

Extraction ratio of ^{125}I-thalamate (Ethal) = glomerular filtration rate / renal plasma flow.

The extraction ratios can be written as follows:

$\mathbf{RPF_{tr}} = ERPF_{tr} / Ehip_{tr}$ (1)

$\mathbf{RPF_{cl}} = ERPF_{cl} / Ehip_{cl}$ (2)

$\mathbf{GFR_{tr}} = RPF_{tr} * Ethal_{tr}$ (3)

$\mathbf{GFR_{cl}} = RPF_{cl} * Ethal_{cl}$ (4)

In which the suffices 'tr' and 'cl' stand for the treated and contralateral side, respectively.

The renal plasma flow ratio between the two kidneys is given by:

$\mathbf{RPF_{tr} / RPF_{cl}} = Flowcounts_{tr} / Flowcounts_{cl}$ (5)

In which Flowcounts = the area of the time-activity curve during the first 60 seconds, thereby assuming that this part of the curve is determined solely by the renal plasma flow.

From equations (1), (2) and (5), it follows that:

$\mathbf{ERPF_{tr} / ERPF_{cl}} = (Ehip_{tr} / Ehip_{cl}) * (Flowcounts_{tr} / Flowcounts_{cl})$ (6)

Total effective renal plasma flow is defined as:

$\mathbf{ERPF_{tr} + ERPF_{cl}}$ = total C-hip (7)

In which total C-hip = total clearance of ^{131}I-hippuran.

From equations (1), (2), (5), (6) and (7) it follows that:

$\mathbf{RPF_{tr}} = Flowcounts_{tr} * \text{total C-hip} / (Ehip_{tr} * Flowcounts_{tr} + Ehip_{cl} * Flowcounts_{cl})$ (8)

$\mathbf{RPF_{cl}} = Flowcounts_{cl} * \text{total C-hip} / (Ehip_{tr} * Flowcounts_{tr} + Ehip_{cl} * Flowcounts_{cl})$ (9)

From equations (1), (2), (8) and (9) it follows that:

$\mathbf{ERPF_{tr}} = Flowcounts_{tr} * Ehip_{tr} * \text{total C-hip} / (Ehip_{tr} * Flowcounts_{tr} + Ehip_{cl} * Flowcounts_{cl})$ (10)

$\mathbf{ERPF_{cl}} = Flowcounts_{cl} * Ehip_{cl} * \text{total C-hip} / (Ehip_{tr} * Flowcounts_{tr} + Ehip_{cl} * Flowcounts_{cl})$ (11)

From equations (3), (4), (8) and (9) it follows that:

$\mathbf{GFR_{tr}} = Flowcounts_{tr} * Ethal_{tr} * \text{total C-hip} / (Ehip_{tr} * Flowcounts_{tr} + Ehip_{cl} * Flowcounts_{cl})$ (12)

$\mathbf{GFR_{cl}} = Flowcounts_{cl} * Ethal_{cl} * \text{total C-hip} / (Ehip_{tr} * Flowcounts_{tr} + Ehip_{cl} * Flowcounts_{cl})$ (13)

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To identify pre-intervention parameters that predict one-year clinical outcome of stent placement for renal artery stenosis, regression analysis was performed using anatomical parameters from angiography and intravascular ultrasound and functional parameters from single-kidney renal function tests and renal scintigraphy as independent variables. Clinical success of renal artery stent placement at one-year follow-up was better in patients treated for hypertension than for renal function impairment (85% and 35% of the patients, respectively). In the latter group, lateralization to the affected kidney on the scintigram appeared to be a positive predictor of clinical success.

Chapter 10

PREDICTORS FOR CLINICAL SUCCESS AT ONE YEAR FOLLOWING RENAL ARTERY STENT PLACEMENT

Renal artery stent placement has become a common procedure to treat atherosclerotic renal artery stenosis (RAS). The usual indications for stent placement are drug resistant hypertension or renal function impairment.
However, from clinical practice it is known that renal artery stenting may benefit some - but not all - patients.[1,2] To avoid unnecessary interventions, it is desirable to predict which patients will achieve long-term clinical success. To the best of our knowledge, however, such predictors for clinical success of renal artery stent placement are scarcely available.
The aim of the present study was, therefore, to identify pre-interventional parameters that may predict one-year clinical success after renal artery stent placement. We considered anatomical parameters of RAS obtained with angiography and intravascular ultrasound (IVUS) and functional parameters obtained by renal scintigraphy and renal vein blood sampling.

METHODS

Patients

Forty consecutive patients (29 men, 11 women; aged 60±9.1 years [mean±SD]) were treated with stent placement for angiographically proven atherosclerotic RAS of more than 50% diameter reduction. For each patient the indication for intervention was recorded as hypertension and/or renal function impairment. Serum creatinine did not exceed 455 µmol/l. All patients underwent renal scintigraphy and single-kidney renal function tests within one month before stent placement. Angiography and IVUS were performed at the time of stent placement. Medication regimen (in defined daily doses), blood pressure and serum creatinine were recorded from six months before intervention up to one-year follow-up. The following characteristics were recorded: age, sex, signs and symptoms of atherosclerotic vascular disease (angina pectoris, intermittent claudication, cerebrovascular disease or vascular surgery), duration of hypertension (<2 or ≥2 years), smoking history (ever or never), obesity (body mass index ≥25 kg/m^2), diabetes mellitus (absent or present) and serum creatinine concentration. The Local Committee Human Research approved the investigation. Written informed consent was obtained from all patients.

Definitions of treatment indication and clinical success

Hypertension was defined as an averaged diastolic blood pressure ≥95 mmHg measured at two to four separate visits in the outpatient clinic from six months before intervention to the day of intervention. Renal function impairment was defined as an averaged serum creatinine ≥110 µmol/l measured in the six months period before intervention.[3] For determination of clinical success, averaged data on diastolic blood pressure and serum creatinine obtained in the period from six to twelve months follow-up were used. Clinical success at follow-up was defined as: 1. a normalization of diastolic blood pressure or a ≥10 mmHg decrease of diastolic blood pressure with the same or lower number of defined daily doses of antihypertensive medication[4] in patients treated for hypertension, 2. a normalization of serum creatinine values (<110 µmol/l), or a ≥20% decrease of serum creatinine[2,5,6] in patients treated for renal function impairment, and 3. a normalization of

diastolic blood pressure or a ≥10 mmHg decrease of diastolic blood pressure with the same or lower number of defined daily doses of antihypertensive medications and/or a normalization of serum creatinine values (<110 µmol/l), or a ≥20% decrease of serum creatinine in patients treated for both hypertension and renal function impairment.

Renal scintigraphy

Data derived from captopril enhanced renal scintigraphy were used to obtain information on the contribution of the affected and the contralateral kidneys to the total renal blood flow. Renal scintigraphy was performed with the patient in a supine position with the detector placed posteriorly. Patients received 25 or 50 mg of captopril orally at one hour before the examination. After intravenous administration of 74 MBq ^{99m}Tc-MAG$_3$, data were collected in 10-second frames during a 20-minute period. The number of total counts accumulated in the first 60 seconds were quantified and were taken as a measure of the renal blood flow to the affected and the contralateral kidneys. This method is based on the assumption that the early part of the time-activity curve is determined solely by the renal blood flow. The contribution of the renal blood flow of the individual kidneys to the total renal blood flow was recorded. Based on this value, we recorded whether the kidney to be stented had an abnormal contribution to the total renal blood flow. To account for normal variability in contribution of the individual kidneys, we defined abnormal contribution of the affected kidney as an affected kidney-to-two-kidney countratio ≤0.45.

Peripheral and renal vein blood sampling

Concentrations of active renin and ^{131}I-hippuran and ^{125}I-thalamate in the left and right renal veins were measured and assayed as described by Wenting et al.[7] Constant infusions of ^{131}I-hippuran and ^{125}I-thalamate were given via an antecubital vein. After reaching the steady state, a renal venous blood sample was taken at each side simultaneously with a sample from the abdominal aorta. Samples from these sites were also used for renin measurements. Additional blood samples were taken at 15-minute intervals from a peripheral vein to estimate the total (two-kidney) clearances of ^{131}I-hippuran and ^{125}I-thalamate. All blood samples were immediately centrifuged and measurements were made in plasma. Determination of blood oxygen saturation served to assure that blood samples were taken from the renal veins. Single-kidney extraction ratios of ^{131}I-hippuran and ^{125}I-thalamate were defined as (A-V)/A, where A = activity in the abdominal aorta and V = activity in renal vein. The total clearances of ^{131}I-hippuran and ^{125}I-thalamate were taken as a measure of total effective renal plasma flow and glomerular filtration rate (GFR), respectively. The concentration of active renin in plasma was measured by radioimmunoassay.[8] We defined the vein-to-artery renin ratio of the affected side as 'elevated' in case of values >1.48.[9]

Stent placement procedure

Pre-intervention digital subtraction angiograms were obtained using aortic-flush injections. The stenosis was then crossed with a 5F selective catheter and, if possible, pre-interventional IVUS was performed over a 0.020-in flexible tip guide wire (Boston Scientific). After predilation, angiography and IVUS were repeated. A Palmaz stent (type p104, p154 or p204; Johnson & Johnson Interventional Systems, New York) was placed

whereby the stent sizing was based on the angiographic and IVUS findings. Stent placement was considered technically successful when angiography and IVUS showed complete stent-vessel wall apposition, complete lesion covering and <20% residual diameter stenosis.[10] If necessary, additional stent dilatation was performed. During the procedure, the patients received 5,000 IU of heparin. Heparin infusion was continued for 48 hours after the procedure (20,000-30,000 IU per day). Oral acetylsalicylic acid (100 mg daily) was started at the day of the procedure and continued during the entire follow-up period.

Intravascular ultrasound

For IVUS examination a 30 MHz mechanical imaging system with 4.3F catheters ("Princeps", Endosonics, Rijswijk, The Netherlands) was used.[11] The IVUS catheter was positioned distally from the stenosis in a second-order renal artery branch. Real-time cross-sectional images of the main renal artery obtained during slow pullback of the IVUS catheter, were displayed on a monitor and stored on S-VHS videotape. Quantitative analysis on lumen, vessel and plaque area was performed at the most stenotic site and at a distal reference site in the main renal artery just before the first major side-branch. Previously we have described two lesion types in atherosclerotic RAS based on IVUS-criteria: one due to accumulation of atherosclerotic plaque with or without adaptive remodeling (adaptive remodeling lesion), and the other due to focal narrowing of the vessel wall without plaque accumulation (coarctation lesion).[12] Lesions in which RAS was considered to be caused by an adaptive remodeling lesion, had a larger vessel area at the target site than at the reference site (relative target to reference vessel area of >85%). Following the previously published definition, lesions were considered to be of the coarctation type when the relative target to reference vessel area was ≤85%.

Data analysis

The following parameters obtained immediately prior to or at the time of stent placement were considered in the analysis:

Angiography:

- percentage diameter stenosis

Intravascular ultrasound:

- Relative target to reference vessel area (coarctation vs. adaptive remodeling lesions)
- Plaque area at the target site
- Minimal stent lumen area after stent placement
- Vessel area at the distal reference site

Renal scintigraphy:

- Affected kidney-to-two-kidney countratio (abnormal or normal)

Peripheral and renal vein blood sampling:

- Two-kidney glomerular filtration rate
- Extraction ratios of ^{131}I-hippuran and ^{125}I-thalamate of the affected kidney
- Vein-to-artery renin ratio of the affected kidney (elevated or non-elevated)

All analyses were initially performed for the whole patient group and repeated for the subgroups of patients with hypertension and renal function impairment separately. Differences in baseline variables between patients with success or failure were assessed using the two-tailed chi-squared or Student's *t*-tests where appropriate, at $p=0.05$. Univariate logistic regression analysis was used to determine which of the above-mentioned parameters was predictive for clinical success. For continuous variables, the beta-coefficient was given and for categorical variables the odds ratio was computed. The variables that reached the significance level in the univariate regression analysis were subsequently entered in a multivariate model. Model selection was performed by a backward selection procedure. Data are presented as a proportion or as mean ± SD. All statistical analyses were performed using the SPSS software package for Windows, version 9.0.

RESULTS

The indication for renal artery stent placement was hypertension in 14 patients, renal function impairment in 14, and hypertension combined with renal function impairment in 12 patients. Stent placement was technically successful in all patients. Clinical success was seen in 27/40 patients at one-year follow-up (Table 1).

Table 1. Number of patients (n) with clinical success or failure according to their treatment indication.

	Success (n)	Failure (n)
Hypertension (n=14)	12	2
Renal function impairment (n=14)	4	10
Both (n=12)	11	1
Hypertension	10	2
Renal function impairment	5	7

Of the 26 procedures performed for hypertension, 22 (85%) were considered clinically successful based on the predefined criteria, as were 9 of 26 procedures (35%) done for renal function impairment. Clinical success for hypertension was not influenced by the presence of renal function impairment (p=NS), but clinical success for renal function impairment was significantly influenced by the presence of hypertension ($p=0.002$). Comparison of baseline characteristics in patients with clinical success or failure showed that a lower serum creatinine at baseline was associated with clinical success at follow-up (116 ± 41.6 µmol/l vs. 209 ± 119.0, $p=0.02$; Table 2).

Table 2. Characteristics of patients with clinical success or failure one year after renal artery stent placement.

	Success n=27	Failure n=13	*p*-value*
Age, years	58 ± 4.9	62 ± 8.2	0.26
Sex, % males	70	77	0.66
Atherosclerotic vascular disease, %	81	100	0.10
Recent onset of hypertension†, %	37	23	0.38
Ever smoked, %	85	77	0.52
Obesity§ ,%	48	54	0.74
Diabetes mellitus, %	7	15	0.43
Serum creatinine, μmol/l	116 ± 41.6	209 ± 119.0	**0.02**

Values are expressed as mean ± SD or proportions.
* Chi-squared tests or Student's *t*-test where appropriate.
† Onset of hypertension < 2 years before intervention.
§ Body mass index ≥25 kg/m^2.
% Percentage.

In the whole group, regression analysis indicated a high two-kidney GFR as a statistically significant predictor of clinical success at one-year follow-up (p=0.03; Table 3). In addition, an abnormal affected kidney-to-two-kidney countratio and an elevated vein-to-artery renin ratio were borderline statistically significant predictors for one-year clinical success (p=0.058 for both). Neither angiographic nor IVUS parameters were predictive for clinical. Since only one parameter was significantly predictive for success, a multivariate analysis could not be performed.

In the subgroup of patients treated for hypertension, there were no differences in baseline clinical characteristics between patients with and without clinical success. Regression analysis indicated the relative target to reference vessel area measured with IVUS as a borderline significant predictor for clinical outcome, (β-coefficient (SE): 0.06 (0.03); p=0.07). Patients with a clinically successful result after stent placement had a lower value of the target to reference vessel area (consistent with coarctation-type RAS lesions) than patients with clinical failure at follow-up (85% ± 23.4 vs. 121% ± 28.6, respectively).

In patients treated for renal function impairment, baseline serum creatinine was different between patients who had clinical success or failure; patients with clinical success had less impaired renal function at baseline (serum creatinine 139 ± 25.4 vs. 207 ± 98.2 µmol/l, p=0.014). Regression analysis implicated an abnormal affected kidney-to-two-kidney countratio as a significant predictor for clinical success (odds ratio: 15; 95%-confidence interval: 1-218; p=0.048). An abnormal affected kidney-to-two-kidney countratio was present in 83% and 25% of the patients with clinical success and failure, respectively.

Table 3. Data on pre-intervention parameters and regression coefficients of univariate logistic regression analysis predicting clinical success or failure one year following renal artery stent placement.

	Success n=27	Failure n=13	β-Coefficient (SE)	Odds ratio (95% CI)	p
Angiography					
Diameter stenosis, %	70 ± 14.1	67 ± 17.7	- 1.00 (2.34)		0.67
Intravascular ultrasound					
Relative vessel area (target/reference), %	90 ± 24.0	95 ± 42.2	0.01 (0.01)		0.71
Plaque area at the target site, mm^2	22 ± 9.1	19 ± 13.8	-0.03 (0.04)		0.47
Lumen area in the stent, mm^2	24 ± 4.3	25 ± 8.2	0.03 (0.07)		0.62
Reference vessel area, mm^2	39 ± 16.2	37 ± 13.0	-0.01 (0.03)		0.76
Renal scintigraphy					
Abnormal affected kidney to two kidney countratio, %	78	29		9 (1 - 63)	0.06
Peripheral renal vein blood sampling					
Glomerular filtration rate, ml/min	71 ± 27.3	40 ± 13.2	- 0.08 (0.04)		**0.03**
Extraction ratio of ^{131}I-hippuran	0.46 ± 0.21	0.42 ± 0.18	-1.03 (2.16)		0.63
Extraction ratio of ^{125}I-thalamate	0.13 ± 0.07	0.11 ± 0.05	-5.09 (7.17)		0.48
Elevated vein-to-artery renin ratio of the affected kidney, %	65	17		9 (1 - 95)	0.06

Values are means ± SD or proportions; GFR = Glomerular filtration rate; SE = standard error; % = percentage.

DISCUSSION

Previous studies have shown that, in terms of blood pressure and renal function, renal artery stent placement benefits some but not all patients.[1,2,13] An earlier study reported that, apart from the fact that the greatest improvement of systolic blood pressure occurred in patients with the highest baseline systolic blood pressure, there were no clinical parameters predictive for improvement of blood pressure and renal function.[14] The present study investigated whether parameters derived from angiography, IVUS, renal scintigraphy and renal vein blood sampling could be used as predictors for one-year clinical outcome.

As a first finding, our results showed a better clinical success at one-year follow-up in patients treated for hypertension than in patients treated for renal function impairment, with success rates of 85% and 35%, respectively. Although the results are critically dependent on the particular criteria to define clinical success in these subgroups, our results are in agreement with the previously reported findings of Blum et al.[1] for stent placement to treat hypertension and of White et al.[15] for treatment of renal function impairment.

In the whole patient group, a high serum creatinine and low GFR at baseline correlated with clinical failure of renal artery stenting at follow-up. This seems to echo the above mentioned finding of poorer outcome in patients treated for renal function impairment. However, even in the subgroup of patients treated for renal function impairment, a higher serum creatinine at baseline was associated with clinical failure. This finding corroborates the observation of others that clinical benefit of renal artery stent placement in patients with severe renal insufficiency is limited.[5] It seems, therefore, that treatment of RAS should preferably be performed before renal function becomes severely impaired.

In patients treated for hypertension, we found no significant predictors of clinical success. However, the coarctation lesion type of RAS as determined with IVUS tended to be predictive at $p=0.07$. This lesion is characterized by a small relative vessel area at the target site.

The ability to predict the clinical outcome of renal artery stent placement may be most desirable in the patients with renal function impairment, because clinical success was obtained in only 35% of the patients. An interesting finding was that the presence of an abnormal affected kidney-to-two-kidney countratio (lateralization) on the scintigram before stent placement emerged as a highly significant predictor of clinical success, particularly in the subgroup of patients treated for renal function impairment. Patients with lateralization on the scintigram had a 15-fold increased chance of having one-year clinical success. Since our scintigraphic data referred to the first 60 seconds after count detection, lateralization on the scintigram may reflect a difference in blood blood flow between the affected and contralateral kidney. This agrees with the finding that an elevated vein-to-artery renin ratio of the affected kidney was borderline predictive for clinical success; under steady state conditions, an increased vein-to-artery renin ratio of a kidney supplied by a stenosed artery is caused by decreased renal blood flow.

At first glance, the presence of lateralization to the affected kidney seems trivial, and a logical consequence of RAS. It should be pointed out, however, that RAS in our study was not associated with lateralization in all patients. This observation accords with results of Peters et al.[16] who measured renal blood flow with Technetium-99m-DTPA renography and found that 22-33% of the patients with RAS showed no evidence of decreased renal blood flow to the affected kidney. An alternative explanation may be that the absence of lateralization is related to the presence of bilateral RAS. However, bilateral RAS was present in only five patients in our study, two of whom did not have lateralization to the affected kidney. Decreased renal function at the so-called non-affected side could also have obscured the lateralization to the affected side. Interestingly, it has been reported earlier that success of revascularization was associated with a normal contralateral renal plasma flow as determined by measuring single-kidney clearances of p-aminohippurate after ureter catheterization.[17]

Some limitations of the present study need to be addressed. First, the current results should be interpreted with caution, because of the limited size of our patient group. Second, as an estimate of renal blood flow, we measured the counts accumulated in the first 60 seconds after count detection on MAG_3-scintigraphy, thereby ignoring that this part of the curve is also determined by the extraction ratios of the individual kidneys. But, irrespective of the exact physiological interpretation, the observation that this scintigraphic parameter may predict clinical success at one-year follow-up remains valid.

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Although much has been published about stent placement for renal artery stenosis (RAS), little is known about the indication for intervention and the mechanisms responsible for vessel patency and clinical outcome. This thesis showed that revascularization of asymptomatic RAS is not necessary. In addition, we studied 38 consecutive patients with symptomatic RAS before stent placement and at one-year follow-up. Intravascular ultrasound showed that RAS could be due to plaque accumulation or coarctation. At follow-up, in-stent restenosis was due to plaque accumulation without stent recoil. The distal main renal artery showed unexpected shrinkage (25%). Single-kidney function tests, on average, showed improvement in function of the treated kidney. Hypertension was successfully treated in 85% of patients after stent placement but renal functional impairment in only 35%. In the latter patients, renal blood flow data may serve as predictor of clinical success.

Chapter 11

SUMMARY AND CONCLUSIONS

This thesis addresses several issues with regard to stent placement for renal artery stenosis (RAS). First, in Chapter 2, we retrospectively studied the natural history of incidentally found RAS in patients with peripheral vascular disease. To decide whether revascularization is necessary to prevent end-stage renal failure, patients with untreated asymptomatic RAS were studied during eight to ten years of follow-up. None of the 126 patients with asymptomatic RAS developed end-stage renal failure or needed dialysis. Therefore, it seems that there is no clear indication for revascularization of RAS in these patients.

Another issue of concern is that stent placement appears to benefit some - but not all - patients treated for symptomatic RAS. Chapter 3 presents a review plus meta-analysis of studies on the effect of balloon angioplasty and stent placement for RAS. The results of this meta-analysis showed that stent placement was associated with a higher initial success rate and a lower restenosis rate than balloon angioplasty (98% vs. 77% and 17% vs. 26%, respectively). Based on this meta-analysis, the two treatment modalities were found to be roughly equivalent with regard to clinical success for blood pressure and renal function in approximately 60% and 70% of the patients, respectively.

To identify vessel characteristics that may be responsible for success or failure of renal artery stent placement, Chapter 4 describes the morphology of renal arteries with and without stenosis as seen with IVUS. First, IVUS images obtained in renal artery specimens obtained at autopsy were validated with the corresponding histologic cross-sections. There was a good agreement between IVUS images and histologic findings for the assessment of renal artery lesions with or without calcifications. Second, and as a novel finding, quantitative analysis of IVUS images revealed that renal artery lumen narrowing could not only be caused by accumulation of atherosclerotic plaque (with or without adaptive remodeling), but also by focal narrowing of an otherwise normal renal arterial wall (coarctation).
In Chapter 5 we assessed whether coarctation could be found clinically in patients with symptomatic RAS. Analysis of patients with symptomatic atherosclerotic RAS undergoing renal artery stent placement showed that coarctation lesions were responsible for the artery obstruction in about half of the patients.

Chapter 6 describes the potential additional value of IVUS to enhance the technical quality of the procedure of stent placement. After predilatation a larger-sized balloon than suggested by angiography was selected for stent placement, based on the IVUS data. Even when a satisfactory angiographic end-result was obtained after stent placement, IVUS information prompted the interventionist to perform additional dilatation or additional stent placement in 33% of the patients studied.

Chapter 7 presents a preliminary report on the behavior of stents placed in renal and femoropopliteal arteries assessed with IVUS. Lumen area reduction in renal artery stents

was solely due to accumulation of plaque. Lumen area reduction in femoropopliteal stents, however, was due to a combination of plaque accumulation and stent recoil.

Chapter 8 describes the results of a serial study in a cohort of 38 consecutive patients undergoing renal artery stent placement using IVUS and angiography. Angiographic restenosis in the stent was present in 14% of the patients. Besides some plaque accumulation inside the stent seen with IVUS, a significant lumen area reduction was evidenced in the main renal artery distal to the stent, which was not caused by plaque accumulation but by a 25% decrease in vessel area. This shrinkage was confirmed by angiography and was limited to the ipsilateral main renal artery only.

To better understand the origin of the heterogeneous clinical results after stent placement, it is useful to study the effect of stent placement on the function of the treated kidney in isolation. Since conventional renal function measurements do not provide this information, single-kidney function measurements were performed and are presented in Chapter 9. Prior to stent placement and at one-year follow-up, patients underwent selective renal vein blood sampling using a constant infusion method. After reaching the steady state, renal vein-to-artery renin ratios and extraction ratios of ^{131}I-hippuran (a measure for effective renal plasma flow; ERPF) and ^{125}I-thalamate (a measure for glomerular filtration rate; GFR) of both the treated and the contralateral kidneys were measured. This, combined with renal blood flow measurements on renal scintigraphy, allowed determination of single-kidney renal plasma flow, ERPF and GFR. One-year after stent placement, the function of the treated kidney had, on average, significantly improved as shown by normalized vein-to-artery renin ratios, increased extraction ratios and increased single-kidney ERPF and GFR.

To improve patient selection for renal artery stenting, Chapter 10 addresses an attempt to find pre-intervention parameters predictive for clinical success at one-year follow-up using regression analysis. Clinical success for blood pressure, using previously published definitions, was obtained in 85% of the hypertensive patients; for treatment of renal function impairment, success was obtained in 35% of patients. A high initial GFR emerged as a significant predictor for clinical success. Subgroup analysis showed that impaired contribution of the affected kidney to the total renal blood flow was predictive for success in patients treated for renal functional impairment.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE STUDIES

From the present study it is concluded that asymptomatic RAS as an incidental finding in patients with peripheral vascular disease will seldomly lead to end-stage renal failure. Preventive revascularization seems, therefore, not necessary.

With regard to morphology of symptomatic RAS, two forms of so-called 'atherosclerotic' RAS could be distinguished on the basis of our IVUS observations. The first was due to

plaque accumulation with or without adaptive remodeling, and the second to vessel coarctation without plaque accumulation. The etiology of this coarctation could not be determined in the present study. Since coarctation was also found in post-mortem renal arteries of asymptomatic subjects, further studies may use histologic sections and more specific staining techniques, e.g. to determine whether apoptosis is present in coarctation lesions.

In our experience, IVUS used during renal artery stent placement provided additional information that led to adjunctive intervention in 33% of the procedures. Whether these additional interventions had a beneficial influence on the final technical or clinical outcome, was not addressed in the present work. To address this question, a randomized study comparing the results of stenting with and without the use of IVUS should be performed.

At one-year follow-up IVUS showed some neointimal hyperplasia in the stent but no stent recoil. Remarkably, the renal artery distal to the stent, which had increased in size immediately after stent placement, at follow-up showed shrinkage without plaque accumulation.

Single-kidney function measurements showed improvement in function of the treated kidney one year after stent placement. Clinical success of renal artery stent placement was obtained in 85% and 35% of the patients treated for hypertension and renal functional impairment, respectively. The lower success rate in patients with renal functional impairment seems to contradict the fact that stent placement, on average, improved the function of the treated kidney. Although the exact figures of clinical success are critically dependent on the definitions used, the observed functional improvement of the treated kidney may have too small an impact to result in improvement of the overall renal function. We attempted to identify predictors of clinical success of renal artery stenting, which is especially important in patients treated for renal functional impairment. Data on renal blood flow, derived from the inflow curve of MAG_3-scintigraphy, appeared to be predictive for clinical success in patients treated for renal functional impairment. The renal blood flow data, however, should be interpreted with caution and the conclusions of the study should be prospectively tested in future studies.

Alhoewel er veel geschreven is over stent-plaatsing bij nierarterie-stenose, is er nog weinig bekend over indicaties voor behandeling en de factoren die het uiteindelijke resultaat bepalen. In dit proefschrift werd aangetoond dat revascularisatie van nierarterie-stenose bij asymptomatische patiënten weinig zinvol is. Daarnaast bestudeerden we 38 patiënten met symptomatische nierarterie-stenose voorafgaand aan stent-plaatsing en na een jaar. Intravasculaire echografie toonde aan dat een nierarterie-stenose kan worden veroorzaakt door plaque-ophoping of door coarctatie. Vernauwing van het lumen van de stent na een jaar was enkel het gevolg van plaque-ophoping. Daarnaast viel op dat de nierarterie aansluitend aan de stent verkleind was met 25%. Gemiddeld gezien leidde stent-plaatsing tot een verbetering van de functie van de behandelde nier. Klinisch succes werd behaald bij 85% van de patiënten met hypertensie en in 35% van de patiënten met nierfunctiestoornissen. Bij patiënten behandeld vanwege nierfunctiestoornissen kunnen bloedstroommetingen mogelijk het klinisch succes voorspellen.

Hoofdstuk 12

SAMENVATTING EN CONCLUSIES

In dit proefschrift worden resultaten gepresenteerd met betrekking tot onderzoek naar stent-plaatsing als behandeling van patiënten met een nierarterie-stenose (d.i. vernauwing van de nierslagader). Als eerste staan in Hoofdstuk 2 de resultaten van een retrospectief onderzoek naar het natuurlijk beloop van de bij toeval gevonden nierarterie-stenose bij patiënten met perifeer vaatlijden beschreven. Om te kunnen beslissen of revascularisatie nodig is ter voorkoming van nierfalen, werden 126 patiënten met asymptomatische nierarterie-stenose gedurende een periode van acht tot tien jaar gevolgd. Geen van deze patiënten bleek in aanmerking te komen voor nierdialyse. Er lijkt dus geen indicatie te bestaan voor de revascularisatie van nierarterie-stenosen bij deze groep patiënten.

Een ander belangrijk onderwerp betreft het feit dat niet alle patiënten met symptomatische nierarterie-stenose op de lange termijn baat hebben bij stent-plaatsing. Hoofdstuk 3 presenteert een overzicht en een meta-analyse van studies inzake het effect van ballon-angioplastiek en stent-plaatsing als behandeling van patiënten met een nierarterie-stenose. De resultaten van de meta-analyse toonden aan dat stent-plaatsing een hoger technisch succespercentage had en een lager percentage restenose (d.i. hervernauwing) dan ballon-angioplastiek (respectievelijk 98% versus 77%, en 17% versus 26%). Uit de meta-analyse bleek verder dat de twee behandelingsmethodes ongeveer gelijk waren voor wat betreft het klinisch succes t.a.v. bloeddruk en nierfunctie (in ongeveer 60% en 70% van de patiënten).

Om vaatwandeigenschappen te identificeren, die verantwoordelijk kunnen zijn voor succes of falen van stent-plaatsing voor nierarterie-stenose, werd de morfologie van nierarteriën met en zonder stenose bestudeerd met behulp van intravasculaire echografie (IVUS) en beschreven in Hoofdstuk 4. Eerst werden de IVUS-beelden van nierarteriën, verkregen bij obductie, vergeleken met de bijbehorende histologische coupes. Bij kwalitatieve analyse bleek er overeenstemming te zijn tussen IVUS en histologie voor wat betreft het detecteren van plaques met of zonder kalk. Kwantitatieve analyse van de IVUS-beelden toonde aan dat vernauwingen van de nierarterie niet alleen veroorzaakt konden worden door een ophoping van atherosclerotische plaque in de vaatwand (al dan niet met compensatoire vergroting van de vaatwand), maar ook door een lokale vaatwandvernauwing van een verder normale nierarterie (coarctatie). Deze laatste bevinding was nieuw, en tot dusver niet beschreven.

In Hoofdstuk 5 wordt beschreven of coarctatie ook klinisch gevonden kon worden bij patiënten met nierarterie-stenose. Analyse van IVUS-beelden, verkregen bij symptomatische patiënten met nierarterie-stenose voorafgaand aan stent-plaatsing, liet zien dat coarctatie verantwoordelijk was voor de obstructie bij ongeveer de helft van de patiënten.

Hoofdstuk 6 beschrijft de mogelijk additionele waarde van IVUS om de technische kwaliteit van de plaatsing van een stent bij patiënten met een nierarterie-stenose te verbeteren. Na predilatatie werden op basis van IVUS-informatie grotere ballonnen gebruikt voor stent-plaatsing dan nodig leek op het angiogram. Zelfs wanneer de stent-plaatsing angiografisch succesvol was, werd op basis van de IVUS informatie bij 33% van de patiënten een extra dilatatie of stent-plaatsing uitgevoerd.

In Hoofdstuk 7 geeft een beschrijving van onderzoek m.b.v. IVUS naar het mechanisme dat verantwoordelijk was voor de verkleining van het lumen (d.i. doorstroomopening) van stents in nier - en femoropopliteale arteriën in de tijd. Het lumen van stents in de nierarterie werd kleiner als gevolg van plaque-ophoping. Verkleining van het lumen in femoropopliteale stents, daarentegen, werd veroorzaakt door een combinatie van plaque-ophoping en een verkleining van de stent.

In Hoofdstuk 8 staan de resultaten beschreven van een onderzoek in een groep van 38 patiënten die stent-plaatsing in de nierarterie ondergingen en die na een jaar weer onderzocht werden met behulp van IVUS en angiografie. Angiografische restenose in de stent was aanwezig in 14% van de patiënten. Met IVUS werd vastgesteld dat, naast een geringe ophoping van plaque in de stent, het lumen van de nierarterie stroomafwaarts van de stent significant verkleind was. Dit laatste werd niet veroorzaakt door plaque-ophoping maar door een verkleining van de vaatwand zelf met 25%. Dit werd bevestigd door angiografie en bleek beperkt te zijn tot de hoofdtak van de behandelde nierarterie.

Om de oorzaak van de verschillen in klinisch resultaat na stent-plaatsing beter te kunnen begrijpen, is het van belang om het effect van stent-plaatsing op de behandelde nier zelf te bestuderen. Omdat de conventionele nierfunctie bepalingen deze informatie niet kunnen geven, werden gescheiden nierfunctie bepalingen uitgevoerd. De resultaten hiervan zijn beschreven in Hoofdstuk 9. Voorafgaand aan stent-plaatsing en een jaar daarna werden na toediening van van de stoffen ^{131}I-hippuran en ^{125}I-thalamaat, bloedmonsters afgenomen uit de niervene en -arterie van beide nieren afzonderlijk. Uit deze bloedmonsters werd de renine ratio (veneus/arterieel) bepaald, samen met de extractie-ratio's van ^{131}I-hippuran (een maat voor de effectieve nierdoorstroming; ERPF) en van ^{125}I-thalamaat (een maat voor de glomerulaire filtratie snelheid; GFR) van zowel de behandelde als de contralaterale nier. Dit - gecombineerd met bloedstroommetingen, afkomstig van nierscintigrafie - maakte het mogelijk om de gescheiden ERPF en GFR te berekenen. Gemiddeld genomen was de functie van de behandelde nier een jaar na stent-plaatsing verbeterd. Dit bleek uit genormaliseerde renine-ratio's, verhoogde extractie-ratio's en verbetering van de ERPF en GFR van de behandelde nier.

Om de selectie van patiënten voor stent-plaatsing van nierarterie-stenose te verbeteren, werd in Hoofdstuk 10 beschreven in hoeverre parameters, voorafgaand aan de interventie

verkregen, het klinisch succes na een jaar konden voorspellen. Hiertoe werd gebruik gemaakt van regressie-analyse. Klinisch succes t.a.v. bloeddruk, gedefinieerd naar aanleiding van eerder gepubliceerde criteria, werd verkregen in 85% van de patiënten met hypertensie; het klinisch succes t.a.v. nierfunctie was 35% bij patiënten met nierfunctiestoornissen. Een hoge GFR was een significante voorspeller van klinisch succes. Analyse in subgroepen toonde aan dat een beperkte bijdrage van de te behandelen nier aan de totale bloedstroom voorspellend was voor klinisch succes bij patiënten met nierfunctiestoornissen.

CONCLUSIES EN AANBEVELINGEN VOOR VERDER ONDERZOEK

Uit deze studie kan worden geconcludeerd dat de asymptomatische nierarterie-stenose, die bij toeval gevonden wordt bij patiënten met perifeer vaatlijden, zelden zal leiden tot eind-stadium nierfalen. Preventieve revascularisatie voor deze groep patiënten is daarom niet geïndiceerd.

Wat betreft de morfologie van symptomatische nierarterie-stenose, werden op basis van de IVUS observaties twee vormen van zogenaamde "atherosclerotische" nierarterie-stenose onderscheiden. De eerste was het gevolg van plaque-ophoping, al dan niet met compensatoire vergroting van de vaatwand. De tweede was het gevolg van coarctatie zonder plaque-ophoping. De oorzaak van coarctatie kon in dit onderzoek niet worden vastgesteld. Omdat coarctatie ook aanwezig was in nierarteriën verkregen bij obductie, zou in verder onderzoek histologie gebruikt kunnen worden met specifieke kleuringstechnieken, bijvoorbeeld om te onderzoeken of apoptose (d.i. geprogrammeerde celdood) aanwezig is bij de nierarterie-stenoses veroorzaakt door coarctatie.

Uit onze ervaring met het gebruik van IVUS tijdens stent-plaatsing bleek dat de verkregen additionele informatie aanleiding gaf tot extra interventie in 33% van de procedures. Of deze extra interventies een positieve invloed hadden op het uiteindelijke technische en klinische resultaat, kon niet worden vastgesteld. Het antwoord op deze vraag kan alleen volgen uit een gerandomiseerde studie waarin de resultaten van stent-plaatsing met en zonder gebruik van IVUS worden vergeleken.

Een jaar na stent-plaatsing liet IVUS enige plaque-ophoping zien in de stent, maar geen verkleining van de stent zelf. Opvallend genoeg was het nierarterie-segment stroomafwaarts van de stent na een jaar significant kleiner geworden door krimp van de vaatwand zonder plaque-ophoping.

Gescheiden nierfunctie bepalingen toonden een verbetering aan van de functie van de behandelde nier een jaar na stent-plaatsing. Klinisch succes werd behaald bij 85% van de patiënten met hypertensie en in 35% van de patiënten met nierfunctiestoornissen. Het beperkte succes bij patiënten met nierfunctiestoornissen lijkt de constatering dat stent-plaatsing, gemiddeld gezien, leidt tot een verbetering van de functie van de

behandelde nier, tegen te spreken. Alhoewel de klinische succespercentages sterk afhankelijk zijn van de gebruikte definities, zou het best zo kunnen zijn dat de verbetering in functie van de behandelde nier te weinig bijdraagt om een verbetering van de totale nierfunctie te bewerkstelligen in de patiënten behandeld met het doel om de nierfunctie te stabiliseren of te verbeteren. Onze poging om predictors voor klinisch succes van stent-plaatsing te vinden, is uiteraard speciaal van belang bij de laatstgenoemde groep patiënten met nierfuntiestoornissen. Bloedstroommetingen op de inflow-curve van het MAG_3-scintigram bleken voorspellend te zijn voor klinisch succes, in het bijzonder bij patiënten behandeld voor nierfunctiestoornissen. Deze bloedstroommetingen moeten echter behoedzaam worden geïnterpreteerd en de conclusies van deze analyse moeten prospectief worden getest in verder onderzoek.

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CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 23 augustus 1974 te Lekkerkerk. Na het behalen van het VWO-diploma aan de Reformatorische Scholengemeenschap 'Guido de Brès' te Rotterdam in 1992, werd de keuze gemaakt voor de studie geneeskunde. Wegens uitloting deed zij de propaedeuse geneeskunde aan de Rijksuniversiteit Antwerpen. In 1993 kon zij na inloting herstarten aan de Erasmus Universiteit Rotterdam, en behaalde het doctoraal examen in 1997.
Gedurende het laatste half jaar werd afstudeeronderzoek gedaan op de afdeling Experimentele Echocardiografie onder begeleiding van mw. dr. E.J. Gussenhoven. Besloten werd om de studie te onderbreken om de onderzoeksactiviteiten, die de basis vormen voor dit proefschrift, voort te kunnen zetten.
In april 1999 is de auteur begonnen met de co-assistentschappen geneeskunde.