Restenosis after elective coronary balloon angioplasty in patients with end stage renal disease: a case-control study using quantitative coronary angiography

Frank-Chris Schoebel, Frank Gradaus, Katrin Ivens, Peter Heering, Thomas Walter Jax, Bernd Grabensee, Bodo-Eckehard Strauer, Matthias Leschke

Abstract

Objective—To assess the rate of angiographic restenosis in patients with end stage renal disease after elective coronary angioplasty.

Design—A retrospective case-control study of 20 patients with end stage renal disease and 20 sex and age matched controls without renal disease, who had undergone primarily successful coronary angioplasty. Control coronary angiography was performed regardless of worsening or renewed incidence of anginal symptoms.

Main outcome measures—Group comparison of coronary morphology, as evaluated by quantitative coronary angiography, and of cardiovascular risk factors.

Results—The rate of angiographic restenosis was 60% in patients with renal disease and 35% in controls. In patients with end stage renal disease the following differences (mean (SD)) were found versus controls: raised plasma fibrinogen (483 (101) *v* 326 (62) mg/dl, p < 0.001); raised plasma triglyceride (269 (163) *v* 207 (176) mg/dl, p < 0.01); smaller diameter of the coronary reference segment (2.59 (0.87) *v* 2.90 (0.55) mm, p < 0.10); smaller minimum luminal diameter of the dilated stenosis (0.77 (0.46) *v* 0.97 (0.27) mm, p < 0.05). Discriminant analysis showed that minimum luminal diameter before angioplasty (*r* = −0.79) and fibrinogen (*r* = +0.34) had the highest statistical association with restenosis.

Conclusions—The high rate of angiographic restenosis in patients with end stage renal disease seems to be related to the size of the vessel dilated and to an increased prothrombotic risk, as indicated by higher fibrinogen concentrations.

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Medizinische Klinik und Poliklinik B, Klinik für Kardiologie, Pneumologie und Angiologie, Heinrich-Heine Universität Düsseldorf, Moorenstraβe 5, 40225 Düsseldorf, Germany
F C Schoebel
F Gradaus
T W Jax
B E Strauer
M Leschke

Medizinische Klinik und Poliklinik F, Klinik für Nephrologie und Rheumatologie, Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany
K Ivens
P Heering
B Grabensee

Correspondence to:
Dr med Schoebel; email:
Frank-Chris.Schoebel@
uni-duesseldorf.de

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Patients with end stage renal disease have an increased risk of developing coronary artery disease. Their rate of cardiovascular mortality is approximately 50%—five to 10 times higher than in the general population.[1–4] Efforts to optimise the medical management of these patients in order to improve their quality of life and survival prospects are thus warranted.

Percutaneous transluminal coronary angioplasty (PTCA) has proved effective in reducing myocardial ischaemia and clinical symptoms in patients with coronary artery disease. In the general population the primary success rate is high, ranging between 90% and 95%, but late haemodynamically relevant restenosis occurs after a period of about 12 weeks in 30–45% of the cases.[5–7] In patients with end stage renal disease an increased risk of procedural complications, an adverse long term clinical outcome, and a high rate of clinical and angiographic restenosis (60–82% and 69–100%, respectively) have been reported.[8–10] These studies were biased towards a high rate of angiographic restenosis, as only patients with recurrent anginal symptoms were included for angiographic follow up.

In an attempt to supply more valid data on the true rate of angiographic restenosis, we compared suitable patients with end stage renal disease who had undergone their first, primarily successful coronary balloon angioplasty with age and sex matched controls for coronary morphology, angiographic variables, and cardiovascular risk factors.

Methods

PATIENTS

In a retrospective case-control study, 20 patients with end stage renal disease who had undergone first, elective, and primarily successful coronary angioplasty were compared with 20 age and sex matched controls who had been randomly selected from the PTCA registry of our institution. As standard clinical practice, all patients had been followed up angiographically regardless of subjective and objective signs of myocardial ischaemia. The following were not included in the analysis: (1) patients with unstable angina, as defined by a recent onset or change of clinical symptoms (frequency, intensity, and characteristics of anginal pain); (2) patients who presented with complete occlusion of the target vessel or suffered procedural complications like large, flow limiting dissections or early reocclusion of the vessel dilated.

LABORATORY VARIABLES

Total cholesterol and triglycerides were determined with colorimetric tests (Boehringer Mannheim, Germany)—the CHOD-PAP

Table 1   Patient characteristics

	ESRD (n=20)		Controls (n=20)		p value
History					
Male (n)	16		16		NS
Age (years) (mean (SD))	56	(10)	57	(10)	NS
Angina pectoris before PTCA (n)	17		16		NS
Myocardial infarction (n)	5		9		NS
Risk factors					
Arterial hypertension (n)	20		14		<0.01
Hyperlipidaemia (n)	15		15		NS
Diabetes mellitus (n)	7		2		NS
Smoker/ex-smoker (n)	16		12		NS
No of risk factors per patient (mean (SD))	2.9	(0.7)	2.2	(0.8)	<0.01
Laboratory variables					
Total cholesterol (mg/dl) (mean (SD))	262	(50)	238	(39)	<0.10
LDL cholesterol (mg/dl) (mean (SD))	191	(50)	172	(38)	NS
HDL cholesterol (mg/dl) (mean (SD))	36	(15)	42	(12)	<0.10
Triglycerides (mg/dl) (mean (SD))	269	(163)	207	(176)	<0.01
Fibrinogen (mg/dl) (mean (SD))	483	(101)	326	(62)	<0.001
Data on maintenance dialysis					
Haemodialysis	13				
Continuous ambulatory peritoneal dialysis	7				
Duration (months) (mean (SD))	35	(40)			

ESRD, end stage renal disease.

method and the GPO-PAP method, respectively. High density lipoprotein (HDL) cholesterol was measured after precipitation with phosphotungistic acid/MgCl$_2$, and low density lipoprotein (LDL) cholesterol after precipitation with heparin at pH 5.12 (Merck, Darmstadt, Germany).

Plasma fibrinogen was measured with a modified method according to Clauss[11] in 9 ml of whole blood added to 1 ml of sodium citrate (Multifibren, Behringwerke AG, Marburg, Germany).

CORONARY ANGIOGRAPHY AND ANGIOPLASTY

Selective coronary angiography was performed following the administration of intracoronary glyceryl trinitrate, and at least six standardised projections of the left coronary artery and two of the right coronary artery were obtained. The severity of coronary artery disease was determined visually and was classified as single, double, or triple vessel disease, defined by the presence of haemodynamically relevant stenoses (stenosis > 50% of the luminal diameter) in one of the three major coronary vessels. Complexity of the target lesion was characterised as concentric, eccentric, and multiple irregular stenosed.[12]

Coronary balloon angioplasty was performed with balloon sizes ranging from 2.5–3.5 mm. Before the procedure patients received 500 mg of aspirin and 10 000 IU of heparin plus an extra 5000 IU intravenously after the intervention, regardless of the regular daily oral medication, which included aspirin in all patients. Follow up coronary angiography was carried out as a routine procedure after approximately six months, regardless of the presence of clinical symptoms or results from non-invasive measurements of myocardial ischaemia.

QUANTITATIVE CORONARY ANGIOGRAPHY

All cineangiograms were evaluated with respect to quantitative coronary morphology by means of computer assisted contour analysis (Cardio 500, Kontron, Munich, Germany) and measurements were made without knowledge of the patient's history or clinical data. The image of the first angiogram which showed the most severe coronary narrowing at end diastole was compared with identical projections of the same region obtained immediately after angioplasty and at long term follow up. The computer measured the absolute values of the stenosis and reference locations, using the known catheter diameter as a scaling device.

A single observer trained in quantitative coronary angiography performed the analysis. Intraobserver variability was determined from 20 randomly selected films. Repeated measurements were made after a three month interval without preselection of images. The variability in measurements of coronary angiograms was expressed by the standard deviation of the difference between paired measurements and ranged within the known limits (0.20 mm for the minimum luminal diameter, 0.31 mm for the reference luminal diameter, 4.9% for per cent diameter stenosis).[13]

As further dependent variables of coronary angioplasty, acute luminal gain (minimum luminal diameter immediately after angioplasty minus minimum luminal diameter before angioplasty), late luminal loss (minimum luminal diameter immediately after angioplasty minus minimum luminal diameter at follow up), and net luminal gain (minimum luminal diameter at follow up minus minimum luminal diameter before angioplasty) were calculated in absolute changes (mm). Restenosis was defined by the presence of a stenosis > 50% luminal diameter at the time of follow up.

STATISTICS

The data were analysed with the Statistical Package for Social Sciences (SPSS for Windows; SPSS, Munich, Germany). For comparison of two groups the Mann-Whitney U test was used, and for analysis of non-continuous data the two tailed Fisher exact test was employed. Correlation coefficients were generated with the Spearman test. A significant difference between groups was assumed at a level of error of < 5%, test results between 5% and 10% were considered as statistical trends. All variables with a potential influence on restenosis which were either significantly different or showed a statistical trend between patients with end stage renal disease and controls were entered into discriminant analysis to assess their influence on angiographic restenosis.

Results

PATIENTS

The numbers of symptomatic patients were comparable in the two groups before the intervention. More patients in the control group than in the maintenance dialysis group had had a myocardial infarct before angioplasty (table 1). The cardiovascular risk profile in patients with end stage renal disease differed from controls, as there were significantly more risk factors per patient in the former, as well as a higher prevalence of diabetes mellitus and arterial hypertension. The underlying disease processes which led to end stage renal disease

Table 2 Results of coronary angiography, quantitative coronary evaluation, and clinical and angiographic restenosis

	ESRD (n=20)	Controls (n=20)	p value
Coronary angiography			
Single vessel disease (n)	5	6	NS
Double vessel disease (n)	8	12	NS
Triple vessel disease (n)	7	2	NS
Vessel of intervention			
Left anterior descending coronary artery (n)	11	9	NS
Left circumflex coronary artery (n)	3	5	NS
Right coronary artery (n)	6	6	NS
Location of intervention			
Major branch: proximal part	10	8	NS
Major branch: mid part	9	10	NS
Major branch: distal part	1	2	NS
Side branch	0	0	NS
Morphology of the target lesion			
Concentric stenosis (n)	10	11	NS
Eccentric stenosis (n)	3	4	NS
Multiple irregular stenosis (n)	7	5	NS
Angulated vessel (<45%) (n)	2	1	NS
Calcified stenoses (n)	7	4	NS
Procedural variables of coronary angioplasty			
Diameter of balloon (mm) (mean (SD))	2.7 (0.3)	2.7 (0.3)	NS
Total time of inflation (s) (mean (SD))	178 (75)	221 (85)	NS
Maximal pressure (bar) (mean (SD))	7.7 (2.3)	7.9 (2.0)	NS
Quantitative coronary angiography before PTCA			
Minimum luminal diameter (mm) (mean (SD))	0.77 (0.46)	0.97 (0.27)	<0.05
Reference diameter (mm) (mean (SD))	2.59 (0.87)	2.90 (0.55)	<0.10
Stenosis (%) (mean (SD))	69.7 (12.0)	65.8 (6.3)	NS
Immediately after PTCA			
Minimum luminal diameter (mm) (mean (SD))	1.64 (0.64)	1.82 (0.53)	NS
Reference diameter (mm) (mean (SD))	2.57 (0.82)	2.80 (0.57)	NS
Stenosis (%) (mean (SD))	37.1 (8.7)	35.3 (11.3)	NS
At follow up			
Time to control (months)	6.7 (2.8)	6.4 (2.4)	NS
Minimal luminal diameter (mm)	1.23 (0.70)	1.53 (0.66)	NS
Reference diameter (mm)	2.69 (0.87)	2.93 (0.63)	NS
Stenosis (%)	58.2 (20.5)	47.1 (17.3)	<0.10
Change in minimum luminal diameter			
Acute luminal gain (mm) (mean (SD))	0.89 (0.48)	0.86 (0.46)	NS
Late loss (mm) (mean (SD))	0.43 (0.56)	0.26 (0.56)	NS
Net gain (mm) (mean (SD))	0.46 (0.50)	0.56 (0.52)	NS
Restenosis			
Angiographic restenosis (n)	12	7	NS
Clinical restenosis (n)	13	7	NS

ESRD, end stage renal disease.

included diabetic nephropathy in seven patients, glomerulonephritis in eight, pyelonephritis in five, and polycystic disease in one.

LABORATORY VARIABLES

Quantitative assessment of cardiovascular risk factors reflected changes in the cardiovascular risk profile, as patients with renal disease showed increases in total cholesterol as well as reductions in HDL cholesterol (table 1). Increases in triglycerides and fibrinogen were highly significant in patients on maintenance dialysis compared with the controls.

QUANTITATIVE CORONARY ANGIOGRAPHY, ANGIOPLASTY, AND RESTENOSIS

The predominant target vessel for intervention was the left anterior descending coronary artery, and there were no significant differences between the two groups in the complexity and angulation of the stenoses that were dilated (table 2). Target vessels in patients with end stage renal disease were smaller, as indicated by the differences in reference diameter and minimum luminal diameter, but stenoses were comparable in their severity (per cent diameter stenosis) and location (proximal, middle, or distal part of a major vessel).

Angiographic restenosis, defined by the presence of a haemodynamically relevant stenosis (> 50% luminal diameter) was present in 60% of patients with renal disease and in 35% of controls on angiographic follow up but did not differ between groups, probably because of the small sample size (table 2) Per cent diameter stenosis showed a statistical trend towards a higher average degree of stenosis in the group with renal disease at the time of follow up.

Clinical restenosis, as defined by recurrence or aggravation of angina, occurred in 65% of patients with renal disease and in 35% of the controls. While the diagnostic sensitivity of clinical symptoms for the occurrence of angiographic restenosis was comparable in the two groups (75% in patients with renal disease and 71% in controls), diagnostic specificity was higher in patients on maintenance dialysis (85% versus 63%; table 2).

Analysis of quantitative angiographic variables for both groups combined showed that the severity of the coronary stenosis (per cent diameter stenosis) before the intervention was positively correlated with acute luminal gain ($r = 0.57$, $p < 0.001$) and acute luminal gain was positively correlated with late luminal loss ($r = 0.39$, $p = 0.05$) indicating that the severity of vessel injury is a promoter of restenosis. Procedural variables such as the size of the balloon, maximum inflation pressure, and total time of inflation were not related to restenosis.

There were no significant correlations between late luminal loss and fibrinogen or lipid values. Discriminant analysis showed that minimum luminal diameter before angioplasty ($r = -0.79$) had the highest influence on the occurrence of angiographic restenosis when analysed for both groups combined, followed by fibrinogen ($r = +0.34$), luminal vessel size as defined by the diameter of the reference segment before angioplasty ($r = +0.32$), and total cholesterol ($r = +0.20$).

Discussion

In this first controlled study which included age and sex matched patients without renal disease, the rate of angiographic restenosis in patients with renal disease was 60%, compared with 35% in controls. Results from this study indicate that prothrombotic factors and procedural variables—vessel size in particular—may be of relevance for angiographic restenosis in patients with end stage renal disease.

LABORATORY VARIABLES

Fibrinogen concentrations were significantly raised in patients with end stage renal disease compared with the controls, and statistical analysis showed that this haemostatic factor affected the rate of angiographic restenosis. Fibrinogen is the substrate of thrombin and is a major determinant of platelet aggregation and rheological blood properties.[14 15] Linear interrelations between fibrinogen, thrombin generation, and enhanced endogenous fibrinolytic activity have also been demonstrated.[16 17]

Table 3 Observational studies on percutaneous transluminal coronary angioplasty in patients with end stage renal disease

	Kahn 1990[10]	Ahmed 1994[9]	Rinehart 1995[11]
Patients (n)	17	21	24
Short term clinical success (n)	15/17	15/21	*23/25
Clinical restenosis (n)	12/15	9/11	13/22
Angiographic follow up (months)	1–12	1–12	<12
Repeat angiography (n)	11/12	7/9	13/22
Angiographic restenosis (n)	*26/32	7/7	9/13

*No of lesions dilated.

Patients on maintenance dialysis have been found to have a higher plasma fibrinogen than patients without renal disease,[18] which suggests a marked procoagulant disease state in the former.[19] Therefore patients with end stage renal disease share some of the haemostatic features of patients with acute coronary syndromes,[20] in whom there is also an increased risk of restenosis following coronary angioplasty.[21 22] As secondary thrombosis following mechanical injury plays a major role in the pathogenesis of restenosis,[23–25] it is conceivable that a systemic hypercoagulable disease state contributes to this process in patients with end stage renal disease.

Indices of lipid metabolism were pathologically altered in patients with end stage renal disease in comparison with the controls. It has been shown previously that HDL cholesterol is reduced in the general population of patients with restenosis,[25] while there is no convincing evidence that increases in LDL cholesterol or triglycerides are of particular relevance.

PROCEDURAL VARIABLES IN CORONARY ANGIOGRAPHY AND ANGIOPLASTY
Previous studies which evaluated the follow up of patients with renal disease who underwent PTCA are not comparable with ours because of the heterogeneity of the cohorts chosen and because of different clinical and angiographic end points[8–10] (table 3). In these studies clinical restenosis, presumably defined by recurrence or aggravation of angina pectoris, occurred in 60% to 82% of the cases. While data presented by Kahn *et al*[9] and by Ahmed *et al*[8] imply that angina is a very good indicator of angiographic restenosis (all symptomatic patients investigated angiographically showed significant renarrowing), the data of Rinehart *et al*[10] suggested that angina predicted restenosis in 69% of cases. The latter results are more comparable with our current findings, where angina had a sensitivity of 75% in detecting angiographic restenosis. It should be borne in mind, though, that angina was present in 85% of patients with end stage renal disease before the intervention. Therefore these results only reflect the potential for clinical symptoms to detect restenosis in symptomatic patients; they are not relevant to the primary detection of coronary artery disease where increased numbers of asymptomatic patients are to be expected because of the high prevalence of neuropathy.[26]

The rate of angiographic restenosis is lower than that reported in previous studies (69% to 100%).[8–10] This is probably a result of selection bias, as in these studies only patients with clinical symptoms were re-evaluated angiographically. Given the high specificity of clinical symptoms for the occurrence of angiographic restenosis in patients with end stage renal disease, as documented by our study, the restenosis rate would have been lower in the other studies if all the patients had been followed up angiographically. Furthermore in earlier investigations restenosis was assessed visually while this is the first study employing computer assisted quantitative coronary angiography at baseline and on follow up. It is known that visual evaluation of coronary stenoses is particularly unreliable in the medium range (between 50% and 90% diameter stenosis),[27] which is also the predominant range in which restenoses occur. It is therefore quite likely that the restenosis rate was overestimated in previous investigations.

In the patients with end stage renal disease in our study the changes in quantitative angiographic variables reflected the smaller luminal vessel size and the smaller minimum luminal diameter before angioplasty compared with the controls, which have both been described as predictors of restenosis.[28 29] Diffuse thickening of the coronary intima and media has been shown to be a dominant feature in experimental models of uraemia.[30] This has recently been confirmed in human coronary arteries and in internal mammary arteries from patients with end stage renal disease, harvested either postmortem or intraoperatively (K Amann, personal communications). This may account for smaller luminal diameters despite comparable locations of the stenosis in the coronary arterial system in patients with end stage renal disease, as the luminal view on coronary angiography gives an incomplete reflection of coronary atherosclerosis.[31]

The acute gain in lumen size did not differ between the two groups. This suggests a more severe degree of vessel injury in relation to vessel size in the patients with end stage renal disease. This is supported by the finding of a greater degree of late luminal loss in patients with renal disease, though that did not reach statistical significance. In conjunction with increased wall stiffness from diffuse narrowing of the vascular wall, this may have led to an increased amount of secondary thrombosis and to the induction of more pronounced proliferative processes.[32–34]

LIMITATIONS OF THE STUDY
The number of patients included in this retrospective study was small and the quality of the data therefore does not allow us to draw the conclusions that might be derived from a large scale prospective trial. As PTCA is not often performed in patients with end stage renal disease, as indicated by the small case numbers reported from other large centres, the number of patients in this investigation probably reflects the best that can be achieved by a single centre. Therefore prospective trials with a multicentre design are warranted to draw more valid conclusions.

In this study, results based on angiographic vascular morphology have to be viewed with

particular care. The size of the target vessel and the minimum luminal diameter were smaller in patients with end stage renal disease than in the controls. Since these two features are well accepted predictors of restenosis in the general population, this could represent an error in the selection of the control group. On the other hand a more pronounced narrowing of the vascular lumen may suggest specific features in the pathology of atherosclerosis in patients with end stage renal disease. Given that the control group was also representative in terms of cardiovascular risk profile, our results probably reflect the true situation presenting to the clinician. Definitive answers will only be provided by future investigations with more specific imaging techniques like coronary intravascular ultrasound or angioscopy. Such techniques may clarify the role of vascular calcium content, the lumen to wall ratio, and primary thrombosis at the site of intervention as potential vascular risk factors for coronary restenosis in patients with end stage renal disease.

CLINICAL IMPLICATIONS

Results from this study imply that procedural and prothrombogenic factors, which are regarded as having an impact on restenosis in the general population, may also contribute to the pathogenesis of restenosis following PTCA in patients with end stage renal disease. Revasularisation procedures which enlarge the vascular lumen more completely, for example stent implantation,[35][36] may therefore be of particular therapeutic benefit. Although the prolonged administration of antithrombotic treatment such as aspirin, coumarins, and heparin has not proved to be successful in preventing restenosis in the general population, patients with end stage renal disease are a promising target group for novel antithrombotic interventions because of their high prothrombotic risk. It is therefore premature to rule out PTCA as a revascularisation procedure in patients with end stage renal disease, and prospective interventional trials are warranted which address the specific risk factors in this cardiovascular high risk group.

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IMAGES IN CARDIOLOGY

An unusual palliative shunt for cyanotic congenital heart disease

An 11 year old boy was referred for surgical correction of tetralogy of Fallot, having undergone a palliative aortopulmonary shunt in eastern Europe seven years previously. Clinical examination revealed severe central cyanosis and a continuous shunt murmur, as well as a short ejection murmur from the right ventricular outflow tract. Selective angiography of the right subclavian artery demonstrated a direct anastomosis to the right upper pulmonary vein. From the clinical history he had been surprisingly well palliated for several years. The severe stenosis at the anastomotic site had protected the right lung from high pressure and pulmonary oedema, allowing successful repair.

Selective angiogram of the right subclavian artery (SA) in the frontal projection, demonstrated filling of the right upper pulmonary vein (PV) and subsequently the left atrium

(LA). The arrow denotes the area of severe stenosis at the anastomotic site.

N SREERAM
H HENNEVELD
J F HITCHCOCK