

Shrinkage of the distal renal artery 1 year after stent placement as evidenced with serial intravascular ultrasound

¹T C GILL-LEERTOUWER, MD, ^{2,4}E J GUSSENHOVEN, MD, ³J DEINUM, MD,
¹L C VAN DIJK, MD and ¹P M T PATTYNAMA, MD

Departments of ¹Radiology, ²Cardiology and ³Internal Medicine, Erasmus Medical Center, Rotterdam and ⁴Interuniversity Cardiology Institute of The Netherlands, The Netherlands

Abstract. The objective of this study was to determine the quantitative intravascular ultrasound (IVUS) and angiographic changes that occur during 1 year follow-up after renal artery stent placement, given that restenosis continues to be a limitation of renal artery stent placement. 38 consecutive patients with symptomatic renal artery stenosis treated with Palmaz stent placement were studied prospectively. IVUS and angiography were performed at the time of stent placement and at 1 year follow-up. At follow-up, angiographic restenosis was seen in 14% of patients. The lumen area in the stent, seen with IVUS, was significantly decreased from $24 \pm 5.6 \text{ mm}^2$ to $17 \pm 5.6 \text{ mm}^2$ ($p < 0.001$) solely due to plaque accumulation. The distal main renal artery showed a significant decrease in lumen area owing to a significant vessel area decrease from $39 \pm 14.0 \text{ mm}^2$ to $29 \pm 9.3 \text{ mm}^2$ ($p < 0.001$) without plaque accumulation. Angiographic analysis confirmed this reduction in luminal diameter and showed that the distal renal artery diameter at follow-up was significantly smaller than before stent placement ($86 \pm 23.0\%$ vs $104 \pm 23.9\%$ of the contralateral renal artery diameter; $p = 0.003$). Besides plaque accumulation in the stent, unexplained shrinkage of the distal main renal artery was evidenced with IVUS and angiography 1 year following stent placement.

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 8 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 allows monitoring of 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 1 year follow-up in a series of consecutive patients who underwent renal artery stenting for atherosclerotic RAS.

Received 17 January 2002 and in revised form 25 June 2002, accepted 3 July 2002.

Address correspondence to Trude C Gill-Leertouwer, MD, PhD, Department of Radiology, University Hospital Rotterdam-Dijkzigt, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

This project was supported by a grant from Revolving Fund (1996-26) of the Erasmus University Medical Center, Rotterdam and Cordis (a Johnson & Johnson Company).

Methods

Patients

Between September 1996 and December 1998, 41 consecutive patients (27 men, 14 women; aged 60 ± 9 years (mean \pm standard deviation unless stated)) presenting with symptomatic RAS of $\geq 50\%$ diameter stenosis were treated with stent placement. One patient underwent stenting of both renal arteries on two separate occasions, therefore, a total of 42 renal arteries were treated. Patients had renal function impairment (serum creatinine $\geq 110 \mu\text{mol l}^{-1}$; $n = 26$) and/or drug resistant hypertension, defined as a diastolic blood pressure $\geq 95 \text{ mmHg}$ while receiving two “defined daily doses” of antihypertensive drug treatment ($n = 26$). The defined daily dose 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. At 1 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 5 F selective catheter. Pre-intervention IVUS imaging was performed over a 0.020 inch flexible tip guide-wire (Terumo, Tokyo, Japan). The lesion was pre-dilated with an angioplasty balloon 5 mm or 6 mm in diameter. A Palmaz stent (Johnson & Johnson Interventional Systems, New York, NY) was then placed (p104 (10.4 mm stent length), p154 (15.4 mm) or p204 (20.4 mm) stents). 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 6 mm or 7 mm balloon. During the procedure, patients received 5000 IU of heparin, after which heparin infusion was continued for 48 h (20 000–30 000 IU day⁻¹). 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 (Princept, Endosonics, Rijswijk, The Netherlands) [4] with 4.3 F 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 a super video home system. 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. In addition, after IVUS and successful angiographic stent placement, and at 1 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). Quantitative measurements of IVUS cross-sections were performed using a digital video analyser system [5]. 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–LA, or SA–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 1 year follow-up was defined as a $\geq 50\%$ diameter reduction in the stent, compared with the distal main renal artery. After stent placement, and at follow-up, angiographic lumen diameter of the ipsilateral 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.

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. A *p*-value ≤ 0.05 was considered statistically significant.

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 \pm standard deviation)) 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. In one of these two patients, only IVUS was performed. Eight patients were lost to follow-up owing to dialysis ($n=3$), patient refusal ($n=4$) and 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 4 of 28 patients (14%) and these patients underwent additional balloon angioplasty.

LA in the stent decreased significantly during follow-up from $24 \pm 5.6 \text{ mm}^2$ to $17 \pm 5.6 \text{ mm}^2$

Table 1. Intravascular ultrasound measurements in 30 renal arteries obtained immediately after stent placement and at 1 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)	<i>p</i> -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

N.B. Values are mean ± standard deviation. NS, not significant.

($p<0.001$) (Table 1), which was entirely owing to an increase of plaque area in the stent. Stent area and diameter remained unchanged. In the renal artery distal to the stent, LA decreased significantly owing to a decrease in vessel area (39 ± 14.0 mm² immediately after stent placement to 29 ± 9.3 mm² at follow-up; $p<0.001$) without plaque accumulation (Figure 1). Of all reference cross-sections after stent placement, 42 showed VA decrease, 11 showed a less than 10% change and 7 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 prior to intervention in five patients, had less than 10% change in two patients, and was larger (>10%) in three patients. There was good observer agreement for IVUS measurements, with a high correlation coefficient

Table 2. Angiographic measurements obtained immediately after stent placement and at 1 year follow-up ($n=28$)

	After stent placement (mm)	Follow-up (mm)	<i>p</i> -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

N.B. Values are mean ± standard deviation. NS, not significant.

($r=0.978$; observer 2 = $(0.99 \times \text{observer 1}) - 0.01$) and an overall coefficient of variation of 6.3%.

Similar to IVUS measurements, quantitative angiographic measurements of the distal main renal artery showed a significantly decreased diameter at 1 year follow-up when compared with diameters measured immediately after stent placement ($p<0.001$) (Table 2). In contrast, the diameters of the intrarenal branches and the contralateral renal artery remained unchanged. Whereas immediately after stent placement there was no significant difference between the diameter of the ipsilateral 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 ($86 \pm 5.1\%$ (mean ± standard error of the mean) vs $104 \pm 5.3\%$ of the contralateral renal artery diameter; $p=0.003$) (Figure 2).

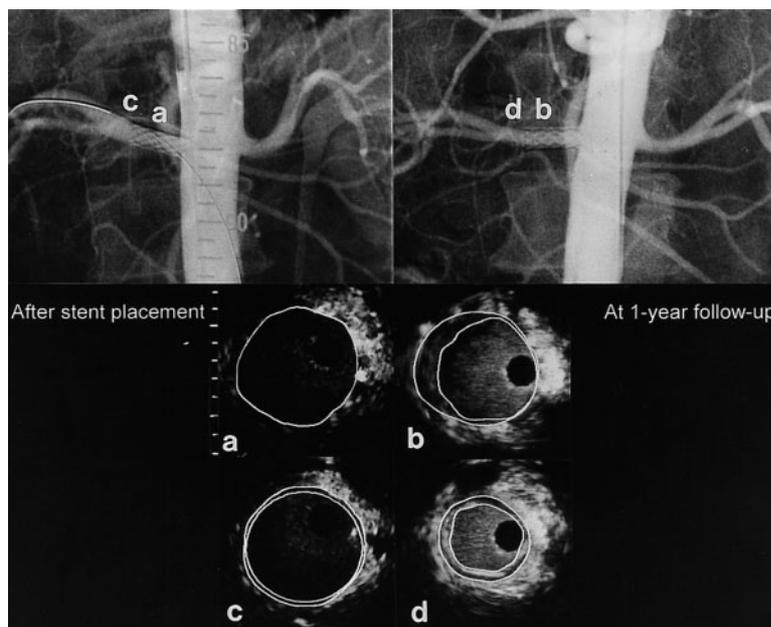


Figure 1. Intravascular ultrasound and angiographic images (a, c) after stent placement and (b, d) at 1 year follow-up. The inner contour of the intravascular images presents the lumen area, the outer contour the stent or vessel area. At follow-up, plaque accumulation was evidenced in the stent (b),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

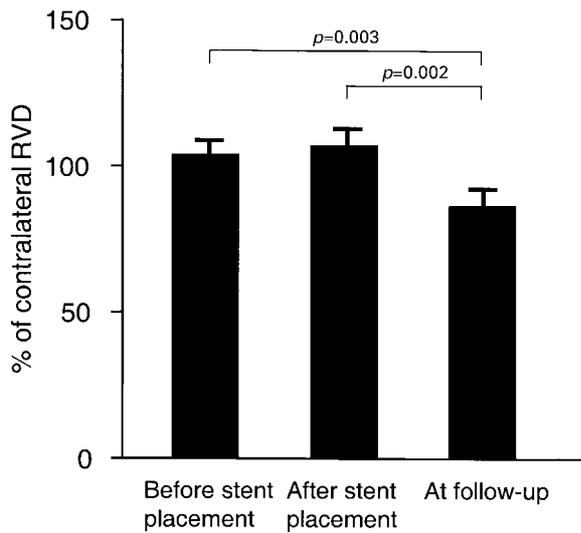


Figure 2. Renal vessel diameter (RVD) of the affected side before and after stent placement and at follow-up, expressed as percentage of the contralateral artery diameter. The relative diameter at follow-up was significantly smaller than pre-interventional values. Mean \pm standard error of the mean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

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 1 year follow-up there was a significant decrease in LA in the stent, which was solely owing 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 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; previously we showed that in 33% of patients, additional dilatation or stent placement was warranted to achieve accurate stent placement [3]. However, a randomized study is required to assess the true beneficial role of IVUS on 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 VA 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 with 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 owing 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 = $4 \times \text{blood viscosity} \times (\text{flow}/\pi r^3)$]. 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 both with data previously presented by others [8] and with our previously presented findings that pre-dilatation and stent placement resulted in enlargement of the distal renal artery [3]. At follow-up, however, shrinkage of the distal renal artery instead of dilatation was experienced. Conversely, 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. In the long-term the kidney may have adapted its vascular resistance, which might have resulted in a decrease of renal blood flow thereby decreasing 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.

Aside from the issue of the pathophysiologic mechanism underlying the encountered shrinkage, the data raise some concern over the clinical value of stent placement for RAS. Should shrinkage be progressive over time, this itself might lead to stenosis and could make stent placement a less useful treatment for RAS in the long-term. This should be determined in future studies using a longer follow-up period. In addition, the possible (patho)physiological mechanism underlying the described phenomenon should be further investigated. 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.

In conclusion, renal artery stent placement resulted in shrinkage of the distal main renal artery at 1 year follow-up. The explanation for this phenomenon, evidenced both by IVUS and angiography, is at present unknown and should be further investigated.

References

1. Rees CR, Palmaz JC, Becker GJ, Ehrman KO, Richter GM, Noeldge G, et al. Palmaz stent in atherosclerotic stenoses involving the ostia of the renal arteries: preliminary report of a multicenter study. *Radiology* 1991;181:507–14.
2. WHO Collaborating Centre for Drug Statistics Methodology. Main principles for the establishment of Defined Daily Doses. In: Guidelines for ATC classification and DDD assignment. Oslo, Norway: WHO Collaborating Centre for Drug Statistics Methodology 1995:22–31.
3. Leertouwer TC, Gussenhoven EJ, van Overhagen H, Man in't Veld AJ, van Jaarsveld BC. Stent placement for treatment of renal artery stenosis guided by intravascular ultrasound. *J Vasc Interv Radiol* 1998;9:945–52.
4. Bom N, ten Hoff H, Lancee CT, Gussenhoven WJ, Bosch JG. Early and recent intraluminal ultrasound devices. *Int J Cardiac Imaging* 1989;4:79–88.
5. Wenguan L, Gussenhoven WJ, Zhong Y, The SHK, Di Mario C, Madretsma S, et al. Validation of quantitative analysis of intravascular ultrasound images. *Int J Card Imaging* 1991;6:247–53.
6. Painter JA, Mintz GS, Wong C, Popma JJ, Pichard AD, Kent KM, et al. Serial intravascular ultrasound studies fail to show evidence of chronic Palmaz-Schatz stent recoil. *Am J Cardiol* 1995;75:398–400.
7. Dussaillant GR, Mintz GS, Pichard AD, Kent KM, Satler LF, Popma JJ, et al. Small stent size and intimal hyperplasia contribute to restenosis: a volumetric intravascular ultrasound analysis. *J Am Coll Cardiol* 1995;26:720–4.
8. White CJ, Ramee SR, Collins TJ, Jenkins JS, Escobar A, Shaw D. Renal artery stent placement: utility in lesions difficult to treat with balloon angioplasty. *J Am Coll Cardiol* 1997;30:1445–50.
9. Peters AM, Brown J, Crossman D, Brady AJ, Hemingway AP, Roddie ME. Noninvasive measurement of renal blood flow with technetium-99m-DTPA in the evaluation of patients with suspected renovascular hypertension. *J Nucl Med* 1990; 31:1980–5.
10. Glagov S, Zarins C, Giddens DP, Ku DN. Hemodynamics and atherosclerosis. Insights and perspectives gained from studies of human arteries. *Arch Pathol Lab Med* 1988;112:1018–31.
11. Hofma SH, Whelan DM, van Beusekom HM, Verdouw PD, van der Giessen WJ. Increasing arterial wall injury after long-term implantation of two types of stent in a porcine coronary model. *Eur Heart J* 1998;19:601–9.