PREVENTION AND TREATMENT OF HEMODIALYSIS ACCESS THROMBOSIS

J.H.M. Smits

Cover design: Sithabile Mlotshwa; “Heart Beat” and “Life Giver”, 2001

Layout: Audiovisuele Dienst, UMC, Utrecht
Printing: Budde Elinkwijk Grafische Producties B.V., Nieuwegein

Prevention and treatment of hemodialysis access thrombosis
J.H.M. Smits; Universiteit Utrecht, Faculteit Geneeskunde
Thesis Utrecht University – with a summary in Dutch
ISBN 90-393-2837-4
Subject headings: Vascular access, Hemodialysis, Thrombosis, Prevention, Treatment

PREVENTION AND TREATMENT OF HEMODIALYSIS ACCESS THROMBOSIS

PREVENTIE EN BEHANDELING VAN HEMODIALYSE VAATTOEGANG TROMBOSE

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de Rector Magnificus, Prof. Dr. W.H. Gispen
ingevolge het besluit van het College voor Promoties
in het openbaar te verdedigen op
dinsdag 30 oktober 2001 des middags te 2.30 uur

door

Johannes Henricus Maria Smits

geboren op 8 augustus 1971 te Deurne

Promotor: Prof. Dr. H.A. Koomans

Co-promotor: Dr. P.J. Blankestijn

Studies in this thesis were supported by a grant from the Dutch Kidney Foundation (C97.1643). Publication of this thesis was supported by Transonic Systems, Inc., Ithaca, NY, USA, Merck Sharpe & Dohme B.V., Janssen-Cilag B.V., and GlaxoWellcome B.V. Financial support by the Dutch Kidney Foundation and the Netherlands Heart Foundation for the publication of the thesis is gratefully acknowledged.

Aan mijn ouders

List of abbreviations

ACA	anticardiolipin antibody
ADP	adenosine diphosphate
AVF	arteriovenous fistula
AVG	arteriovenous graft
bFGF	basic fibroblast growth factor
CDF	color Doppler flow
CV	central vein
DL	double-lumen
DSA	digital subtraction angiography
ESRD	end-stage renal disease
FV	femoral vein
HD	hemodialysis
INR	international normalized ratio
K/DOQI	kidney disease outcomes quality initiative
LA	lupus anticoagulant
MAP	mean arterial pressure
(CE)-MRA	(contrast-enhanced) magnetic resonance angiography
NKF-DOQI	national kidney foundation - dialysis outcome quality initiative
NS	not significant
P_{IA}	intra-access pressure
PDGF	platelet-derived growth factor
PTA	percutaneous transluminal angiography
PTFE	polytetrafluoroethylene
Qa	access flow
SBP	systolic blood pressure
SCVIR	society of cardiovascular and interventional radiology
SEM	standard error of the mean
SL	single-lumen
URR	urea reduction ratio
VP	venous pressure
vWF	von Willebrand factor

Contents

Chapter 1

Introduction

Introduction

"As we did not know at all how our first patient would react to the dialysis we started with repeatedly dialysing small portions of blood. In the end we succeeded in keeping the percentage of urea at the same level for 26 days, after that no more serviceable veins were available." The 29-year old patient died 34 days after initiating her dialysis treatment. Since those problematic but promising hemodialysis sessions with the first artificial kidney performed by Dr. Willem J. Kolff in the Municipal Hospital of Kampen, The Netherlands, in 1943, many of the hemodialysis-related problems have been solved [1].

Kolff's first effective dialysis treatment of an end-stage renal disease (ESRD) patient came to an end because of problems gaining access to the bloodstream. After depleting the readily accessible veins and disappointing artery punctures, no adequate access to the bloodstream could be established for transporting blood to and from the artificial kidney [1]. "We believe to be able to keep patients suffering from uremia and anuria alive so long as blood vessels for punction are available", he wrote. Since those early dialysis pioneering days, dialysis equipment has improved dramatically. Also, attempts were made to sustain and improve access to the blood stream. However, it was not until the 1960s when the first papers appeared describing novel methods for gaining access to the blood stream [2,3], that long-term hemodialysis would become a reality. In 1966, Brescia and Cimino published an article describing an arteriovenous (AV) fistula between the radial artery and cephalic vein, which could function as a vascular access [4]. First, they made an anastomosis between the artery and the vein. Then, the day after surgery, the vein downstream from the anastomosis was engorged by a tourniquet, and therefore allowed for cannulation to gain access to the blood stream. The investigators noted that with time, the vessels became "even more prominent and thicker-walled, making venepuncture even easier" [4,5]. Because of its low infection and thrombosis rate, the Brescia-Cimino (radio-cephalic) fistula is still regarded as the first choice for the creation of a vascular access for hemodialysis [6]. Other forms of AV fistula include the brachio-cephalic fistula and the transposed brachio-basilic fistula [7-9]. Nowadays, AV fistulae are allowed to mature for a period of at least 1 month until there is sufficient dilatation and "arterialization" on physical examination [5,6]. Unfortunately, not all patients have suitable vessels to construct an AV fistula, mainly because of their insufficient caliber or sclerosis due to prior venipunctures. Therefore, a modification of the AV fistula was found in constructing an interposition graft between an artery and a vein. The interposition AV graft could then function as a vascular access by itself. Several materials were studied on their ability to function as an AV graft, like bovine carotid artery grafts, autogenous and homologous vein grafts, and human umbilical cord grafts [10-15]. AV grafts of synthetic materials were also developed to function as vascular access [16]. Nowadays, AV grafts are predominantly manufactured from expanded polytetrafluoroethylene (PTFE).

Unfortunately, these PTFE AV grafts show a thrombosis rate of 0.5 - 2.5 per patient-year [6,17-20] resulting in considerable morbidity and even mortality [21,22]. For the United States, it was calculated that vascular access morbidity is responsible for an estimated annual cost of close to $1 billion and accounts for 17 - 25% of all dialysis patients hospitalizations [23-26]. Because of these complications the NKF-K/DOQI guidelines on vascular access suggest that vascular access using AV grafts may only be considered, if it is not possible to establish either a radio-cephalic or a brachio-cephalic AV fistula [6,27]. Despite the higher rate of thrombosis and its subsequent morbidity, an increasing number of patients depend on an AV graft. In some populations in the United States, AV grafts account for as many as 83% of access placements [28]. Because of the increasing age of the hemodialysis patients, establishment of an AV fistula in those patients becomes difficult due to insufficient vessels. Also, the number of patients with end-stage renal disease (ESRD) requiring hemodialysis is increasing worldwide [29]. In The Netherlands the use of AV grafts is increasing at the expense of AV fistulae [30]. As a consequence, patients and physicians alike are more frequently confronted with vascular access complications, particularly thrombosis.
This thesis focuses on the prevention and treatment of hemodialysis access thrombosis.

AV graft thrombosis: cause and prevention

In almost all cases, thrombosis is associated with the presence of one or more stenoses in the AV graft. Usually, they are located at or near the venous anastomosis of the AV graft or elsewhere in the venous outflow tract [31-34]. They show the typical histology of intimal hyperplasia [35,36]. The presence of a stenosis results in both anatomical (for instance reduction of the vessel lumen) and functional changes. These functional changes include an increase in resistance and pressure gradient over the stenosis, and a subsequent decline in access blood flow. The logical approach would be prevention of the development of intimal hyperplasia. At present, this is not possible in clinical practice, although interesting experimental work is being conducted [37,38]. Therefore, the second best approach is identifying patients at risk of thrombosis and referring them for corrective intervention. This indeed reduces thrombosis rate dramatically and prolongs vascular access patency [31,39-45]. Percutaneous transluminal angioplasty (PTA) or surgical correction can be considered for elective intervention [6,46].
Thrombosis rate can also be reduced by decreasing coagulability. Both dipyridamole and coumarin reduced the risk of thrombosis in patients with PTFE grafts [47,48]. Although specific antiproliferative effects of these agents can not be excluded, it is possible that these drugs only bring the risk for thrombosis to a lower level of flow.
All presently used vascular access monitoring methods focus on detecting the anatomical and/or the functional changes that are induced by stenosis.

Monitoring techniques to detect accesses at risk of thrombosis

Physical examination

Physical examination includes inspection, palpation, and possibly auscultation [6]. Collateral vessel formation or edema of an extremity may indicate the presence of stenosis. Palpation and auscultation can be useful for detecting stenosis. Trerotola *et al.* claimed that it is possible to rule out low flows by palpation alone [49]. Safa *et al.* used auscultation as tool in a surveillance program [33]. Others have included physical examination in monitoring programs as well [18,50].

Although physical examination is easily performed and inexpensive, many clinicians will feel that its value is limited, because results are highly investigator dependent.

Venous pressure (VP)

As a result of the presence of a stenosis, resistance over the outflow tract increases and the pressure upstream from the stenosis will rise. Most dialysis devices are capable of measuring the venous drip chamber pressure, which is an indirect derivative of the true intra-access pressure. Schwab *et al.* described a method to monitor vascular access by evaluating venous drip chamber pressure with a pump flow rate of 200 - 225 mL/min, the so-called dynamic venous pressure. When PTA was done of stenoses in patients who had a dynamic VP > 150 mmHg, thrombosis rate was 0.20 per patient-year. This study included patients with AVF and PTFE grafts [43]. Cayco *et al.* used dynamic VP for surveillance of grafts and reported a thrombosis rate of 0.29 events per year [18].

Besarab *et al.* further refined the concept [39] and recently introduced the equalized intra-access VP measurement corrected for height and mean arterial pressure (eqP_{IA}/MAP) [51]. $EqP_{IA}/MAP \geq 0.5$ was associated with hemodynamically significant (i.e. low flow) and angiographically confirmed stenosis. They showed that treating stenoses in patients identified by P_{IA}/SBP resulted in a thrombosis rate of 0.17 per patient-year [39]. This study group consisted of both AV grafts and fistulae.

Access flow

Increased resistance due to stenosis causes low flow, which has been shown to be predictive for thrombosis in early studies (reviewed in [52,53]). A variety of devices has now been developed which are capable of measuring or calculating flow during dialysis treatment [54-60]. So far, the ultrasound dilution technique seems to be the best-validated technique [53,54].

Several questions, however, have not been addressed yet. The optimal frequency of measurements and the optimal threshold level for intervention have not been determined. It was shown that in a group of patients with AV grafts monitored by venous pressures,

almost all thromboses occurred within 2 months after measurements in patients with a flow < 600 mL/min [61]. Others have suggested 500 mL/min [62], 650 ml/min [46] or 750 ml/min [20] as threshold level, when flow is measured every 4 to 8 weeks. May *et al.* reported that relative risk of thrombosis in grafts within 3 months after measurements was 1.36, 1.51 and 1.67 when flow was 850, 750 and 650 mL/min respectively [63]. Venous pressure did not predict thrombosis. Sands *et al.* found that patients with PTFE grafts and flow rates < 800 mL/min had a 93% incidence of thrombosis during the 6 months following the measurements [64]. These data seem to support the idea that by decreasing the frequency of flow assessment the cut-off value indicating increased risk for thrombosis increases.

This points to another deficiency in our knowledge. Basically, there are no data on the natural history of stenosis development and therefore on the change of risk of thrombosis over time. It seems likely that the absolute value of flow is related to the risk of thrombosis, whereas the decrease in flow over time reflects development of stenosis. In a recent study it was shown that especially a decrease in flow over time was predictive for imminent thrombosis [65]. Factors that influence the speed of development of stenosis are hardly known. It is conceivable that patients with initially high but decreasing flow need to be evaluated more frequently than patients with stable flow.

Some investigators have measured flow in AV fistulae. Flow may be as low as 130 mL/min and as high as 3600 mL/min. Bouchouareb *et al.* reported in 9 of their 90 patients with native arm fistulae flows > 2000 mL/min [66]. Recently, it was argued that flow measurement in AV fistulae with the ultrasound dilution method poses problems [54], because needle placement is very critical. The arterial needle has to be placed in the main branch. AV fistulae may have side branches. Placement of the needles in two minor branches makes it impossible to measure flow.

More important is the question whether it is at all useful to monitor the functional status of the AV fistulae. Once fully matured, thrombosis is a rare complication. Besarab *et al.* already noted that venous pressure monitoring was not useful in native accesses [39]. Sands *et al.* showed that monthly flow measurements in AV fistulae resulted in a minimal reduction of the already very low thrombosis rate [20].

Recirculation

Recirculation occurs when dialyzed blood that comes out of the "venous" needle of the extracorporeal circuit is taken up again through the "arterial" needle bypassing the systemic circulation.

Several methods are available to measure recirculation. Using urea samples poses serious methodological problems [67,68], and has poor stenosis predictability [69]. When compared with a method using a non-urea indicator, it became clear that values of > 10%

mean true access recirculation in most cases. Many devices are capable of measuring recirculation using non-urea based methods [55,58,59,67,70-72]. Most devices have been clinically validated and are able to differentiate between cardiopulmonary and true access recirculation.
Because recirculation only occurs when spontaneous blood flow through the graft approaches the blood flow through the extracorporeal circuit [73] it should be considered at best as a late sign for access dysfunction.

Identifying stenosis location: vascular access imaging

The gold standard for vascular access imaging is contrast angiography. However, its use as a singular prospective monitoring tool is not possible for obvious reasons.
Color Doppler flow (CDF) imaging enables the physician to non-invasively obtain an anatomical and a functional image of the access. Several studies have shown a good correlation between stenosis detection by Color Doppler imaging and angiography [74-78]. Sands *et al.* reported a thrombosis rate of 0.19 in patients referred for PTA when a ≥ 50% stenosis was detected by CDF imaging, whereas it was 1.26 per patient-year in controls [79].
Two other recent studies are worth mentioning. Lumsden *et al.* randomized patients with greater than 50% stenosis to have either a PTA or no PTA and found that outcome did not differ [80]. Later the same authors re-analyzed their data and reported that patency did improve but only in grafts without prior angioplasty or thrombosis [81].

Magnetic resonance angiography (MRA) is able to quantify flow [82] and to provide anatomical information in AV fistulae [83]. However, anatomical information still leaves much to be desired with the current phase-contrast and time-of-flight MR techniques, even when the image is enhanced by gadolinium contrast [84,85]. MRA guided angioplasty was performed in a limited number of patients [86,87]. Whether MRA will indeed turn out to be the ideal one-stop-shop approach for both diagnosis and treatment of grafts at risk of thrombosis, remains to be established.

Stenosis correction and prevention of restenosis

Radiological series report a patency of 6 months after PTA of 40 - 60% and of 20 - 40% after thrombolysis combined with PTA [31,40,45,88]. These results are not convincingly different from surgical treatment. Data on comparison of radiological series with surgical treatment mainly come from uncontrolled or retrospective studies [88]. Also stent placement did not result in clear improvement of results, except for central venous stenoses [89]. Marston *et al.* evaluated 123 cases of PTFE graft thrombosis who were randomized to surgical or radiological management [90]. Patency in the surgical group was

significantly better than in the other group, 36% and 25% versus 11% and 9% after 6 and 12 months respectively. Nevertheless, many clinicians will feel that PTA is the primary choice of treatment of stenoses. Surgical correction often means the creation of a new anastomosis. For a particular graft this can only be done once or a few times, whereas PTA of a lesion can be done repeatedly [40]. It can be carried out without regional or general anesthesia and it is usually done as an outpatient procedure.

Restenosis is an imminent danger after PTA. PTA injures the vessel wall. The proliferative response to this injury is implicated as cause for restenosis. Some years ago, the hypothesis was tested that increasing the luminal diameter by sharp and regular endovascular surgical incisions instead of circular dilatation by a conventional balloon, would increase the success of the angioplasty [91]. Indeed, in an animal model the cutting balloon produced less intimal proliferation than a standard balloon [91,92]. Early results in coronary arteries seem to indicate that this hypothesis is indeed worth studying in humans [93,94]. Limited, uncontrolled data in hemodialysis patients indicate that this device may be useful in clinical practice [95].

A most exciting development is the emerging potential of gene therapy for the treatment of vasculoproliferative disease, including possible pharmacological inhibition of restenosis after angioplasty [96-98]. It has been shown that vascular smooth muscle cell proliferation and lesion formation can be prevented by the blockade of genes regulating cell cycle progression. It seems that hemodialysis AV grafts offer an attractive in vivo model for this therapy, because they are relatively easily accessible and periodic imaging during follow up is not a great burden to the patient.

Treatment of the thrombosed access

Despite vascular access surveillance, thrombosis still occurs [18,20,32,33,39,43,50,79]. No consensus has been established to resolve thrombosis in AV fistulae [6]. For AV grafts, there are basically two ways to restore the patency after thrombosis: by surgical thrombectomy or radiologically by pharmacomechanical or mechanical thrombolysis. Comparative studies show conflicting results [17,99-103]. When a surgical thrombectomy is performed, the only way to treat a possible underlying stenosis is to revise the access. In many cases this means that the (venous) anastomosis is constructed more proximally. As a consequence, after several surgical revisions there is no more space to construct an anastomosis. The advantage of radiological thrombolysis is the possibility to evaluate the access after the thrombolytic procedure by angiogram and to treat the underlying stenosis directly after thrombolysis by angioplasty [99]. There is no need to revise the anastomosis and

angioplasty can be performed repeatedly to preserve the access [40].
Of course, while the patient is waiting for restoration of the access, there is still the need for dialysis and therefore for an access. One possibility is to insert a temporary catheter in a large vein, i.e. a femoral or internal jugular vein. These catheters can also be used to act as an access, while they are waiting for the first construction of an access, or while in need for an acute access.

In summary, since the introduction of the AV fistula and the PTFE AV graft for vascular access, little improvement in vascular access has been made. Unfortunately, not all patients can receive the preferred AV fistula, and depend on PTFE AV grafts instead. The main problem with these AV grafts is thrombosis, mostly caused by intimal hyperplasia. This leads to a huge burden for patient, nurses and physicians. Not only does it require salvage of the access, but also in the meantime the patients receives other types of accesses, in most cases a temporary catheter, that can lead to insufficient dialysis and infection. Therefore, it is paramount to prevent thrombosis. In the unfortunate case that thrombosis does occur, all has to be done to resolve the thrombosis as soon as possible, and to reestablish a patent access.

References

1. Kolff WJ, Berk HTh: The artificial kidney: a dialyzer with a great area. *Acta Med Scand* 117: 121-134, 1944
2. Quinton WE, Dillard D, Scribner BH: Cannulation of blood vessels for prolonged hemodialysis. *Trans Am Soc Artif Intern Organs* 104-113, 1960
3. Cimino JE, Brescia M.J.: Simple venipuncture for hemodialysis. N Engl J Med 267: 608-609, 1962
4. Brescia MJ, Cimino JE, Appel K, Hurwich BJ: Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. *N Engl J Med* 275: 1089-1092, 1966
5. Kapoian T, Sherman RA: A brief history of vascular access for hemodialysis: an unfinished story. *Semin Nephrol* 17: 239-245, 1997
6. National Kidney Foundation. K/DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 37 (Suppl 1): S137-S181, 2001
7. Dunlop MG, Mackinlay JY, Jenkins AM: Vascular access: experience with the brachiocephalic fistula. *Ann R Coll Surg Engl* 68: 203-206, 1986
8. Cantelmo NL, LoGerfo FW, Menzoian JO: Brachiobasilic and brachiocephalic fistulas as secondary angioaccess routes. *Surg Gynecol Obstet* 155: 545-548, 1982
9. Stonebridge PA, Edington D, Jenkins AM: 'Brachial/basilic vein' transposition for vascular access. *J R Coll Surg Edinb* 40: 219-220, 1995

10. Yokoyama T, Bower R, Chinitz J, Schwartz A, Swartz C: Experience with 100 bovine arteriografts for maintenance hemodialysis. *Trans Am Soc Artif Intern Organs* 20A: 328-333, 1974
11. Butler HG, Baker LD, Jr., Johnson JM: Vascular access for chronic hemodialysis: polytetrafluoroethylene (PTFE) versus bovine heterograft. *Am J Surg* 134: 791-793, 1977
12. May J, Tiller D, Johnson J, Stewart J, Sheil AG: Saphenous-vein arteriovenous fistula in regular dialysis treatment. *N Engl J Med* 280: 770, 1969
13. Bonnaud P, Messier D, Man NK: Manufactured homologous vein graft for creation of arteriovenous fistula. *Proc Eur Dial Transplant Assoc* 17: 303-305, 1980
14. Rubio PA, Farrell EM: Modified human umbilical vein arteriovenous fistula for maintenance hemodialysis: a 3 1/2-year experience. *Arch Surg* 117: 943-945, 1982
15. Bosman PJ: Secondary vascular access for hemodialysis. Thesis University Utrecht, ISBN 90-393-2022-5, 1997
16. Baker LD, Jr., Johnson JM, Goldfarb D: Expanded polytetrafluoroethylene (PTFE) subcutaneous arteriovenous conduit: an improved vascular access for chronic hemodialysis. *Trans Am Soc Artif Intern Organs* 22: 382-387, 1976
17. Beathard GA: Thrombolysis for the treatment of thrombosed dialysis access grafts: a nephrologist's view. *Semin Dial* 8: 162-165, 1995
18. Cayco AV, Abu-Alfa AK, Mahnensmith RL, Perazella MA: Reduction in arteriovenous graft impairment: results of a vascular access surveillance protocol. *Am J Kidney Dis* 32: 302-308, 1998
19. Bosman PJ, Blankestijn PJ, van der Graaf Y, Heintjes RJ, Koomans HA, Eikelboom BC: A comparison between PTFE and denatured homologous vein grafts for haemodialysis access: a prospective randomised multicentre trial. The SMASH Study Group. *Eur J Vasc Endovasc Surg* 16: 126-132, 1998
20. Sands JJ, Jabyac PA, Miranda CL, Kapsick BJ: Intervention based on monthly monitoring decreases hemodialysis access thrombosis. *ASAIO J* 45: 147-150, 1999
21. Powe NR, Jaar B, Furth SL, Hermann J, Briggs W: Septicemia in dialysis patients: incidence, risk factors, and prognosis. *Kidney Int* 55: 1081-1090, 1999
22. Schwab SJ, Beathard G: The hemodialysis catheter conundrum: hate living with them, but can't live without them. *Kidney Int* 56: 1-17, 1999
23. U.S. Renal Data System. The economic cost of ESRD, vascular access procedures, and Medicare spending for alternative modalities of treatment. *Am J Kidney Dis* 30 (Suppl 1): S160-S177, 1997
24. Feldman HI, Kobrin S, Wasserstein A: Hemodialysis vascular access morbidity. *J Am Soc Nephrol* 7: 523-535, 1996
25. Feldman HI, Held PJ, Hutchinson JT, Stoiber E, Hartigan MF, Berlin JA: Hemodialysis vascular access morbidity in the United States. *Kidney Int* 43: 1091-1096, 1993
26. Schwab SJ: Vascular access for hemodialysis. *Kidney Int* 55: 2078-2090, 1999

27. National Kidney Foundation. NKF-DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 30 (Suppl 3): S152-S191, 1997
28. Windus DW: Permanent vascular access: a nephrologist's view. *Am J Kidney Dis* 21: 457-471, 1993
29. U.S. Renal Data System. USRDS 1999 Annual Data Report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 1999
30. Ezzahiri R, Lemson MS, Kitslaar PJ, Leunissen KM, Tordoir JH: Haemodialysis vascular access and fistula surveillance methods in The Netherlands. *Nephrol Dial Transplant* 14: 2110-2115, 1999
31. Kanterman RY, Vesely TM, Pilgram TK, Guy BW, Windus DW, Picus D: Dialysis access grafts: anatomic location of venous stenosis and results of angioplasty. *Radiology* 195: 135-139, 1995
32. Roberts AB, Kahn MB, Bradford S, Lee J, Ahmed Z, Fitzsimmons J, Ball D: Graft surveillance and angioplasty prolongs dialysis graft patency. *J Am Coll Surg* 183: 486-492, 1996
33. Safa AA, Valji K, Roberts AC, Ziegler TW, Hye RJ, Oglevie SB: Detection and treatment of dysfunctional hemodialysis access grafts: effect of a surveillance program on graft patency and the incidence of thrombosis. *Radiology* 199: 653-657, 1996
34. Smits HF, Van Rijk PP, Van Isselt JW, Mali WP, Koomans HA, Blankestijn PJ: Pulmonary embolism after thrombolysis of hemodialysis grafts. *J Am Soc Nephrol* 8: 1458-1461, 1997
35. Swedberg SH, Brown BG, Sigley R, Wight TN, Gordon D, Nicholls SC: Intimal fibromuscular hyperplasia at the venous anastomosis of PTFE grafts in hemodialysis patients. Clinical, immunocytochemical, light and electron microscopic assessment. *Circulation* 80: 1726-1736, 1989
36. Hofstra L: Intimal hyperplasia in human vascular grafts. A study in peripheral bypasses and arteriovenous fistulas. Thesis Rijksuniversiteit Limburg Maastricht, ISBN 90-5278-190-7, 1995
37. Neville RF, Sidawy AN: Myointimal hyperplasia: basic science and clinical considerations. *Semin Vasc Surg* 11: 142-148, 1998
38. Svensson EC, Schwartz LB: Gene therapy for vascular disease. *Curr Opin Cardiol* 13: 369-374, 1998
39. Besarab A, Sullivan KL, Ross RP, Moritz MJ: Utility of intra-access pressure monitoring in detecting and correcting venous outlet stenoses prior to thrombosis. *Kidney Int* 47: 1364-1373, 1995
40. Beathard GA: Percutaneous transvenous angioplasty in the treatment of vascular access stenosis. *Kidney Int* 42: 1390-1397, 1992
41. Beathard GA: Thrombolysis versus surgery for the treatment of thrombosed dialysis access grafts. *J Am Soc Nephrol* 6: 1619-1624, 1995

42. Windus DW, Audrain J, Vanderson R, Jendrisak MD, Picus D, Delmez JA: Optimization of high-efficiency hemodialysis by detection and correction of fistula dysfunction. *Kidney Int* 38: 337-341, 1990
43. Schwab SJ, Raymond JR, Saeed M, Newman GE, Dennis PA, Bollinger RR: Prevention of hemodialysis fistula thrombosis. Early detection of venous stenoses. *Kidney Int* 36: 707-711, 1989
44. Sands JJ, Miranda CL: Prolongation of hemodialysis access survival with elective revision. *Clin Nephrol* 44: 329-333, 1995
45. Turmel-Rodrigues L, Pengloan J, Blanchier D, Abaza M, Birmele B, Haillot O, Blanchard D: Insufficient dialysis shunts: improved long-term patency rates with close hemodynamic monitoring, repeated percutaneous balloon angioplasty, and stent placement. *Radiology* 187: 273-278, 1993
46. Jindal KK, Ethier JH, Lindsay RM, Barre PE, Kappel JE, Carlisle EJ, Common A: Clinical practice guidelines for vascular access. *J Am Soc Nephrol* 10 (Suppl 13): S297-S305, 1999
47. Sreedhara R, Himmelfarb J, Lazarus JM, Hakim RM: Anti-platelet therapy in graft thrombosis: results of a prospective, randomized, double-blind study. *Kidney Int* 45: 1477-1483, 1994
48. Tevlin MT, Portner ME, Kraus MG, Dulaney JT: Clotting frequency of hemodialysis accesses before and after systemic anticoagulation with coumadin. [Abstract] *J Am Soc Nephrol* 7 (ASN Program and Abstracts): A1421, 1996
49. Trerotola SO, Scheel PJ, Jr., Powe NR, Prescott C, Feeley N, He J, Watson A: Screening for dialysis access graft malfunction: comparison of physical examination with US. *J Vasc Interv Radiol* 7: 15-20, 1996
50. Allon M, Bailey R, Ballard R, Deierhoi MH, Hamrick K, Oser R, Rhynes VK, Robbin ML, Saddekni S, Zeigler ST: A multidisciplinary approach to hemodialysis access: prospective evaluation. *Kidney Int* 53: 473-479, 1998
51. Besarab A, Frinak S, Sherman RA, Goldman J, Dumler F, Devita MV, Kapoian T, Al-Saghir F, Lubkowski T: Simplified measurement of intra-access pressure. *J Am Soc Nephrol* 9: 284-289, 1998
52. Smits JHM, Blankestijn PJ: Thrombosis-free hemodialysis grafts: a possibility for the next century? *Semin Dial* 12: 44-49, 1999
53. Blankestijn PJ, Smits JH: How to identify the haemodialysis access at risk of thrombosis? Are flow measurements the answer? *Nephrol Dial Transplant* 14: 1068-1071, 1999
54. Krivitski NM, Depner TA: Development of a method for measuring hemodialysis access flow: from idea to robust technology. *Semin Dial* 11: 124-130, 1998
55. Lindsay RM, Bradfield E, Rothera C, Kianfar C, Malek P, Blake PG: A comparison of methods for the measurement of hemodialysis access recirculation and access blood flow rate. *ASAIO J* 44: 62-67, 1998

56. Steuer RR, Harris DH, Conis JM: A new optical technique for monitoring hematocrit and circulating blood volume: its application in renal dialysis. *Dial Transpl* 22: 260-265, 1993
57. Lindsay RM, Burbank J, Brugger J, Bradfield E, Kram R, Malek P, Blake PG: A device and a method for rapid and accurate measurement of access recirculation during hemodialysis. *Kidney Int* 49: 1152-1160, 1996
58. Schneditz D, Fan Z, Kaufman A, Levin NW: Measurement of access flow during hemodialysis using the constant infusion approach. *ASAIO J* 44: 74-81, 1998
59. Schneditz D, Wang E, Levin NW: Validation of haemodialysis recirculation and access blood flow measured by thermodilution. *Nephrol Dial Transplant* 14: 376-383, 1999
60. Gotch FA, Buyaki R, Panlilio F, Folden T: Measurement of blood access flow rate during hemodialysis from conductivity dialysance. *ASAIO J* 45: 139-146, 1999
61. Bosman PJ, Boereboom FTJ, Eikelboom BC, Koomans HA, Blankestijn PJ: Graft flow as a predictor of thrombosis in hemodialysis grafts. *Kidney Int* 54: 1726-1730, 1998
62. Wang E, Schneditz D, Nepomuceno C, Lavarias V, Martin K, Morris AT, Levin NW: Predictive value of access blood flow in detecting access thrombosis. *ASAIO J* 44: M555-M558, 1998
63. May RE, Himmelfarb J, Yenicesu M, Knights S, Ikizler TA, Schulman G, Hernanz Schulman M, Shyr Y, Hakim RM: Predictive measures of vascular access thrombosis: a prospective study. *Kidney Int* 52: 1656-1662, 1997
64. Sands J, Young S, Miranda C: The effect of Doppler flow screening studies and elective revisions on dialysis access failure. *ASAIO J* 38: M524-M527, 1992
65. Neyra NR, Ikizler TA, May RE, Himmelfarb J, Schulman G, Shyr Y, Hakim RM: Change in access blood flow over time predicts vascular access thrombosis. *Kidney Int* 54: 1714-1719, 1998
66. Bouchouareb D, Saveanu A, Bartoli JM, Olmer M: A new approach to evaluate vascular access in hemodialysis patients. *Artif Organs* 22: 591-595, 1998
67. Lindsay RM, Blake PG, Malek P, Posen G, Martin B, Bradfield E: Accuracy and precision of access recirculation measurements by the hemodynamic recirculation monitor. *Am J Kidney Dis* 31: 242-249, 1998
68. Schneditz D: Recirculation, a seemingly simple concept. *Nephrol Dial Transplant* 13: 2191-2193, 1998
69. Paulson WD, Gadallah MF, Bieber BJ, Altman SD, Birk CG, Work J: Accuracy and reproducibility of urea recirculation in detecting haemodialysis access stenosis. *Nephrol Dial Transplant* 13: 118-124, 1998
70. Depner TA, Krivitski NM, MacGibbon D: Hemodialysis access recirculation measured by ultrasound dilution. *ASAIO J* 41: M749-M753, 1995
71. Lindsay RM: Assessment of access recirculation during haemodialysis. *Curr Opin Nephrol Hypertens* 6: 570-574, 1997

72. Alloatti S, Molino A, Bonfant G, Ratibondi S, Bosticardo GM: Measurement of vascular access recirculation unaffected by cardiopulmonary recirculation: evaluation of an ultrasound method. *Nephron* 81: 25-30, 1999
73. Besarab A, Sherman R: The relationship of recirculation to access blood flow. *Am J Kidney Dis* 29: 223-229, 1997
74. Tordoir JH, Hoeneveld H, Eikelboom BC, Kitslaar PJ: The correlation between clinical and duplex ultrasound parameters and the development of complications in arterio-venous fistulae for haemodialysis. *Eur J Vasc Surg* 4: 179-184, 1990
75. Older RA, Gizienski TA, Wilkowski MJ, Angle JF, Cote DA: Hemodialysis access stenosis: Early detection with color Doppler US. *Radiology* 207: 161-164, 1998
76. Gadallah MF, Paulson WD, Vickers B, Work J: Accuracy of Doppler ultrasound in diagnosing anatomic stenosis of hemodialysis arteriovenous access as compared with fistulography. *Am J Kidney Dis* 32: 273-277, 1998
77. Robbin ML, Oser RF, Allon M, Clements MW, Dockery J, Weber TM, Hamrick-Waller KM, Smith JK, Jones BC, Morgan DE, Saddekni S: Hemodialysis access graft stenosis: US detection. *Radiology* 208: 655-661, 1998
78. Passman MA, Criado E, Farber MA, Risley GL, Burnham CB, Marston WA, Burnham SJ, Keagy BA: Efficacy of color flow duplex imaging for proximal upper extremity venous outflow obstruction in hemodialysis patients. *J Vasc Surg* 28: 869-875, 1998
79. Sands J, Gandy D, Finn M, Johnson A, Burrows S, Miranda C: Ultrasound-angioplasty program decreases thrombosis rate and cost of PTFE graft maintenance. [Abstract] *J Am Soc Nephrol* 8 (ASN Program and Abstracts): 171A, 1997
80. Lumsden AB, MacDonald MJ, Kikeri D, Cotsonis GA, Harker LA, Martin LG: Prophylactic balloon angioplasty fails to prolong the patency of expanded polytetrafluoroethylene arteriovenous grafts: results of a prospective randomized study. *J Vasc Surg* 26: 382-390, 1997
81. Martin LG, MacDonald MJ, Kikeri D, Cotsonis GA, Harker LA, Lumsden AB: Prophylactic angioplasty reduces thrombosis in virgin ePTFE arteriovenous dialysis grafts with greater than 50% stenosis: subset analysis of a prospectively randomized study. *J Vasc Interv Radiol* 10: 389-396, 1999
82. Bakker CJ, Bosman PJ, Boereboom FT, Blankestijn PJ, Mali WP: Measuring flow in hemodialysis grafts by non-triggered 2DPC magnetic resonance angiography. *Kidney Int* 49: 903-905, 1996
83. Laissy JP, Menegazzo D, Debray MP, Loshkajian A, Viron B, Mignon F, Schouman-Claeys E: Failing arteriovenous hemodialysis fistulas: assessment with magnetic resonance angiography. *Invest Radiol* 34: 218-224, 1999
84. Thurnher S: Magnetic resonance angiography of hemodialysis fistulas and grafts. *Semin Interv Radiol* 14: 101-110, 1997

85. Bos C, Smits JH, Zijlstra JJ, van der Mark WA, Blankestijn PJ, Bakker CJ, Viergever MA, Mali WP: MRA of hemodialysis access grafts and fistulae using selective contrast injection and flow interruption. *Magn Reson Med* 45: 557-561, 2001
86. Bakker CJ, Smits HF, Bos C, van der Weide R, Zuiderveld KJ, van Vaals JJ, Hurtak WF, Viergever MA, Mali WP: MR-guided balloon angioplasty: in vitro demonstration of the potential of MRI for guiding, monitoring, and evaluating endovascular interventions. *J Magn Reson Imaging* 8: 245-250, 1998
87. Smits HFM: Radiological diagnosis and treatment of hemodialysis access graft dysfunction. Thesis University Utrecht, ISBN 90-6464-5329, 2000
88. Turmel-Rodrigues L, Pengloan J, Baudin S, Testou D, Abaza M, Dahdah G, Mouton A, Blanchard D: Treatment of stenosis and thrombosis in haemodialysis fistulas and grafts by interventional radiology. *Nephrol Dial Transplant* 15: 2029-2036, 2000
89. Gray RJ: Percutaneous intervention for permanent hemodialysis access: a review. *J Vasc Interv Radiol* 8: 313-327, 1997
90. Marston WA, Criado E, Jaques PF, Mauro MA, Burnham SJ, Keagy BA: Prospective randomized comparison of surgical versus endovascular management of thrombosed dialysis access grafts. *J Vasc Surg* 26: 373-380, 1997
91. Barath P, Fishbein MC, Vari S, Forrester JS: Cutting balloon: a novel approach to percutaneous angioplasty. *Am J Cardiol* 68: 1249-1252, 1991
92. Barath P: Microsurgical dilatation concept: animal data. *J Invas Cardiol* 8 (Suppl A): 2A-5A, 1996
93. Molstad P, Myreng Y, Golf S, Sirnes PA, Kassis E, Abilgaard U, Andersen PE, Thuesen L: The Barath Cutting Balloon versus conventional angioplasty. A randomized study comparing acute success rate and frequency of late restenosis. *Scand Cardiovasc J* 32: 79-85, 1998
94. Kondo T, Kawaguchi K, Awaji Y, Mochizuki M: Immediate and chronic results of cutting balloon angioplasty: a matched comparison with conventional angioplasty. *Clin Cardiol* 20: 459-463, 1997
95. Vorwerk D, Adam G, Müller-Leisse C, Günther RW: Hemodialysis fistulas and grafts: use of cutting balloons to dilate venous stenoses. *Radiology* 201: 864-867, 1996
96. Braun-Dullaeus RC, Mann MJ, Dzau VJ: Cell cycle progression: new therapeutic target for vascular proliferative disease. *Circulation* 98: 82-89, 1998
97. Holmes D, Fitzgerald P, Goldberg S, LaBlanche J, Lincoff AM, Savage M, Serruys PW, Willerson J, Granett JR, Chan R, Shusterman NH, Poland M: The PRESTO (Prevention of restenosis with tranilast and its outcomes) protocol: a double-blind, placebo-controlled trial. *Am Heart J* 139: 23-31, 2000
98. Kaufman JS, Fiore L, Hasbargen JA, O'Connor TZ, Perdriset G: A pharmacodynamic study of clopidogrel in chronic hemodialysis patients. *J Thromb Thrombolysis* 10: 127-131, 2000

99. Gray RJ, Sacks D, Martin LG, Trerotola SO: Reporting standards for percutaneous interventions in dialysis access. Technology Assessment Committee. *J Vasc Interv Radiol* 10: 1405-1415, 1999
100. Schuman E, Quinn S, Standage B, Gross G: Thrombolysis versus thrombectomy for occluded hemodyalisis grafts. *Am J Surg* 167: 473-476, 1994
101. Schwartz CI, McBrayer CV, Sloan JH, Meneses P, Ennis WJ: Thrombosed dialysis grafts: comparison of treatment with transluminal angioplasty and surgical revision. *Radiology* 194: 337-341, 1995
102. Brotman DN, Fandos L, Faust GR, Doscher W, Cohen JR: Hemodialysis graft salvage. *J Am Coll Surg* 178: 431-434, 1994
103. Middlebrook MR, Amygdalos MA, Soulen MC, Haskal ZJ, Shlansky Goldberg RD, Cope C, Pentecost MJ: Thrombosed hemodialysis grafts: percutaneous mechanical balloon declotting versus thrombolysis. *Radiology* 196: 73-77, 1995

Chapter 2

Outline of the thesis

Outline of the thesis

Vascular access thrombosis is associated with stenosis, particularly in polytetrafluoroethylene (PTFE) arteriovenous (AV) grafts [1]. These stenoses cause an increased resistance over the access tract. Because the graft has no auto-regulating capacities, this leads to a decrease in vascular access blood flow (Qa), and to an increase in intra-access pressure, which is commonly expressed as venous pressure (VP) [2,3]. Consequently, both parameters (i.e. Qa and VP) can be used as predictors for impending vascular access failure [4]. Theoretically, Qa provides more information about the vascular access than the intra-access VP measurement, because it provides information about the total access tract. The VP measurement only provides information about the access upstream from the venous needle. We have to realize that surveillance using VP is without extra cost and results are very easy to obtain. In ***chapter 3*** we investigated whether Qa measurements are better than VP measurements in identifying patients at risk for thrombosis. Furthermore, we looked whether referral of patients for corrective interventions (stenosis treatment with percutaneous transluminal angioplasty, PTA) based on Qa measurements alone or on the combination of VP and Qa reduces thrombosis rate more than referral based on VP alone.

After the clinical detection of an impaired vascular access it is imminent to localize and treat a stenosis before thrombosis occurs [5]. Conventional imaging of the access mainly consists of digital subtraction angiography (DSA). However, the radiation load and the use of iodinated contrast agents needed for DSA are considered the major disadvantages of this imaging modality. Magnetic resonance angiography (MRA) offers the opportunity to provide an image of the access without these less desirable features of DSA. However, because of turbulent blood flow some segments of the MR image can present as a void, especially near the anastomoses [6,7]. Even with contrast-enhancement there are still substantial artifacts, because of the presence of flow [8]. Therefore, we designed a flow-interrupted contrast-enhanced MR imaging sequence. In ***chapter 4*** we compared this novel MRA imaging of the vascular access with DSA.

After detection of a failing access, it is important to intervene before thrombosis occurs [9]. The common approach for intervention nowadays is PTA [4,10]. Several studies demonstrated that the overall survival of the access can be prolonged by repetitive PTA [5,11]. In ***chapter 5*** we studied the short-term effect of PTA on Qa, Qa patterns after PTA, and which factors had an influence on Qa after PTA.

If, despite the efforts of detecting failing accesses timely, thrombosis still occurs, the dialysis patient comes in an undesirable situation. Namely, the patient cannot get access to the hemodialysis treatment. When this happens, it is paramount to re-establish a patent vascular access as soon as possible. This can be done by surgical thrombectomy or radiologically by percutaneous thrombolysis [4]. The latter has become the treatment of

choice for thrombosed hemodialysis grafts [10,12,13]. In ***chapter 6*** we compared three devices for percutaneous thrombolysis with respect to their efficacy in removing thrombus from hemodialysis access grafts. Treatment should be initiated immediately after diagnosing thrombosis [14]. In many cases this cannot be done immediately and the patients rely on other types of accesses, mostly a temporary catheter in the internal jugular or femoral vein [15]. These catheters are also used as vascular access, when the arteriovenous graft or fistula is not constructed or ready for puncture at the onset of dialysis treatment. Basically, there are two types of temporary catheters: the single-lumen and the double-lumen catheters. Single-lumen catheters do not allow for a continuous blood flow to and from the dialysis machine, whereas double-lumen catheters do. Although it is presumed that single-lumen catheters have a lower dialysis adequacy than double-lumen catheters, this has not been formally investigated yet. In ***chapter 7*** we present a randomized prospective trial comparing dialysis adequacy and overall performance in single-lumen versus double-lumen catheters.

Not all decreases in access blood flow are related to intimal hyperplasia or stenosis formation. Other causes for low access flow leading to access thrombosis have been proposed. Hypotension, hypovolaemia, or external compression may be involved in these non-stenotic thrombotic events [16]. Also, there has been a growing appreciation of the role of increased hypercoagulability found in these patients. In ***chapter 8*** we discuss coagulability abnormalities in relation to haemodialysis access thrombosis.

References

1. Kanterman RY, Vesely TM, Pilgram TK, Guy BW, Windus DW, Picus D: Dialysis access grafts: anatomic location of venous stenosis and results of angioplasty. *Radiology* 195: 135-139, 1995
2. Schwab SJ, Raymond JR, Saeed M, Newman GE, Dennis PA, Bollinger RR: Prevention of hemodialysis fistula thrombosis. Early detection of venous stenoses. *Kidney Int* 36: 707-711, 1989
3. Besarab A, Sullivan KL, Ross RP, Moritz MJ: Utility of intra-access pressure monitoring in detecting and correcting venous outlet stenoses prior to thrombosis. *Kidney Int* 47: 1364-1373, 1995
4. National Kidney Foundation. K/DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 37 (Suppl 1): S137-S181, 2001
5. Beathard GA: Percutaneous transvenous angioplasty in the treatment of vascular access stenosis. *Kidney Int* 42: 1390-1397, 1992
6. Bradley WGJ: Flow phenomena. In: Stark DD, Bradley WGJ, eds. Magnetic Resonance Imaging, 2nd ed. St. Louis: Mosley Year Book, 1992; pp 253-298

7. Gehl HB, Bohndorf K, Gladziwa U, Handt S, Gunther RW: Imaging of hemodialysis fistulas: limitations of MR angiography. *J Comput Assist Tomogr* 15: 271-275, 1991
8. Thurnher S: Magnetic resonance angiography of hemodialysis fistulas and grafts. *Semin Interv Radiol* 14: 101-110, 1997
9. Beathard GA: Percutaneous angioplasty for the treatment of venous stenosis: a nephrologist's view. *Semin Dial* 8: 166-170, 1995
10. Gray RJ: Percutaneous intervention for permanent hemodialysis access: a review. *J Vasc Interv Radiol* 8: 313-327, 1997
11. Turmel-Rodrigues L, Pengloan J, Baudin S, Testou D, Abaza M, Dahdah G, Mouton A, Blanchard D: Treatment of stenosis and thrombosis in haemodialysis fistulas and grafts by interventional radiology. *Nephrol Dial Transplant* 15: 2029-2036, 2000
12. Davis GB, Dowd CF, Bookstein JJ, Maroney TP, Lang EV, Halasz N: Thrombosed dialysis grafts: efficacy of intrathrombic deposition of concentrated urokinase, clot maceration, and angioplasty. *Am J Roentgenol* 149: 177-181, 1987
13. Beathard GA: Thrombolysis versus surgery for the treatment of thrombosed dialysis access grafts. *J Am Soc Nephrol* 6: 1619-1624, 1995
14. Roberts AC, Valji K, Bookstein JJ, Hye RJ: Pulse-spray pharmacomechanical thrombolysis for treatment of thrombosed dialysis access grafts. *Am J Surg* 166: 221-225, 1993
15. Schwab SJ: Vascular access for hemodialysis. *Kidney Int* 55: 2078-2090, 1999
16. Windus DW: Permanent vascular access: a nephrologist's view. *Am J Kidney Dis* 21: 457-471, 1993

Chapter 3

Graft surveillance: venous pressure, access flow, or the combination?

Johannes H.M. Smits[1], Joke van der Linden[2], E. Chris Hagen[3], Esther C. Modderkolk-Cammeraat[4], Geert W. Feith[5], Hein A. Koomans[1], Marinus A. van den Dorpel[2], Peter J. Blankestijn[1]

1 Department of Nephrology, University Medical Center, Utrecht
2 Department of Internal Medicine, Medisch Centrum Rijnmond-Zuid, Rotterdam
3 Department of Internal Medicine, Eemland Hospital, Amersfoort
4 Dianet, Utrecht
5 Department of Internal Medicine, Gelderse Vallei, Wageningen

Abstract

Background. Increased venous pressure (VP) and decreased access flow (Qa) are predictors of dialysis access graft thrombosis. VP is easily obtainable. Qa assessment requires a special device and takes more time. Aims of our randomized multi-center studies were to compare outcome in patients with grafts monitored by VP or Qa (study A) or monitored by VP or the combination of VP *and* Qa (study B).

Methods. We performed VP measurements that consisted of weekly VP at a pumpflow of 200 mL/min (VP200) and the ratio of VP0/MAP. Qa was measured every 8 weeks with the Transonic HD01 hemodialysis monitor. Threshold levels for referral for angiography were VP200 > 150 mmHg or VP0/MAP > 0.5 (both at 3 consecutive dialysis sessions), or Qa < 600 mL/min. Subsequent therapy consisted of either PTA or surgery.

Results. Total follow-up was 80.5 patient-years for 125 grafts. The vast majority of a total of 131 positive tests was followed by angiography and corrective intervention. In study A, the rate of thromboses not preceded by a positive test was 0.19 and 0.24 per patient-year (P = NS) and in study B it was 0.32 versus 0.28 per patient-year (P = NS). Survival curves were not significantly different between the subgroups.

Conclusions. These data demonstrate that standardized monitoring of either VP or Qa or the combination of both and subsequent corrective intervention can reduce thrombosis rate in grafts to below the recommended quality of care standard (i.e. 0.5 per patient-year, NKF-DOQI). These surveillance strategies are equally effective in reducing thrombosis rates.

Introduction

Thrombosis remains a major problem in vascular access for hemodialysis, particularly in polytetrafluoroethylene (PTFE) grafts. It accounts for considerable morbidity and mortality with an annual cost of close to $1 billion in the United States and is responsible for 17 - 25% of all hospitalizations in dialysis patients [1-3].

Thrombosis occurs at a rate of 0.5 to 2.5 events per patient-year [4-8]. In most cases thrombosis is associated with the presence of stenoses at the venous anastomosis or in the outflow tract [9-13]. Stenosis increases resistance over the flow tract. Because the graft has no autoregulating capacities, blood flow (Qa) drops and venous pressures (VP) rise. These variables have been shown to predict thrombosis. More importantly, several studies demonstrated that referral for corrective intervention based on these parameters can prevent thrombosis [14-18].

We and others confirmed that patients with outflow stenosis have on average a higher VP and/or lower Qa [14,19]. However, VP did not correlate with Qa. In other words not all patients with high VP had low Qa, indicating that not all patients who are at risk for thrombosis can be identified by VP measurements. We also showed that inflow resistance (that is resistance of the flow tract upstream of the venous needle) comprises a substantial and very variable part of total graft resistance. Indeed, several studies have indicated that in up to 29% of thrombosis cases, stenoses may be located in the arterial part of the graft [13,20-23]. The inflow resistance is not reflected by VP measurements, whereas Qa measurements are a reflection of total graft resistance. This could make VP less effective as selection parameter for patients at risk for thrombosis than Qa. In contrast to Qa measurements, VP can be measured by the dialysis machine, is easy to obtain and requires little time investment. Furthermore, some studies have convincingly indicated that the use of VP measurements as a selection variable for diagnostic and subsequent corrective procedures, results in thrombosis rates between 0.2 and 0.4 events per patient-year [6,14,16]. Although we provided the theoretical basis that Qa measurements are better than VP measurements, the question is whether Qa measurements really confer additional benefit in patients who are monitored by VP. In other words, when simple clinical variables such as VP are used, is there any additional benefit when periodic Qa measurements are added to the surveillance protocol?

Our hypothesis for the present studies was as follows: Qa measurements are better than VP measurements in identifying patients at risk for thrombosis. As a consequence: referral of patients for corrective interventions based on Qa measurements alone or on the combination of VP and Qa reduces thrombosis rate more than referral based on VP alone.

Patients and methods

Five dialysis centers participated in this study. All patients with a hemodialysis access PTFE graft were eligible to enter into the study. Exclusion criteria were inability to give informed consent and contrast allergy. Studies were approved by the Institutional Ethical Review Committees. Informed consent was obtained from all patients.

Surveillance protocols

Two surveillance studies were conducted concurrently. In study A patients were assigned to weekly VP measurements (Group A1) or periodic Qa measurements (Group A2). In study B, patients were assigned to weekly VP measurements (Group B1) or the combination of VP measurements and periodic Qa measurements (Group A2). Study A was instituted in one center (Rotterdam) and study B in four. Within the centers the patients were prospectively and at random allocated to one of the subgroups of each study (Fig. 1).

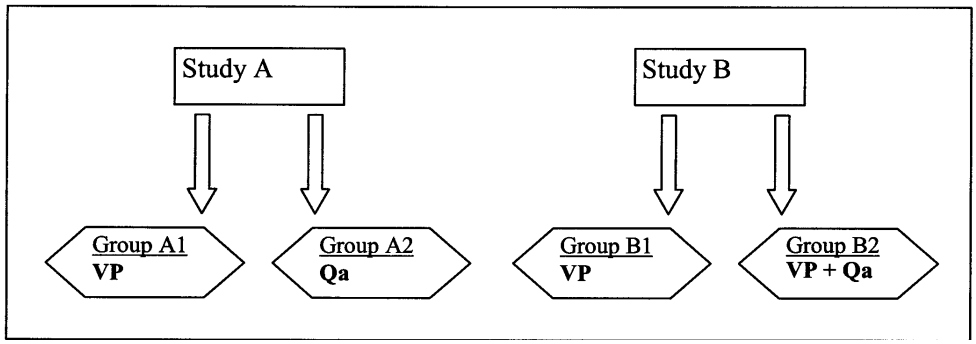

Figure 1. Study design

Venous pressure monitoring

Measurements were done once weekly, within the first half-hour of dialysis, and included both dynamic and static VP measurements. When one or both measurements were positive (see **Indication for referral for angiography**), measurements were repeated the next dialysis session. All centers had dialysis machines with digital pressure displays. Maintenance and calibration was done according to the manufacturer's recommendations on a regular basis by an experienced technician.

Dynamic venous pressure
Digitally displayed dynamic VPs were assessed with a fixed pump flow set at 200 mL/min (VP200), as described by Schwab *et al.* [16]. Ten subsequent readings on the dialyzer display were averaged. After the measurement the pump flow was set to the original level.

Static venous pressure
Static VP (VP0) was assessed with zero pump flow with the tubing out of the air lock in order to avoid automatic closure of the tubing after the pump was shut off. VP0 was divided by mean arterial pressure (MAP) to correct for blood pressure differences as described by Besarab *et al.* [14]. No correction for height differences was made. MAP was calculated by taking two times diastolic pressure plus systolic pressure divided by three.

Access flow measurement

Measurements were done every eight weeks. Qa was measured with the Transonic Hemodialysis Monitor (Transonic Systems Inc, Ithaca, NY). The theoretical background, bench validation and in vivo validation are described in detail in previous papers [24,25]. Periodic calibration was done by the local distributor. Qa determination consisted of the average of three consecutive measurements. If Qa levels reached between 600 and 800 mL/min the measurement was repeated after one month. All measurements were done with a dialyzer blood flow of more than 200 mL/min.

Indication for referral for angiography

Referral of Group A1 patients for angiography was based on three consecutive dialysis sessions with elevated static and/or dynamic VP. Patients in Group A2 underwent angiography when Qa fell below 600 mL/min. Indication for referral of Group B1 patients for angiography was an elevated static and/or dynamic VP, similar to Group A1. In Group B2 an elevated static and/or dynamic VP and/or Qa below 600 mL/min were reasons for referral. The threshold level for the static VP ratio was 0.5, according to the method described by Besarab *et al.* [14]. Threshold for dynamic VP was 150 mmHg.
Angiography was done to determine presence and location of the stenosis. If a stenosis of > 50% was present, the primary choice of treatment was percutaneous transluminal angioplasty (PTA). After an intervention patients continued the same surveillance mode as before. All thrombotic events and interventions (elective or therapeutic) were recorded.

Data analysis

Thrombosis-free survival rates between the subgroups in both groups were tested with the log rank test. Curves were made with Kaplan-Meier survival analysis showing event-

free graft survival. An event was defined as a thrombotic event without a preceding positive test, either VP (Group A1, B1 and B2) or Qa (Group A2 and B2). Differences between incidence rates of thrombosis and of intervention were calculated with Poisson regression analysis. A *P* value of less than 0.05 was considered significant.

Power analysis

For calculation of group sizes we made the following assumptions. Our historical thrombosis rate was 1.2 event per patient-year [7], but improved after intensifying access surveillance using dynamic VP measurements to approximately 0.85. At that time however, no specific surveillance protocol was used. We expected the thrombosis rate in the Qa groups to be lower than in the VP groups based on considerations described in the Introduction. We calculated that with a follow-up of 100 patient-year a thrombosis rate difference of 0.25 could be demonstrated ($\alpha = 0.05$, $\beta = 0.20$). Obviously, for differences greater than 0.25 less follow-up is needed.

Results

Data were evaluated after a follow-up of approximately two times 40 patient-years. An interim analysis showed that results in VP monitored grafts were much better than anticipated. This justified the conclusion that continuation of the study was not likely to result in clinically significant differences.

Patient characteristics

Study A included 53 PTFE grafts (51 patients). Twenty-five grafts were monitored by VP (Group A1) and 28 grafts by Qa measurements (Group A2). Study B included 72 grafts (68 patients). Thirty-one grafts were assigned to Group B1 (VP) and 41 grafts to Group B2 (VP + Qa) (Fig. 1).

In study A 19 patients were lost during follow up (8 in Group A1, 11 in Group A2). Reasons included death or abstinence of dialysis therapy (n = 12), transplantation (n = 3), refusal of further graft monitoring (n = 2), change to peritoneal dialysis (n = 1) or to another center (n = 1). In study B 15 patients were lost to follow-up (8 in Group B1, 7 in Group B2). Reasons were death (n = 8), transplantation (n = 4), abstinence of dialysis therapy (n = 1), and change to peritoneal dialysis (n = 2).

Demographic patient characteristics for both studies are depicted in Table 1. There were no significant differences in age, percentage diabetics, race, or time on hemodialysis therapy, in either study A or B.

Outcome

Study A

Total follow up was 37.8 patient-years. Graft monitoring resulted 59 times in positive tests followed by 55 angiograms, which subsequently resulted in 48 PTA procedures and 7 surgical interventions. Table 2 shows which test(s) led to these interventions. In all cases of Group A1 it was an increased VP0/MAP, which led to the intervention. In the vast majority of angiograms venous stenoses were present (Table 3). Graft characteristics and outcomes of individual patient groups are outlined in Table 4 and 5.

Table 1. Patient characteristics

	Study A			Study B		
	VP (A1)	Qa (A2)	*P*	VP (B1)	VP + Qa (B2)	*P*
Patients	24	27	NS	31	37	NS
Median age *years* (range)	65(26-86)	66(21-84)	NS	65(19-80)	61(21-87)	NS
Mean age *years* (SD)	61 (17)	61 (18)		62 (14)	60 (17)	
Gender						
male	9	18	0.04	15	16	NS
female	15	9		16	21	
Cause of renal failure						
diabetes	4 (16%)	7 (26%)	NS	8 (26%)	4 (11%)	NS
hypertension	8	8		2	2	
glomerulonephritis	3	2		3	2	
polycystic kidney disease	3	0		0	5	
other	4	7		13	19	
unknown	2	3		5	5	
Race						
Caucasian	18 (75%)	23 (85%)	NS	30 (97%)	30 (81%)	NS
black	5	4		0	4	
Asian	1	0		1	3	
Median HD therapy *months* (range)	18.1 (2.3-88.8)	13.9 (0.9-116.7)	NS	22.0 (0.0-281.0)	24.8 (0.2-302.1)	NS
Mean HD therapy *months* (SD)	27.9 (26.9)	22.6 (28.2)		43.9 (58.2)	44.3 (69.6)	

During the follow-up, 12 thrombotic events occurred (6 in each patient group), resulting in a thrombosis frequency of 0.31 per patient-year. In both subgroups thrombosis was predicted by a positive test (VP or Qa) in 2 occasions, but thrombosis occurred pending the angiography (2 - 15 days after obtaining positive tests). In 8 grafts thrombosis was not preceded by an abnormal VP or flow, which resulted in an unpredicted thrombosis rate of 0.19 and 0.24 per patient-year (P = NS). No anatomical information is available from these 8 grafts with thrombosis. Reasons included: no attempt to reestablish patency or surgical thrombectomy without intra-operative angiography.

Table 2. Which positive test led to intervention?

	Study A		Study B	
	VP (A1)	Qa (A2)	VP (B1)	VP + Qa (B2)
VP0/MAP	15	-	12	6
VP200	0	-	4	0
VP0/MAP + VP200[a]	15	-	9	8
Qa	-	25	-	3
Qa +VP[b]	-	-	-	13
Total (PTA)	30 (26)	25 (22)	25 (23)	30 (26)

[a] both tests were positive

[b] VP means either a positive VP0/MAP, or a positive VP200, or both

Table 3. Localization of stenotic lesions in grafts of patients referred for PTA

	Study A		Study B	
	VP (A1)	Qa (A2)	VP(B1)	VP + Qa (B2)
Localization				
Venous graft +/- outflow[a]	24 (92%)	19 (86%)	22 (96%)	20 (77%)
Arterial graft[b]	0 (0%)	1 (5%)	0 (0%)	1 (4%)
Venous + arterial graft[c]	2 (8%)	2 (9%)	1 (4%)	5 (19%)
Total PTA	26	22	23	26

[a] stenosis at or near the venous anastomosis and/or in the venous outflow tract

[b] stenosis at or near the arterial anastomosis

[c] combination of [a] and [b], i.e. a stenosis at or near the venous anastomosis and/or in the venous outflow tract **and** a stenosis at or near the arterial anastomosis

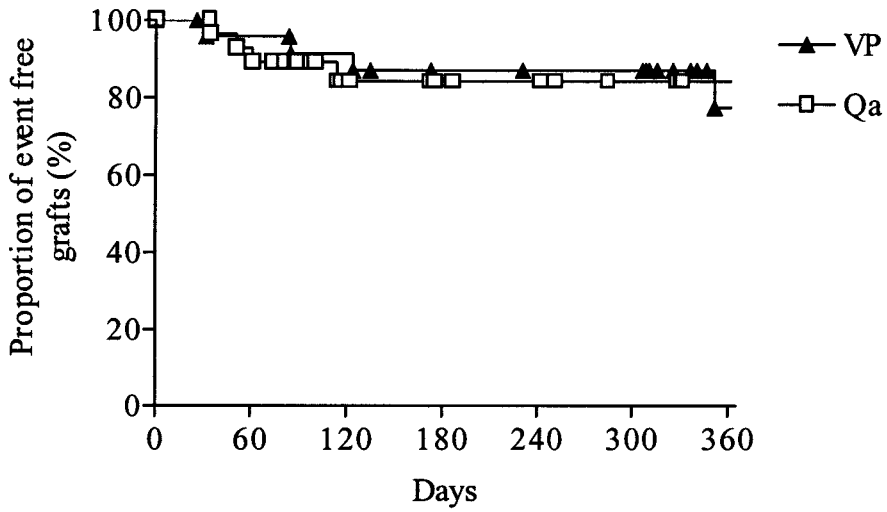

Figure 2. Study A. Graft survival with non-predicted thrombosis

Kaplan-Meier survival curves did not show a significant difference between the subgroups (Table 5, Fig. 2). The 6 months event-free survival (an event equals thrombosis not predicted by the test) was 87% for the VP group, and 84% for the Qa group (P = NS).

Study B

The total follow up period was 42.7 patient-years. Graft monitoring resulted 72 times in positive tests followed by 55 angiograms, which subsequently resulted in 49 PTA procedures and 6 surgical interventions. Table 2 shows which positive test(s) led to an intervention. In 90% of cases there was an elevated VP0/MAP. Venous stenosis (at or near the venous anastomosis or in the venous outflow tract) was present in 98% of the grafts treated with PTA (see Table 3). Graft characteristics and outcomes of individual patient groups are outlined in Table 4 and 5.

Thirty thrombotic events occurred (12 in the VP group, 18 in the VP + Qa group), that is 0.7 per patient-year. Five out of the 12 thrombosis in the Group B1 were preceded by a positive test, but thrombosis occurred after 2 - 15 days pending the angiography. In all five cases thrombectomy was done and a venous stenosis was found. In Group B2, 12 out of 18 thromboses were predicted by one or more positive tests. In 7 cases thrombosis occurred after 3 - 20 days pending the angiography (all of these seven grafts showed a venous stenosis after thrombectomy), and in 5 cases intervention was not done for vari-

ous reasons, including graft infection, poor clinical condition and switch to peritoneal dialysis. In 13 cases thrombosis was not preceded by a positive test, resulting in a thrombosis frequency of 0.32 (Group B1) and 0.28 (Group B2) (*P* = NS). Ten of these 13 thromboses were treated by radiological thrombolysis. Stenoses were found at the venous anastomosis (n = 5, Group B1; n = 3, Group B2), at the arterial anastomosis (n = 1, Group B2), or at both anastomoses (n = 1, Group B2). In 3 grafts it was impossible to obtain anatomical information, because no attempt was made to reestablish patency.

Kaplan-Meier survival curves did not show a significant difference between the subgroups (Table 5, Fig. 3). The 6 months event-free survival (an event equals thrombosis not predicted by the test) was 85% for the VP group, and 88% for the VP + Qa group (*P* = NS).

Table 4. Graft characteristics

	Study A			Study B		
	VP (A1)	Qa (A2)	*P*	VP (B1)	VP + Qa (B2)	*P*
Grafts	25	28		31	41	
Median age graft	6.7	4.6		11.6	6.0	
months (range)	(1.0-49.7)	(1.2-28.4)	NS	(0.0-73.6)	(0.0-100.0)	NS
Mean age graft	12.8	8.3		18.1	16.4	
months (SD)	(13.8)	(7.6)		(20.9)	(24.8)	
Configuration graft						
looped, forearm	23	26	NS	31	37	NS
straight, upperarm	2	2		0	4	
Anticoagulant therapy						
acenocoumerol	14	15		20	23	
aspirin	5	2		3	5	
combination	1	0		2	0	
none	5	11		6	13	
Follow-up						
patient-years	21.3	16.5		21.6	21.1	
median *months*	11.2	5.8		5.9	5.1	
(range)	(0.9-15.5)	(1.1-15.2)	0.016	(1.7-20.4)	(0.4-20.4)	NS
mean *months*	10.4	7.2		8.4	6.2	
(SD)	(4.4)	(4.9)		(5.7)	(4.9)	

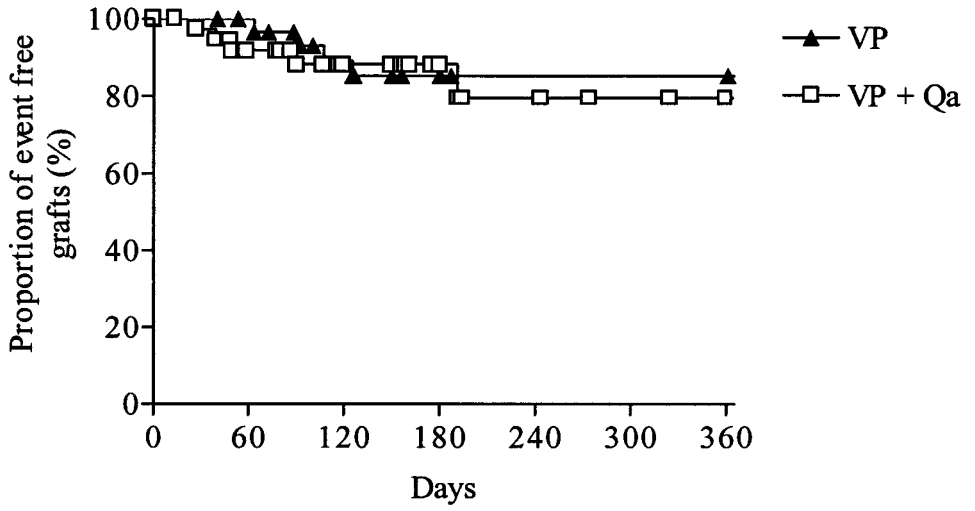

Figure 3. Study B. Graft survival with non-predicted thrombosis

Table 5. Results

	Study A			Study B		
	VP (A1)	Qa (A2)	*P*	VP (B1)	VP + Qa (B2)	*P*
Interventions/ pt.-yr. (n pts)	1.41 (17)	1.52 (11)		1.16 (16)	1.42 (20)	
balloon angioplasty (n)	26	22		23	26	
surgical (n)	4	3		2	4	
Thromboses total (n pts)	6(4)	6(4)		12(10)	18(16)	
predicted / unpredicted	2/4	2/4		5/7	12/6	
Unpredicted thromboses/ pt.-yr.	0.19	0.24	NS	0.32	0.28	NS
6 mnth. event-free[a] surv. rate (%)	87	84	NS	85	88	NS
12 mnth. event-free[a] surv. rate (%)	77	84	NS	85	80	NS

[a] an event is defined as an unpredicted thrombosis

Discussion

This randomized, prospective multi-center trial allows a number of important conclusions. Firstly, we confirm that thrombosis rates in patients monitored and selected for corrective interventions based on VP or Qa can be maintained below the quality of care standards formulated by the NKF-DOQI committee [4]. Secondly, we show that thrombosis rates in groups monitored by VP or Qa alone or by the combination of tests do not differ. Thirdly, only a small minority of patients was selected for corrective interventions by Qa alone in the group with combined monitoring of VP and Qa. Fourthly, after obtaining abnormal tests subsequent diagnostic and interventional procedures should be instituted on short notice. It seems likely that the number of thromboses during the waiting time can be reduced. Finally, we confirm that static VP is more effective than dynamic VP for monitoring dialysis grafts.

The present study confirms the usefulness of VP and Qa measurements as access surveillance variables. Previously, we have presented the theoretical basis for the assumption that Qa measurements are better than VP (i.e. dynamic) measurements as a monitoring tool (summarized in [26]). This is based on the fact that some stenoses are located in the arterial flow tract that is upstream of the venous needle. These lesions increase resistance and reduce Qa without increasing VP, possibly even decreasing VP. Several studies have indicated that arterial stenoses occur in up to 29% of thrombosis cases [20-23]. In the present study, we found a strong predominance of venous lesions in the patients referred for angiography. In some patients having a graft thrombosis without a preceding positive test, thrombectomy was done. Also, in those patients venous lesions were more likely than arterial lesions.

Qa measurements have already been recognized as the preferred monitoring tool for vascular access surveillance [4,27]. However, these recommendations are primarily based on clinical studies with a non-randomized or observational setup [19,25,28-30]. To our knowledge, only one study compared Qa with static VP as surveillance variable. Sands *et al.* [8] showed that intervention based on monthly Qa measurement or on monthly static VP measurements reduced thrombosis rates in comparison with non-monitored controls. Some important differences between the two studies exist. The present study also includes a program combining VP and Qa. Theoretically, this combination is likely to be the most effective program [18]. Furthermore, the study population of Sands *et al.* consisted predominantly of AV fistulae (almost two-third in the control and monitored groups) which are less likely to clot. Also, threshold for referral for angiogram (750 mL/min vs. 600 mL/min in our Qa groups), and frequency of measurements (monthly VP vs. weekly in our VP groups) differed. There is some controversy about the optimal frequency. Some advocate the use of dynamic pressures weekly and static VP every two

weeks [4], others suggest to measure dynamic VP every dialysis [27], or static VP every week [31]. In the present study, we measured both dynamic and static VP once weekly during the same dialysis session. Our results indicate that graft surveillance using VP or Qa measurements strictly organized as in the present study results in identical thrombosis rates. This does not exclude the possibility that in patients who develop more arterial lesions for whatever reason, surveillance using Qa would result in lower thrombosis rates than using VP measurements.

In our study most referrals for intervention in patients monitored by VP measurements alone (Group A1 and B1) were based on static VP measurements. Although dynamic VP was successfully used as part of an access surveillance program in some studies [6,11,16,32], there is convincing evidence that dynamic VP does not accurately reflect true intra-access pressure, and therefore, does not reflect resistance caused by stenosis formation [14]. Dynamic VP is highly biased by pump flow, blood tubing, needle size, and blood pressure [33]. Static VP measurements, on the other hand, particularly when corrected for mean arterial pressure, avoid these potential confounders.
Also in Group B2 (combination of VP and Qa measurements) most referrals were based on VP and only 3 out of 30 referrals were based on Qa alone. These data indicate that when VP measurements are well organized, adding periodic Qa measurements is of limited value (Group B1 versus B2). On the other hand, study A clearly shows that when no VP measurements are done periodic Qa measurements result in identical thrombosis rates, proving the effectiveness of Qa as surveillance variable.

In this study 21 of the 42 thromboses occurred despite preceding positive tests. Sixteen thromboses occurred 2 to 20 days after obtaining the abnormal tests pending further diagnostic and correctional interventions. These results further support the idea that an increased VP and/or low Qa indeed predict imminent thrombosis. It seems likely that immediate institution of further treatment could have decreased the number of thromboses.
The 21 thromboses, which were not preceded by positive tests, should not all be considered as failures of the tests. Flow is directly related to blood pressure. Blood pressure may show considerable variability in hemodialysis patients and is likely to reach its lowest levels in the first hours after the hemodialysis session and especially during the night [34]. Therefore, it is possible that flow is adequate at the time measurements are done, but reaches levels associated with thrombosis in the interdialytic period.

Several issues need to be addressed with respect to the present study.
Firstly, our power calculations were based on the assumption that there would be a dif-

ference in thrombosis rates between VP and Qa monitored patients. However, the strict adherence to the surveillance protocols improved our results using VP measurements when compared to our historic controls. Differences in the present study were not statistically significant. The results indicated that continuation of the study was not likely to result in clinically relevant differences.

Secondly, we measured Qa every two months, but repeated the measurement after one month if Qa reached levels between 600 and 800 mL/min. This frequency was mainly based on feasibility considerations. It remains unclear, whether a higher frequency of Qa measurements, as was suggested by others [8,27] would decrease the already low thrombosis rate further. Furthermore, we can not exclude the possibility that decreasing the frequency of VP measurements, for instance every 2 weeks, as was suggested elsewhere [4], would result in identical results.

Additionally, threshold levels for selection for referral may vary. We used a level of 600 mL/min as Qa threshold level for referral. We based our choice on earlier results [35] and the NKF-DOQI considerations [4]. Others have chosen 650 or 750 mL/min [8,27]. This may affect outcome. A recent meta-analysis by Paulson *et al.* [36] concluded that a single Qa measurement did not appear to have enough accuracy to be a clinically useful predictor of graft thrombosis or failure. Furthermore, it has been suggested that a decrease in Qa over time of > 15% is particularly predictive of impending graft failure [29]. The present study was not specifically designed to study that issue. However, in the patients who were monitored by Qa measurements (Group A2 and B2) none of the unpredicted thromboses were preceded by a decrease in Qa of more than 15%. As a consequence, none of these thromboses would have been predicted by this criterion. Furthermore, in the patients who did not reach the threshold levels of the present study but did show a decrease in Qa of more than 15% (n = 11 (A2), n = 8 (B2); average decrease: 1090 mL/min to 740 mL/min) none experienced thrombosis. So, our data do not support the hypothesis that a decrease in Qa of > 15% as selection parameter would confer any benefit when added to either of the Qa protocols. Also, a recent study showed that a decrease in Qa over time had little predictive value [37].

In unmonitored PTFE grafts the total graft access event rate related to thrombosis or stenosis was 1.51 per patient-year [7] of which 1.24 event per patient-year (82%) was caused by thrombosis. In the present studies the total graft event rate (related to thrombosis and stenosis) was 1.88 (range 1.69-2.27). On average, all thrombotic episodes accounted for 0.52 event per patient-year (28%) and the unpredicted thromboses accounted for 0.26 event per patient-year (14%). So, the introduction of a well structured surveillance program resulted in a substantial decrease in interventions for treatment of thrombosis at the expense of an increase of the number of elective interventions, mainly PTA. Our study was not designed as a cost effectiveness analysis. It seems likely, however,

that this shift in type of interventions is associated with a decrease in access related morbidity and mortality.

What may be the implications of the present study for everyday clinical practice? We showed that using the surveillance protocol of this study outcome with respect to thrombosis rate is equal in Qa monitored grafts and in VP monitored grafts and that there is no rationale in combining the two methods. It is important to note that our population contained fewer diabetics than the average US dialysis population. It is possible that this affects outcome, since inflow stenosis (which will not be detected by VP measurements) may occur more frequently in diabetics. Each dialysis center should decide which method is best suitable for their dialysis practice. VP measurements are easy to obtain and require little time investment. However, they need discipline. Qa measurements are more time consuming and a special device is needed. We showed that by measuring Qa every 4 to 8 weeks identical results can be obtained as with weekly VP assessments. The decision which method to use, will be primarily based on the preferences of those involved in the access care and on the possibilities to implement a certain surveillance strategy.

In conclusion, our studies show that standardized monitoring of VP or Qa or the combination of both and subsequent corrective intervention can decrease thrombosis rates to below 0.5 per patient-year, which is recommended by the Vascular Access Task Force of the NKF-DOQI Committee as quality of care standard [4]. When applying the present protocol, VP, Qa, or the combination as variables for selection of patients for corrective intervention are equally effective in reducing thrombosis rates in hemodialysis access grafts.

Acknowledgements

Presented at the 32nd Annual Meeting of the American Society of Nephrology, Miami Beach, Florida, USA, November 5-8, 1999. The authors would like to acknowledge the following contributors: Adri Diepenbroek, Eemland Hospital, Amersfoort; Carry M. van der Beek, Monique M. Harskamp, Eddy van der Weele, Gelderse Vallei, Wageningen; Menno P. Kooistra, Jaap A. Vos, Pieter F. Vos, Dianet, Utrecht; Cees Haaring, UMC, Utrecht.

References

1. Feldman HI, Kobrin S, Wasserstein A: Hemodialysis vascular access morbidity. *J Am Soc Nephrol* 7: 523-535, 1996
2. USRDS. The economic cost of ESRD, vascular access procedures, and Medicare spending for alternative modalities of treatment. United States Renal Data System: *Am J Kidney Dis* 30 (Suppl 1): S160-S177, 1997
3. Feldman HI, Held PJ, Hutchinson JT, Stoiber E, Hartigan MF, Berlin JA: Hemodialysis vascular access morbidity in the United States. *Kidney Int* 43: 1091-1096, 1993
4. NKF-DOQI clinical practice guidelines for vascular access. National Kidney Foundation: *Am J Kidney Dis* 30 (Suppl 3): S152-S191, 1997
5. Beathard GA: Thrombolysis for the treatment of thrombosed dialysis access grafts: a nephrologist's view. *Semin Dial* 8: 162-165, 1995
6. Cayco AV, Abu-Alfa AK, Mahnensmith RL, Perazella MA: Reduction in arteriovenous graft impairment: results of a vascular access surveillance protocol. *Am J Kidney Dis* 32: 302-308, 1998
7. Bosman PJ, Blankestijn PJ, van der Graaf Y, Heintjes RJ, Koomans HA, Eikelboom BC: A comparison between PTFE and denatured homologous vein grafts for haemodialysis access: a prospective randomised multicentre trial. The SMASH Study Group. *Eur J Vasc Endovasc Surg* 16: 126-132, 1998
8. Sands JJ, Jabyac PA, Miranda CL, Kapsick BJ: Intervention based on monthly monitoring decreases hemodialysis access thrombosis. *ASAIO J* 45: 147-150, 1999
9. Bassiouny HS, White S, Glagov S, Choi E, Giddens DP, Zarins CK: Anastomotic intimal hyperplasia: mechanical injury or flow induced. *J Vasc Surg* 15: 708-716, 1992
10. Kanterman RY, Vesely TM, Pilgram TK, Guy BW, Windus DW, Picus D: Dialysis access grafts: anatomic location of venous stenosis and results of angioplasty. *Radiology* 195: 135-139, 1995
11. Roberts AB, Kahn MB, Bradford S, Lee J, Ahmed Z, Fitzsimmons J, Ball D: Graft surveillance and angioplasty prolongs dialysis graft patency. *J Am Coll Surg* 183: 486-492, 1996
12. Safa AA, Valji K, Roberts AC, Ziegler TW, Hye RJ, Oglevie SB: Detection and treatment of dysfunctional hemodialysis access grafts: effect of a surveillance program on graft patency and the incidence of thrombosis. *Radiology* 199: 653-657, 1996
13. Smits HF, Van Rijk PP, Van Isselt JW, Mali WP, Koomans HA, Blankestijn PJ: Pulmonary embolism after thrombolysis of hemodialysis grafts. *J Am Soc Nephrol* 8: 1458-1461, 1997
14. Besarab A, Sullivan KL, Ross RP, Moritz MJ: Utility of intra-access pressure monitoring in detecting and correcting venous outlet stenoses prior to thrombosis. *Kidney Int* 47: 1364-1373, 1995
15. Beathard GA: Percutaneous transvenous angioplasty in the treatment of vascular access stenosis. *Kidney Int* 42: 1390-1397, 1992

16. Schwab SJ, Raymond JR, Saeed M, Newman GE, Dennis PA, Bollinger RR: Prevention of hemodialysis fistula thrombosis. Early detection of venous stenoses. *Kidney Int* 36: 707-711, 1989
17. Sands JJ, Miranda CL: Prolongation of hemodialysis access survival with elective revision. *Clin Nephrol* 44: 329-333, 1995
18. Smits JHM, Blankestijn PJ: Haemodialysis access: the case for prospective monitoring. *Curr Opin Nephrol Hypertens* 8: 685-690, 1999
19. Bosman PJ, Boereboom FT, Smits HF, Eikelboom BC, Koomans HA, Blankestijn PJ: Pressure or flow recordings for the surveillance of hemodialysis grafts. *Kidney Int* 52: 1084-1088, 1997
20. Beathard GA: Mechanical versus pharmacomechanical thrombolysis for the treatment of thrombosed dialysis access grafts. *Kidney Int* 45: 1401-1406, 1994
21. Roberts AC, Valji K, Bookstein JJ, Hye RJ: Pulse-spray pharmacomechanical thrombolysis for treatment of thrombosed dialysis access grafts. *Am J Surg* 166: 221-225, 1993
22. Valji K, Bookstein JJ, Roberts AC, Oglevie SB, Pittman C, O'Neill MP: Pulse-spray pharmacomechanical thrombolysis of thrombosed hemodialysis access grafts: long-term experience and comparison of original and current techniques. *Am J Roentgenol* 164: 1495-1500, 1995
23. Swan TL, Smyth SH, Ruffenach SJ, Berman SS, Pond GD: Pulmonary embolism following hemodialysis access thrombolysis/thrombectomy. *J Vasc Interv Radiol* 6: 683-686, 1995
24. Krivitski NM: Theory and validation of access flow measurement by dilution technique during hemodialysis. *Kidney Int* 48: 244-250, 1995
25. Bosman PJ, Boereboom FT, Bakker CJ, Mali WP, Eikelboom BC, Blankestijn PJ, Koomans HA: Access flow measurements in hemodialysis patients: in vivo validation of an ultrasound dilution technique. *J Am Soc Nephrol* 7: 966-969, 1996
26. Blankestijn PJ, Smits JH: How to identify the haemodialysis access at risk of thrombosis? Are flow measurements the answer? *Nephrol Dial Transplant* 14: 1068-1071, 1999
27. Jindal KK, Ethier JH, Lindsay RM, Barre PE, Kappel JE, Carlisle EJ, Common A: Clinical practice guidelines for vascular access. *J Am Soc Nephrol* 10 (Suppl 13): S297-S305, 1999
28. May RE, Himmelfarb J, Yenicesu M, Knights S, Ikizler TA, Schulman G, Hernanz Schulman M, Shyr Y, Hakim RM: Predictive measures of vascular access thrombosis: a prospective study. *Kidney Int* 52: 1656-1662, 1997
29. Neyra NR, Ikizler TA, May RE, Himmelfarb J, Schulman G, Shyr Y, Hakim RM: Change in access blood flow over time predicts vascular access thrombosis. *Kidney Int* 54: 1714-1719, 1998
30. Wang E, Schneditz D, Nepomuceno C, Lavarias V, Martin K, Morris AT, Levin NW: Predictive value of access blood flow in detecting access thrombosis. *ASAIO J* 44: M555-M558, 1998
31. Besarab A, Frinak S, Sherman RA, Goldman J, Dumler F, Devita MV, Kapoian T, Al-Saghir F, Lubkowski T: Simplified measurement of intra-access pressure. *J Am Soc Nephrol* 9: 284-289, 1998

32. Allon M, Bailey R, Ballard R, Deierhoi MH, Hamrick K, Oser R, Rhynes VK, Robbin ML, Saddekni S, Zeigler ST: A multidisciplinary approach to hemodialysis access: prospective evaluation. *Kidney Int* 53: 473-479, 1998
33. Besarab A, Dorrell S, Moritz M, Michael H, Sullivan K: Determinants of measured dialysis venous pressure and its relationship to true intra-access venous pressure. *ASAIO Trans* 37: M270-M271, 1991
34. Luik AJ, Struijk DG, Gladziwa U, von Olden RW, von Hooff JP, de Leeuw PW, Leunissen KM: Diurnal blood-pressure variations in haemodialysis and CAPD patients. *Nephrol Dial Transplant* 9: 1616-1621, 1994
35. Bosman PJ, Boereboom FTJ, Eikelboom BC, Koomans HA, Blankestijn PJ: Graft flow as a predictor of thrombosis in hemodialysis grafts. *Kidney Int* 54: 1726-1730, 1998
36. Paulson WD, Ram SJ, Birk CG, Work J: Does blood flow accurately predict thrombosis or failure of hemodialysis synthetic grafts? A meta-analysis. *Am J Kidney Dis* 34: 478-485, 1999
37. Paulson WD, Ram SJ, Birk CG, Zapczynski M, Martin SR, Work J: Accuracy of decrease in blood flow in predicting hemodialysis graft thrombosis. *Am J Kidney Dis* 35: 1089-1095, 2000

Chapter 4

Hemodialysis access imaging: comparison of flow-interrupted contrast-enhanced MR angiography and digital subtraction angiography

Johannes H.M. Smits[1], Clemens Bos[2], Otto E.H. Elgersma[2],
Wil A.M.A. van der Mark[1], Peter J. Blankestijn[1], Chris J.G. Bakker[2],
Jan J. Zijlstra[2], Willem P.Th.M. Mali[2]

[1] Department of Nephrology, University Medical Center, Utrecht
[2] Department of Radiology, University Medical Center, Utrecht

Abstract

Background. To compare flow-interrupted contrast-enhanced magnetic resonance angiography (CE-MRA) in hemodialysis access imaging with conventional digital subtraction angiography (DSA).

Methods. Twenty-two accesses (14 AVG, 8 AVF) in eighteen patients were imaged with flow-interrupted CE-MRA and subsequent conventional DSA. Anastomotic diameters in AVG and post-anastomotic diameter in AVF were measured and set out against an adjacent normal segment. Lumen reduction at MRA and DSA was assessed independently by two radiologists. Lumen reductions were compared with Pearson correlation. Inter-observer agreement was analyzed with Kappa (κ) statistics.

Results. Image quality obtained with flow-interrupted CE-MRA was considered excellent in 77%, and good in 23%. Pearson correlation coefficient between MRA and DSA was 0.79 (Obs. 1) and 0.82 (Obs. 2) ($P < 0.0001$). Inter-observer agreement showed a κ of 0.67 for MRA and 0.93 for DSA. MRA lumen reductions were on average slightly higher than DSA scores by both observers (3.7% and 5.7%).

Conclusion. Flow-interrupted CE-MRA is capable of adequate hemodialysis vascular access imaging. Flow-interrupted CE-MRA image quality and anatomical depiction is comparable with DSA.

Introduction

Thrombosis remains the most important complication in hemodialysis arteriovenous fistulae (AVF) and grafts (AVG) with an incidence of 0.5 - 2.5 per patient-year [1-6]. Stenosis due to progressive intimal hyperplasia is associated with vascular access thrombosis [7-11]. Several surveillance tools have been introduced that offer the ability to identify vascular accesses at risk of thrombosis [1,12,13]. To treat a failing access (either by percutaneous transluminal angioplasty (PTA) or by surgical intervention [1]), it is necessary to identify the underlying problem, i.e. in most cases one or more stenoses, predominantly found at the anastomosis of an AVF and at the venous anastomosis of an AVG [7-11]. The conventional technique to identify and locate stenosis has predominantly been digital subtraction angiography (DSA). However, there are several drawbacks: the radiation load for the patient and radiology personnel, the use of potentially nephrotoxic iodinated contrast agents, and limited spatial information [14]. Magnetic resonance angiography (MRA) does not have these disadvantages and could offer an attractive alternative. In addition, MRA offers the possibility to measure access flow. Access flow has been shown to be a better parameter for impending vascular access failure than anatomical information alone [6,12,15].

However, a major problem with flow-based approaches to MRA, such as phase-contrast (PC) and time-of-flight (TOF), has always been the frequent occurrence of flow artifacts

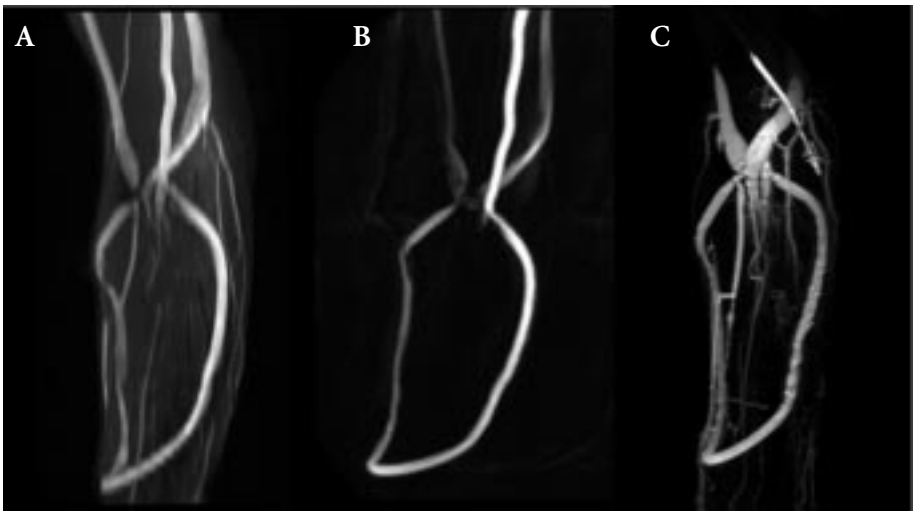

Figure 1. Evolution in MRA of the hemodialysis access: A.) time-of-flight MRA, B.) phase-contrast MRA, C.) flow-interrupted contrast-enhanced MRA

in regions with disturbed flow that complicate interpretation of the MR angiograms. Especially near stenoses (but also near bends and cusps [16]), the appearance of the lumen is distorted by a combination of dephasing, displacement and, for TOF methods, saturation artifacts [17]. Application of PC and TOF to hemodialysis accesses, i.e. both AVF and AVG, also suffers from the above types of inaccuracies [18,19], but interpretation of the angiograms is further complicated by the large range of flow rates that occurs in these vessels: roughly 100 - 3000 ml/min. As flow disturbances tend to increase with flow rate, signal voids may easily arise at mild narrowings or sharp-angled anastomoses, when a high flow rate is present [20].
Contrast-enhanced (CE) MR angiography is less sensitive to these artifacts [21], and has been reported to improve hemodialysis access visualization, when compared to TOF and PC [22]. However, flow related artifacts remain present under the extreme flow conditions that occur in hemodialysis accesses [23]. To eliminate these artifacts, we borrow from the procedure used for DSA of the hemodialysis access, and use a cuff to obstruct the blood flow temporarily (Figure 1) [24,25]. We recently described the technical details of this flow-interrupted CE-MRA imaging technique [23].
This study was designed to validate our MRA technique anatomically, and for this purpose we compared anastomotic (AVG) and post-anastomotic diameters (AVF) of MRA images obtained with flow-interruption and selective contrast administration with those diameters scored on conventional DSA imaging of hemodialysis accesses.

Patients and methods

Between March 2000 and March 2001 18 hemodialysis patients with functioning vascular accesses were included. Twenty-two MRA/DSA series were made in these patients. Eleven patients (3 M, 8 F) had an AVG. A total of 14 MRA/DSA series were made in these patients. Seven patients had an AVF (all male), with eight MRA/DSA series. Mean age for the AVG patients was 56.1 ± 16.3 years, and 59.9 ± 16.9 for the AVF patients. The study was approved by our institutional ethical review board. Informed consent was obtained from all patients. All patients underwent MR angiography including MR flow measurement and subsequent DSA on the same day.

Imaging Techniques

MRA

All examinations were performed on a 1.5-T clinical scanner (Gyroscan ACS-NT, Philips Medical Systems, Best, The Netherlands). Patients were imaged in supine position, entering the scanner feet-first to facilitate communication with the physician at the front of the scanner. A 17-gauge plastic needle (Clampcath, Medikit Co., Tokyo) was inserted in

the hemodialysis access and fixed with tape. Two luerlock syringes, 20 or 30 ml each, containing twentyfold diluted Gd-DTPA (Magnevist, Schering, Berlin, Germany) in saline were connected to the needle via 100-cm luerlock tubing. An MR-compatible cuff was wrapped around the upper arm and fixed with a strap. A rectangular surface coil of 10 × 40 cm was positioned on the forearm of the patient for signal reception.
First, three orthogonal two-dimensional (2D) phase-contrast surveys were obtained. Filling of the access with contrast was monitored using a fast 2D spoiled gradient echo sequence with complex mask subtraction, providing one image every 0.9 seconds. Care was taken to select an imaging plane showing the arterial and venous limbs of the access well separated.
The images were reconstructed immediately and were presented to the radiologist on an LCD-screen in the scanner room. A 3D image of the access was acquired using a spoiled gradient echo with centric k-space order. Scan parameters included: repetition time 6.1 msec, echo time 1.8 msec, excitation angle 45º, field-of-view 400 × 100 mm, acquisition matrix 512 × 100. The volume consisted of 64 1.0-mm partitions that were zero-filled and reconstructed every 0.5 mm. The volume had a sagittal orientation to prevent overlap from the trunk. More slices were added if necessary to cover the left-right extent of the access. Scan time was 38 to 48 seconds.

We first reduced access flow by inflating the cuff to diastolic blood pressure. Then, contrast was hand-injected until the access downstream of the puncture site was adequately filled. Next, the flow in the access was blocked, by increasing the cuff pressure to well above the systolic pressure, enabling retrograde filling of the upstream part of the access, the arterial anastomosis and the native artery. When the filling of the access was sufficient and stable on the complex subtraction images, we proceeded to the 3D acquisition. After completion of the acquisition, the cuff was released.

DSA
DSA was performed on dedicated angiography equipment (DVI-s and Integris 3000, Philips Medical Systems, Best, The Netherlands). The DSA studies were performed by experienced radiologists who were aware of the clinical information regarding vascular access function and with access to previously performed DSA studies. Our standard DSA imaging strategy comprises of at least four DSA series in fistulae and five in grafts. One series was made to visualize the loop of the graft. The second series visualized the arterial anastomosis by injecting iodinated contrast agent (Ultravist, Schering, Berlin, Germany) into the arterial limb of the graft during upper arm cuff compression of about 200 mmHg. This ensured adequate filling of the arterial anastomosis. Then the venous anastomosis and part of the upper arm veins were visualized. A further two series were per-

formed to visualize the veins up to the superior caval vein. In case of overprojection of the anastomoses, additional projections of the anastomotic areas were made.

Image Analysis

Image quality was assessed on the scale of excellent, good, or non-diagnostic. Both the DSA and MRA multi-planar reformat (MPR) images were blindly reviewed by two experienced vascular radiologists independently. For the DSA, all lumen diameters were measured on the hard-copies with a mechanical caliper with a digital display (PAV Electronics, Vaduz, Liechtenstein). For MRA, the data were presented on a console (EasyVision, Philips Medical Systems, Best, The Netherlands). The lumen diameters were measured from vessel cross-sections that were created by multi-planar reformatting of the volume data perpendicular to the vessel axis.

For comparison, we took the vascular access segments that were easily definable and were responsible for most clinical problems. For AVF, we only scored the narrowest diameter near the anastomosis (within three centimeter) and compared it with the diameter of a normal segment of the vein downstream. This resulted in one ratio number for the AVF, from which the relative degree of stenosis was calculated.

For AVG, the narrowest diameter of the arterial anastomosis was divided by a normal arterial graft segment nearby the anastomosis, and the narrowest segment of the venous anastomosis was divided by a close-by normal segment of the graft. Therefore, two ratio measurements were done per AVG per observer per imaging method. The degree of stenosis was calculated from these ratios.

Statistical analysis

Correlations between the imaging methods were assessed with calculation of the Pearson correlation coefficients (r). Furthermore, findings were categorized in the following lumen reduction percentages: 0% - 49%, 50% - 74%, and 75% - 99%, and 100%. Kappa (κ) coefficients were calculated based on these categories. Inter-observer variation was measured for MRA and DSA. A P value < 0.05 was considered statistically significant.

Results

Twenty-two vascular accesses in 18 patients were depicted with conventional DSA and contrast-enhanced flow-interrupted MR angiography. In one case, patient movement during the scan resulted in non-diagnostic image quality of the MRA image. Five of the MRA series were considered of good diagnostic quality, and 16 were considered to be of excellent quality for diameter assessment. Therefore, 21 MRA series remained for comparison. For AVF, seven lumen reductions were measured for each imaging method per

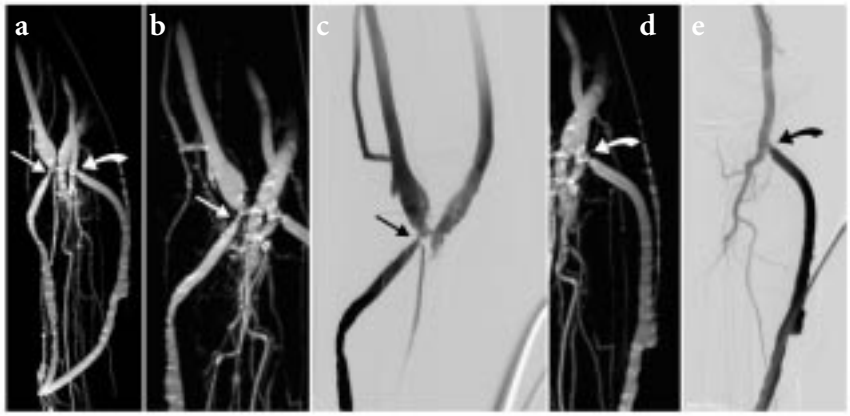

Figure 2. Contrast-enhanced MRA and DSA of an AV graft. Coronal maximum intensity projection provides an overview of the graft (a). Oblique maximum intensity projection of the CE-MRA data set (b) and conventional angiogram (c) demonstrate a stenosis at the venous anastomosis (straight arrows). At the arterial anastomosis (curved arrows), oblique maximum intensity projection of the CE-MRA data set (d) and conventional angiogram (e) show a mild stenosis. In addition, CE-MRA clearly delineates the narrowing of the venous limb of the graft, the puncture aneurysm at the arterial limb, and the dilated native veins downstream of the anastomosis.

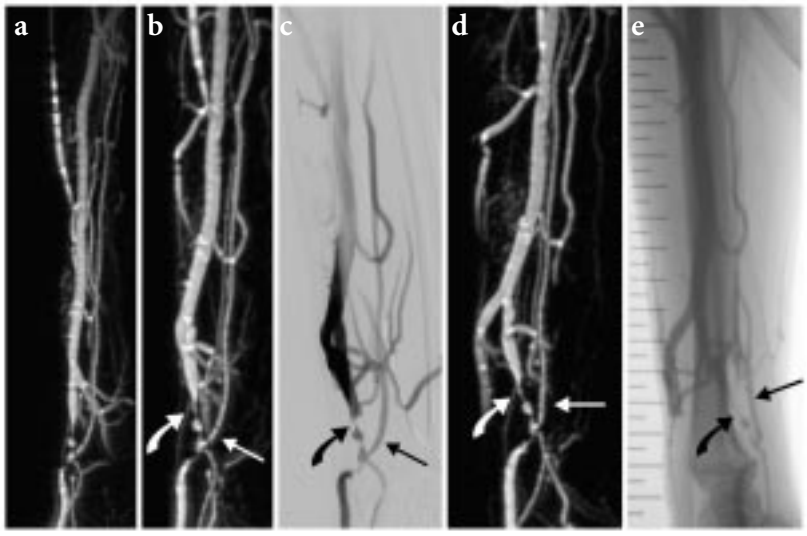

Figure 3. Contrast-enhanced MRA and DSA of a AV Brescia-Cimino fistula. Coronal maximum intensity projection provides an overview of the fistula (a). Oblique coronal view of the CE-MRA data (b) with corresponding conventional angiogram (c), and oblique saggital view of the CE-MRA data (d) with corresponding conventional angiogram (e). The images clearly show the native artery (straight arrows), the side-to-side anastomosis and the stenoses in the venous part of the access (curved arrows).

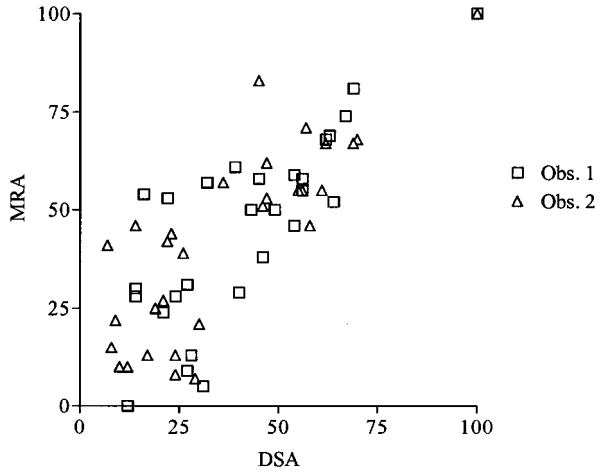

Figure 4. Scatter plots show measurements of maximum stenosis percentage obtained at MRA versus those obtained at conventional DSA by observer 1 (r = 0.79) and observer 2 (r = 0.82)

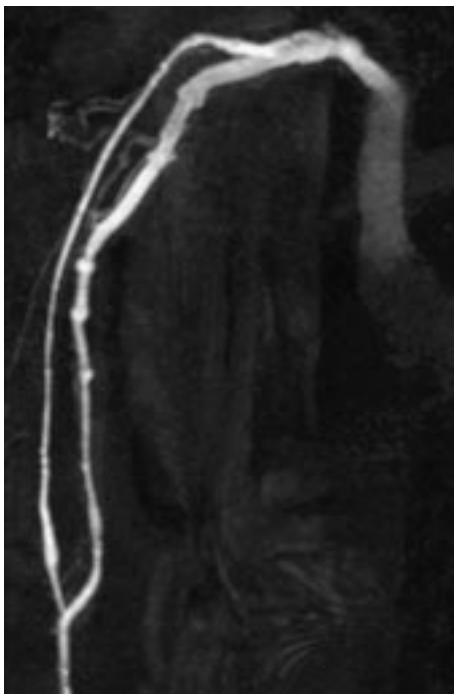

Figure 5. Example of the CE-MRA of an outflow tract up to the superior vena cava

Table 1. Inter-observer agreement shown as categorized lumen reduction measurements of maximum stenosis scores at MRA ($\kappa = 0.67$) versus DSA ($\kappa = 0.93$)

	MRA Obs. 2				
MRA Obs. 1	0% - 49%	50% - 74%	75% - 99%	100%	Total
0% - 49%	**11**	1	0	0	12
50% - 74%	4	**11**	0	0	15
75% - 99%	0	0	**0**	0	0
100%	0	0	0	**1**	1
Total	15	12	0	1	**28**

	DSA Obs. 2				
DSA Obs. 1	0% - 49%	50% - 74%	75% - 99%	100%	Total
0% - 49%	**21**	0	0	0	21
50% - 74%	1	**9**	0	0	10
75% -99%	0	0	**0**	0	0
100%	0	0	0	**0**	0
Total	22	9	0	0	**31**

observer. In AVG, MRA stenotic ratios could be calculated in 21 segments (28 expected): seven could not be measured because of the following reasons: 3 venous anastomoses were extended to the axilla and were therefore not imaged, 3 arterial anastomoses were not depicted because fill-up was not complete, and one venous anastomosis was compressed under the cuff during MRA examination. DSA stenotic ratios could be calculated in 24 segments (28 expected); four ratios could not be calculated because the AV grafts were extended to more proximal veins and these segments were not adequately depicted. Access flow measured with MRA was 890 ± 449 mL/min in AVG, and 677 ± 384 mL/min in AVF. Examples of the image quality are given in Figure 2 and 3 for AVG and AVF respectively.

Pearson analysis of the MRA data sets with the corresponding DSA data sets revealed a significant correlation between both methods by both observers (Figure 4, $r = 0.79$ and $r = 0.82$ respectively, both $P \leq 0.0001$). The observers measured on average more severe lumen reductions at the MRA when compared to DSA: +3.7% (2.8% SEM) for observer 1, and +5.7% (2.6% SEM) for observer 2. Categorical scores are shown in Table 1. Inter-observer categorical analysis revealed a κ of 0.67 for MRA and 0.93 for DSA.

Discussion

This study shows that a selective MR angiography technique is able to deliver high quality visualization of hemodialysis AVG and AVF. Flow artifacts are eliminated by temporarily interrupting the blood flow, as is common practice in DSA examinations of hemodialysis accesses [25]. Up to now, flow artifacts have seriously hampered MRA of AVG and AVF [18,20], since the large variation of flow rates in these vessels, between patients but also in the course of time, made it hard to assess whether a signal narrowing was realistic or flow related.

Compared to DSA, flow-interrupted contrast-enhanced MRA shows an excellent correlation when the most problematic areas (i.e. the anastomoses) are evaluated. This finding was expected, since both imaging methods fill-up the lumen of the graft with contrast-agents. In some early experiments with this new technique, we found contrast layering along the vessel wall. After adjusting the technique by injecting the contrast solution more rapidly, this artifact disappeared. Also, the time required for an entire MRA sequence decreased from about 40 minutes in the early cases of this study to 30 minutes after obtaining more experience. This difference in duration can be explained by improvements in planning of the sequence.

Previous studies that compared non-contrast-enhanced MRA in vascular accesses [18,19] or contrast-enhanced non-flow interrupted MRA in other vascular beds [26] showed an overestimation of stenosis assessment. In this study a slightly higher degree of stenosis (maximally about 5.7%) by MRA when compared to DSA still exists. Possibly, DSA underestimates lumen reduction, which is conceivable, since the percentage stenosis can only be assessed by DSA in one or two directions. Another explanation for this phenomenon could be that MRA overestimates the real stenosis because of the limited spatial resolution [27]. However, the differences between both techniques were minimal and for clinical stenosis assessment both techniques suffice.

This study further shows that direct injection strongly reduces the required contrast dose, and thus offers the possibility to repeat the exam without the need for large contrast dosages. The issue of synchronizing acquisition and peak contrast concentration, which is a problem of intravenously injected 3D CE-MRA, is circumvented.

MRA has a number of benefits with respect to DSA, the present method of choice for anatomic hemodialysis access evaluation. The images acquired are three-dimensional and can be reformatted to show the access from arbitrary projection angles. As stated in a previous paragraph, this is very useful, as it is hard to define a standard view for these vascular constructs of varying geometry [25]. A major asset of MR is its capability of a functional evaluation of the access by measuring the flow rate [5]. Low values of the access flow rate are indicative of increased risk of thrombosis [5,28-30], and may prompt for radiological intervention in case of an underlying stenosis [6]. Ideally, when a low

access flow is measured and the underlying stenosis is located by MRA, a PTA procedure is done during the same procedure. Some attempts have been made to provide this one-shop-stop approach with MRA [20].
The contrast agent used, Gd-DTPA, has an excellent safety profile and is considered at least as safe as iodinated contrast agents [31]. Gd-DTPA is not contraindicated for use in patients with impaired renal function [32,33], and can be removed by hemodialysis [34]. Finally, patients and physicians are not exposed to ionizing radiation.
A clear advantage of DSA over MRA is the possibility to perform the corrective intervention on the spot, should a hemodynamically significant stenosis be detected. Techniques for MR-guided endovascular interventions still have to be developed further to provide a clinically attractive alternative [35]. In addition, a complete angiographic evaluation of the graft or fistula on DSA includes visualization of the run off vessels to the superior vena cava [25]. Indeed, several studies show that in a small number of patients stenoses are found in the venous outflow tract [7,36]. A recent report indicates that images of the run off veins of the extremities can be obtained using CE-MRA, as well [37]. The acquisition is started directly after intravenous injection of the contrast agent, instead of waiting for the venous phase following the first arterial passage.
Although our study was not primarily focused on imaging of the outflow tract to the superior vena cava, we nevertheless performed outflow tract examination by injecting 30 - 40 ml of diluted Gd-DTPA in 6 patients. Figure 5 shows an example of the CE-MRA of an outflow tract. The results were quite promising. The total outflow tract was visualized in a single scan, whereas a typical DSA outflow tract image would require at least two images.
In conclusion, selective flow-interrupted CE-MRA imaging can provide excellent quality images of hemodialysis AVF and AVG, which are free of flow artifacts. The high image quality of the MR angiograms is comparable with DSA. In combination with MR flow quantification and imaging of the outflow tract, our approach may provide a complete anatomical and functional evaluation of hemodialysis accesses on MR.

Acknowledgements

Parts of this paper were presented at the ASN/ISN World Congress of Nephrology, San Francisco, California, USA, October 13-17, 2001. The authors would like to acknowledge the participating radiology personnel, and especially Tineke Kievit from the Radiology Trialbureau for the planning of the MRA and DSA sessions.

References

1. National Kidney Foundation. K/DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 37 (Suppl 1): S137-S181, 2001
2. Beathard GA: Thrombolysis versus surgery for the treatment of thrombosed dialysis access grafts. *J Am Soc Nephrol* 6: 1619-1624, 1995
3. Wilson SE: Vascular access: principles and practice, 3rd ed. Missouri: Mosby-Year Book, Inc., 1996
4. Cayco AV, Abu-Alfa AK, Mahnensmith RL, Perazella MA: Reduction in arteriovenous graft impairment: results of a vascular access surveillance protocol. *Am J Kidney Dis* 32: 302-308, 1998
5. Bosman PJ, Boereboom FTJ, Eikelboom BC, Koomans HA, Blankestijn PJ: Graft flow as a predictor of thrombosis in hemodialysis grafts. *Kidney Int* 54: 1726-1730, 1998
6. Sands JJ, Jabyac PA, Miranda CL, Kapsick BJ: Intervention based on monthly monitoring decreases hemodialysis access thrombosis. *ASAIO J* 45: 147-150, 1999
7. Kanterman RY, Vesely TM, Pilgram TK, Guy BW, Windus DW, Picus D: Dialysis access grafts: anatomic location of venous stenosis and results of angioplasty. *Radiology* 195: 135-139, 1995
8. Roberts AB, Kahn MB, Bradford S, Lee J, Ahmed Z, Fitzsimmons J, Ball D: Graft surveillance and angioplasty prolongs dialysis graft patency. *J Am Coll Surg* 183: 486-492, 1996
9. Safa AA, Valji K, Roberts AC, Ziegler TW, Hye RJ, Oglevie SB: Detection and treatment of dysfunctional hemodialysis access grafts: effect of a surveillance program on graft patency and the incidence of thrombosis. *Radiology* 199: 653-657, 1996
10. May RE, Himmelfarb J, Yenicesu M, Knights S, Ikizler TA, Schulman G, Hernanz Schulman M, Shyr Y, Hakim RM: Predictive measures of vascular access thrombosis: a prospective study. *Kidney Int* 52: 1656-1662, 1997
11. Smits HF, Van Rijk PP, Van Isselt JW, Mali WP, Koomans HA, Blankestijn PJ: Pulmonary embolism after thrombolysis of hemodialysis grafts. *J Am Soc Nephrol* 8: 1458-1461, 1997
12. Smits JHM, Blankestijn PJ: Haemodialysis access: the case for prospective monitoring. *Curr Opin Nephrol Hypertens* 8: 685-690, 1999
13. Smits JHM, van der Linden J, Hagen EC, Modderkolk-Cammeraat EC, Feith GW, Koomans HA, van den Dorpel MA, Blankestijn PJ: Graft surveillance: venous pressure, access flow, or the combination? *Kidney Int* 59: 1551-1558, 2001
14. Bettmann MA, Heeren T, Greenfield A, Goudey C: Adverse events with radiographic contrast agents: results of the SCVIR Contrast Agent Registry. *Radiology* 203: 611-620, 1997
15. Lumsden AB, MacDonald MJ, Kikeri D, Cotsonis GA, Harker LA, Martin LG: Prophylactic balloon angioplasty fails to prolong the patency of expanded polytetrafluoroethylene arteriovenous grafts: results of a prospective randomized study. *J Vasc Surg* 26: 382-390, 1997

16. Saloner D, van Tyen R, Dillon WP, Jou LD, Berger SA: Central intraluminal saturation stripe on MR angiograms of curved vessels: simulation, phantom, and clinical analysis. *Radiology* 198: 733-739, 1996
17. Bradley WGJ: Flow phenomena. In: Stark DD, Bradley WGJ, eds. Magnetic Resonance Imaging, 2nd ed. St. Louis: Mosley Year Book, 1992; pp 253-298
18. Gehl HB, Bohndorf K, Gladziwa U, Handt S, Gunther RW: Imaging of hemodialysis fistulas: limitations of MR angiography. *J Comput Assist Tomogr* 15: 271-275, 1991
19. Waldman GJ, Pattynama PM, Chang PC, Verburgh C, Reiber JH, de Roos A: Magnetic resonance angiography of dialysis access shunts: initial results. *Magn Reson Imaging* 14: 197-200, 1996
20. Smits HFM: Radiological diagnosis and treatment of hemodialysis access graft dysfunction. Thesis University Utrecht, ISBN 90-6464-5329, 2000
21. Prince MR: Gadolinium-enhanced MR aortography. *Radiology* 191: 155-164, 1994
22. Thurnher S: Magnetic resonance angiography of hemodialysis fistulas and grafts. *Semin Interv Radiol* 14: 101-110, 1997
23. Bos C, Smits JH, Zijlstra JJ, van der Mark WA, Blankestijn PJ, Bakker CJ, Viergever MA, Mali WP: MRA of hemodialysis access grafts and fistulae using selective contrast injection and flow interruption. *Magn Reson Med* 45: 557-561, 2001
24. Anderson CB, Gilula LA, Harter HR, Etheredge EE: Venous angiography and the surgical management of subcutaneous hemodialysis fistulas. *Ann Surg* 187: 194, 1977
25. Chait A: Angiography of dialysis shunts. In: Baum S, ed. Abram's angiography; vascular and interventional radiology, 4th ed. Boston: Little, Brown and Company, 1997; pp 1767-1778
26. Arlart IP, Bongartz GM, Marchal G: Magnetic resonance angiography, 1st ed. Berlin: Springer-Verlag, 1996
27. Hoogeveen RM, Bakker CJ, Viergever MA: Limits to the accuracy of vessel diameter measurement in MR angiography. *J Magn Reson Imaging* 8: 1228-1235, 1998
28. Sands J, Young S, Miranda C: The effect of Doppler flow screening studies and elective revisions on dialysis access failure. *ASAIO J* 38: M524-M527, 1992
29. Wang E, Schneditz D, Nepomuceno C, Lavarias V, Martin K, Morris AT, Levin NW: Predictive value of access blood flow in detecting access thrombosis. *ASAIO J* 44: M555-M558, 1998
30. Jindal KK, Ethier JH, Lindsay RM, Barre PE, Kappel JE, Carlisle EJ, Common A: Clinical practice guidelines for vascular access. *J Am Soc Nephrol* 10 (Suppl 13): S297-S305, 1999
31. Niendorf HP, Haustein J, Cornelius I, Alhassan A, Clauss W: Safety of gadolinium-DTPA: extended clinical experience. *Magn Reson Med* 22: 222-228, 1991
32. Runge VM: Safety of approved MR contrast media for intravenous injection. *J Magn Reson Imaging* 12: 205-213, 2000
33. Prince MR, Arnoldus C, Frisoli JK: Nephrotoxicity of high-dose gadolinium compared with iodinated contrast. *J Magn Reson Imaging* 6: 162-166, 1996

34. Choyke PL, Girton ME, Vaughan EM, Frank JA, Austin HA, III: Clearance of gadolinium chelates by hemodialysis: an in vitro study. *J Magn Reson Imaging* 5: 470-472, 1995
35. Smits HF, Bos C, van der Weide R, Bakker CJ: Interventional MR: vascular applications. *Eur Radiol* 9: 1488-1495, 1999
36. Turmel-Rodrigues L, Pengloan J, Baudin S, Testou D, Abaza M, Dahdah G, Mouton A, Blanchard D: Treatment of stenosis and thrombosis in haemodialysis fistulas and grafts by interventional radiology. *Nephrol Dial Transplant* 15: 2029-2036, 2000
37. Li W, David V, Kaplan R, Edelman RR: Three-dimensional low dose gadolinium-enhanced peripheral MR venography. *J Magn Reson Imaging* 8: 630-633, 1998

Chapter 5

Short- and long-term functional effect of percutaneous transluminal angioplasty in hemodialysis vascular access

Johannes H.M. Smits[1], Joke van der Linden[2], Jan H. Assink[3], Derk W. Wolterbeek[4], Jan J. Zijlstra[5,6], Gijs M.Th. de Jong[3], Marinus A. van den Dorpel[2], Peter J. Blankestijn[1]

1 Department of Nephrology, University Medical Center, Utrecht
2 Department of Internal Medicine, Medisch Centrum Rijnmond-Zuid, loc. Clara, Rotterdam
3 Department of Internal Medicine, Albert Schweitzer Ziekenhuis, Dordrecht
4 Department of Radiology, Medisch Centrum Rijnmond-Zuid, loc. Clara, Rotterdam
5 Department of Radiology, University Medical Center, Utrecht
6 Department of Radiology, Albert Schweitzer Ziekenhuis, Dordrecht

Abstract

Background. Efficacy of percutaneous transluminal angioplasty (PTA) is usually expressed as the angiographic result. Access flow (Qa) offers a means to quantify the functional effect. This study was performed to evaluate the short-term functional and angiographic effect of PTA and to determine the longevity of the functional effect during follow-up.

Methods. Patients with an arteriovenous graft (AVG) or fistula (AVF) eligible for PTA (Qa < 600 mL/min) were included. Ultrasound-dilution derived Qa was measured shortly before PTA and periodically after PTA, starting 1 week after the procedure. The short-term effect was expressed as the increase in Qa and as the reduction of stenosis. The long-term effect was expressed as patency and as the decline in Qa after PTA.

Results. Ninety-eight PTA procedures in 60 patients (65 AVG, 33 AVF) were analyzed. Qa improved from 371 ± 17 to 674 ± 30 mL/min in AVG, and from 304 ± 24 to 638 ± 51 mL/min in AVF (both $P < 0.0001$). In 66% (AVG) and 50% (AVF) flow increased to levels > 600 mL/min. Degree of stenosis decreased from 65 ± 3% to 17 ± 2% in AVG and from 72 ± 5% to 23 ± 7% in AVF (both $P < 0.005$). Reduction of stenosis did not correlate with ΔQa ($r^2 = 0.066$). Six-month unassisted patency after PTA was 25% for AVG and 50% for AVF. Decline in Qa was 3.7 ± 0.8 ml/min/day in AVG and 1.8 ± 0.9 ml/min/day in AVF. Qa before PTA and ΔQa correlated with the subsequent decline in Qa ($P < 0.005$).

Conclusions. Access flow increases after PTA, however in a substantial percentage not to a level > 600 mL/min. Qa before PTA and the increase in Qa correlated with long-term outcome, whereas angiographic results did not. The present data combined with the literature suggest that there is an optimal timing for PTA.

Introduction

Vascular access complications account for considerable morbidity and mortality in hemodialysis patients. In the United States they are responsible for up to 25% of all hospitalizations in dialysis patients [1-3]. The European Dialysis and Transplant Association does not collect data on this issue, but it is likely that data in Europe and elsewhere will be comparable.

Thrombosis is the leading cause of vascular access complication. It is almost always associated with the presence of stenosis. Percutaneous transluminal angioplasty (PTA) is an accepted treatment of stenotic lesions [3]. Routine surveillance programs for the early detection of stenoses followed by angioplasty have been shown to substantially reduce the number of thromboses per patient year [4-7]. However, repetitive PTA treatment is often necessary, since re-stenosis frequently occurs. Although the short term success rates of PTA range from 85% to 98% [8], patency at 6 months follow-up varies from 38% to 63% [4,9-11].

Several studies have shown that angiographic degree of the stenotic lesion before and after PTA is poorly related with its subsequent patency [9,11-14]. Recently, the SCVIR Technology Assessment Committee recommended that PTA efficacy should be expressed by both angiographic and functional parameters [15]. In particular, access flow (Qa) measurements offer the opportunity to quantify and follow up the functional effect of PTA.

The purpose of this study is to assess access function of patients undergoing PTA. We quantified the short-term functional and angiographic effect of PTA. Additionally, we determined the longevity of the functional effect during follow-up. Finally, we addressed the question whether functional variables are predictive for long-term outcome.

Patients and methods

This prospective observational intervention study was done in 9 Dutch hemodialysis centers, in which a well-defined surveillance protocol was instituted as part of the routine patient care. All chronic hemodialysis patients with permanent arteriovenous grafts (AVG) and fistulae (AVF), who were referred for angiography because predetermined Qa threshold levels were reached, were eligible to enter the study. The surveillance protocol included periodic Qa measurements and angiography with PTA in thus selected patients.

Qa surveillance protocol

Qa was measured at least every 8 weeks using the ultrasound hemodilution technique (Transonic Systems Inc, Ithaca NY). The bench and clinical validations are presented elsewhere [16,17]. The surveillance protocol has been discussed in detail previously [7]. In brief, Qa determination consisted of the average of three single measurements within

the first 30 minutes of the dialysis session at a fixed pump flow (> 200 mL/min). If Qa levels reached values between 600 and 800 mL/min the measurement was repeated at least every 4 weeks. Patients were referred for angiography whenever Qa was below 600 mL/min. Patients referred for angiography based on other criteria, for instance frequent miscanulation, swelling of the arm or high venous pressure, were excluded. Patients with a history of allergy to iodinated contrast agents were also not included into the study.

Angiography and percutaneous transluminal angioplasty (PTA)

Angiography and PTA procedures were done as soon as possible (usually < 7 days) after the low Qa level (< 600 mL/min) was diagnosed. Digital subtraction angiography was performed to visualize the complete vascular access and to locate the stenosis. Any luminal reduction of 50% or more was treated by percutaneous transluminal angioplasty (PTA) during the same session. The same PTA technique was used for all patients. First, the stenotic lesion was crossed with a guide wire (Boston Scientific Corporation, Watertown, MA). Then a sheath was introduced (Cordis Europe N.V., Roden, The Netherlands). The PTA balloon catheter was then passed over the guide wire to the location of the stenosis. In general, the high-pressure balloons had a diameter of 6 mm although larger balloons (up to 10 mm) could be used for large proximal veins (Bülach, Switzerland). At the stenotic site the balloon was inflated to at least 10 atmospheres of pressure and held for approximately 2 minutes. In resistant cases pressures up to 20 atmospheres were used and held for 10 minutes. No heparin, vasodilators or local anesthetics were given during the procedure. Immediately after PTA an angiogram was obtained to evaluate the result of the procedure. The interventional radiologist considered the PTA procedure successful when the residual diameter of the stenosis was less than 25%. After PTA, Qa measurements were done within one week and then at least at 4 weeks intervals. In case Qa fell below 600 mL/min, patients were referred for angiography and repeat PTA was performed if necessary.

Outcome variables and statistical analysis

The short-term functional effect of PTA on Qa was evaluated by calculation of ΔQa, i.e. the difference between Qa before (Qa_{pre}) and just after PTA (Qa_{post}). The long-term functional effect was assessed as the time to the next intervention, if applicable. When there were 3 or more Qa measurements after the PTA, the decline in Qa was determined (in ml/min/day). Resistance was calculated as the ratio of mean arterial blood pressure (MAP) and Qa. Angiographic data were analyzed by an independent radiologist. Only cases that had adequate biplanar angiograms available of the stenotic areas both before and after PTA were included. Stenosis degree was assessed before (baseline) and after PTA (post-PTA) as the ratio of maximal lumen reduction and an adjacent normal

graft/vessel diameter (expressed in percentage: 0% = no stenosis, 100% = occlusion). Stenosis reduction due to PTA was calculated by the difference between baseline stenosis and post-PTA stenosis.
Data are presented as mean ± SEM, unless indicated otherwise. Differences of Qa and ΔQa values between different time points and subgroups of patients were calculated with two-tailed t-tests. Pearson analysis was used for correlation purposes. Post-PTA primary patency, i.e. the period of time that elapsed following intervention until access thrombosis or re-intervention (surgical and/or radiological), was calculated using life-table analysis. To compare post-PTA survival of AVF and AVG the (two-sided) log-rank test was performed. *P* values of less than 0.05 were considered significant.

Results

Sixty patients referred for angiogram were included. A total of 98 PTA procedures were performed. In 35 patients with an AVG, 65 PTA procedures were done. In the remaining 25 patients with an AVF, 33 PTA procedures were performed. Patient and graft characteristics are shown in Table 1.

Functional results

Short-term. In all cases the first Qa measurement was done within 7 days after PTA, usually during the first dialysis session after PTA.

Table 1. Patient and access characteristics

	AVG	AVF	Total
Patients	35	25	60
Mean age in years (range)	62.7 (37.2 - 82.6)	66.8 (34.6 - 83.7)	64.4 (34.6 - 83.7)
Gender			
Male	6	16	22
Female	29	9	38
Diabetes	9 (26%)	4 (16%)	13 (22%)
Coumarin therapy	19 (54%)	10 (40%)	29 (48%)
Mean age access in days (range)	629 (2 - 1893)	1088 (30 - 2926)	806 (2 - 2926)
Lower arm / upper arm	31 / 4	21 / 4	52 / 8

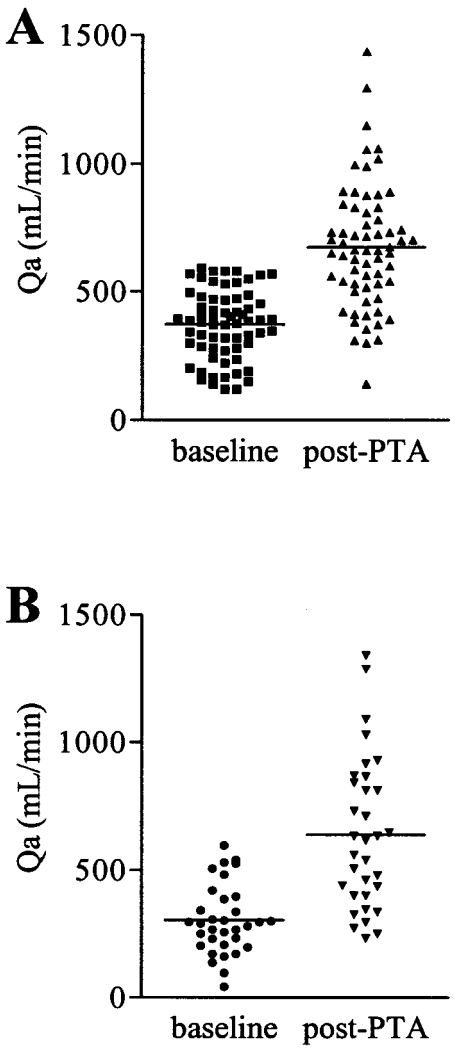

Figure 1. Qa results within one week after PTA in A.) AVG and B.) AVF (both $P < 0.0001$)

In AVG, Qa improved from 371 ± 17 to 674 ± 30 mL/min ($P < 0.0001$). MAP remained stable after PTA (97 ± 2 vs 96 ± 2 mmHg), indicating that the increase in Qa represents a decrease in resistance. Qa_{post} values greater than 600 mL/min were reached in 62% (40/65) (Figure 1A). A negative correlation was found between Qa_{pre} and the ΔQa ($P = 0.0019$, r = -0.38). In diabetics Qa_{pre} did not differ from non-diabetics (340 ± 32 mL/min

Table 2. Number of patients with single and multiple PTA procedures

	AVG	AVF	Total
Single PTA	20 (20)	19 (19)	39 (39)
Multiple PTA	15 (45)	6 (14)	21 (59)
2	5 (10)	4 (8)	9 (18)
3	6 (18)	2 (6)	8 (24)
4	3 (12)	-	3 (12)
5	1 (5)	-	1 (5)
Total	35 (65)	25 (33)	60 (98)

versus 386 ± 19, $P = 0.20$). PTA in diabetics tended to be less effective than in non-diabetics (ΔQa, 228 ± 50 and 337 ± 41 mL/min respectively, $P = 0.06$). The age of the AVG and of the patient did not correlate with ΔQa. In 15 patients multiple procedures were done (Table 2). In patients who were treated twice, ΔQa was 355 ± 68 ml/min and 424 ± 79 ml/min after the first and second PTA respectively (n = 15, P = NS). In patients who were treated 3 times, ΔQa was 315 ± 98, 484 ± 112 and 345 ± 51 ml/min after the first, second and third PTA respectively (n = 10, P = NS). In 15 patients, the PTA was the first intervention on the AVG. ΔQa in those patients did not differ from those who had a second or later PTA (287 ± 61 vs. 313 ± 41 mL/min, $P = 0.72$). Unassisted patency did not differ either.

In AVF, Qa improved from 304 ± 24 to 638 ± 51 mL/min ($P < 0.0001$) (Figure 1B), 52% (17/33) of PTA procedures resulted in Qa_{post} levels of more than 600 mL/min. The ΔQa was not related to Qa_{pre} in AVF (r = -0.06). Diabetes or age of the AVF or patient did not significantly affect the results in AVF. Only four patients underwent 2 PTA procedures (Table 2) and showed a ΔQa of 541 ± 173 mL/min and 285 ± 144 mL/min after the first and second PTA respectively ($P = 0.09$).

Long-term. In 35% of all patients (21/60) multiple procedures were performed. In AVG, repeat PTA was more common than in AVF (43% (15/35) versus 24% (6/25) Table 2). In AVG, the mean time interval to re-PTA was shorter than in AVF (109 ± 12 and 169 ± 32 days, $P = 0.04$). In those with two PTA procedures, time interval between the first and second PTA was 113 ± 18 days (n = 15). In those with three PTA procedures, time interval between the first and second and second and third PTA was 122 ± 26 and 101 ± 21 days respectively (n = 10, P = NS).

Decline in Qa after PTA was 3.7 ± 0.8 ml/min/day in AVG (n = 38) and 1.8 ± 0.9 ml/min/day in AVF (n = 24) ($P = 0.06$). Coumarin use and diabetes did not affect the

decline in Qa after PTA. However, there was a correlation between Qa_{pre} levels and the subsequent decline in Qa after PTA (r = -0.43, $P < 0.005$). Also, ΔQa correlated with the decline in Qa after PTA (r = -0.48, $P = 0.0009$).
The median primary patency after PTA in AVG was 97 days. The post-PTA primary patency rates for AVG were at 1, 3 and 6 months 100%, 56% and 25% respectively. The median patency of AVF was 161 days. Post-PTA primary patency rates for AVF were at 1, 3 and 6 months 100%, 92% and 50% respectively.
Log-rank comparison analysis of intervention-free survival curves demonstrated a significant difference in favor of the AVF ($P = 0.031$).
During the available follow-up period no unpredicted thrombotic events (i.e. accesses thrombosed with a Qa > 600 mL/min) occurred. In 6 AVG with a Qa that remained below 600 mL/min after PTA, thrombosis occurred within weeks after PTA. These are considered predicted thromboses. Furthermore, some thromboses occurred in patients with low Qa while waiting for PTA. These accesses were not included in this analysis, because no PTA procedure was performed.

Angiographic results

In AVG, 48 (74%) PTA procedures were performed on single lesions (38 (58%) venous, 9 (14%) midgraft, and 1 (2%) arterial stenosis). Seventeen (26%) PTA procedures were done on two stenotic lesions (12 (18%) showed a venous and midgraft stenosis, and 5 (8%) had an arterial and venous stenosis). Log rank survival analysis showed no difference in patency between AVG with a single lesion versus those with multiple lesions ($P = 0.74$). Seven (21%) PTA procedures in AVF were of true anastomotic lesions, twenty (61%) were performed on venous lesions (in most cases located within the first few centimeters from the anastomosis) and 6 (18%) on combined (venous and anastomotic) lesions. In 92% of all PTA procedures, angiographic improvement of the stenosis was achieved using a 6-mm balloon. Larger balloons were occasionally needed for proper dilatation of stenoses in proximal AVF veins. In all cases PTA was reported to be successful, i.e. residual luminal reduction of 25% or less.
In AVG, baseline stenosis was 65 ± 3% and post-PTA stenosis 17 ± 2% (n = 33, $P < 0.0001$). No correlation was found between baseline stenosis and post-PTA stenosis (r = -0.14, $P = 0.47$) or Qa_{post} (r = -0.05, $P = 0.76$). Baseline stenosis correlated with Qa_{pre} (r = -0.48, $P = 0.008$). No correlation was found between angiographic (i.e. stenosis reduction) and functional (ΔQa) improvement ($r^2 = 0.066$) or between baseline stenosis and subsequent decline in Qa (r = -0.02, $P = 0.93$). Additionally, neither the stenosis reduction ($P = 0.29$) or the post-PTA stenosis ($P = 0.07$) correlated with the decline in Qa after PTA. Log rank survival analysis of the lower and upper 50th percentile baseline stenosis revealed no difference in survival ($P = 0.90$).

When the AVG group was divided in a group with Qa_{post} < 600 mL/min (n = 24) and a group with Qa_{post} > 600 mL/min (n = 41), we found that there was no difference in angiographic results between both groups. The group with Qa_{post} < 600 mL/min showed a stenosis of 66 ± 4% before and 19 ± 4% after PTA, while the group with Qa_{post} > 600 mL/min had a stenosis of 63 ± 4% before and 14 ± 3% after PTA (*P* = NS). The group with Qa_{post} < 600 mL/min had a Qa_{pre} of 336 ± 24 mL/min and a Qa_{post} of 441 ± 22 mL/min (ΔQa = 105 ± 24 mL/min). Those with Qa_{post} > 600 mL/min had a Qa_{pre} of 392 ± 22 mL/min and a Qa_{post} of 811 ± 29 mL/min (ΔQa = 419 ± 40 mL/min). Of the 24 patients with Qa_{post} < 600 mL/min, 6 thrombosed within 4 weeks after PTA, 8 had a surgical correction without repeat angiogram, in 10 cases repeat angiograms showed 61% stenosis. Two of those patients were subsequently referred for surgical revision, and eight had another PTA.
For the AVF, baseline stenosis was 72 ± 5% and post-PTA stenosis was 23 ± 7% (n = 8, *P* = 0.0039).

Discussion

To our knowledge this is the first study in AVG and AVF reporting both angiographic and functional results of PTA. The present data contain novel information. We show that angiographic results do not correlate with functional results. Importantly, we demonstrate that functional variables are predictive for long-term outcome, whereas angiographic results are not. The study confirms recent data indicating that PTA results in a direct increase in Qa of approximately 250 mL/min [18]. We also confirm that a substantial percentage of PTA is not successful. Finally, time to repeat PTA in the present study is substantially shorter than in other studies [9,18,19]. This suggests a more rapid recurrence of stenosis in the present study. The combined data of these studies suggest that there is an optimal moment of PTA.

Based on the vast experience reported in the literature the NKF-K/DOQI taskforce has suggested PTA as one of the preferred treatments of vascular access stenosis [3]. In most studies, the post-PTA stenosis is used to express the efficiency of a PTA procedure. However, the post-PTA stenosis poorly predicts patency after PTA [9,11-14]. Recently, the SCVIR Technology Assessment Committee recommended reporting both angiographic and functional data as efficacy variables of PTA [15].
Our patients all had a Qa below 600 mL/min, which especially in grafts is a strong predictor for imminent thrombosis [3,20-23]. They all had a baseline stenosis of 50% or more, which was treated by PTA. We confirm earlier data that on average Qa increases with approximately 250 - 300 mL/min [18,24]. In the patients with adequate

angiograms, the post-PTA stenosis in AVG was in almost all cases 25% or less. This is considered to be an adequate angiographic result [3]. However, the decrease in resistance did not correlate with the stenosis reduction, indicating that angiographic improvement does not necessarily represent functional improvement. Preliminary data in a small group of patients also indicated that the stenosis reduction did not correlate with the increase in Qa [14]. Results in diabetics did not differ from those in non-diabetics. The percentage of PTA procedures resulting in a Qa_{post} above the threshold value of 600 mL/min, was 66% in AVG and 50% in AVF. Schwab *et al.* defined failure of PTA as an increase in Qa of less than 20%, which occurred in 21% of grafts [18]. This lack of effect may be caused by rapid recoil of the stenotic lesion, occurring in the period between PTA and first Qa measurement. Intravascular ultrasound after PTA showed that immediate elastic recoil occurred in 50% of the stenotic lesions [25]. The present findings may also indicate that other stenotic lesions, which importantly contribute to overall resistance, were not identified and not treated. Qa measurements during or immediately after PTA in the intervention room could be helpful to optimize procedure results [24].
In patients who needed multiple procedures, similar increases in Qa were obtained in subsequent PTA procedures. This finding supports earlier data indicating that patency after repeat PTA does not decrease [9]. Lumsden *et al.* randomized patients with greater than 50% stenosis to have either a PTA or no PTA and found that outcome did not differ [12]. Later the same authors re-analyzed their data and reported that patency did improve but only in grafts without prior angioplasty or thrombosis [13]. In the present study only in a minority of AV grafts, the PTA included in this study was the first intervention. We were unable to confirm the earlier results, that outcome of a first intervention is better than that of a second or later intervention.

Usually, long-term results of PTA are quantified as primary patency. In AVG, it varies from 38 - 64% at 6 months and 10 - 40% at 12 months [8]. We found an intervention-free primary patency at 6 months of 25% in AVG. The median time to next PTA was 97 days, as compared to 5.8 months in the study by Schwab *et al.* [18]. Their results seem substantially better than the present results, whereas the short-term functional effects in the two studies are comparable. Some of the differences between these studies may be important in this respect. In the present study, AV grafts were almost exclusively localized in the lower arm, whereas Schwab's study mainly included upper arm AVG. We selected patients when the threshold of 600 mL/min was reached, whereas in the other study most patients were referred when Qa showed a decrease of more than 20% or more. As a result, both Qa before and after PTA differed considerably, i.e. in the present study 371 ± 17 to 674 ± 30 mL/min and in the previous study approximately 750 and 950 mL/min [18]. The decline in Qa after PTA correlated with the Qa_{pre} level, suggesting that the

severity of stenosis before PTA is predictive for the rate of stenosis recurrence. In patients with a Qa_{pre} level between 100 and 350 mL/min the decline in Qa was 4.1 ± 1.0 ml/min/day versus 2.7 ± 1.2 ml/min/day for the patients with a Qa_{pre} level between 350 and 600 ml/min. Further support for this notion comes from patients who underwent PTA because of high venous pressure and who were not included in this study. In these patients (n = 12) who had Qa_{pre} levels between 600 and 800 ml/min, the decline in Qa was 1.6 ± 1.8 ml/min/day, which perfectly corresponds with the 5.8 months between consecutive interventions as reported by Schwab *et al.* [18]. Whereas baseline stenosis correlated with Qa_{pre}, post-PTA results (both post-PTA stenosis and stenosis reduction) did not correlate with the subsequent decline in Qa. These data suggest that Qa and therefore resistance is more predictive for longevity of effect of PTA than the angiographic variables.

Also, the correlation between the ΔQa and the decline in Qa deserves comment. It is likely that a higher ΔQa is an indication of a greater dilation of the stenosis, probably corresponding with more tissue injury. This may favor more rapid stenosis recurrence. Indeed, there is some indication that a less traumatic dilation, for instance by a cutting balloon, results in less activation of growth factors (reviewed in [23]).

The combined results of the present study and the study by Schwab *et al.* [18] warrant the start of a new discussion on the optimal timing of PTA. It is tempting to hypothesize that post-PTA patency in AVG is related to Qa_{pre} and/or the functional result of the PTA. If this turns out to be the case, PTA should be done as soon as a decrease in Qa is found, as is advocated by some [18,26], instead of when a low Qa level is reached as is proposed by others [7,27]. In such cases a "mild" PTA may result in a better long-term outcome than a more vigorous one. Quality of patient care and cost effectiveness of PTA may benefit importantly from properly designed studies addressing this hypothesis.

Possibly the best way of quantifying the long-term effect of PTA is by calculating secondary patencies. However, the present study was not designed to address this question. Many patients were included in the surveillance and intervention program of the present study long after the day they had the access implanted. Some of them had undergone interventions before their inclusion in the study, making it impossible the express true secondary patency of AV grafts followed by the surveillance and intervention program as in the present study. However, survival estimation of our secondary patency rates for AVG revealed a 6-month patency of 85%, a 1-year patency of 79%. In AVF, survival analysis showed a 6-month patency of 89% and a 1-year patency of 82%. With the limitation outlined above in mind, we can conclude that our secondary patency is comparable to the data in the literature on secondary patency rates [3,8].

The association between Qa and risk for thrombosis in AVF is less well documented than in AVG. AVF with Qa levels less than 300 to 500 mL/min can still remain patent [3]. K/DOQI recommends that AVF should be monitored as AVG. The efficacy of PTA in AVF was comparable to that in AVG. The long-term effect in AVF seems substantially better than in AVG. Primary (post-PTA) patency in AVF ranges from 47 - 67% at 6 months and 16 - 62% after 12 months [8]. We found intervention-free primary patencies at 6 months of 50% and a median survival of 161 days for AVF. None of the investigated variables were predictive for the long-term result in AVF.
In conclusion, access flow increases after PTA, however in a substantial percentage not to a level > 600 mL/min. Qa before PTA and the increase in Qa correlated with long-term outcome, whereas angiographic results did not. The present data combined with the literature suggest that there is an optimal timing for PTA.

Acknowledgements

Parts of this paper were presented at the 33rd Annual Scientific Meeting of the American Society of Nephrology, Toronto, Ontario, Canada, October 13-16, 2000 and at the ASN/ISN World Congress of Nephrology, San Francisco, California, USA, October 13-17, 2001. The authors acknowledge the following contributors: E.C. Hagen, A. Diepenbroek, Eemland Hospital, Amersfoort; G.W. Feith, Gelderse Vallei, Wageningen; M. Kooistra, P. Vos, Dianet, Utrecht; M.M. van Loon, H.H. Burger, E.F.H. van Bommel, Albert Schweizer Ziekenhuis, Dordrecht; M.I. Koolen, P.M. van der Zee, Medicentrum, Den Bosch; L. van den Broek, Rijnstate Ziekenhuis, Arnhem; B.J. Potter van Loon, Sint Lucas Andreas Ziekenhuis, Amsterdam.

References

1. Churchill DN, Taylor DW, Cook RJ, LaPlante P, Barre P, Cartier P, Fay WP, Goldstein MB, Jindal K, Mandin H: Canadian Hemodialysis Morbidity Study. *Am J Kidney Dis* 19: 214-234, 1992
2. Feldman HI, Held PJ, Hutchinson JT, Stoiber E, Hartigan MF, Berlin JA: Hemodialysis vascular access morbidity in the United States. *Kidney Int* 43: 1091-1096, 1993
3. National Kidney Foundation. K/DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 37 (Suppl 1): S137-S181, 2001
4. Schwab SJ, Raymond JR, Saeed M, Newman GE, Dennis PA, Bollinger RR: Prevention of hemodialysis fistula thrombosis. Early detection of venous stenoses. *Kidney Int* 36: 707-711, 1989

5. Besarab A, Sullivan KL, Ross RP, Moritz MJ: Utility of intra-access pressure monitoring in detecting and correcting venous outlet stenoses prior to thrombosis. *Kidney Int* 47: 1364-1373, 1995
6. Safa AA, Valji K, Roberts AC, Ziegler TW, Hye RJ, Oglevie SB: Detection and treatment of dysfunctional hemodialysis access grafts: effect of a surveillance program on graft patency and the incidence of thrombosis. *Radiology* 199: 653-657, 1996
7. Smits JHM, van der Linden J, Hagen EC, Modderkolk-Cammeraat EC, Feith GW, Koomans HA, van den Dorpel MA, Blankestijn PJ: Graft surveillance: venous pressure, access flow, or the combination? *Kidney Int* 59: 1551-1558, 2001
8. Gray RJ: Percutaneous intervention for permanent hemodialysis access: a review. *J Vasc Interv Radiol* 8: 313-327, 1997
9. Beathard GA: Percutaneous transvenous angioplasty in the treatment of vascular access stenosis. *Kidney Int* 42: 1390-1397, 1992
10. Glanz S, Gordon DH, Butt KM, Hong J, Lipkowitz GS: The role of percutaneous angioplasty in the management of chronic hemodialysis fistulas. *Ann Surg* 206: 777-781, 1987
11. Kanterman RY, Vesely TM, Pilgram TK, Guy BW, Windus DW, Picus D: Dialysis access grafts: anatomic location of venous stenosis and results of angioplasty. *Radiology* 195: 135-139, 1995
12. Lumsden AB, MacDonald MJ, Kikeri D, Cotsonis GA, Harker LA, Martin LG: Prophylactic balloon angioplasty fails to prolong the patency of expanded polytetrafluoroethylene arteriovenous grafts: results of a prospective randomized study. *J Vasc Surg* 26: 382-390, 1997
13. Martin LG, MacDonald MJ, Kikeri D, Cotsonis GA, Harker LA, Lumsden AB: Prophylactic angioplasty reduces thrombosis in virgin ePTFE arteriovenous dialysis grafts with greater than 50% stenosis: subset analysis of a prospectively randomized study. *J Vasc Interv Radiol* 10: 389-396, 1999
14. Ahya SN, Windus DW, Vesely TM, Lattimore BA: Utility of radiologic criteria for predicting access flow after percutaneous transluminal angioplasty. [Abstract] *J Am Soc Nephrol* 10 (ASN Program and Abstracts): 200A, 1999
15. Gray RJ, Sacks D, Martin LG, Trerotola SO: Reporting standards for percutaneous interventions in dialysis access. Technology Assessment Committee. *J Vasc Interv Radiol* 10: 1405-1415, 1999
16. Krivitski NM: Theory and validation of access flow measurement by dilution technique during hemodialysis. *Kidney Int* 48: 244-250, 1995
17. Bosman PJ, Boereboom FT, Bakker CJ, Mali WP, Eikelboom BC, Blankestijn PJ, Koomans HA: Access flow measurements in hemodialysis patients: in vivo validation of an ultrasound dilution technique. *J Am Soc Nephrol* 7: 966-969, 1996
18. Schwab SJ, Oliver MJ, Suhocki P, McCann R: Hemodialysis arteriovenous access: detection of stenosis and response to treatment by vascular access blood flow. *Kidney Int* 59: 358-362, 2001

19. Turmel-Rodrigues L, Pengloan J, Baudin S, Testou D, Abaza M, Dahdah G, Mouton A, Blanchard D: Treatment of stenosis and thrombosis in haemodialysis fistulas and grafts by interventional radiology. *Nephrol Dial Transplant* 15: 2029-2036, 2000
20. Bosman PJ, Boereboom FT, Smits HF, Eikelboom BC, Koomans HA, Blankestijn PJ: Pressure or flow recordings for the surveillance of hemodialysis grafts. *Kidney Int* 52: 1084-1088, 1997
21. Blankestijn PJ, Smits JH: How to identify the haemodialysis access at risk of thrombosis? Are flow measurements the answer? *Nephrol Dial Transplant* 14: 1068-1071, 1999
22. Smits JHM, Blankestijn PJ: Thrombosis-free hemodialysis grafts: a possibility for the next century? *Semin Dial* 12: 44-49, 1999
23. Smits JHM, Blankestijn PJ: Haemodialysis access: the case for prospective monitoring. *Curr Opin Nephrol Hypertens* 8: 685-690, 1999
24. Vesely T, Gherardini D, Starostin D, Krivitski N: Preliminary experiences using intravascular blood flow monitor (IBFM) during vascular access angioplasty. [Abstract] *J Am Soc Nephrol* 10 (ASN Program and Abstracts): 221A, 1999
25. Davidson CJ, Newman GE, Sheikh KH, Kisslo K, Stack RS, Schwab SJ: Mechanisms of angioplasty in hemodialysis fistula stenoses evaluated by intravascular ultrasound. *Kidney Int* 40: 91-95, 1991
26. Neyra NR, Ikizler TA, May RE, Himmelfarb J, Schulman G, Shyr Y, Hakim RM: Change in access blood flow over time predicts vascular access thrombosis. *Kidney Int* 54: 1714-1719, 1998
27. Sands JJ, Jabyac PA, Miranda CL, Kapsick BJ: Intervention based on monthly monitoring decreases hemodialysis access thrombosis. *ASAIO J* 45: 147-150, 1999

Chapter 6

Percutaneous thrombolysis of thrombosed hemodialysis access grafts: comparison of three mechanical devices

Henk F.M. Smits[1], Johannes H.M. Smits[2], Aloys F.J. Wüst[1],
Erik Buskens[3], Peter J. Blankestijn[2]

1 Department of Radiology, University Medical Center, Utrecht
2 Department of Nephrology, University Medical Center, Utrecht
3 Department of Clinical Epidemiology, University Medical Center, Utrecht

Abstract

Background. Percutaneous thrombolysis has become an accepted treatment of thrombosed hemodialysis grafts. Several devices have been developed for mechanical thrombolysis, which macerate the clot using different mechanisms such as aspiration and fragmentation. The aim of our study was to compare the efficacy of three devices for mechanical thrombolysis in removing thrombus from thrombosed hemodialysis access grafts and to determine the initial technical and clinical success, complication rates of each device, and graft patency after the procedure.

Methods. Thrombolysis (i.e. clot removal followed by percutaneous transluminal angioplasty (PTA)) was performed in 68 thrombosed hemodialysis grafts using the Cragg brush catheter combined with urokinase in 13, the Hydrolyser in 18 and the Arrow-Trerotola PTD in 37. Clot removal scores (CRSs, the ability to thoroughly remove clot from the access), initial technical success, clinical success, patency at 30, 60 and 90 days and complication rates were evaluated.

Results. CRSs for the Cragg brush, Hydrolyser and PTD were good in 92%, 44% and 95% of cases, respectively. Initial technical (85%, 83%, 95%) and clinical success (62%, 67%, 86%), mean patency rates at 30 (73%, 60%, 55%), 60 (61%, 53%, 49%) and 90 (49%, 40%, 43%) days, stenosis after PTA (33%, 46%, 21%) and complication rates (8%, 6%, 0%) were not different for the three devices. Success rates and graft patency depended on the effect of PTA, irrespective of the device used.

Conclusions. The rotational devices removed clot more effectively than the Hydrolyser, with the PTD having the advantage of not requiring urokinase. However, the result of PTA in the treatment of underlying stenoses was the only predictive value for graft patency.

Introduction

Percutaneous thrombolysis has become an accepted treatment of thrombosed hemodialysis grafts [1]. A number of techniques have been described. In pharmacological thrombolysis a lytic agent such as streptokinase or urokinase is administered intravenously or directly into the graft [2]. With pulse spray pharmacomechanical thrombolysis, lysis is accelerated by injecting the lytic agent into the clot, using a dedicated multi side hole infusion catheter [3,4]. More recently, mechanical devices have been developed for mechanical thrombolysis which macerate the clot using different mechanical actions such as aspiration and fragmentation [5].

Comparison of the efficacy of these devices is difficult. Most studies report on a single device only. Thrombolytic devices may be effective in removing thrombus material, however, they do not treat the underlying causes for clot formation, i.e. stenoses compromising blood flow [6-10]. Often, patency rates are given as a measure for determining efficacy of mechanical devices. However, patency of a graft after mechanical thrombolysis is likely to depend on the result of the treatment of the underlying stenoses [11,12], and clot removal is only part of the treatment. Comparison of reported procedure times and complication rates is also difficult because the methods vary among institutions, and differences in study results are therefore difficult to assess.

Over the last four years we applied three techniques for thrombolysis of hemodialysis grafts using mechanical devices for clot removal. The goal of our study was to compare the efficacy of each method in removing thrombus from hemodialysis access grafts and to determine the initial technical and clinical success, complication rates of each device, and graft patency after the procedure.

Patients and methods

All patients with a thrombosed vascular access graft were eligible to enter the study. Informed consent was obtained from all patients. The study was approved by the institute's Medical Ethical Committee. In its original design it was a prospective study to evaluate the efficacy of the rotating brush catheter. However, when this device was withdrawn by the manufacturer, a second (the hydrodynamic catheter) and later a third device (rotating basket catheter) were prospectively examined.

Clot removal procedures

All procedures were performed with the crossed catheter technique [13]. Access puncture was performed under local anesthesia with lidocaine 2%. In the standard procedure, no sedatives, systemic analgesics or antibiotics were used. In one third of cases ultrasonography was used at the operators discretion to guide puncture of the graft. A guide wire was

advanced and navigated across the venous anastomosis. Subsequently, a sheath was introduced towards the venous anastomosis (venous sheath). By contrast agent injection through a straight catheter, the central venous outflow tract and venous anastomosis of the graft were evaluated for the presence of stenoses. Also, the central end of the thrombus was determined. A second sheath was then introduced towards the arterial anastomosis (arterial sheath). Care was taken to avoid overlap of the sheaths. The actual thrombus treatment was then initiated using one of the following mechanical devices (chronological order).

Rotating brush catheter (Cragg brush)

The first mechanical device exploited was the Cragg brush catheter (Cragg Thrombolytic Brush, Micro Therapeutics, San Clemente, CA). Before employing the Cragg brush catheter 125.000 IU of urokinase mixed with 5000 IU heparin in 20 ml saline was injected into the clotted graft with the pulse-spray technique using a multi-side hole infusion catheter (Cook Inc, Bloomington, IN) [14]. During slow withdrawal of the brush and catheter, an additional 125.000 IU of urokinase mixed with 60 ml of 1:1 diluted iodinated contrast agent (30 ml per limb) were administered through a sidearm of the catheter, allowing real time visualization of clot fragmentation and subsequent restoration of the graft lumen. When the Cragg brush was temporarily withdrawn from clinical tests because of technical problems, we started to use a hydrodynamic catheter.

Hydrodynamic catheter (Hydrolyser)

The second device we employed for mechanical thrombolysis was a hydrodynamic catheter (Hydrolyser, Cordis Europa NV, Roden, The Netherlands). The Hydrolyser consisted of a 7-F double-lumen catheter with a 6-mm side hole at the tip [15,16]. The device was introduced over a 0.025-inch guide wire. Saline was injected with a power injector through the smaller of the two lumens. The resultant high-velocity jet was directed retrogradely in the catheter, along the side hole into a wider discharge channel. Due to the resultant underpressure (Venturi effect) the thrombus was aspirated into the side hole, fragmented and evacuated via the discharge channel. The injection of 150 ml saline at a flow rate of 4 ml/s resulted in an activation time of 37 seconds per run, during which the catheter was slowly withdrawn. Each limb of the graft was treated with a minimum of two runs. Any residual clot was removed by repeated passes with the Hydrolyser.

Rotating basket catheter (PTD)

In the third period, mechanical thrombolysis was performed with a rotating basket (Arrow-Trerotola Percutaneous Thrombolytic Device, PTD. Arrow International, Reading, PA). The PTD incorporates a self-expandable basket made of Nitinol wires,

attached to a drive cable. It was described in detail previously [17]. The PTD was introduced in its closed position through the sheaths. Once in place, the PTD was deployed. The PTD was rotated by a handheld disposable motor unit at 3,000 rpm and slowly withdrawn. After each pass, the PTD was removed in the deployed position and thoroughly cleaned and flushed before closure. The slurry was aspirated and small amounts of contrast material were injected to evaluate the effectiveness of mechanical thrombolysis in the venous limb. The arterial limb was then treated in the same way. The white clot at the arterial anastomosis was removed with the PTD and not with a separate Fogarty thrombectomy catheter. This modification of the original technique has recently been described [17,18]. Any residual clot was removed by repeated PTD passes or, if unsuccessful, by mobilization of residual clot using a slightly inflated balloon catheter.

PTA procedure

PTA was performed immediately following mechanical thrombolysis when a stenosis greater than 50% of the vessel diameter was present. We routinely used 6-mm diameter balloon catheters (Opta, Cordis Europa NV, Roden, The Netherlands) for intragraft stenoses. For PTA at the anastomoses the size of the balloon was adapted to the size of the artery and vein. Balloon catheters were inflated at maximum pressure of 12 ATM. Attempts were made to achieve the greatest stenosis reduction possible. In case of recoil, repeated PTA was performed with an oversized balloon. When the balloon did not unfold because of rigidity of the stenosis, a non-compliant high-pressure balloon was used with pressures up to 20 ATM. (Blue Max, Boston Scientific Corporation, Watertown, MA). Angiography was performed at the end of each procedure. Patients were scheduled for additional angiography and PTA within two weeks after the procedure in case flow in the graft was restored only moderately because of considerable residual thrombus and/or unsatisfactory effect of balloon dilation.

Definitions

Success of treatment was assessed by angiography. Using a two-point scale, the clot removal score (CRS) allowed discrimination between complete (successful) clot removal (minimal to no residual clot, CRS = 1) and incomplete clot removal (considerable residual thrombus material, CRS = 0). Minimal residual clot was defined as non-circumferential wall-adherent thrombus involving only a small portion (one third or less) of the graft. Any clot greater than minimal was graded as considerable. Initial technical success was defined as the restoration of flow within the graft at the end of the procedure, thus after clot removal and PTA. This criterion was met when a test bolus of iodinated contrast material disappeared rapidly with the blood stream. Clinical success was defined as at least one successful hemodialysis session using the graft after mechanical thrombolysis.

PTA results were measured on hardcopy images. For intragraft stenoses and stenoses at the anastomoses, the diameter in the stenosis was compared to the diameter of the graft. For native vein stenoses, the diameter in the stenosis was compared to the diameter of a non-stenotic part of the vein. Stenoses with a diameter reduction of more than 50% were treated with PTA. The result of PTA was expressed as the percent residual stenosis after PTA. When more than one stenosis was present, the part with the highest grade of residual stenosis was taken for residual stenosis rate of that graft.
Major complications were defined as: major bleeding necessitating surgery or transfusion, symptomatic pulmonary or arterial embolization, severe contrast agent reaction, injury to the graft necessitating surgery and mechanical defects of the device affecting technical success [17]. Minor complications were defined as: minor contrast agent reaction, adverse reactions to urokinase, asymptomatic arterial or pulmonary embolization, self-limited hematomas treated by local compression and mechanical defects of the device that did not affect technical success.
Total procedure time was defined as the time from beginning of local anesthesia, given at initiation of the procedure until completion of hemostasis, applied to the graft at the end of the procedure.
Primary patency rate was defined as the percentage of grafts that functioned well without any additional intervention for graft failure. Follow-up time was censored for patients who died or were otherwise lost to follow-up and patients who received a kidney transplant.

Statistical methods

The difference in proportion with successful clot removal was calculated, including 95% confidence intervals (CI). Ordinal data were analyzed by means of Chi-square tests. Multiple logistic regression analysis was used to assess the independent association of various clinical parameters. Primary patency was studied using Kaplan-Meier survival curves. Differences in the patency rates were tested using the log rank test. In addition, Cox's proportional hazards model was used to analyze primary patency in relation to the various clinical parameters comparable to the multivariate analysis of clinical success. Procedure time in relation to number of stenoses per graft was analyzed using Pearson's correlation coefficient.

Results

Between January 1996 and January 2000, 73 consecutive cases (60 patients) with a thrombosed hemodialysis access graft were referred for mechanical thrombolysis, consisting of clot removal followed by percutaneous transluminal angioplasty (PTA).
In five of the 73 cases, the procedure was ended before clot removal had begun, as the venous anastomosis (n = 4) or the arterial anastomosis (n = 1) could not be passed with a guide wire. Mechanical thrombolysis was performed in the remaining 68 cases (55 patients) (Table 1). Thirty-eight of the 68 access sites were PTFE grafts (Gore-Tex; Gore, Flagstaff, Ariz.) and 30 were homologous vein grafts (Varivas; Vascogref BV, Bussum, The Netherlands) (Table 1). Table 1 shows type and location of the grafts and the distribution of graft material in the three device groups. In 67 of 68 cases mechanical thrombolysis was completed; in one case clot removal was terminated because of technical failure of the device. In 66 of 67 cases PTA followed clot removal. In the remaining case there was no identifiable stenosis requiring PTA. The mean period grafts had been functioning was 15 months (range 3 - 60 months). Mechanical thrombolysis was performed between 8 hours and two weeks after diagnosing graft thrombosis, and in the vast majority (50 cases) treatment was started within 24 hours.

Table 1. Number, type and location of grafts with distribution per device

			Device					
	Total		Cragg Brush		Hydrolyser		PTD	
Number of grafts	**68**		**13**		**18**		**37**	
patients	55		13		14		28	
	Vein*	PTFE‡	Vein	PTFE	Vein	PTFE	Vein	PTFE
Type of graft	**30**	**38**	**11**	**2**	**13**	**5**	**6**	**31**
Location of grafts								
Fore-arm loop	25	28	11	-	9	2	5	26
Upper arm loop	3	2	-	-	3	-	-	2
Axillo-axillary	-	6	-	2	-	3	-	1
Fore-arm straight	2	2	-	-	1	-	1	2

* homologous vein graft

‡ polytetrafluoroethylene

Clot removal

Clot removal scores are shown in Table 2. The rotational devices (Cragg brush catheter and PTD) had a similar clot removal score (92 versus 95%). Both had a significantly ($P < 0.05$) better clot removal score than the non-rotational device (Hydrolyser, 44%). CRS was not associated to initial technical success ($P = 0.72$). In univariate analysis, CRS seemed to have a significant association with clinical success (odds ratio 4.3, 95% CI 1.2 - 16). Using multivariate regression analysis, however, the association between residual clot material and clinical success could not be confirmed. Cox proportional hazard analysis revealed no relation between clot removal score and primary patency.

Table 2. Results of mechanical thrombolysis by device

	Device		
	Cragg Brush	Hydrolyser	PTD
Clot Removal Score*			
1	92% (11/12)‡	44% (8/18)	95% (35/37)
0	8% (1/12)	56% (10/18)	5% (2/37)
Initial technical success	85% (11/13)	83% (15/18)	95% (35/37)
CI†	55 - 98%	59 - 96%	82 - 99%
Clinical success	62% (8/13)	67% (12/18)	86% (32/37)
CI	32 - 86%	41 - 87%	71 - 96%
Patency at 30 days	67% ± 14¥	50% ± 12	52% ± 8
60	56% ± 15	39% ± 12	46% ± 8
90	44% ± 16	33% ± 11	40% ± 8
Mean procedure time (min)	118 ± 27	132 ± 16	119 ± 43
Range	80 - 150	105 - 150	70 - 168
Major complications	8% (1/13)	6% (1/18)	0%
Minor complications	31% (4/13)	56% (10/18)	43% (16/37)
Mean number of stenoses per grafts	2.2	2.5	1.9

Note.- Thirteen brush procedures; in one procedure the brush broke off, so twelve clot removal scores remained. For calculation of success rates and patency, the broken brush was considered as a failure.

* CRS 1 = minimal to no residual thrombus. CRS 0 = considerable residual thrombus.

‡ numbers of patients are given in parentheses

† CI = 95% confidence interval

¥ standard error of the mean

Initial technical success and clinical success

Cragg brush

Initial technical success was achieved in 11 (85%) of the 13 patients (Table 2). In one case the brush broke off before clot removal was completed and in another case blood flow could not be restored because of bleeding complications after clot removal. Successful hemodialysis after mechanical thrombolysis could be performed in 8 of 13 patients, indicating a clinical success rate of 62%. In three of the 11 patients with initial technical success, re-occlusion of the grafts occurred before the first post-procedural hemodialysis following mechanical thrombolysis could be performed.

Hydrolyser

Initial technical success was reached in 83% (15 of 18 cases). In the remaining three, restoration of blood flow could not be achieved because of a long rigid stenosis in the native vein of the upper arm, which was resistant to PTA (n = 1); a 60% residual stenosis with a small dissection after PTA at the arterial anastomosis (n = 1); and bleeding complications during mechanical thrombolysis that was performed one-day after shunt revision (n = 1). In three of the remaining 15 cases with initial technical success, re-occlusion of the grafts occurred before the first hemodialysis following mechanical thrombolysis could be performed, resulting in a clinical success rate of 67% (12/18 cases).

PTD

With the PTD, the initial technical success was 95% (35/37 cases). In one of the two unsuccessful cases, restoration of blood flow could not be achieved due to a rigid stenosis at the arterial anastomosis resistant to PTA, and in the other one there was occlusion of the graft by overlapping sheaths and residual white clot material. In three of the 35 cases with initial technical success, re-occlusion of the grafts occurred before the first post-procedural hemodialysis could be performed, resulting in a clinical success rate of 86% (32/37 cases).

Using multivariate logistic regression analysis and Cox's regression analysis respectively, no association was found between type of device used and clinical success and between type of device used and primary patency.

Distribution and treatment of stenoses

A total of 142 stenoses were encountered in 67 grafts treated. Sixty-two of the 67 grafts showed a stenosis at the venous anastomosis (93%) and 29 at the arterial anastomosis (43%). Twenty-three (34%) were located in the upper arm and central vein and 28 stenoses were in the graft itself (42%). Mean number of stenoses was 1.8 in the PTFE group and 2.5 in the homologous vein group. As is shown in table 1, there was an uneven

distribution of types of graft material in the three device groups. Accordingly, the number of stenoses per device group was also distributed unevenly. The mean number of vascular stenoses per graft in the Cragg brush group, the Hydrolyser group and the PTD group were 2.2, 2.5 and 1.9 respectively.
In fourteen of 67 cases PTA of the underlying stenosis resulted in residual stenosis of more than 50% (mean 75% residual stenosis, range 55 to 99% residual stenosis). Six of seven procedures with initial technical failure were found in the last group. Seven cases were scheduled for control angiography because of unsatisfactory results due to the presence of residual clot and/or stenosis after the procedure. Four of these cases showed clinical evidence of re-occlusion within 24 hours. These were not re-entered in the study. The other three cases were evaluated with angiography 6 - 14 days after the procedure. All three showed complete resolution of residual clot. One of the three showed 60% residual stenosis, which was treated with PTA. One case showed 55% residual stenosis which was not treated and one showed no residual stenosis.
Independent of the type of device used, multiple logistic regression analysis showed a strong relationship between residual stenosis and clinical success (odds ratio 0.92, 95% C.I. 0.87 - 0.96). Cox's regression analysis also showed that residual stenosis was the only parameter that determined follow-up.

Complications

Cragg brush

One major complication occurred: the brush broke off its drive cable at the curve of the loop graft during withdrawal of the brush. The loose brush was retrieved using a goose neck catheter with successive graft damage. Four minor complications included rupture of the venous anastomosis after PTA (n = 1), asymptomatic retrograde arterial embolism, which was treated with additional local urokinase infusion (n = 1), and spontaneous hematomas occurred in two cases at previously used puncture sites for hemodialysis. These hematomas were treated with manual compression.

Hydrolyser

One patient had symptomatic, scintigraphically proven pulmonary embolism. Minor complications occurred in ten cases. These included seven patients with a total of nine hematomas. Two of these nine hematomas were caused by unsuccessful needle punctures of the graft at the beginning of the procedure. Three of the nine hematomas occurred at PTA sites. In three patients asymptomatic retrograde arterial emboli were seen at control angiography after mechanical thrombolysis. These three patients showed no clinical signs; the emboli were not treated and there were no long-term sequelae.

PTD

No major complications occurred in the 37 cases treated with the PTD. Minor complications occurred in 16 with 9 of those experiencing minor bleeding. In four of these 9 cases, there were hematomas at prior puncture sites. In the remaining five, minor bleeding occurred at the site of balloon dilation, which were treated by local manual compression. Minor mechanical problems with the device occurred in seven cases. In three of these, one of the wires of the PTD broke at the proximal connection. A broken wire hampered withdrawal of the PTD in the covering catheter. In two cases, the 5-F guiding catheter, in which the PTD was housed, wrinkled near the motor unit and in two other cases, the cover catheter broke. These mechanical defects occurred chiefly in the first half of the procedures and were less common after the manufacturer had modified the basket and its housing catheter.

Procedure time

As shown in Table 2 procedure times were comparable for each type of device. Length of the procedure as such was mainly determined by the number of stenoses ($r = 0.47$).

Patency rates

Mean survival time was 144 ± 31 days (median 59 days). Ten patients were lost to follow-up. Six of them died. Five of these six died as a result of unrelated disease 6 to 790 days after the procedure with an intact shunt. One patient died four days after mechanical thrombolysis due to sepsis, which was thought to be related to central catheters, but may also have been related to shunt infection. Four patients were censored because of renal transplant, 22 to 377 days after the procedure. Figure 1 shows the Kaplan-Meier survival curves of each device (P = NS). Primary patency rates are shown in table 2. For all procedures, primary patency rates were 53 ± 6% at 30 days, 46 ± 6% at 60 days and 39 ± 6% at 90 days. Using Cox's proportional hazard model, long-term patency rates were significantly related to residual stenosis (hazard ratio 1.025, 95% CI 1.009 to 1.041), meaning that each percent of rest stenosis induces a risk for graft failure of 2.5% (CI 0.9 - 4.1%) per day. Patency rates were not related to type of device nor to clot removal score.

Discussion

In this study, in which we evaluated three devices used for mechanical thrombolysis, we found that the rotating devices -the Cragg brush and the PTD- performed significantly better than the Hydrolyser in removing thrombus from hemodialysis access grafts. When applying the Cragg brush or the PTD, the original contour of the graft wall was restored. Removal of thrombus with the aid of the Hydrolyser often resulted in an irregular lumen

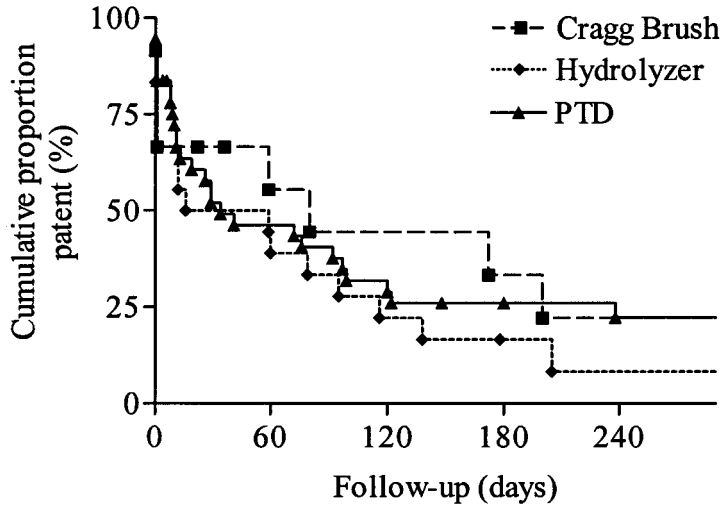

Figure 1. Kaplan-Meier survival curves of mechanical thrombolysis using the Cragg Brush, the Hydrolyser and the PTD. The curves were not significantly different.

with residual thrombus material adherent to the wall. The most likely explanation for the superior clot removal scores that the rotating devices achieved is that both use the same principle of a self-expanding wall-contact mechanism, in which the device is centered in the vessel lumen with the device's hairs or wires rubbing against the vessel wall to remove the clot [19]. The main action of the Hydrolyser, however, is exerted through the side hole of the catheter, often resulting in removal of only the clot facing the side hole and leaving the remaining clot in place. As a result, thrombus removal achieved with the Hydrolyser frequently is incomplete. Vesely *et al.* showed similar results with respect to thrombus removal between the different devices. However, no patency rates were given for their thrombolysis procedures [19].

Using univariate analysis, we found that successful clot removal seemed to be associated with clinical success. However, after adjusting for residual stenosis, the association with clot removal could not be confirmed. In addition, there was no association between clot removal and long-term patency. These results add to the discussion of the relevance of residual thrombus in the graft after clot removal [20,21]. Large fragments of residual clot will obstruct the lumen and hamper initial technical success. These large fragments can easily be identified and removed using additional mechanical thrombolysis or by means of the balloon catheter. Small amounts of residual clot appeared to be insignificant because they disappeared completely 1 to 2 weeks after treatment. This refers to the

inherent thrombolytic capability of the normal bloodstream and, probably, is the result of adequate restoration of blood flow through the graft.

Percutaneous transluminal angioplasty (PTA) adds substantially to initial technical success [3,8,22]. In our study, using Cox's regression analysis, residual stenosis after PTA appeared to be the single, most important factor predictive of primary patency after mechanical thrombolysis. Therefore, we believe that the main goal of a mechanical thrombolysis procedure should be adequate reduction of stenosis with subsequent restoration of blood flow. Clot removal is a sine qua non, but the presence of small amounts of residual thrombus seems to be insignificant because they are likely to be cleared by the bloodstream.

Each device appeared to be relatively safe to use in our experience although the number of procedures per device was relatively small. Major complications were rarely encountered with no clear relation to type of device. In only one of our group of 68 cases, there were clinical signs of pulmonary embolism, which was confirmed with scintigraphy. The number of minor complications was relatively high, however, occurring in 31% to 56% of the cases and comparable for each device group. There were four patients (6%) in whom asymptomatic arterial embolism was identified, the first of whom was treated with intra-arterial infusion of urokinase. The following three patients with asymptomatic arterial embolism were not treated and none developed late sequelae. Distal arterial mapping was not routinely performed and, thus, the true incidence of arterial embolism may have been higher. It is well recognized that, in many instances, pulmonary or arterial embolism occurs after mechanical thrombolysis without becoming clinically evident. In a previous study it was shown that in 35% of patients who had undergone the procedure, there was scintigraphic evidence of new pulmonary emboli, although almost all of these patients were asymptomatic [23]. In another series of patients who underwent surgical thrombectomy, arterial embolization was found in eight (12%) of cases. In only one of the eight cases was the condition symptomatic [24]. Thus, the risk of embolism of the clot fragments is a potential complication of the procedure no matter what thrombolysis treatment is used. Fortunately, the clinical implications are limited [25,26].

A limitation of our study is that we did not randomize the application of the three devices throughout the patient population. Each device was used at a different period of time, according to its availability during the course of the study. Another shortcoming is that the type of graft changed during the course of the study as the surgeons who created the grafts changed their primary choice of graft material from homologous vein to PTFE. This lead to an unbalanced distribution of graft types among the various treatment groups. However, in the calculation of success, we used type of graft as one of the parameters in the multivariate analysis and found that graft type did not affect the results.

In conclusion, in our evaluation of three mechanical devices used to declot thrombosed hemodialysis access grafts, we found that the success of mechanical thrombolysis was determined more by the success of PTA of underlying stenoses than by the results of clot removal. The rotating devices performed significantly better than the Hydrolyser in removing thrombus from hemodialysis access grafts. The effectiveness of the two rotating devices was comparable.

References

1. Gray RJ: Percutaneous intervention for permanent hemodialysis access: a review. *J Vasc Interv Radiol* 8: 313-327, 1997
2. Cohen MA, Kumpe DA, Durham JD, Zwerdlinger SC: Improved treatment of thrombosed hemodialysis access sites with thrombolysis and angioplasty. *Kidney Int* 46: 1375-1380, 1994
3. Valji K, Bookstein JJ, Roberts AC, Davis GB: Pharmacomechanical thrombolysis and angioplasty in the management of clotted hemodialysis grafts: early and late clinical results. *Radiology* 178: 243-247, 1991
4. Davis GB, Dowd CF, Bookstein JJ, Maroney TP, Lang EV, Halasz N: Thrombosed dialysis grafts: efficacy of intrathrombic deposition of concentrated urokinase, clot maceration, and angioplasty. *Am J Roentgenol* 149: 177-181, 1987
5. Sharafuddin MJ, Hicks ME: Current status of percutaneous mechanical thrombectomy. Part II. Devices and mechanisms of action. *J Vasc Interv Radiol* 9: 15-31, 1998
6. Kanterman RY, Vesely TM, Pilgram TK, Guy BW, Windus DW, Picus D: Dialysis access grafts: anatomic location of venous stenosis and results of angioplasty. *Radiology* 195: 135-139, 1995
7. Beathard GA: Mechanical versus pharmacomechanical thrombolysis for the treatment of thrombosed dialysis access grafts. *Kidney Int* 45: 1401-1406, 1994
8. Smith TP, Cragg AH, Castaneda F, Hunter DW: Thrombosed polytetrafluoroethylene hemodialysis fistulas: salvage with combined thrombectomy and angioplasty. *Radiology* 171: 507-508, 1989
9. Smits JHM, Blankestijn PJ: Thrombosis-free hemodialysis grafts: a possibility for the next century? *Semin Dial* 12: 44-49, 1999
10. Blankestijn PJ, Smits JH: How to identify the haemodialysis access at risk of thrombosis? Are flow measurements the answer? *Nephrol Dial Transplant* 14: 1068-1071, 1999
11. Sharafuddin MJ, Hicks ME: Current status of percutaneous mechanical thrombectomy. Part I. General principles. *J Vasc Interv Radiol* 8: 911-921, 1997
12. Beathard GA: Percutaneous transvenous angioplasty in the treatment of vascular access stenosis. *Kidney Int* 42: 1390-1397, 1992

13. Trerotola SO, Lund GB, Scheel PJ, Jr., Savader SJ, Venbrux AC, Osterman FA, Jr.: Thrombosed dialysis access grafts: percutaneous mechanical declotting without urokinase. *Radiology* 191: 721-726, 1994
14. Castaneda F, Wyffels PL, Patel JC, Swischuk JL, Li R, Cole BA, Cragg AH: New thrombolytic brush catheter in thrombosed polytetrafluoroethylene dialysis grafts: preclinical animal study. *J Vasc Interv Radiol* 9: 793-798, 1998
15. Vorwerk D, Schurmann K, Muller-Leisse C, Adam G, Bucker A, Sohn M, Kierdorf H, Gunther RW: Hydrodynamic thrombectomy of haemodialysis grafts and fistulae: results of 51 procedures. *Nephrol Dial Transplant* 11: 1058-1064, 1996
16. Pattynama PM, van Baalen J, Verburgh CA, van der Pijl JW, Schultze Kool LJ: Revascularization of occluded haemodialysis fistulae with the Hydrolyser thrombectomy catheter: description of the technique and report of six cases. *Nephrol Dial Transplant* 10: 1224-1227, 1995
17. Trerotola SO, Vesely TM, Lund GB, Soulen MC, Ehrman KO, Cardella JF: Treatment of thrombosed hemodialysis access grafts: Arrow-Trerotola percutaneous thrombolytic device versus pulse-spray thrombolysis. Arrow-Trerotola Percutaneous Thrombolytic Device Clinical Trial. *Radiology* 206: 403-414, 1998
18. Lazzaro CR, Trerotola SO, Shah H, Namyslowski J, Moresco K, Patel N: Modified use of the arrow-trerotola percutaneous thrombolytic device for the treatment of thrombosed hemodialysis access grafts. *J Vasc Interv Radiol* 10: 1025-1031, 1999
19. Vesely TM, Hovsepian DM, Darcy MD, Brown DB, Pilgram TK: Angioscopic observations after percutaneous thrombectomy of thrombosed hemodialysis grafts. *J Vasc Interv Radiol* 11: 971-977, 2000
20. Overbosch EH, Pattynama PM, Aarts HJ, Schultze Kool LJ, Hermans J, Reekers JA: Occluded hemodialysis shunts: Dutch multicenter experience with the hydrolyser catheter. *Radiology* 201: 485-488, 1996
21. Turmel-Rodrigues L, Sapoval M, Pengloan J, Billaux L, Testou D, Hauss S, Mouton A, Blanchard D: Manual thromboaspiration and dilation of thrombosed dialysis access: mid-term results of a simple concept. *J Vasc Interv Radiol* 8: 813-824, 1997
22. National Kidney Foundation. K/DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 37 (Suppl 1): S137-S181, 2001
23. Smits HF, Van Rijk PP, Van Isselt JW, Mali WP, Koomans HA, Blankestijn PJ: Pulmonary embolism after thrombolysis of hemodialysis grafts. *J Am Soc Nephrol* 8: 1458-1461, 1997
24. Trerotola SO, Johnson MS, Shah H, Namyslowski J, Filo RS: Incidence and management of arterial emboli from hemodialysis graft surgical thrombectomy. *J Vasc Interv Radiol* 8: 557-562, 1997
25. Swan TL, Smyth SH, Ruffenach SJ, Berman SS, Pond GD: Pulmonary embolism following hemodialysis access thrombolysis/thrombectomy. *J Vasc Interv Radiol* 6: 683-686, 1995

26. Dolmatch B: Risk of pulmonary emboli from mechanical thrombolysis. *Semin Dial* 8: 321-322, 1995

Chapter 7

Single-lumen versus double-lumen catheters for temporary hemodialysis access: a randomized prospective trial

Johannes H.M. Smits, Wil A.M.A. van der Mark, Theo van Berkel, Juliette Verwey, Walther H. Boer, Peter J. Blankestijn

Department of Nephrology, University Medical Center, Utrecht

Abstract

Background. Double-lumen (DL) catheters are advised as temporary vascular access in hemodialysis. No data are available indicating that urea reduction ratios (URR) using DL are better than when using single-lumen (SL) catheters. Aim of the present study was to compare URR obtained using SL and DL catheters.

Methods. Patients, who needed a temporary access, were prospectively randomized to have a SL or DL catheter, either in the femoral vein (FV) or in a central vein (CV). With DL catheters blood flow was targeted on 200 mL/min and with SL on 300 mL/min (150 mL/min effectively). URR was calculated using the formula 1 minus urea post-dialysis/urea pre-dialysis.

Results. 118 catheters were placed in 81 patients, 33 SL catheters and 28 DL catheters in a FV, and 30 SL catheters and 27 DL catheters in a CV. During 4 hour dialysis the percentage of dialysis sessions providing a URR $\geq$ 65 % was greater using DL catheters (FV: 25% versus 4%, CV: 29% versus 11%, both $P < 0.05$). During 3 hour dialysis differences were not significant. After increasing flow in DL catheters to 300 mL/min URR improved in CV and FV with 0.08 ± 0.01 and 0.08 ± 0.02.

Conclusion. Many dialysis treatments using catheters do not result in a URR $\geq$ 65%. DL catheters in CV position were most likely to obtain an URR $\geq$ 65%.

Introduction

Catheters are widely used for temporary vascular access in hemodialysis patients [1]. Two types of catheters are available: the single-lumen (SL) catheter and the double-lumen (DL) catheter. The Vascular Access Committee of the NKF-K/DOQI recommends the DL catheter for temporary vascular access [2]. Originally, the DL catheter was designed to alleviate the need for a double-pump system required for SL catheter dialysis. Presently, most dialysis machines are equipped with a double-pump for SL dialysis. From a theoretical point of view, it is reasonable to assume that dialysis using DL catheters offer a more effective treatment, because higher effective blood flows can be achieved. However, data substantiating this assumption are lacking. Therefore, we designed a prospective randomized study comparing SL and DL catheters in terms of adequacy of dialysis and overall performance.

Methods

The present study was done in a university hospital based dialysis department and a free standing dialysis center, in which approximately 150 hemodialysis patients are treated. All patients requiring temporary venous catheters for vascular access for intermittent hemodialysis during a certain 6 months period could be included. The Ethical Committee of the University Medical Center Utrecht approved the trial protocol. Informed consent was obtained from all participating patients. Catheters placed for plasmapheresis or for dialysis treatment on the ICU were excluded.

Materials and Study design

Indications for catheter insertion were graft or AV fistula thrombosis, need for dialysis before the AV fistula matured or before the graft could be punctured, or the need for acute dialysis without other means of vascular access. Patients were prospectively randomized to either insertion of a SL catheter or a DL catheter.

The standard dialysis prescription included a pump flow of 200 mL/min for DL catheters and 300 mL/min (150 mL/min effectively) for SL catheter. These flows were chosen because it was our clinical experience that in the majority of dialysis sessions these flows can indeed be obtained without too many inflow problems and alarms of the dialysis machine.

Dialysis efficacy was quantified as the urea reduction ratio (URR). The formula for URR is 1 minus urea post-dialysis/urea pre-dialysis. A blood sample was taken out of the extracorporeal circuit at the beginning of the dialysis (urea pre-dialysis). After dialysis a blood sample was drawn after approximately 20 minutes after stopping the dialysis (urea post-dialysis) [1]. Blood was analyzed by the hospital laboratory using standard procedures.

The processed blood volume as indicated by the dialysis machine was also monitored. In all cases Gambro AK 100 or 200 devices were used.
Variables for over all performance were infection, removal for poor flow or inability to obtain any flow, bleeding and dislocation.

Catheters: insertion, maintenance and removal

The catheters were inserted either in the internal jugular vein, the subclavian vein or the femoral vein. The attending physician performing the catheter placement was responsible for the choice of location. The catheter placement was done on the dialysis ward under sterile conditions. If necessary, ultrasound equipment was used for localizing the vein. In the case of subclavian or internal jugular vein canulation, a chest X-ray was made afterwards to assure the right positioning of the catheter tip. We used the following catheters: Quinton DL 19.5 cm and Vascath SL 20.0 cm for the femoral and subclavian vein, the Arrow DL 13.0 cm and Medcomp SL 15.0 cm for the jugular vein.
Catheter maintenance included inspection and cleaning with povidone iodine ointment of the exit side before each dialysis session and coverage with dry gauze afterwards. After dialysis catheters were filled with pure heparin.
Catheters were removed if: 1) the catheter was no longer needed; 2) a major complication occurred, e.g. a bleeding, high suspicion of catheter related infection (fever and/or redness around exit site); 3) catheter occlusion or dysfunction. Femoral vein catheters were removed after approximately one week according to the NKF-K/DOQI recommendations [1].

Statistical analysis

Proportions were compared using the χ^2 test using Yates' correction. URR comparison tests were conducted using two-way ANOVA with the Student-Newman-Keuls method. Target blood volumes were compared with a t-test using the Mann-Whitney Rank Sum test. Survival analysis to calculate complication-free survival in central vein catheters was performed with log rank analysis. A *P*-value of less than 0.05 was considered significant.

Results

Randomization was done for 118 catheters in 81 patients. 33 SL catheters and 28 DL catheters were placed in a femoral vein (FV), and 30 SL catheters and 27 DL catheters were placed in a central vein (CV). In the vast majority of cases the internal jugular vein was used as central vein. Results of subclavian and jugular vein catheters are presented as one group. A total of 647 dialyses were done on these catheters resulting in 1338 catheter days, 723 days for SL and 615 for DL. URR was obtained from 478 dialyses, 246 from SL

catheter dialysis and 232 from DL catheter dialysis.
The Table shows URR for 3-hour and 4-hour dialysis. Use of CV catheters for dialysis resulted in a higher URR than FV catheters ($P < 0.01$), except for the 3 h SL dialysis. During 4-hour dialysis URR using DL catheters was greater than using SL catheters, whereas this was not the case for 3-hour dialysis sessions. For a given location and catheter type, URR during 4-hour dialysis was significantly better ($P < 0.05$) than that of 3-hour dialysis, except for the SL FV catheter dialysis ($P = 0.083$). DL catheters were more likely to process the target volume of blood than SL catheters (Table). Only 5.7% of the SL and 9.2% of the DL dialyses resulted in an URR of ≥ 65%.
FV catheters remained in place for approximately one week (SL 7.7 ± 5.6 and DL 6.3 ± 4.5 days, respectively 3.2 ± 1.9 and 2.7 ± 1.7 dialysis sessions) and the CV catheters were present for approximately 25 days (SL 25.5 ± 13.7 and DL 25.5 ± 10.1 days, respectively 7.7 ± 4.7 and 8.1 ± 6.4 dialysis sessions). The majority of the catheters was removed, because they were no longer needed. Other reasons were thrombosis, bleeding, dislocation, (suspected) infection, and a group with other reasons such as death, or lost to follow-up. There were no statistical differences in reasons for removal between both types of catheters.
Catheter survival curves (Kaplan-Meier analysis) with an event defined as one of the complications (i.e. thrombosis, bleeding, dislocation, or (suspected) infection) were not different ($P = 0.13$).

Table 1. Urea reduction ratio for 3- and 4-hour dialysis and achieved percentage of target blood volume and percentage (between brackets) of dialysis sessions reaching URR of ≥ 65%.

	SL	n	DL	n	*P*
URR 3h FV	0.46 ± 0.15 (6%)	32	0.45 ± 0.13 (4%)	26	NS
URR 3h CV	0.50 ± 0.10 (5%)	84	0.51 ± 0.07 (1%)	100	NS
P	NS		< 0.001		
URR 4h FV	0.47 ± 0.13 (4%)	46	0.52 ± 0.11 (25%)	26	0.030
URR 4h CV	0.55 ± 0.09 (11%)	84	0.58 ± 0.09 (29%)	80	0.041
P	< 0.001		0.006		
% target vol. FV	87 ± 14		95 ± 9		< 0.001
% target vol. CV	92 ± 11		95 ± 15		< 0.001

Finally, we tested the option that increasing the flow in the DL catheters from 200 to 300 mL/min would result in improvement of URR. In 25 cases (16 central vein and 9 femoral vein) paired observations were made within the same patient with dialysis time unchanged. URR increased with 0.08 ± 0.01 in CV catheters and with 0.08 ± 0.02 in FV catheters. In 28% (7/25) of the patients (4 central vein and 3 femoral vein catheters) were unable to obtain 300 mL/min and one case (central vein) could not even reach the 200 mL/min when the target was 300 mL/min.

Discussion

To our knowledge this is the first study comparing in a prospective randomized trial dialysis adequacy obtained using DL and SL catheters for temporary use. This study allows a number of clinically relevant conclusions. In vast majority of cases the URR of 0.65, recommended by the NKF-K/DOQI Committee as indication for adequate dialysis, was not obtained using either the SL or DL catheters [1]. Dialysis using catheters in CV position is more effective than catheters in FV position. During 4 h of dialysis DL catheters provide a higher URR than SL catheters. Although some comparisons were statistically significant favoring the use of DL catheters, differences were clinically not very impressive. Overall performance did not differ.

During the use of temporary catheters an important obstacle in the effort to achieve an adequate URR is the inability to obtain the prescribed flow and recirculation of processed blood. In the present study DL catheters were more likely to process the prescribed blood volume than SL catheters. Furthermore with DL catheters, in present settings of the dialysis machines, the processed volume of blood was one third greater than SL catheters. During 4 hours of dialysis this resulted in a higher URR. Although statistically significant, the obtained differences were not very great. The clinical relevance is difficult to establish, but likely to be limited.

We confirm earlier data that adequacy of FV catheters is lower than that of CV catheters [3]. This is probably due to an anatomic factor. Blood flow in the central vein close to the right atrium is higher than in the iliac vein or inferior caval vein, resulting in a lower probability of recirculation.

Adequacy of DL catheters can be improved by increasing blood flow of the dialysis machine. Especially in femoral catheters, this may be associated with an increase in recirculation, partially off setting the beneficial effect [4]. However, in the present study URR increased with approximately 15% in both CV and FV catheters.

Several limitations of this study need to be discussed. We tested a limited number of catheters only. We can not exclude the possibility that other types would result in other results. Especially longer catheters (25 cm) in the FV position are likely to produce more

effective dialysis than the 19.5 cm catheter we used. We also did not explore the possibility that increasing flow in SL catheters or prolonging the dialysis time would be of benefit. The present settings and dialysis time were a compromise between the number of alarms by the dialysis machine (with respect to flow) and the acceptability of dialysis treatment by the patient (time).

What may be the implications of the present study for the every day clinical practice? The present study shows that many dialysis sessions, using the present setting of dialysis machines, do not meet the standards suggested by the NKF-K/DOQI Work Group. Dialysis sessions using DL catheters in CV position were most likely to reach the standard. URR could be further improved by increasing flow. In 25% of cases it was not possible to obtain a flow of 300 mL/min. Whether the inability to reach an URR $\geq$ 65% is of any clinical relevance, when it only concerns a limited number of treatments is questionable. The present data do not support the conclusion that DL catheters, processing blood at 200 mL/min, provide a much more effective treatment than SL catheters. Especially when short-term (arbitrarily defined as some days to one or two weeks) use is expected, it seems unlikely that adequacy differences will be of any relevance. In such cases one may conclude that SL catheters are preferable. DL catheters should then be reserved when longer duration is expected (up to several weeks), which in the case of femoral vein location would mean repeated cannulation. In addition, it is conceivable that SL catheters cause less vascular damage, resulting in less risk for stenosis. We were unable to find studies addressing the issue. Finally, SL catheters are much cheaper, although dialysis lines necessary for SL catheter dialysis are more expensive than those used with DL catheters. Therefore, especially when only a limited number of dialysis sessions are anticipated, the use of SL catheters might turn out to be cheaper. Taken these considerations together it seems that SL catheters are, at least in selected cases, an acceptable alternative to DL catheters in providing a temporary vascular access.

In conclusion, the present study shows that using DL catheters often results in better URR. Differences obtained with SL catheters are limited and, especially when only a limited number of dialysis sessions are performed using catheters, of questionable clinical relevance.

Acknowledgements

Parts of this paper were presented at the 33rd Annual Scientific Meeting of the American Society of Nephrology, Toronto, Ontario, Canada, October 13-16, 2000. The authors would like to acknowledge the medical and nursing staff of Dianet Utrecht for their contributions to the present study.

References

1. Schwab SJ, Beathard G: The hemodialysis catheter conundrum: hate living with them, but can't live without them. *Kidney Int* 56: 1-17, 1999
2. National Kidney Foundation. K/DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 37 (Suppl 1): S137-S181, 2001
3. Leblanc M, Fedak S, Mokris G, Paganini EP: Blood recirculation in temporary central catheters for acute hemodialysis. *Clin Nephrol* 45: 315-319, 1996
4. Kelber J, Delmez JA, Windus DW: Factors affecting delivery of high efficiency dialysis using temporary vascular access. *Am J Kidney Dis* 22: 24-29, 1993

Chapter 8

Coagulation and haemodialysis access thrombosis

Johannes H.M. Smits[1], Joke van der Linden[2],
Peter J. Blankestijn[1], Ton J. Rabelink[3]

[1] Department of Nephrology, University Medical Center, Utrecht
[2] Department of Internal Medicine, Medisch Centrum Rijnmond-Zuid, location Clara, Rotterdam
[3] Department of Vascular Medicine, University Medical Center, Utrecht

Introduction

An increased thrombotic tendency is an important cause of complications in patients on chronic hemodialysis leading not only to possibly fatal complications like ischaemic heart disease, or stroke, but also to thrombosis of the vascular access [1]. This latter complication remains the main problem in vascular access for haemodialysis, particularly in polytetrafluoroethylene (PTFE) grafts. It accounts for considerable morbidity and mortality with an estimated annual cost of close to $1 billion in the United States. Moreover, vascular access complications mainly consisting of thrombotic events are responsible for 17 - 25% of all hospitalizations in dialysis patients [2-4].

In most cases thrombosis is associated with low access blood flow [5-7]. The most important reason for a decreasing access blood flow is intimal hyperplasia formation at the venous anastomosis or in the outflow tract of the graft [8-13]. However, not all decreases in access blood flow are related to intimal hyperplasia or stenosis formation. Other causes for low access flow leading to access thrombosis have been proposed (Table 1). Hypotension, hypovolaemia, or external compression may be involved in these non-stenotic thrombotic events [14]. Also, there has been a growing appreciation of the role of increased hypercoagulability found in these patients.

This review will discuss coagulability abnormalities in relation to haemodialysis access thrombosis. First, an outline will be given regarding normal haemostatic and fibrinolytic responses. Subsequently, we will focus on coagulation abnormalities leading to the thrombotic tendency in chronic haemodialysis patients. And finally, preventative measures for these coagulation defects will be discussed.

Normal haemostasis and fibrinolysis

Normal haemostatic responses are initiated by damage of the vessel wall with exposure of subendothelial structures to flowing blood and results in the formation of a solid haemostatic plug. The first step of this haemostatic response involves platelet adherence to the

Table 1. Possible causes of vascular access thrombosis

Low access blood flow
-intimal hyperplasia
-hypotension
-hypovolaemia
-external compression
Hypercoagulability

subendothelium [15-17]. The number of platelets available for this process is determined by platelet count. It is however, even more dependent on red blood cell-mediated transport of circulating platelets towards the vessel wall [17-19]. The adhesion of platelets to the site of injury is initially mediated by interactions between specific platelet receptors (e.g. glycoprotein Ib) and adhesive proteins in or deposited on the subendothelium (e.g. von Willebrand factor, vWF) [20-22]. The quality of the platelet adhesion, however, depends strongly on subsequent platelet activation. Platelet activation is initiated by stimuli originating from the vessel wall but is sustained by products released from activated platelets themselves, for example thromboxane and adenosine diphosphate (ADP) [22]. Platelet activation leads to expression of additional receptors on platelet membranes which support platelet interaction with subendothelium (e.g. glycoprotein IIb/IIIa) [22-25]. Most importantly, however, these receptors mediate platelet-platelet interactions resulting in aggregate formation.

Normal haemostasis also involves initiation of coagulation at sites of vessel wall injury that starts with activation of factor VII from flowing blood by tissue factor present in the vessel wall. The key products of the coagulation cascade are thrombin and fibrinogen. Thrombin proteolytically converts fibrinogen to insoluble fibrin, which in its turn activates factor XIII that causes cross-linking of fibrin fibres [26]. With collagen, thrombin is also a main stimulus of platelet activation and aggregation [22]. Fibrin is able to stabilize platelet aggregates and other cellular elements in a shear stress resistant network. Pathological thrombin formation is prevented by natural anticoagulant systems, of which antithrombin III and the vitamin K-dependent protein C systems are the most important ones. In addition to these anticoagulant systems the fibrinolytic system generates plasmin by the action of tissue plasminogen activator on plasminogen. Plasmin dissolves the fibrin clot and thereby prevents pathological thrombus formation. Thus, normal haemostatic responses require both coagulation and platelet-dependent processes.

In haemodialysis patients complex coagulation abnormalities occur ranging from bleeding to thrombosis [1,27]. On the one hand, the enhanced bleeding tendency in these patients is primarily based on functional platelet abnormalities and defective adhesion to the vessel wall [28,29]. On the other hand, a variety of coagulation abnormalities contribute to an increased thrombotic tendency.

Factors in chronic haemodialysis patients contributing to thrombotic tendency

Hypercoagulability in patients on chronic haemodialysis can be caused by a variety of factors, mainly consisting of platelet abnormalities and plasma factor abnormalities (Table 2).

Platelet abnormalities

Platelet abnormalities are common in patients on haemodialysis. Paradoxically, most studies on platelet abnormalities in haemodialysis patients have focused on adhesion defects leading to an increased bleeding tendency. So, first of all, do these platelets actually play a role in the thrombotic tendency seen in patients on haemodialysis? In other words, are there abnormal circumstances leading to an increase of thromboembolic complications in a setting of dysfunctional platelets? Indeed, there are indications that this is the case. Although these platelet abnormalities exist which favour a bleeding tendency, other circumstances may actually lead to an increase in thrombotic complications. First of all, although some studies suggest a decreased membrane expression or an abnormal activation of platelet receptors (glycoprotein Ib and IIb/IIIa) [30,31], an increase in platelet receptor number may be related to frequent access obstruction [32]. Also, haemodialysis is thought to activate platelets by adherence to the extracorporeal circuit [33,34]. In addition to extracorporeal activation, high shear stress and turbulence in the vascular access may be responsible for further platelet activation [35,36]. Another condition favouring vascular access clotting is that the artificial surface of the PTFE graft, and to a lesser extent the native arteriovenous (AV) fistula, promotes the adhesion of fibrinogen [37,38]. Serum fibrinogen, which is increased in haemodialysis patients, adheres to glycoprotein IIb/IIIa on the surface of the platelet. Once attached to the surface (solid

Table 2. Factors contributing to an increased thrombotic tendency in patients on chronic haemodialysis

Platelet factors
-blood - artificial surface interaction
-treatment with recombinant human erythropoetin
-increased platelet count
-platelet activation due to high shear stress in the vascular access
Plasma factor abnormalities
-increased levels of vWF
-hyperfibrinogenaemia
-increased thrombin formation
-reduced levels of protein C anticoagulant activity
-high levels of factor VIII procoagulant
-decreased levels and reduced activity of antithrombin III
-impaired release of plasminogen activator
-increased levels of antiphospholipid antibodies
-increased levels of homocysteine

phase fibrinogen) it can also bind to inactivated platelets, thereby activate them, and further enhance platelet deposition on the surface [37]. Indeed, Windus *et al.* [39] have shown that platelets are deposited along the vascular access surface. Another possible complementary explanation could be that clotting factor (contact factors like factor XII) deposition may lead to local thrombin formation, platelet activation, and enhanced platelet deposition [40].
Adherent platelets may release factors (platelet-derived growth factor (PDGF), for example) which lead to or enhance intimal hyperplasia in the vascular access and thereby reduce blood flow through the access, which allows other activated or non-activated platelets to aggregate more easily. This creates, despite a bleeding tendency, a favourable situation for thrombosis.

Plasma factor abnormalities

Uraemic subjects have higher levels of fibrinogen while at the same time thrombin formation is increased [41,42]. Song *et al.* [43] showed that a high plasma fibrinogen level is an independent risk factor for vascular access failure in haemodialysis patients. In addition, levels of antithrombin III may be decreased and antithrombin III activity may be reduced [44,45]. The subsequent increase of in vivo fibrinogen-fibrin transformation is reflected by increased fibrinopeptide A formation.
Erdem *et al.* [46] also provided evidence for a substantial contribution of the vascular access itself to the modulation of the thrombotic tendency. By taking blood samples from the vascular access and from contralateral large veins in end-stage renal disease (ESRD) patients and from peripheral veins in control subjects, they showed not only a difference in parameters of thrombotic tendency between peripheral vein samples in ESRD patients and controls, but more importantly, also between vascular access samples and peripheral vein samples in the same ESRD patient group.
Others have shown that in antiphospholipid antibodies are predictive of vascular access thrombosis [45,47-49]. These antibodies include lupus anticoagulant (LA), anticardiolipin antibodies (ACA), and antiphosphatidyl serine antibodies. Higher titres of both ACA and LA antibodies have been demonstrated in patients with ESRD than in the general population [48,50,51]. Elevated LA antibody titres are present in up to one-third of haemodialysis patients [48]. Elevated ACA antibody titres have been found in 0 - 29% of them [48,52,53], with a greater prevalence in patients with AV grafts (22%) than with native AV fistulae (6%) [47]. However, the association between elevated ACA antibody titre and increased access thrombosis is not fully established yet. While several studies found no association [48,52,54], Prakash *et al.* [47] demonstrated in a retrospective study a 3.7 times increased risk of recurrent thrombosis in patients with PTFE grafts having elevated ACA antibody titres. The latter finding was recently confirmed in a prospec-

tive study: the survival time of PTFE grafts in patients with elevated titres was significantly shorter than in patients with normal titres. Interestingly, this difference was not found in patients with native AV fistula [53].
Hyperhomocysteinaemia is an independent risk factor for recurrent and early-onset venous thrombosis in patients with normal renal function [55-57]. Fasting homocysteine levels have been shown to be elevated in patients with ESRD [58] and may contribute to atherosclerosis and subsequent cardiovascular events in haemodialysis patients [59,60]. The underlying mechanism by which hyperhomocysteinaemia provokes thrombosis is uncertain. It may involve a change in factor V and protein C complex activity as well as effects on platelet function [56,61,62].
Studies on the association of homocysteine and access thrombosis are limited and the results are controversial. In a retrospective study by Manns *et al.* [52] no association between homocysteine level and access thrombosis was found. Two recent prospective studies showed conflicting results. Shemin *et al.* [63] demonstrated a 4% increase in the risk of access thrombosis with each 1 µmol/l increase of plasma homocysteine concentration for both AV fistulae and grafts. Similarly, Ducloux *et al.* [64] suggested that hyperhomocysteinaemia is a risk factor for vascular access thrombosis. However, such an association could not be demonstrated in a population of 96 patients with only native AV fistulae. The patients with the lowest levels even appeared to have an increased mortality risk [65]. These conflicting differences in outcome may be related to the type of fistula, to the length of follow-up, and to other variables. Obviously, long-term prospective studies with serial, instead of occasional, determinations of plasma homocysteine are needed to solve this issue.

Therapeutic considerations

Anti-platelet therapy

The usefulness of antiplatelet therapy for the maintenance of internal haemodialysis access devices was reviewed by the Antiplatelet Trialists' Collaboration Group [66]. Outcomes of nine placebo-controlled randomized trials showed an occlusion rate of 17% in the antiplatelet groups vs 39% in the control groups. Antiplatelet regimens consisted of ticlopidine (five studies), aspirin (two studies), and sulphinpyrazone (two studies). Unfortunately, most of the evaluated studies were conducted in the late 1970s and the beginning of the 1980s. At that time some of the achievements in modern dialysis were not yet available, and dialysis populations differed from those of today. Moreover, these studies had only a short follow-up (mean 2 months). Finally, the analysis report was difficult to interpret in terms of excess bleeding due to antiplatelet therapy.
Only one randomized, placebo-controlled clinical trial comparing access thrombosis fre-

quency in patients treated with antiplatelet therapy (dipyridamole 75 mg orally 3 times a day, or aspirin 325 mg orally daily) was conducted in the last decade. Surprisingly, dipyridamole alone, which is considered a relatively weak platelet inhibitor, had the best outcome, while patients on aspirin had the highest frequency of thrombosis, even higher than with placebo or the combination of dipyridamole and aspirin [67]. The results of this study became more understandable after the authors conducted a series of in vitro experiments using vascular smooth muscle cells [68,69]. They could show that aspirin potentiated PDGF-induced vascular smooth-muscle cell proliferation by shunting arachidonic acid from cyclo-oxygenase into lipoxygenase pathways. On the other hand, dipyridamole profoundly inhibited PDGF- and bFGF-induced vascular smooth-muscle cell proliferation. This suggests that the observed direct effect of aspirin and dipyridamole on vascular smooth-muscle cell proliferation (rather than the antiplatelet effect) is a better explanation for the reported clinical efficiency of dipyridamole. Gastrointestinal bleeding occurred in 16% of the treated patients vs 8% in the placebo group. Unfortunately, no anatomical data or functional data (e.g. vascular access flow) was collected in the randomized trial [67]. This could have provided further in vivo evidence for the experimental in vitro data.
Finally, Windus *et al.* [70] showed that aspirin and ticlopidine both reduced dialysis-associated platelet deposition in PTFE grafts, although they did not completely prevent it.

Oral anticoagulation

Current opinions on the use of systemic anticoagulant therapy to improve access patency is primarily based on personal belief rather than on evidence. Not surprisingly, the reason is that systematic data on this subject are very limited. Interestingly, despite the lack of consensus nephrologists do not refrain from prescribing anticoagulants. As a consequence numerous different anticoagulant strategies exist from centre to centre as to patient selection, dosing scheme, and treatment duration.
In 1967, the effect of coumadin in reducing the clotting frequency of AV Scribner shunts was first reported in three dialysis patients [71]. A few years later coumadin was shown to prolong cannula shunt life in non-uraemic sheep [72]. However, in several recent studies aimed at evaluating risk factors for vascular access dysfunction, anticoagulants were either not used in the study population or their use was not mentioned. Nevertheless, the use of anticoagulants was advocated based on the hypercoagulable state often found in the dialysis patients under study [48,73]. In a recent Japanese study in 83 dialysis patients with AV fistula dysfunction, no association was found with prior anticoagulant use or prothrombin time [74]. However, the criteria mentioned for fistula dysfunction were vague and the distribution of various access types (AV fistula or PTFE) in this population

was not mentioned. Dialysis patients with a history of early vascular access graft loss or frequent thrombosis showed a twofold prolongation of access survival time and less frequent clotting after initiation of coumadin [53,75]. However, these results were based on small numbers and obtained with patients being their own controls. Bleeding complications seen in these studies occurred in patients with high international normalized ratio (INR) levels. Also, LeSar *et al.* [45] showed in a subgroup of dialysis patients with frequent PTFE graft thrombosis and a hypercoagulable state (i.e. prevalence of antiphospholipid antibodies, anti-thrombin III and protein C system abnormalities), that oral anticoagulant therapy effectively decreased thrombosis frequency, particularly with INR values maintained at 2.7 - 3.0. However, the incidence of significant bleeding complications in this subset of patients was 10% per year. By administering coumadin, Valeri *et al.* [53] increased the survival of access grafts in 16 patients with elevated ACA antibody titres and frequent access thrombosis. However, the absolute duration of graft survival in the treated group was not impressive (48 ± 12 days in the untreated group vs 103 ± 26 days in the patients on coumadin with target INR values of 2.0 - 3.0). Two patients suffered major bleeding complications, although both had an overshoot of target INR (> 8).

Conclusion

Despite the bleeding tendency of chronic haemodialysis patients, vascular access thrombosis is a frequent complication. Hypercoagulability is one of the causes contributing to the high frequency of access thrombosis. The hypercoagulable state can be explained by platelet and coagulation factor abnormalities. Unfortunately, few randomized placebo-controlled trials were conducted using antiplatelet or oral anticoagulation therapy. Therefore, no evidence-based consensus has been established regarding pharmacological prevention of access thrombosis. It still needs to be determined whether the potential benefits of anticoagulation and antiplatelet therapy outweigh the risk of adverse events. In the meantime it seems reasonable to give some form of anticoagulant therapy based on pathophysiological considerations and the high incidence of thrombotic complications. Our group recently demonstrated that graft flow measurements could effectively predict thrombotic vascular access events [76]. Risk tables that take into account such parameters as well as plasma markers of hypercoagulability may help to develop rationally designed trials and guidelines.

References

1. Lindner A, Charra B, Sherrard DJ, Scribner BH: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 290: 697-701, 1974
2. Feldman HI, Kobrin S, Wasserstein A: Hemodialysis vascular access morbidity. *J Am Soc Nephrol* 7: 523-535, 1996
3. U.S. Renal Data System. The economic cost of ESRD, vascular access procedures, and Medicare spending for alternative modalities of treatment. *Am J Kidney Dis* 30 (Suppl 1): S160-S177, 1997
4. Feldman HI, Held PJ, Hutchinson JT, Stoiber E, Hartigan MF, Berlin JA: Hemodialysis vascular access morbidity in the United States. *Kidney Int* 43: 1091-1096, 1993
5. Bosman PJ, Boereboom FTJ, Eikelboom BC, Koomans HA, Blankestijn PJ: Graft flow as a predictor of thrombosis in hemodialysis grafts. *Kidney Int* 54: 1726-1730, 1998
6. Smits JHM, Blankestijn PJ: Haemodialysis access: the case for prospective monitoring. *Curr Opin Nephrol Hypertens* 8: 685-690, 1999
7. Diskin CJ, Stokes TJJ, Pennell AT: Pharmacologic intervention to prevent hemodialysis vascular access thrombosis. *Nephron* 64: 1-26, 1993
8. Bassiouny HS, White S, Glagov S, Choi E, Giddens DP, Zarins CK: Anastomotic intimal hyperplasia: mechanical injury or flow induced. *J Vasc Surg* 15: 708-716, 1992
9. Kanterman RY, Vesely TM, Pilgram TK, Guy BW, Windus DW, Picus D: Dialysis access grafts: anatomic location of venous stenosis and results of angioplasty. *Radiology* 195: 135-139, 1995
10. Roberts AB, Kahn MB, Bradford S, Lee J, Ahmed Z, Fitzsimmons J, Ball D: Graft surveillance and angioplasty prolongs dialysis graft patency. *J Am Coll Surg* 183: 486-492, 1996
11. Safa AA, Valji K, Roberts AC, Ziegler TW, Hye RJ, Oglevie SB: Detection and treatment of dysfunctional hemodialysis access grafts: effect of a surveillance program on graft patency and the incidence of thrombosis. *Radiology* 199: 653-657, 1996
12. Smits HF, Van Rijk PP, Van Isselt JW, Mali WP, Koomans HA, Blankestijn PJ: Pulmonary embolism after thrombolysis of hemodialysis grafts. *J Am Soc Nephrol* 8: 1458-1461, 1997
13. Smits JHM, Blankestijn PJ: Thrombosis-free hemodialysis grafts: a possibility for the next century? *Semin Dial* 12: 44-49, 1999
14. Windus DW: Permanent vascular access: a nephrologist's view. *Am J Kidney Dis* 21: 457-471, 1993
15. Sakariassen KS, Bolhuis PA, Sixma JJ: Platelet adherence to subendothelium of human arteries in pulsatile and steady flow. *Thromb Res* 19: 547-559, 1980
16. Baumgartner HR: The role of blood flow in platelet adhesion, fibrin deposition, and formation of mural thrombi. *Microvasc Res* 5: 167-179, 1973
17. Turitto VT, Weiss HJ, Baumgartner HR: Rheological factors influencing platelet interaction with vessel wall surfaces. *J Rheol* 23: 735-749, 1979

18. Aarts PA, Bolhuis PA, Sakariassen KS, Heethaar RM, Sixma JJ: Red blood cell size is important for adherence of blood platelets to artery subendothelium. *Blood* 62: 214-217, 1983
19. Aarts PA, Heethaar RM, Sixma JJ: Red blood cell deformability influences platelets—vessel wall interaction in flowing blood. *Blood* 64: 1228-1233, 1984
20. Stel HV, Sakariassen KS, de Groot PG, van Mourik JA, Sixma JJ: Von Willebrand factor in the vessel wall mediates platelet adherence. *Blood* 65: 85-90, 1985
21. Coller BS, Peerschke EI, Scudder LE, Sullivan CA: Studies with a murine monoclonal antibody that abolishes ristocetin-induced binding of von Willebrand factor to platelets: additional evidence in support of GPIb as a platelet receptor for von Willebrand factor. *Blood* 61: 99-110, 1983
22. Sixma JJ, Wester J: The hemostatic plug. *Semin Hematol* 14: 265-299, 1977
23. Niiya K, Hodson E, Bader R, Byers-Ward V, Koziol JA, Plow EF, Ruggeri ZM: Increased surface expression of the membrane glycoprotein IIb/IIIa complex induced by platelet activation. Relationship to the binding of fibrinogen and platelet aggregation. *Blood* 70: 475-483, 1987
24. Ruggeri ZM, De Marco L, Gatti L, Bader R, Montgomery RR: Platelets have more than one binding site for von Willebrand factor. *J Clin Invest* 72: 1-12, 1983
25. Solum NO: Procoagulant expression in platelets and defects leading to clinical disorders. *Arterioscler Thromb Vasc Biol* 19: 2841-2846, 1999
26. Furie B, Furie BC: Molecular and cellular biology of blood coagulation. *N Engl J Med* 326: 800-806, 1992
27. Eberst ME, Berkowitz LR: Hemostasis in renal disease: pathophysiology and management. *Am J Med* 96: 168-179, 1994
28. Castillo R, Lozano T, Escolar G, Revert L, Lopez J, Ordinas A: Defective platelet adhesion on vessel subendothelium in uremic patients. *Blood* 68: 337-342, 1986
29. Escolar G, Cases A, Bastida E, Garrido M, Lopez J, Revert L, Castillo R, Ordinas A: Uremic platelets have a functional defect affecting the interaction of von Willebrand factor with glycoprotein IIb-IIIa. *Blood* 76: 1336-1340, 1990
30. Sloand JA, Sloand EM: Studies on platelet membrane glycoproteins and platelet function during hemodialysis. *J Am Soc Nephrol* 8: 799-803, 1997
31. Benigni A, Boccardo P, Galbusera M, Monteagudo J, De Marco L, Remuzzi G, Ruggeri ZM: Reversible activation defect of the platelet glycoprotein IIb-IIIa complex in patients with uremia. *Am J Kidney Dis* 22: 668-676, 1993
32. Liani M, Salvati F, Tresca E, Di Paolo G, Vitacolonna L, Golato M, Velussi C: Arteriovenous fistula obstruction and expression of platelet receptors for von Willebrand factor and for fibrinogen (glycoproteins GPIb and GPIIb/IIIa) in hemodialysis patients. *Int J Artif Organs* 19: 451-454, 1996
33. Hakim RM, Schafer AI: Hemodialysis-associated platelet activation and thrombocytopenia. *Am J Med* 78: 575-580, 1985

34. Cases A, Reverter JC, Escolar G, Sanz C, Lopez-Pedret J, Revert L, Ordinas A: Platelet activation on hemodialysis: influence of dialysis membranes. *Kidney Int* 43 (Suppl 41): S217-S220, 1993
35. Turitto VT, Hall CL: Mechanical factors affecting hemostasis and thrombosis. *Thromb Res* 92 (Suppl 2): S25-S31, 1998
36. Viener A, Aviram M, Better OS, Brook JG: Enhanced in vitro platelet aggregation in hemodialysis patients. *Nephron* 43: 139-143, 1986
37. Savage B, Ruggeri ZM: Selective recognition of adhesive sites in surface-bound fibrinogen by glycoprotein IIb-IIIa on nonactivated platelets. *J Biol Chem* 266: 11227-11233, 1991
38. Salzman EW, Lindon J, McManama G, Ware JA: Role of fibrinogen in activation of platelets by artificial surfaces. *Ann N Y Acad Sci* 516: 184-195, 1987
39. Windus DW, Santoro S, Royal HD: The effects of hemodialysis on platelet deposition in prosthetic graft fistulas. *Am J Kidney Dis* 26: 614-621, 1995
40. Colman RW, Scott CF, Schmaier AH, Wachtfogel YT, Pixley RA, Edmunds LHJ: Initiation of blood coagulation at artificial surfaces. *Ann N Y Acad Sci* 516: 253-267, 1987
41. Sagripanti A, Cupisti A, Baicchi U, Ferdeghini M, Morelli E, Barsotti G: Plasma parameters of the prothrombotic state in chronic uremia. *Nephron* 63: 273-278, 1993
42. Tomura S, Nakamura Y, Deguchi F, Ando R, Chida Y, Marumo F: Coagulation and fibrinolysis in patients with chronic renal failure undergoing conservative treatment. *Thromb Res* 64: 81-90, 1991
43. Song IS, Yang WS, Kim SB, Lee JH, Kwon TW, Park JS: Association of plasma fibrinogen concentration with vascular access failure in hemodialysis patients. *Nephrol Dial Transplant* 14: 137-141, 1999
44. Lai KN, Yin JA, Yuen PM, Li PK: Effect of hemodialysis on protein C, protein S, and antithrombin III levels. *Am J Kidney Dis* 17: 38-42, 1991
45. LeSar CJ, Merrick HW, Smith MR: Thrombotic complications resulting from hypercoagulable states in chronic hemodialysis vascular access. *J Am Coll Surg* 189: 73-79, 1999
46. Erdem Y, Haznedaroglu IC, Celik I, Yalcin AU, Yasavul U, Turgan C, Caglar S: Coagulation, fibrinolysis and fibrinolysis inhibitors in haemodialysis patients: contribution of arteriovenous fistula. *Nephrol Dial Transplant* 11: 1299-1305, 1996
47. Prakash R, Miller CC, Suki WN: Anticardiolipin antibody in patients on maintenance hemodialysis and its association with recurrent arteriovenous graft thrombosis. *Am J Kidney Dis* 26: 347-352, 1995
48. Brunet P, Aillaud MF, San Marco M, Philip-Joet C, Dussol B, Bernard D, Juhan-Vague I, Berland Y: Antiphospholipids in hemodialysis patients: relationship between lupus anticoagulant and thrombosis. *Kidney Int* 48: 794-800, 1995
49. Prieto LN, Suki WN: Frequent hemodialysis graft thrombosis: association with antiphospholipid antibodies. *Am J Kidney Dis* 23: 587-590, 1994

50. Garcia-Martin F, De Arriba G, Carrascosa T, Moldenhauer F, Martin-Escobar E, Val J, Saiz F: Anticardiolipin antibodies and lupus anticoagulant in end-stage renal disease. *Nephrol Dial Transplant* 6: 543-547, 1991
51. Sitter T, Schiffl H: Anticardiolipin antibodies in patients on regular hemodialysis: an epiphenomenon? *Nephron* 64: 655-656, 1993
52. Manns BJ, Burgess ED, Parsons HG, Schaefer JP, Hyndman ME, Scott-Douglas NW: Hyperhomocysteinemia, anticardiolipin antibody status, and risk for vascular access thrombosis in hemodialysis patients. *Kidney Int* 55: 315-320, 1999
53. Valeri A, Joseph R, Radhakrishnan J: A large prospective survey of anti-cardiolipin antibodies in chronic hemodialysis patients. *Clin Nephrol* 51: 116-121, 1999
54. George J, Aron A, Levy Y, Gilburd B, Ben-David A, Renaudineau Y, Zonana-Nachach A, Youinou P, Harats D, Shoenfeld Y: Anti-cardiolipin, anti-endothelial-cell and anti-malondialdehyde-LDL antibodies in uremic patients undergoing hemodialysis: relationship with vascular access thrombosis and thromboembolic events. *Hum Antibodies* 9: 125-131, 1999
55. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG: A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. *JAMA* 274: 1049-1057, 1995
56. den Heijer M, Blom HJ, Gerrits WB, Rosendaal FR, Haak HL, Wijermans PW, Bos GM: Is hyperhomocysteinaemia a risk factor for recurrent venous thrombosis? *Lancet* 345: 882-885, 1995
57. Selhub J, D'Angelo A: Relationship between homocysteine and thrombotic disease. *Am J Med Sci* 316: 129-141, 1998
58. Bostom AG, Lathrop L: Hyperhomocysteinemia in end-stage renal disease: prevalence, etiology, and potential relationship to arteriosclerotic outcomes. *Kidney Int* 52: 10-20, 1997
59. Bostom AG, Shemin D, Verhoef P, Nadeau MR, Jacques PF, Selhub J, Dworkin L, Rosenberg IH: Elevated fasting total plasma homocysteine levels and cardiovascular disease outcomes in maintenance dialysis patients. A prospective study. *Arterioscler Thromb Vasc Biol* 17: 2554-2558, 1997
60. Moustapha A, Naso A, Nahlawi M, Gupta A, Arheart KL, Jacobsen DW, Robinson K, Dennis VW: Prospective study of hyperhomocysteinemia as an adverse cardiovascular risk factor in end-stage renal disease. *Circulation* 97: 138-141, 1998
61. McCully KS, Carvalho AC: Homocysteine thiolactone, N-homocysteine thiolactonyl retinamide, and platelet aggregation. *Res Commun Chem Pathol Pharmacol* 56: 349-360, 1987
62. Graeber JE, Slott JH, Ulane RE, Schulman JD, Stuart MJ: Effect of homocysteine and homocystine on platelet and vascular arachidonic acid metabolism. *Pediatr Res* 16: 490-493, 1982
63. Shemin D, Lapane KL, Bausserman L, Kanaan E, Kahn S, Dworkin L, Bostom AG: Plasma total homocysteine and hemodialysis access thrombosis: a prospective study. *J Am Soc Nephrol* 10: 1095-1099, 1999

64. Ducloux D, Pascal B, Jamali M, Gibey R, Chalopin JM: Is hyperhomocysteinaemia a risk factor for recurrent vascular access thrombosis in haemodialysis patients? *Nephrol Dial Transplant* 12: 2037-2038, 1997
65. Sirrs S, Duncan L, Djurdjev O, Nussbaumer G, Ganz G, Frohlich J, Levin A: Homocyst(e)ine and vascular access complications in haemodialysis patients: insights into a complex metabolic relationship. *Nephrol Dial Transplant* 14: 738-743, 1999
66. Collaborative overview of randomised trials of antiplatelet therapy— II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. Antiplatelet Trialists' Collaboration. *BMJ* 308: 159-168, 1994
67. Sreedhara R, Himmelfarb J, Lazarus JM, Hakim RM: Anti-platelet therapy in graft thrombosis: results of a prospective, randomized, double-blind study. *Kidney Int* 45: 1477-1483, 1994
68. Harvey R, Bredenberg CE, Couper L, Himmelfarb J: Aspirin enhances platelet-derived growth factor-induced vascular smooth muscle cell proliferation. *J Vasc Surg* 25: 689-695, 1997
69. Himmelfarb J, Couper L: Dipyridamole inhibits PDGF- and bFGF-induced vascular smooth muscle cell proliferation. *Kidney Int* 52: 1671-1677, 1997
70. Windus DW, Santoro SA, Atkinson R, Royal HD: Effects of antiplatelet drugs on dialysis-associated platelet deposition in polytetrafluoroethylene grafts. *Am J Kidney Dis* 29: 560-564, 1997
71. Wing AJ, Curtis JR, De Wardener HE: Reduction of clotting in Scribner shunts by long-term anticoagulation. *Br Med J* 3: 143-145, 1967
72. Boyd SJJ, Dennis MB, Nogami RT, Cole JJ, Scribner BH: Prophylactic coumadin and A-V cannula function. *J Appl Physiol* 37: 6-7, 1974
73. Ambühl PM, Wüthrich RP, Korte W, Schmid L, Krapf R: Plasma hypercoagulability in haemodialysis patients: impact of dialysis and anticoagulation. *Nephrol Dial Transplant* 12: 2355-2364, 1997
74. Masaki T, Yorioka N, Kyuden Y, Yamashita K, Taniguchi Y, Yamakido M, Tanaka J, Harada S: Factors influencing arteriovenous fistula dysfunction in Japanese patients on chronic hemodialysis. *Int J Artif Organs* 22: 14-17, 1999
75. Tevlin MT, Portner ME, Kraus MG, Dulaney JT: Clotting frequency of hemodialysis accesses before and after systemic anticoagulation with coumadin. [Abstract] *J Am Soc Nephrol* 7 (ASN Program and Abstracts): A1421, 1996
76. Blankestijn PJ, Smits JH: How to identify the haemodialysis access at risk of thrombosis? Are flow measurements the answer? *Nephrol Dial Transplant* 14: 1068-1071, 1999

Chapter 9

General discussion

General discussion

Nowadays, hemodialysis offers an important treatment modality for patients with end-stage renal disease (ESRD). Many problems with hemodialysis technique and equipment have been dealt with. With hemodialysis, ESRD patients can survive for many years. However, patients on hemodialysis require an access to their bloodstream three times a week. Because of its low infection and thrombosis rate, the Brescia-Cimino (radio-cephalic) fistula is still regarded as the first choice for the creation of a vascular access for hemodialysis [1]. Unfortunately, not all patients have suitable vessels to construct an AV fistula, mainly because of their insufficient caliber or sclerosis due to prior venipunctures. Due to ageing of the dialysis population and prolongation of the dialysis therapy, more and more secondary accesses are used. These secondary accesses can consist of intravenous catheters or, more commonly, a modification of the AV fistula: an interposition graft between an artery and a vein. The interposition AV graft functions as a vascular access by itself. Nowadays, AV grafts are predominantly manufactured from expanded polytetrafluoroethylene (PTFE).

Unfortunately, these PTFE AV grafts show a thrombosis rate of 0.5 - 2.5 per patient-year [1-5] resulting in considerable morbidity and even mortality [6,7]. For the United States, it was calculated that vascular access morbidity is responsible for an estimated annual cost of close to $1 billion and accounts for 17 - 25% of all dialysis patients hospitalizations [8-11]. Because of these complications the NKF-K/DOQI guidelines on vascular access suggest that vascular access using AV grafts may only be considered, if it is not possible to establish either a radio-cephalic or a brachio-cephalic AV fistula [1,12]. Despite the higher rate of thrombosis and its subsequent morbidity, an increasing number of patients depend on an AV graft. In some populations in the United States, AV grafts account for as many as 83% of access placements [13]. Because of the increasing age of the hemodialysis patients, establishment of an AV fistula in those patients becomes difficult due to insufficient vessels. Also, the number of patients with end-stage renal disease (ESRD) requiring hemodialysis is increasing worldwide [14]. In The Netherlands the use of AV grafts is increasing at the expense of AV fistulae [15]. As a consequence, patients and physicians alike are more frequently confronted with vascular access complications, particularly thrombosis.

Vascular access surveillance

In most cases thrombosis is associated with the presence of stenoses at the venous anastomosis or in the outflow tract [16-20]. Stenosis increases resistance over the flow tract. Because the graft has no autoregulating capacities, blood flow (Qa) drops and venous pressures (VP) rise. These variables have been shown to predict thrombosis. More importantly, several studies demonstrated that referral for corrective intervention based on these parameters can prevent thrombosis [21-25].

Patients with outflow stenosis have on average a higher VP and/or lower Qa [21,26]. However, VP does not correlate with Qa. In other words not all patients with high VP had low Qa, indicating that not all patients who are at risk for thrombosis can be identified by VP measurements. It is also shown that inflow resistance (that is resistance of the flow tract upstream of the venous needle) comprises a substantial and very variable part of total graft resistance. Indeed, several studies have indicated that in up to 29% of thrombosis cases, stenoses may be located in the arterial part of the graft [20,27-30]. The inflow resistance is not reflected by VP measurements, whereas Qa measurements are a reflection of total graft resistance. This could make VP less effective as selection parameter for patients at risk for thrombosis than Qa. In contrast to Qa measurements, VP can be measured by the dialysis machine, is easy to obtain and requires little time investment. Furthermore, some studies have convincingly indicated that the use of VP measurements as a selection variable for diagnostic and subsequent corrective procedures, results in thrombosis rates between 0.2 and 0.4 events per patient-year [3,21,23]. Although the theoretical basis was provided that Qa measurements are better than VP measurements, the question is whether Qa measurements really confer additional benefit in patients who are monitored by VP. In other words, when simple clinical variables such as VP are used, is there any additional benefit when periodic Qa measurements are added to the surveillance protocol?

We addressed these questions in ***chapter 3*** with the following hypotheses: Qa measurements are better than VP measurements in identifying patients at risk for thrombosis. As a consequence, referral of patients for corrective interventions based on Qa measurements alone or on the combination of VP and Qa reduces thrombosis rate more than referral based on VP alone.

We found that thrombosis rates in patients monitored and selected for corrective interventions based on VP or Qa can be maintained below the quality of care standards formulated by the NKF-DOQI committee [1]. Secondly, we showed that thrombosis rates in groups monitored by VP or Qa alone or by the combination of tests do not differ. Thirdly, only a small minority of patients was selected for corrective interventions by Qa alone in the group with combined monitoring of VP and Qa. Fourthly, after obtaining abnormal tests subsequent diagnostic and interventional procedures should be instituted

on short notice. It seems likely that the number of thromboses during the waiting time can be reduced. Finally, we confirmed that static VP is more effective than dynamic VP for monitoring dialysis grafts.
What may be the implications of the present study for everyday clinical practice? We showed that using the surveillance protocol of this study outcome with respect to thrombosis rate is equal in Qa monitored grafts and in VP monitored grafts and that there is no rationale in combining the two methods. Each dialysis center should decide which method is best suitable for their dialysis practice. VP measurements are easy to obtain and require little time investment. However, they need discipline. Qa measurements are more time consuming and a special device is needed. We showed that by measuring Qa every 4 to 8 weeks identical results can be obtained as with weekly VP assessments. The decision which method to use, will be primarily based on the preferences of those involved in the access care and on the possibilities to implement a certain surveillance strategy.
So, we have demonstrated that standardized monitoring of VP or Qa or the combination of both and subsequent corrective intervention can decrease thrombosis rates to below 0.5 per patient-year, which is recommended by the Vascular Access Task Force of the NKF-DOQI Committee as quality of care standard [1]. When applying our study protocol, VP, Qa, or the combination as variables for selection of patients for corrective intervention are equally effective in reducing thrombosis rates in hemodialysis access grafts.

Access imaging

To treat a failing access (either by percutaneous transluminal angioplasty (PTA) or by surgical intervention [1]), it is necessary to identify the underlying problem, i.e. in most cases one or more stenoses, predominantly found at the anastomosis of an AVF and at the venous anastomosis of an AVG [17-20,31]. The conventional technique to identify and locate stenosis has predominantly been digital subtraction angiography (DSA). However, there are several drawbacks: the radiation load for the patient and radiology personnel, the use of potentially nephrotoxic iodinated contrast agents, and limited spatial information [32]. Magnetic resonance angiography (MRA) does not have these disadvantages and could offer an attractive alternative. In addition, MRA offers the possibility to measure access flow. Access flow has been shown to be a better parameter for impending vascular access failure than anatomical information alone [5,25,33].
However, a major problem with flow-based approaches to MRA, such as phase-contrast (PC) and time-of-flight (TOF), has always been the frequent occurrence of flow artifacts in regions with disturbed flow that complicate interpretation of the MR angiograms. Especially near stenoses (but also near bends and cusps [34]), the appearance of the lumen is distorted by a combination of dephasing, displacement and, for TOF methods,

saturation artifacts [35]. Application of PC and TOF to hemodialysis accesses, i.e. both AVF and AVG, also suffers from the above types of inaccuracies [36,37], but interpretation of the angiograms is further complicated by the large range of flow rates that occurs in these vessels: roughly 100 - 3000 ml/min. As flow disturbances tend to increase with flow rate, signal voids may easily arise at mild narrowings or sharp-angled anastomoses, when a high flow rate is present [38].
Contrast-enhanced (CE) MR angiography is less sensitive to these artifacts [39], and has been reported to improve hemodialysis access visualization, when compared to TOF and PC [40]. However, flow related artifacts remain present under the extreme flow conditions that occur in hemodialysis accesses [41]. To eliminate these artifacts, we borrow from the procedure used for DSA of the hemodialysis access, and use a cuff to obstruct the blood flow temporarily [42,43]. In ***chapter 4*** we validated this novel MRA technique anatomically, and for this purpose we compared anastomotic (AVG) and post-anastomotic diameters (AVF) of MRA images obtained with flow-interruption and selective contrast administration with those diameters scored on conventional DSA imaging of hemodialysis accesses.
We showed that selective flow-interrupted CE-MRA imaging is able to provide excellent quality images of hemodialysis AVF and AVG, which are free of flow artifacts. The high image quality of the MR angiograms is comparable with DSA. In combination with MR flow quantification and imaging of the outflow tract, our approach may provide a complete anatomical and functional evaluation of hemodialysis accesses on MR.

Access function after PTA

Routine surveillance programs for the early detection of stenoses followed by angioplasty have been shown to substantially reduce the number of thromboses per patient year [19,21,23,44]. However, repetitive PTA treatment is often necessary, since re-stenosis frequently occurs. Although the short term success rates of PTA range from 85% to 98% [45], patency at 6 months follow-up varies from 38% to 63% [17,22,23,46].
Several studies have shown that angiographic degree of the stenotic lesion before and after PTA is poorly related with its subsequent patency [17,22,33,47,48]. Recently, the SCVIR Technology Assessment Committee recommended that PTA efficacy should be expressed by both angiographic and functional parameters [49]. In particular, access flow (Qa) measurements offer the opportunity to quantify and follow up the functional effect of PTA.
In ***chapter 5*** we quantified the short-term functional and angiographic effect of PTA. Additionally, we determined the longevity of the functional effect during follow-up. Finally, we addressed the question whether functional variables are predictive for long-term outcome.

We demonstrated that angiographic results do not correlate with functional results. Importantly, we also showed that functional variables are predictive for long-term outcome, whereas angiographic results are not. The study confirms recent data indicating that PTA results in a direct increase in Qa of approximately 250 mL/min [50]. We also confirm that a substantial percentage of PTA is not successful. Finally, time to repeat PTA in our study is substantially shorter than in other studies [22,50,51]. This suggests a more rapid recurrence of stenosis in the present study. The combined data of these studies suggest that there is an optimal moment of PTA.

Thrombolysis

Thrombosis of the access graft is an acute problem for the patient on chronic hemodialysis and treatment should be initiated immediately after diagnosing graft thrombosis. Usually, patients are referred to the vascular surgeon who performs surgical thrombectomy, i.e. clot removal with a balloon catheter through a small incision in the graft. When this procedure is unsuccessful in restoring graft flow, which is often the case, graft revision is done. Graft revision often means that a new venous anastomosis is created. When revision of the graft is not possible, a new one is created. A patient has only a limited number of sites where a graft can be implanted. Therefore, it is of the utmost importance to preserve functioning access sites as long as possible [17,52]. Percutaneous thrombolysis typically tries to keep the local anatomic situation intact.

Therefore, percutaneous thrombolysis has become an accepted treatment of thrombosed hemodialysis grafts, and in many institutions clotted grafts are primarily referred to the radiologist [45,52]. The main difference with surgical thrombectomy is that the percutaneous techniques visualize the underlying problem, i.e. vascular stenosis. A number of percutaneous techniques have been reported. In pharmacological thrombolysis a lytic agent such as streptokinase or urokinase is administered intravenously or directly into the graft [53,54]. With pulse spray pharmacomechanical thrombolysis, using a dedicated multi side hole infusion catheter, lysis is accelerated by injecting the lytic agent into the clot [29,52]. Lysis of the clot can be accelerated even more by maceration of the clot with a mechanical device. These devices macerate the clot using different mechanical actions such as aspiration and fragmentation [55-57]. Over twenty devices for mechanical thrombolysis have been developed. Comparison of the efficacy of these devices is difficult. Most studies report on a single device only.

In our institution, we gained experience with three mechanical devices for thrombolysis (***chapter 6***). The mechanical devices were compared with respect to their efficacy of removing thrombus from hemodialysis access grafts. The first device was a rotating brush (Cragg brush catheter) that shreds the clot after which small fragments disperse in the bloodstream or embolize to the lungs [58]. According to the instructions of the man-

ufacturer, urokinase is applied to the thrombus before application of the brush to partially lyse the clot and to facilitate fragmentation and dissolution. When the Cragg brush was temporarily withdrawn from the market, we started to use the Hydrolyser, a hydrodynamic catheter [59,60]. The Hydrolyser fragments the thrombus by a high-velocity jet of saline, after which the clot fragments are suctioned and evacuated. The third device was a mechanically driven, rotating basket, which macerates the clot (Arrow-Trerotola PTD) [61]. After maceration of the clot with the PTD, most of the clot fragments are aspirated with a syringe through the device's introducer sheath and removed.
Clot removal was achieved in 66 of 67 cases. Clot removal with the rotational, wall contact type devices (i.e. the Cragg brush and the PTD) provided better clot removal than the Hydrolyser. However, the percent technical success after thrombolysis and the long-term patency rates did not differ between the different devices. Percutaneous thrombus treatment consists of two stages. First the clot is removed with the chosen device. When the graft is cleared of clot material, the underlying cause is visualized and subsequently treated with percutaneous transluminal angioplasty (PTA).
However, PTA was often unsuccessful, independent of the type of device used. In multivariate analysis, the percentage of residual stenosis after PTA was the single factor that determined long-term patency rates. It was concluded that clot removal was successful in almost every case independent of what device was used. The wall contact devices provided better clot removal than the Hydrolyser. The key issue of thrombolysis is the detection and subsequent correction of the underlying stenosis.

Temporary catheters

Catheters are widely used for temporary vascular access in hemodialysis patients [7]. Basically, two types of catheters are available: the single-lumen (SL) catheter and the double-lumen (DL) catheter. The Vascular Access Committee of the NKF-K/DOQI recommends the DL catheter for temporary vascular access [1]. Originally, the DL catheter was designed to alleviate the need for a double-pump system required for SL catheter dialysis [62]. Nowadays, most dialysis machines are equipped with a double-pump for SL dialysis. It has been suggested that SL catheters have several possible advantages over DL catheters. These include the following overall performance parameters: the smaller diameter resulting in easier insertion, a lower rate of infectious complications [62,63], a better patency, and less recirculation [64,65]. Also, it has been stated that the use of SL catheters tends to be cheaper in the short-term, i.e. less than a year [66]. However, to determine whether there is still a place for the SL catheter in modern dialysis, it is important to compare its ability to deliver an adequate dialysis dose to that of the DL catheter. In ***chapter 7***, we describe a prospective randomized study comparing SL and DL catheters in terms of adequacy of dialysis and overall performance.

We could not demonstrate a difference in adequacy for the short-term dialysis (3-hour) between SL versus DL catheters, and only a marginal difference for the longer-term dialysis (4-hour). Overall performance did not differ between SL and DL catheters.
The recommended URR of 0.65 by the NKF-K/DOQI Committee was not reached in either the SL or DL catheters [1]. A possible explanation for this could be that the chosen pump flow was not high enough to achieve sufficient URR. On the other hand, in a subset of patients dialyzing on DL catheters we looked at the URR with a dialysis pump flow of 200 mL/min versus 300 mL/min. Although the URR with a pump flow of 300 mL/min (0.49 ± 0.09) was higher than with a pump flow of 200 mL/min (0.41 ± 0.10), we also found that 28% of the patients could not reach this level of 300 mL/min at all. Maybe an already present recirculation in DL catheters is further enhanced by an increased pump flow, and therefore explains the only slight increase in URR. URR did not differ between SL and DL catheters in the 3-hour dialysis for both the FV and CV position. In all cases CV dialysis showed a higher URR than FV dialysis.
Based on our findings, for the longer lasting catheter dialysis, it is sensible to use the central vein position, preferably the internal jugular vein, because of the reported increased incidence of stenosis in the subclavian vein after catheter dialysis in that position [67]. However, when the catheter is needed for only a short amount of time, a SL femoral vein catheter can also be considered. For example, when a vascular access graft or fistula clots and a declot procedure can be planned within a few days.
Obviously, every effort must be made to minimize the use of temporary catheters. Not only because of the lower adequacy of dialysis, when compared to other accesses. The main indication for temporary catheter dialysis remains vascular access thrombosis. With adequate surveillance techniques and timely intervention, it is possible to decrease thrombosis rates. Also, timely planning of the permanent vascular access may lead to less temporary catheters.
In conclusion, our data do not unequivocally support the preference for the DL catheter for temporary hemodialysis access.

Coagulation and access thrombosis

An increased thrombotic tendency is an important cause of complications in patients on chronic hemodialysis leading not only to possibly fatal complications like ischaemic heart disease, or stroke, but also to thrombosis of the vascular access [68]. In most cases thrombosis is associated with low access blood flow [25,69,70]. The most important reason for a decreasing access blood flow is intimal hyperplasia formation at the venous anastomosis or in the outflow tract of the graft [16-20,71]. However, not all decreases in access blood flow are related to intimal hyperplasia or stenosis formation. Other causes for low access flow leading to access thrombosis have been proposed. Hypotension, hypo-

volaemia, or external compression may be involved in these non-stenotic thrombotic events [13]. Also, there has been a growing appreciation of the role of increased hypercoagulability found in these patients.

In ***chapter 8*** we discussed coagulability abnormalities in relation to haemodialysis access thrombosis. Despite the bleeding tendency of chronic haemodialysis patients, vascular access thrombosis is a frequent complication. Hypercoagulability is one of the causes contributing to the high frequency of access thrombosis. The hypercoagulable state can be explained by platelet and coagulation factor abnormalities. Unfortunately, few randomized placebo-controlled trials were conducted using antiplatelet or oral anticoagulation therapy. Therefore, no evidence-based consensus has been established regarding pharmacological prevention of access thrombosis. It still needs to be determined whether the potential benefits of anticoagulation and antiplatelet therapy outweigh the risk of adverse events. In the meantime it seems reasonable to give some form of anticoagulant therapy based on pathophysiological considerations and the high incidence of thrombotic complications. Our group recently demonstrated that graft flow measurements could effectively predict thrombotic vascular access events [72]. Risk tables that take into account such parameters as well as plasma markers of hypercoagulability may help to develop rationally designed trials and guidelines.

Future perspectives

Since the introduction of the AV fistula in 1966 and the PTFE AV graft a decade later, little improvement has been made in the vascular access field [73,74]. Various variations on both AV fistulae and grafts have been studied, but without much success [75]. The main problem with today's accesses is still thrombosis, mostly caused by intimal hyperplasia. Several efforts have been made to decrease intimal hyperplasia. In experimental settings, pharmacological interventions, improvement of biocompatibility, and influencing graft geometry were quite promising in terms of inhibiting or reducing intimal hyperplasia. To date however, none of these methods were successful in clinical studies [76]. Nonetheless, future research is needed to inhibit intimal hyperplasia formation either pharmacologically or by improving biocompatibility.

Over more than 30 years people have tried to find the perfect vascular access. In my opinion, this ideal access has the following characteristics: 1) easily constructable, 2) easily accessible, 3) no intimal hyperplasia, 4) no infection, 5) no thrombosis, 6) limitless patency, and 7) the ability to deliver a high dialysis dose. Unfortunately, this type of access does not exist (yet). Several researchers have developed a device that can be totally implanted under the pectoral skin [77]. This device has two lines connected to it that are inserted into the subclavian vein. It can be accessed via needles through the skin.

Hopefully, developments like these bring us more towards the ideal access.
However, a major objective over the coming years should be the widespread introduction of access surveillance. Although the NKF-K/DOQI Committee on Vascular Access has formed some recommendations on how to perform the most accurate surveillance, many dialysis centers are still not putting this knowledge into practice [1]. With the developed surveillance strategies, it is possible to decrease thrombosis rates dramatically [25]. With regular access flow or venous pressure measurements and timely intervention, patency rates will increase and, more importantly, patient care improves. Also, the treatment of stenoses might be improved via direct evaluation of PTA by intra-procedural flow measurement. That way it is possible to directly assess the effect of PTA. Another exiting new development is the improved vascular access image quality of magnetic resonance imaging [41]. All together this may lead to an efficient surveillance strategy which benefits all that are involved in the dialysis care.
In summary, for the short-term it is important that every dialysis center not only has an adequate surveillance strategy, but also a team that is dedicated to the vascular access. This team should consist of a nephrologist, a vascular surgeon, a radiologist, and last but certainly not least a nursing team. For the longer term, studies should be focused on inhibiting intimal hyperplasia and thrombosis and on developing better accesses.

References

1. National Kidney Foundation. K/DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 37 (Suppl 1): S137-S181, 2001
2. Beathard GA: Thrombolysis for the treatment of thrombosed dialysis access grafts: a nephrologist's view. *Semin Dial* 8: 162-165, 1995
3. Cayco AV, Abu-Alfa AK, Mahnensmith RL, Perazella MA: Reduction in arteriovenous graft impairment: results of a vascular access surveillance protocol. *Am J Kidney Dis* 32: 302-308, 1998
4. Bosman PJ, Blankestijn PJ, van der Graaf Y, Heintjes RJ, Koomans HA, Eikelboom BC: A comparison between PTFE and denatured homologous vein grafts for haemodialysis access: a prospective randomised multicentre trial. The SMASH Study Group. *Eur J Vasc Endovasc Surg* 16: 126-132, 1998
5. Sands JJ, Jabyac PA, Miranda CL, Kapsick BJ: Intervention based on monthly monitoring decreases hemodialysis access thrombosis. *ASAIO J* 45: 147-150, 1999
6. Powe NR, Jaar B, Furth SL, Hermann J, Briggs W: Septicemia in dialysis patients: incidence, risk factors, and prognosis. *Kidney Int* 55: 1081-1090, 1999
7. Schwab SJ, Beathard G: The hemodialysis catheter conundrum: hate living with them, but can't live without them. *Kidney Int* 56: 1-17, 1999

8. U.S. Renal Data System. The economic cost of ESRD, vascular access procedures, and Medicare spending for alternative modalities of treatment. *Am J Kidney Dis* 30 (Suppl 1): S160-S177, 1997
9. Feldman HI, Kobrin S, Wasserstein A: Hemodialysis vascular access morbidity. *J Am Soc Nephrol* 7: 523-535, 1996
10. Feldman HI, Held PJ, Hutchinson JT, Stoiber E, Hartigan MF, Berlin JA: Hemodialysis vascular access morbidity in the United States. *Kidney Int* 43: 1091-1096, 1993
11. Schwab SJ: Vascular access for hemodialysis. *Kidney Int* 55: 2078-2090, 1999
12. National Kidney Foundation. NKF-DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 30 (Suppl 3): S152-S191, 1997
13. Windus DW: Permanent vascular access: a nephrologist's view. *Am J Kidney Dis* 21: 457-471, 1993
14. U.S. Renal Data System. USRDS 1999 Annual Data Report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 1999
15. Ezzahiri R, Lemson MS, Kitslaar PJ, Leunissen KM, Tordoir JH: Haemodialysis vascular access and fistula surveillance methods in The Netherlands. *Nephrol Dial Transplant* 14: 2110-2115, 1999
16. Bassiouny HS, White S, Glagov S, Choi E, Giddens DP, Zarins CK: Anastomotic intimal hyperplasia: mechanical injury or flow induced. *J Vasc Surg* 15: 708-716, 1992
17. Kanterman RY, Vesely TM, Pilgram TK, Guy BW, Windus DW, Picus D: Dialysis access grafts: anatomic location of venous stenosis and results of angioplasty. *Radiology* 195: 135-139, 1995
18. Roberts AB, Kahn MB, Bradford S, Lee J, Ahmed Z, Fitzsimmons J, Ball D: Graft surveillance and angioplasty prolongs dialysis graft patency. *J Am Coll Surg* 183: 486-492, 1996
19. Safa AA, Valji K, Roberts AC, Ziegler TW, Hye RJ, Oglevie SB: Detection and treatment of dysfunctional hemodialysis access grafts: effect of a surveillance program on graft patency and the incidence of thrombosis. *Radiology* 199: 653-657, 1996
20. Smits HF, Van Rijk PP, Van Isselt JW, Mali WP, Koomans HA, Blankestijn PJ: Pulmonary embolism after thrombolysis of hemodialysis grafts. *J Am Soc Nephrol* 8: 1458-1461, 1997
21. Besarab A, Sullivan KL, Ross RP, Moritz MJ: Utility of intra-access pressure monitoring in detecting and correcting venous outlet stenoses prior to thrombosis. *Kidney Int* 47: 1364-1373, 1995
22. Beathard GA: Percutaneous transvenous angioplasty in the treatment of vascular access stenosis. *Kidney Int* 42: 1390-1397, 1992
23. Schwab SJ, Raymond JR, Saeed M, Newman GE, Dennis PA, Bollinger RR: Prevention of hemodialysis fistula thrombosis. Early detection of venous stenoses. *Kidney Int* 36: 707-711, 1989
24. Sands JJ, Miranda CL: Prolongation of hemodialysis access survival with elective revision. *Clin Nephrol* 44: 329-333, 1995

25. Smits JHM, Blankestijn PJ: Haemodialysis access: the case for prospective monitoring. *Curr Opin Nephrol Hypertens* 8: 685-690, 1999
26. Bosman PJ, Boereboom FT, Smits HF, Eikelboom BC, Koomans HA, Blankestijn PJ: Pressure or flow recordings for the surveillance of hemodialysis grafts. *Kidney Int* 52: 1084-1088, 1997
27. Beathard GA: Mechanical versus pharmacomechanical thrombolysis for the treatment of thrombosed dialysis access grafts. *Kidney Int* 45: 1401-1406, 1994
28. Roberts AC, Valji K, Bookstein JJ, Hye RJ: Pulse-spray pharmacomechanical thrombolysis for treatment of thrombosed dialysis access grafts. *Am J Surg* 166: 221-225, 1993
29. Valji K, Bookstein JJ, Roberts AC, Oglevie SB, Pittman C, O'Neill MP: Pulse-spray pharmacomechanical thrombolysis of thrombosed hemodialysis access grafts: long-term experience and comparison of original and current techniques. *Am J Roentgenol* 164: 1495-1500, 1995
30. Swan TL, Smyth SH, Ruffenach SJ, Berman SS, Pond GD: Pulmonary embolism following hemodialysis access thrombolysis/thrombectomy. *J Vasc Interv Radiol* 6: 683-686, 1995
31. May RE, Himmelfarb J, Yenicesu M, Knights S, Ikizler TA, Schulman G, Hernanz Schulman M, Shyr Y, Hakim RM: Predictive measures of vascular access thrombosis: a prospective study. *Kidney Int* 52: 1656-1662, 1997
32. Bettmann MA, Heeren T, Greenfield A, Goudey C: Adverse events with radiographic contrast agents: results of the SCVIR Contrast Agent Registry. *Radiology* 203: 611-620, 1997
33. Lumsden AB, MacDonald MJ, Kikeri D, Cotsonis GA, Harker LA, Martin LG: Prophylactic balloon angioplasty fails to prolong the patency of expanded polytetrafluoroethylene arteriovenous grafts: results of a prospective randomized study. *J Vasc Surg* 26: 382-390, 1997
34. Saloner D, van Tyen R, Dillon WP, Jou LD, Berger SA: Central intraluminal saturation stripe on MR angiograms of curved vessels: simulation, phantom, and clinical analysis. *Radiology* 198: 733-739, 1996
35. Bradley WGJ: Flow phenomena. In: Stark DD, Bradley WGJ, eds. Magnetic Resonance Imaging, 2nd ed. St. Louis: Mosley Year Book, 1992; pp 253-298
36. Gehl HB, Bohndorf K, Gladziwa U, Handt S, Gunther RW: Imaging of hemodialysis fistulas: limitations of MR angiography. *J Comput Assist Tomogr* 15: 271-275, 1991
37. Waldman GJ, Pattynama PM, Chang PC, Verburgh C, Reiber JH, de Roos A: Magnetic resonance angiography of dialysis access shunts: initial results. *Magn Reson Imaging* 14: 197-200, 1996
38. Smits HFM: Radiological diagnosis and treatment of hemodialysis access graft dysfunction. Thesis University Utrecht, ISBN 90-6464-5329, 2000
39. Prince MR: Gadolinium-enhanced MR aortography. *Radiology* 191: 155-164, 1994
40. Thurnher S: Magnetic resonance angiography of hemodialysis fistulas and grafts. *Semin Interv Radiol* 14: 101-110, 1997

41. Bos C, Smits JH, Zijlstra JJ, van der Mark WA, Blankestijn PJ, Bakker CJ, Viergever MA, Mali WP: MRA of hemodialysis access grafts and fistulae using selective contrast injection and flow interruption. *Magn Reson Med* 45: 557-561, 2001
42. Anderson CB, Etheredge EE, Harter HR, Codd JE, Graff RJ, Newton WT: Blood flow measurements in arteriovenous dialysis fistulas. *Surgery* 81: 459-461, 1977
43. Chait A: Angiography of dialysis shunts. In: Baum S, ed. Abram's angiography; vascular and interventional radiology, 4th ed. Boston: Little, Brown and Company, 1997; pp 1767-1778
44. Smits JHM, van der Linden J, Hagen EC, Modderkolk-Cammeraat EC, Feith GW, Koomans HA, van den Dorpel MA, Blankestijn PJ: Graft surveillance: venous pressure, access flow, or the combination? *Kidney Int* 59: 1551-1558, 2001
45. Gray RJ: Percutaneous intervention for permanent hemodialysis access: a review. *J Vasc Interv Radiol* 8: 313-327, 1997
46. Glanz S, Gordon DH, Butt KM, Hong J, Lipkowitz GS: The role of percutaneous angioplasty in the management of chronic hemodialysis fistulas. *Ann Surg* 206: 777-781, 1987
47. Martin LG, MacDonald MJ, Kikeri D, Cotsonis GA, Harker LA, Lumsden AB: Prophylactic angioplasty reduces thrombosis in virgin ePTFE arteriovenous dialysis grafts with greater than 50% stenosis: subset analysis of a prospectively randomized study. *J Vasc Interv Radiol* 10: 389-396, 1999
48. Ahya SN, Windus DW, Vesely TM, Lattimore BA: Utility of radiologic criteria for predicting access flow after percutaneous transluminal angioplasty. [Abstract] *J Am Soc Nephrol* 10 (ASN Program and Abstracts): 200A, 1999
49. Gray RJ, Sacks D, Martin LG, Trerotola SO: Reporting standards for percutaneous interventions in dialysis access. Technology Assessment Committee. *J Vasc Interv Radiol* 10: 1405-1415, 1999
50. Schwab SJ, Oliver MJ, Suhocki P, McCann R: Hemodialysis arteriovenous access: detection of stenosis and response to treatment by vascular access blood flow. *Kidney Int* 59: 358-362, 2001
51. Turmel-Rodrigues L, Pengloan J, Baudin S, Testou D, Abaza M, Dahdah G, Mouton A, Blanchard D: Treatment of stenosis and thrombosis in haemodialysis fistulas and grafts by interventional radiology. *Nephrol Dial Transplant* 15: 2029-2036, 2000
52. Davis GB, Dowd CF, Bookstein JJ, Maroney TP, Lang EV, Halasz N: Thrombosed dialysis grafts: efficacy of intrathrombic deposition of concentrated urokinase, clot maceration, and angioplasty. *Am J Roentgenol* 149: 177-181, 1987
53. Cohen MA, Kumpe DA, Durham JD, Zwerdlinger SC: Improved treatment of thrombosed hemodialysis access sites with thrombolysis and angioplasty. *Kidney Int* 46: 1375-1380, 1994
54. Duszak RJ, Sacks D: Dialysis graft declotting with very low dose urokinase: is it feasible to use "less and wait?". *J Vasc Interv Radiol* 10: 123-128, 1999
55. Sharafuddin MJ, Hicks ME: Current status of percutaneous mechanical thrombectomy. Part II. Devices and mechanisms of action. *J Vasc Interv Radiol* 9: 15-31, 1998

56. Schmitz-Rode T, Pfeffer JG, Bohndorf K, Gunther RW: Percutaneous thrombectomy of the acutely thrombosed dialysis graft: in vitro evaluation of four devices. *Cardiovasc Intervent Radiol* 16: 72-75, 1993
57. Muller-Hulsbeck S, Bangard C, Schwarzenberg H, Gluer CC, Heller M: In vitro effectiveness study of three hydrodynamic thrombectomy devices. *Radiology* 211: 433-439, 1999
58. Castaneda F, Wyffels PL, Patel JC, Swischuk JL, Li R, Cole BA, Cragg AH: New thrombolytic brush catheter in thrombosed polytetrafluoroethylene dialysis grafts: preclinical animal study. *J Vasc Interv Radiol* 9: 793-798, 1998
59. Overbosch EH, Pattynama PM, Aarts HJ, Schultze Kool LJ, Hermans J, Reekers JA: Occluded hemodialysis shunts: Dutch multicenter experience with the hydrolyser catheter. *Radiology* 201: 485-488, 1996
60. Vorwerk D, Schurmann K, Muller-Leisse C, Adam G, Bucker A, Sohn M, Kierdorf H, Gunther RW: Hydrodynamic thrombectomy of haemodialysis grafts and fistulae: results of 51 procedures. *Nephrol Dial Transplant* 11: 1058-1064, 1996
61. Trerotola SO, Vesely TM, Lund GB, Soulen MC, Ehrman KO, Cardella JF: Treatment of thrombosed hemodialysis access grafts: Arrow- Trerotola percutaneous thrombolytic device versus pulse-spray thrombolysis. Arrow-Trerotola Percutaneous Thrombolytic Device Clinical Trial. *Radiology* 206: 403-414, 1998
62. de los Angeles, Lerner A, Goldstein SJ, Kramer MS, Raja RM: Comparison of coaxial and side-by-side double lumen subclavian catheters with the single lumen catheter. *Am J Kidney Dis* 7: 221-224, 1986
63. Al Wakeel J, Milwalli AH, Malik GH, Huraib S, Al MS, Abu AH, Memon N: Dual-lumen femoral vein catheterization as vascular access for hemodialysis—a prospective study. *Angiology* 49: 557-562, 1998
64. Kelber J, Delmez JA, Windus DW: Factors affecting delivery of high-efficiency dialysis using temporary vascular access. *Am J Kidney Dis* 22: 24-29, 1993
65. Leblanc M, Fedak S, Mokris G, Paganini EP: Blood recirculation in temporary central catheters for acute hemodialysis. *Clin Nephrol* 45: 315-319, 1996
66. Kumwenda MJ: Single or dual lumen long-term hemodialysis catheters—does it matter which? *Clin Nephrol* 48: 61-63, 1997
67. Khanna S, Sniderman K, Simons M, Besley M, Uldall R: Superior vena cava stenosis associated with hemodialysis catheters. *Am J Kidney Dis* 21: 278-281, 1993
68. Lindner A, Charra B, Sherrard DJ, Scribner BH: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 290: 697-701, 1974
69. Bosman PJ, Boereboom FTJ, Eikelboom BC, Koomans HA, Blankestijn PJ: Graft flow as a predictor of thrombosis in hemodialysis grafts. *Kidney Int* 54: 1726-1730, 1998
70. Diskin CJ, Stokes TJJ, Pennell AT: Pharmacologic intervention to prevent hemodialysis vascular access thrombosis. *Nephron* 64: 1-26, 1993

71. Smits JHM, Blankestijn PJ: Thrombosis-free hemodialysis grafts: a possibility for the next century? *Semin Dial* 12: 44-49, 1999
72. Blankestijn PJ, Smits JH: How to identify the haemodialysis access at risk of thrombosis? Are flow measurements the answer? *Nephrol Dial Transplant* 14: 1068-1071, 1999
73. Brescia MJ, Cimino JE, Appel K, Hurwich BJ: Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. *N Engl J Med* 275: 1089-1092, 1966
74. Baker LD, Jr., Johnson JM, Goldfarb D: Expanded polytetrafluoroethylene (PTFE) subcutaneous arteriovenous conduit: an improved vascular access for chronic hemodialysis. *Trans Am Soc Artif Intern Organs* 22: 382-387, 1976
75. Bosman PJ: Secondary vascular access for hemodialysis. Thesis University Utrecht, ISBN 90-393-2022-5, 1997
76. Lemson MS: Intimal hyperplasia in prosthetic vascular access: the effect of flow variation and anastomotic geometry on its development. Thesis University Maastricht, ISBN 90-9013585-5, 2000
77. Canaud B, My H, Morena M, Lamy-Lacavalerie B, Leray-Moragues H, Bosc JY, Flavier JL, Chomel PY, Polaschegg HD, Prosl FR, Megerman J: Dialock: a new vascular access device for extracorporeal renal replacement therapy. Preliminary clinical results. *Nephrol Dial Transplant* 14: 692-698, 1999

Chapter 10

Summary and conclusions

Summary

Patients on hemodialysis require an access to their bloodstream. The Brescia-Cimino (radio-cephalic) arteriovenous (AV) fistula is still regarded as the first choice for the creation of a vascular access for hemodialysis. Unfortunately, not all patients have suitable vessels to construct an AV fistula. An alternative for the AV fistula is the polytetrafluoroethylene (PTFE) AV interposition graft. However, one of the major problems of these AV grafts is a high thrombosis rate. This thesis focuses on the prevention and treatment of hemodialysis access thrombosis.

There are various ways to monitor vascular accesses for impending failure: theoretically, access flow (Qa) measurements provide more information about the vascular access than the intra-access venous pressure (VP) measurement. In ***chapter 3*** we investigated whether Qa measurements are indeed better than VP measurements in identifying patients at risk for thrombosis. Furthermore, we looked whether referral of patients for percutaneous transluminal angioplasty (PTA) based on Qa measurements alone or on the combination of VP and Qa reduces thrombosis rate more than referral based on VP alone.

Magnetic resonance angiography (MRA) offers the opportunity to provide an image of the access without the less desirable features of digital subtraction angiography (DSA). However, because of turbulent blood flow some segments of the MR image can present as a void, especially near the anastomoses. Even with contrast-enhancement there are still substantial artifacts, because of the presence of flow. Therefore, we designed a flow-interrupted contrast-enhanced MR imaging sequence. In ***chapter 4*** we compared this novel MRA imaging of the vascular access with DSA.

After detection of a failing access, it is important to intervene before thrombosis occurs. The common approach for intervention nowadays is PTA. Several studies demonstrated that the overall survival of the access can be prolonged by repetitive PTA. In ***chapter 5*** we studied the short-term effect of PTA on Qa, Qa patterns after PTA, and which factors had an influence on Qa after PTA.

If, despite the efforts of detecting failing accesses timely, thrombosis still occurs, the dialysis patient comes in an undesirable situation. Namely, the patient cannot get access to the hemodialysis treatment. When this happens, it is paramount to re-establish a patent vascular access as soon as possible. This can be done by surgical thrombectomy or radiologically by percutaneous thrombolysis. The latter has become the treatment of choice for thrombosed hemodialysis grafts. In ***chapter 6*** we compared three devices for percuta-

neous thrombolysis with respect to their efficacy in removing thrombus from hemodialysis access grafts.

Treatment should be initiated immediately after diagnosing thrombosis. In many cases this cannot be done immediately and the patients rely on other types of accesses, mostly a temporary catheter in the internal jugular or femoral vein. Basically, there are two types of temporary catheters: the single-lumen and the double-lumen catheters. Single-lumen catheters do not allow for a continuous blood flow to and from the dialysis machine, whereas double-lumen catheters do. Although it is presumed that single-lumen catheters have a lower dialysis adequacy than double-lumen catheters, this has not been formally investigated yet. In ***chapter 7*** we present a randomized prospective trial comparing dialysis adequacy and overall performance in single-lumen versus double-lumen catheters.

Not all decreases in access blood flow are related to intimal hyperplasia or stenosis formation. Other causes for low access flow leading to access thrombosis have been proposed. Hypotension, hypovolaemia, or external compression may be involved in these non-stenotic thrombotic events. Also, there has been a growing appreciation of the role of increased hypercoagulability found in these patients. In ***chapter 8*** we discuss coagulability abnormalities in relation to haemodialysis access thrombosis.

Conclusions

1. Standardized monitoring of VP or Qa or the combination of both and subsequent corrective intervention can decrease thrombosis rates to below 0.5 per patient-year, which is recommended by the Vascular Access Task Force of the NKF-DOQI Committee as quality of care standard. When applying the surveillance protocol, VP, Qa, or the combination as variables for selection of patients for corrective intervention are equally effective in reducing thrombosis rates in hemodialysis access grafts (***chapter 3***).

2. Selective flow-interrupted CE-MRA imaging can provide excellent quality images of hemodialysis AVF and AVG, which are free of flow artifacts. The high image quality of the MR angiograms is comparable with DSA. In combination with MR flow quantification and imaging of the outflow tract, our approach may provide a complete anatomical and functional evaluation of hemodialysis accesses on MR (***chapter 4***).

3. Access flow increases after PTA, however in a substantial percentage not to a level > 600 mL/min. Qa before PTA and the increase in Qa correlated with long-term out-

come, whereas angiographic results did not. The present data combined with the literature suggest that there is an optimal timing for PTA (***chapter 5***).

4. In our evaluation of three mechanical devices used to declot thrombosed hemodialysis access grafts, we found that the success of mechanical thrombolysis was determined more by the success of PTA of underlying stenoses than by the results of clot removal. The rotating devices performed significantly better than the Hydrolyser in removing thrombus from hemodialysis access grafts. The effectiveness of the two rotating devices was comparable (***chapter 6***).

5. The use of double-lumen catheters as temporary access often results in better URR than the use of singe-lumen catheters. However, differences obtained with single-lumen catheters are limited, and, especially when only a limited number of dialysis sessions are performed using catheters, of questionable clinical relevance. Also, many catheter dialysis sessions will not result in adequate dialysis (***chapter 7***).

Samenvatting

Samenvatting

Bij hemodialyse is het noodzakelijk dat bloed van de patiënt naar het dialyse apparaat gebracht wordt, daar gezuiverd wordt, en weer teruggebracht wordt van het apparaat naar de patiënt. Om dit te bereiken heeft de patiënt een zogeheten toegang tot de bloedbaan nodig, een vaattoegang. In veel gevallen is dit een zogeheten Brescia-Cimino fistel. Dit is een verbinding tussen de slagader in de pols en een ader. Nadat de verbinding gelegd is zal de ader in de loop van enkele weken uitzetten, zodat deze geschikt is om herhaaldelijk aangeprikt te worden als vaattoegang. Helaas hebben lang niet alle patiënten geschikte vaten om dit soort fistels te construeren. Een alternatief voor de directe fistel is een vaatprothese die tussen de slagader en een ader geplaatst wordt, meestal in de elleboogsplooi. Deze vaattoegangen worden ook wel dialyse shunts genoemd. Eén van de belangrijkste problemen van dialyse shunts is het ontstaan van vernauwingen, die kunnen leiden tot stolling van het bloed (trombose) in de vaattoegang, waardoor deze (tijdelijk) onbruikbaar wordt. Dit proefschrift gaat over het voorkomen en behandelen van vaattoegang trombose.

Er zijn verschillende manieren om de vaattoegang in de gaten te houden voor wat betreft het opsporen van aankomende trombose. Eén manier is om de hoeveelheid bloed te meten die per tijdseenheid door een vaattoegang stroomt, ook wel bloedstroom genoemd. Een andere veel gebruikte manier is om de druk te meten die het dialyse apparaat moet opbouwen om het bloed weer terug de vaattoegang in te pompen. Dit wordt ook wel de veneuze drukmeting genoemd. Theoretisch gezien biedt de bloedstroom bepaling meer informatie dan de veneuze druk meting bij het opsoren van vernauwingen. In ***hoofdstuk 3*** hebben we onderzocht of de bloedstroom bepaling inderdaad beter is dan de veneuze druk meting bij het identificeren van patiënten die een hoog risico lopen om een vaattoegang trombose te krijgen. Verder hebben we gekeken of er verschil was in trombose frequentie tussen patiënten die verwezen waren voor een dotter behandeling op grond van 1) de bloedstroom bepaling alleen, 2) de veneuze druk bepaling alleen, of 3) de combinatie van de bloedstroom bepaling en de veneuze druk meting. Het bleek dat de trombose frequentie teruggebracht kon worden tot lager dan 0.5 per patiënt jaar na een dotter behandeling op grond van het gestandaardiseerd meten van hetzij de veneuze druk hetzij de bloedstroom hetzij de combinatie van deze twee. Met ons protocol van vaattoegang bewaking is gebleken dat zowel de bloedstroom, als de veneuze druk, als de combinatie hiervan als variabelen voor de selectie van patiënten voor een dotter behandeling de trombose frequentie in dezelfde mate omlaag kunnen brengen.

Magnetische resonantie angiografie (MRA) biedt de mogelijkheid om een afbeelding van de vaattoegang te geven zonder de nadelen van de 'normale' röntgen angiografie (ook wel

digitale subtractie angiografie genoemd, DSA). Echter, vanwege turbulentie in de bloedbaan kunnen sommige segmenten van de MRA afbeelding zich voordoen als uitsparingen in de afbeelding, zeker nabij de verbindingen van de vaten. Zelfs met MR contrast zijn er nog steeds behoorlijke artefacten vanwege de bloedstroming. Daarom hebben we een MRA meting ontwikkeld, waarbij de bloedstroom tijdelijk onderbroken wordt. In ***hoofdstuk 4*** hebben we deze nieuwe methode vergeleken met de conventionele DSA afbeelding. Onze nieuwe methode bood afbeeldingen van uitstekende kwaliteit, vrij van bloedstroom artefacten. De hoge kwaliteit van de MRA afbeeldingen was vergelijkbaar met de DSA afbeeldingen. Een belangrijk voordeel van de MRA is dat hiermee ook de bloedstroom gemeten kan worden. Hiermee zou onze benadering kunnen zorgen voor een complete anatomische en functionele evaluatie van de vaattoegang met MRA.

Wanneer een slecht functionerende vaattoegang is gedetecteerd, is het belangrijk om in te grijpen voordat trombose optreedt. De gangbare behandeling tegenwoordig is de dotter behandeling, waarbij de vernauwing met een ballonnetje verholpen wordt. Verschillende studies hebben aangetoond dat de levensduur van een vaattoegang kan worden verlengd met herhaalde dotter behandelingen. In ***hoofdstuk 5*** hebben we het korte en lange termijn effect bestudeerd van de dotter behandeling op de bloedstroom. Tevens hebben we gekeken welke factoren van invloed waren op de bloedstroom na de dotter behandeling. We vonden dat de bloedstroom toeneemt na de dotter behandeling, echter in een aanzienlijk percentage niet tot boven de 600 mL/min. De bloedstroom bepaling voor de dotter procedure en de toename in bloedstroom correleerde met het lange termijn resultaat. Het anatomische resultaat van de dotter procedure (m.a.w. de afname van de vernauwing) correleerde niet met het lange termijn resultaat. Onze gegevens gecombineerd met gegevens van andere onderzoeken suggereren dat er een optimaal moment is voor een dotter procedure.

Wanneer een vaattoegang stolt moet er snel een ontstopping ofwel trombolyse plaatsvinden. In ***hoofdstuk 6*** worden drie apparaten voor trombolyse met elkaar vergeleken wat betreft hun effectiviteit in het verwijderen van de trombose. De apparaten werkten op verschillende manieren. Het eerste apparaat was een borsteltje dat letterlijk de binnenzijde van de vaattoegang schoon borstelt. Het volgende apparaat was een soort hoge druk spuit die het stolsel in de vaattoegang vernevelt en opzuigt. Het derde apparaat was een zelfontplooiend mandje dat zich tegen de binnenkant van het vat zet en zo het stolsel vermaalt en de binnenzijde van de vaattoegang schoon schraapt. Het schoonmaken van de gestolde prothese lukte in vrijwel alle gevallen, maar de roterende apparaatjes die in fysiek contact staan met de binnenzijde van de vaattoegang gaven de meest volledige verwijdering van stolsels. Na het opruimen van de trombose werd de onderliggende vernau-

wing gedotterd. De keuze van het soort apparaatje was niet van invloed op het lange termijn resultaat van de behandeling. Alleen het resultaat van de dotter behandeling bleek de lange termijn resultaten te beïnvloeden. Dit toont aan dat een goede correctie van de vaatvernauwing het belangrijkste onderdeel van de behandeling is.

In veel gevallen is het niet direct mogelijk om de getromboseerde vaattoegang weer te openen. In dat geval is de patiënt afhankelijk van een ander soort vaattoegang. Dit is dan meestal een tijdelijke catheter in één van de grote aders in de hals of lies. Er zijn twee soorten tijdelijke catheters: catheters met een enkel lumen en catheters met een dubbel lumen. Enkel-lumen catheters kunnen geen continue bloedstroom van en naar de dialyse machine bewerkstelligen, terwijl dubbel-lumen catheters dit wel kunnen. Het wordt daarom wel aangenomen dat enkel-lumen catheters een lagere dialyse effectiviteit bereiken dan dubbel-lumen catheters. Dit is echter nooit formeel onderzocht. In ***hoofdstuk 7*** presenteren we een gerandomiseerde prospectieve trial waarbij we de dialyse effectiviteit en de algehele prestatie hebben vergeleken tussen enkel- en dubbel-lumen catheters. We vonden dat dubbel-lumen catheters beter in staat zijn om het beoogde bloedvolume te verwerken dan enkel-lumen catheters. De effectiviteit van enkel-lumen catheters in een lies ader verschilde niet met die van dubbel-lumen catheters in een lies ader. In een hals ader was de effectiviteit van de dubbel-lumen catheter wel beter. Echter, veel dialyse sessies met een catheter resulteerden niet in een effectieve dialyse. Bovendien waren de verschillen tussen dubbel- en enkel-lumen catheters beperkt, en, zeker gezien de meestal korte duur van de catheter dialyses, van twijfelachtige klinische relevantie.

Niet alle verminderingen van de bloedstroom zijn gerelateerd aan vaatvernauwingen. Een lage bloeddruk, een laag circulerend volume, of externe compressie van de vaattoegang zouden ook oorzaken voor een lage bloedstroom kunnen zijn. Er is tevens een groeiende belangstelling voor de rol van de toegenomen stolbaarheid van het bloed bij hemodialyse patiënten. In ***hoofdstuk 8*** worden deze stollingsafwijkingen bij hemodialyse patiënten besproken in relatie tot vaattoegang trombose.

Bibliography

Bibliography

van Erpecum KJ, **Smits JHM**, van de Meeberg PC, Linn FH, Wolfhagen FH, vanBerge-Henegouwen GP, Algra A: Risk of primary sclerosing cholangitis is associated with non-smoking behavior. *Gastroenterology* 110: 1503-1506, 1996

Smits JHM, Blankestijn PJ: Thrombosis-free hemodialysis grafts: a possibility for the next century? *Semin Dial* 12: 44-49, 1999

Blankestijn PJ, **Smits JHM**: How to identify the haemodialysis access at risk of thrombosis? Are flow measurements the answer? *Nephrol Dial Transplant* 14: 1068-1071, 1999

Smits JHM, Blankestijn PJ: Haemodialysis access: the case for prospective monitoring. *Curr Opin Nephrol Hypertens* 8: 685-690, 1999

Smits JHM, van der Linden J, Blankestijn PJ, Rabelink TJ: Coagulation and haemodialysis access thrombosis. *Nephrol Dial Transplant* 15: 1755-1760, 2000

Bos C, **Smits JHM**, Zijlstra JJ, van der Mark WA, Blankestijn PJ, Bakker CJ, Viergever MA, Mali WP: MRA of hemodialysis access grafts and fistulae using selective contrast injection and flow interruption. *Magn Reson Med* 45: 557-561, 2001

Smits JHM, van der Linden J, Hagen EC, Modderkolk-Cammeraat EC, Feith GW, Koomans HA, van den Dorpel MA, Blankestijn PJ: Graft surveillance: venous pressure, access flow, or the combination? *Kidney Int* 59: 1551-1558, 2001

van der Linden J, **Smits JHM**, Wolterbeek DW, Zijlstra JJ, van den Dorpel MA, Blankestijn PJ: Short- and long-term functional effect of percutaneous transluminal angioplasty in hemodialysis vascular access. *J Am Soc Nephrol* (in press)

Smits JHM, Bos C, Elgersma OEH, van der Mark WAMA, Blankestijn PJ, Bakker CJG, Zijlstra JJ, Mali WPThM: Hemodialysis access imaging: comparison of flow-interrupted contrast-enhanced MR angiography and digital subtraction angiography. *Radiology* (revised)

Smits HFM, **Smits JHM**, Wüst AFJ, Buskens E, Blankestijn PJ: Percutaneous thrombolysis of thrombosed hemodialysis access grafts: comparison of three mechanical devices. *Nephrol Dial Transplant* (revised)

Smits JHM, van der Mark WAMA, van Berkel Th, Verwey J, Boer WH, Blankestijn PJ: Single-lumen versus double-lumen catheters for temporary hemodialysis access: a randomized prospective single center trial. (submitted)

Dankwoord

Dankwoord

Met veel genoegen kijk ik terug op de onderzoeksperiode die heeft geleid tot dit proefschrift. Veel mensen waren hier direct bij betrokken of hebben die periode op een andere manier plezierig gemaakt. Allereerst wil ik de vele dialyse patiënten bedanken die meegewerkt hebben met de onderzoeken die beschreven staan in dit proefschrift. Tevens wil ik alle verpleegkundigen en radiologie laboranten bedanken die zeer behulpzaam en volstrekt onmisbaar waren bij het verzamelen van de gegevens.
Daarnaast wil ik een aantal mensen met name noemen.

Dr. P.J. Blankestijn, geachte co-promotor, beste Peter. Je kunde om zaken ten positieve te keren is bewonderenswaardig. Als ik door de vele beschikbare data het overzicht even verloor, wist jij er altijd zo'n draai aan te geven, dat alle stukjes weer snel in elkaar vielen. Je vastberadenheid bij het analyseren van de data is indrukwekkend en soms vermoeiend, maar leidde vrijwel altijd tot uitstekende resultaten. Het was erg leerzaam om met je te hebben samengewerkt.
Drs. J. van der Linden, beste Joke. Een aanzienlijk deel van dit proefschrift is letterlijk tevens van jou. Zonder de hulp van jou en *Rene van den Dorpel* bij het verzamelen en analyseren van de nodige gegevens, had dit boekje er zeker anders uitgezien. De humorvolle en relativerende gesprekken waren vaak een welkome afwisseling.
Prof. Dr. H.A. Koomans, geachte promotor, beste Hein. Misschien is de versnelde veroudering van hemodialyse patienten ook wel van invloed op de snelle proliferatie van intima hyperplasie in de vaattoegang. Ik weet het niet, maar in ieder geval heb ik van je de waardevolle les geleerd om alles vanuit verschillende invalshoeken te bekijken.
Prof. Dr. W.P.Th.M. Mali. Bedankt voor het ter beschikking stellen van de MR tijd en voor uw scherpe blik op het onderzoek.
Wil van der Mark, beste Wil. Hartelijk dank voor je hulp bij de onderzoeken. Weinig mensen zijn meer geschikt om de resultaten in de praktijk te brengen en over Nederland te verspreiden dan jij. Veel succes hiermee. Toen je me een e-mail liet zien van een thuisdialyse patiënt, die z'n eigen veneuze drukwaarden doormailde, kreeg ik echt het idee dat we aan het begin stonden van een heel mooie nieuwe ontwikkeling.

Drs. C. Bos, beste Clemens, op weg naar de grenzen van de MR mogelijkheden en die dan proberen te overschreiden. Het was een genot om daar deel van uit te maken. Je enthousiasme over de MR werkte erg aanstekelijk. Succes met jouw verdediging. *Dr. C.J.G. Bakker*, beste Chris, wellicht kijken radiologen over 20 jaar terug naar onze tijd met jou als boegbeeld voor de MR interventie. Maar dan moeten er eerst nog wel wat obstakels uit de weg geruimd worden. *Dr. H.F.M. Smits*, beste Henk, als geen ander kun je mensen motiveren. Je vertek was dan ook een groot gemis voor het vaattoegang onderzoek.

Gelukkig was *Dr. J.J. Zijlstra* bereid om het houtje over te nemen. Beste Jan, parttime academisch radioloog, je komst zorgde al snel voor een frisse wind door het vaattoegang onderzoek. Ook al was je maar een dag per week aanwezig, dit was vaak genoeg om ons voor de rest van de week bezig te houden. Met je voortvarendheid kwam er in korte tijd veel tot stand. De beste herinnering bewaar ik aan je opmerkelijke gevoel voor humor. *Dr. O.E.H. Elgersma*, beste Otto, de combinatie met Jan werkte prima. Hij als perifeer gangmaker en jij als academisch geweten.

Tineke en later *Anneke* van het trialbureau van de Radiologie, onmisbaar was jullie uiterst efficiënte planning van de MRA en DSA onderzoeken. Ik kan iedere vakgroep een trialbureau aanraden, zeker met mensen zoals jullie. *Cees Haaring*, bedankt voor de database ontwikkeling, andere computer ondersteuning, en de leerzame gesprekken over nieuwe computersnufjes.
Verder wil ik *Wilma* van de angiokamer bedanken, niet in de laatste plaats voor haar uitstekende rol als beschermengel van eventueel toekomstig nageslacht als ik weer 'ns een loodschort als jas aantrok.

Collega-onderzoekers van de Nefrologie: *Tycho*, goede herinneringen heb ik aan de lunches en vele gesprekken over van alles en nog wat. *Oliver*, soms dacht ik dat m'n verhalen je wel moesten gaan vervelen, maar dit heb ik nooit gemerkt. Je verhalen waren bijzonder en boeiend. Bedankt en veel geluk. *Coes*, eerst werd ik bijna geëlektrocuteerd als proefpersoon bij je onderwater sympathicus onderzoek en nu bel je me regelmatig om zes uur 's ochtends uit bed om een pre-operatief onderzoek te doen. Toch zal ik je nu voor de tweede keer gaan missen. *Ingrid* en *Inge*, niet-mis-te-verstane waarschuwingen van een plaatselijke bewoner ("They'll shoot you on the spot!") weerhielden ons op het nippertje om door Little Havana te fietsen. De andere tocht was zeker zo leuk. *Jacobine, Thi Danh, Diana, Simona, Jutta*, succes met jullie onderzoek.
Collega's van ziekenhuis Gooi-Noord: vanaf nu alleen de opleiding, gelukkig.

Walther, bedankt voor de introductie in het Nefrologie onderzoek. Verder *Ronald, Gerry, Branco, Jaap Beutler, Jaap Joles, Pieter, Menno, Brigitte, Peter Boer, Jaap Vos.* Bedankt voor de belangstelling en steun. *Trees* en *Coby*, zeer behulpzaam.

Alle participanten in de multi-center studies, hartelijk dank voor jullie deelname (in willekeurige volgorde): *Dr E.C. Hagen, Dr. G.W. Feith, A. Diepenbroek, C.M. van der Beek, M.M. Harskamp, E. van der Weele, Dr. G.M.Th. de Jong, Dr. J.H. Assink, D. Wolterbeek, M.M. van Loon, Dr. H.H. Burger, Dr. E.F.H. van Bommel, Dr. M.I. Koolen, P.M. van der Zee, L. van den Broek, Dr. B.J. Potter van Loon.*

Magne, vaak zorgde je voor de nodige afwisseling in de vorm van vakanties, uitstapjes en huisfeesten. De waarde hiervan besefte ik pas echt toen je terug ging naar Noorwegen. Ik hoop je nog vaak op de boerderij te komen bezoeken.
Harm en Sithabile, bedankt voor de interessante, maar nog vaker lachwekkende discussies en voor de luisterende oren. *S'tha*, many thanks for the cover paintings.

Mijn broers, *Edwin, Peter* en *Bart*. Ik mocht maar twee paranimfen meenemen, maar het liefst had ik jullie alledrie gevraagd. Bart, ben jij de volgende promovendus?

Beste ouders, met veel plezier denk ik terug aan de tijd op het Brabantse land aan de rand van de Peel. Daar zijn de eerste schreden gezet op weg naar dit boekje. Zonder jullie was dit niet mogelijk geweest. *Moeder*, ook al neemt je nauwgezetheid vaak verregaande vormen aan, soms hoop ik dat ik daarvan ook maar een klein deel heb meegekregen. *Vader*, voorbeeld in nagenoeg alles. Ik denk dat ik namens m'n broers spreek, als ik zeg, dat we zonder jullie motivatie, stimulatie en steun dit nooit hadden kunnen bereiken.

Sander

Curriculum Vitae

Curriculum Vitae

Sander Smits werd op 8 augustus 1971 geboren te Deurne en is getogen in Liessel. Hij behaalde het Gymnasium-β diploma in 1989 op het St.-Willibrord Gymnasium te Deurne. Wegens uitloting voor de studie Geneeskunde werd hierna aangevangen met de studie Fysiotherapie aan de Hogeschool Limburg te Heerlen. In 1990 werd hij alsnog ingeloot voor de studie Geneeskunde, en wel aan de Universiteit Utrecht. Het doctoraal examen Geneeskunde werd in 1996 gehaald, gevolgd door het artsexamen op 27 maart 1998. Tijdens de opleiding tot arts participeerde hij in diverse wetenschappelijke en klinische stages, te weten bij de afdeling Fysiologie aan de Universiteit van Cádiz, Spanje, de afdeling Gastro-Enterologie van het Academisch Ziekenhuis Utrecht, de afdeling Gynaecologie en Obstetrie van het King Edward VIII Hospital in Durban, Zuid-Afrika, en de afdeling Nefrologie van het Academisch Ziekenhuis Utrecht.

Van maart 1998 tot en met april 2001 was hij als artsonderzoeker werkzaam bij de vakgroep Nefrologie van het Universitair Medisch Centrum Utrecht, alwaar het in dit proefschrift beschreven onderzoek is uitgevoerd. Op 1 mei 2001 is de auteur van dit proefschrift begonnen met de opleiding tot internist in Ziekenhuis Gooi-Noord te Blaricum (opleider: Dr. P. Niermeijer).