Management Strategies in Hemodialysis Vascular Access

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INTRODUCTION

INTRODUCTION

Gaining proper access to the circulation is a prerequisite for hemodialysis in order to transport blood from the patient to the artificial kidney and back to the patient again. In 1943, Dr. Willem J. Kolff first encountered the problem of gaining access to the bloodstream for hemodialysis (1). After 34 days of puncturing readily accessible blood vessels he failed to find further possibilities to enter the bloodstream. As a consequence his patient died.

The chronic hemodialysis era began almost 20 years later, when Quinton and Scribner introduced the first external arterio-venous shunt constructed of Teflon, that allowed repeated access to the vascular system (2). Unfortunately, infection and thrombosis often limited the long-term use of this access type. In 1966 a major breakthrough in vascular access surgery was achieved by the introduction of the first endogenous fistula by Brescia and Cimino (3-5). They created a side-to-side anastomosis between the radial artery and cephalic vein, which ensured function as a vascular access. Later, brachio-cephalic and transposed brachio-basilic fistulae were constructed by Dunlop (6) and Stonebridge (7) respectively. At present the arterio-venous fistula (AVF) is still considered to be the vascular access of choice. After adequate maturation, the AVF has the highest long-term patency rates because of low risk of thrombosis and infection (8,9).

Unfortunately, creation of an AVF is not always possible as a consequence of prior vascular access surgery, or insufficient caliber of forearm vessels. Subsequently, the use of various prosthetic grafts has emerged as an alternative to native fistula. These arterio-venous grafts (AVG) are typically positioned in the forearm, in a looped or straight configuration. Nowadays, polytetrafluoroethylene (PTFE) is the most used graft-material. Unfortunately, AVG appear to be associated with a significantly higher risk of thrombosis and infection as compared with AVF (10-13).

Since the introduction of the AVF and the PTFE AVG, little improvement has been made in the vascular access field. Still, vascular access related complications are one of the most important reasons for patient hospitalisation, morbidity and even mortality (13,14). In the United States access complications are estimated to cost about to $1 billion per annum, and are responsible for 17-30% of all hospital admissions in dialysis patients (15-17). Interestingly, the cost of vascular access related care was found to be more than fivefold higher for patients with AVG compared with patients with a functioning AVF (18). In an attempt to improve overall patency rates and reduce access related costs, the NFK-DOQI committee currently recommends that in any dialysis center the majority of new dialysis patients should have a primary AVF constructed (19).

Despite these recommendations large variations in vascular access practice patterns are found. Fistula use still is much lower in the United States than in Europe (9). AVF use was found to be actually 0% in some facilities in the United States (9). These differences are frequently attributed to unfavourable patient characteristics such as diabetes, peripheral vascular disease, and older age of patients (9,20,21). However, the observed differences persist after adjustment for these patient characteristics. Facility's preferences and approaches to vascular access practice still seem to be major determinants of vascular access use (22).

Endothelial function in chronic renal disease

Cardiovascular complications are a major cause of death and morbidity of ESRD patients (23). Early studies suggested that uremia is associated with accelerated atherosclerosis (24,25). Over the last decade endothelial dysfunction has been identified as an important mediator in this process. Nitric oxide (NO) is one of the main factors involved in the anti-atherosclerotic effects of the endothelium, and chronic renal failure has been associated with impaired NO bioavailability (26,27).

The ability to adjust to high blood flow and proper vasodilatation, needed after creation of AVF, could be strongly influenced by endothelial function of the forearm vessels. Endothelium-dependent vasodilatation of forearm capacitance vessels is affected by many diseases, among which several are known to cause renal failure, like diabetes and hypertension (28). Local infusion of vasodilators causes a less pronounced increase of forearm flow in hypertensive patients as compared to normotensive controls (29-35). Also, the hyperaemic response after temporary arterial occlusion is reduced in hypertensive patients (29-34). Similar results are found in patients with diabetes and congestive heart failure (36,37). In addition, uraemia or so-called uraemic factors like homocysteine or endogenous inhibitors of NO-synthase (ADMA) could be directly toxic to the vascular endothelium (38,39).

In addition to the impaired vasodilatation of capacitance vessels due to endothelial dysfunction, several authors demonstrated reduced venous forearm distensibility in patients with hypertension, diabetes, chronic heart failure and end stage renal disease (40-43). Vein wall distensibility is controlled by collagen, elastin and smooth muscle. Wali et al. demonstrated accumulation of collagen fibres in place of smooth muscle cells in pre-access cephalic veins, which would cause a

decrease in the elasticity of the vein wall (44). These functional properties of the forearm vasculature could interfere with proper maturation of the AVF.

Increasing the placement of AVF and an aggressive policy for vascular access monitoring could improve quality of life and overall outcomes for hemodialysis patients significantly.

Choice of access: preoperative testing

With the recognition of the superiority of the AVF and the increasing comorbidity of the hemodialysis population, efforts are made to evaluate the vasculature of the arm of the patient prior to access surgery. This would help the surgeon to choose the access site and type with the highest likelihood of success in the individual patient. The NKF-DOQI guidelines provide recommendations concerning preoperative evaluation in addition to obtaining careful patient history and physical examination of the patient's venous venous, arterial, and cardiopulmonary systems (10). In patients who meet specified criteria such as edema of the extremity, collateral vein development, or previous subclavian catheter placement, venography is indicated. In compare to Doppler studies, venography has the advantage of accurate evaluation of central vein structures. However, patients with reduced kidney function in whom contrast agents are undesirable, Doppler ultrasound or magnetic resonance imaging may be preferred.

Preoperative Doppler ultrasound

Doppler ultrasound has been the most extensively studied and widely used test to guide access creation (45-51). Several authors demonstrated that vessel size and blood flow are of predictive value for AVF outcome. AVF creation with a cephalic vein and/or radial artery smaller than 1,5-

2,0 mm is likely to fail and may indicate brachio-cephalic or transposed brachio-basilic AVF or insertion of a graft (45,52,53). A pre-operative brachial artery flow of at least 40 mL/min and a flow of 400 mL/min or more in the subclavian vein are associated with better primary patency rates and fistula function (47). Also, the use of a standardized program of preoperative arterial en venous mapping with ultrasonography could increase the use of AVF and reduce early failure rates (48,50,54).

Forearm strain-gauge plethysmography

Venous occlusion strain-gauge plethysmography is a frequently used technique for measurement of forearm blood flow and venous compliance (55). Throughout the years the method has been standardized and computerized, resulting in a reasonably simple and reliable technique (56-58).

It works on the principle that during short-term occlusion of venous return, the rate of distension of the forearm is proportional to the rate of arterial inflow into the forearm. Provided that the arterial blood pressure remains constant, changes in flow reflect changes in smooth muscle tone in small arteries and arterioles. A venous occlusion upper arm cuff is rapidly inflated to 60 mmHg during 4 heartbeats and deflated during 3 heartbeats. Distension of the arm is detected by a length transducer - specifically, a fine rubber tube containing mercury - placed around the maximal circumference of the forearm. The influence of the circulation of the hand on the measurements of forearm blood flow (FBF) is only small, which makes the use of a wrist cuff unnecessary (55). Subjects lay in supine position with the arm supported above heart level.

FBF can be measured at rest and after arterial infusion of drugs. FBF is expressed as mL blood flow/min/100ml forearm. Incremental infusions of acetylcholine, metacholine or serotonine are

frequently used drugs to examine endothelium-dependent vasodilatation. Sodium nitroprusside (SNP) is the most frequent used drug to examine endothelium-independent vasodilatation.

Venous compliance is the change in blood volume for a given change in pressure produced by a cuff around the arms or legs. The cuff pressure restricts blood flow from the tissues and causes the blood to pool. The upper arm cuff is inflated to a cuff pressure of 20 mmHg and is kept inflated during 3 minutes for stabilization of arm volume and venous pressure values. The cuff is deflated for 2 minutes to minimize accumulation of interstitial fluid due to capillary filtration. After repeating the same procedure during cuff pressures of 30, 40, 50 and 60, the obtained volume/pressure ratios are used in a linear regression analysis to obtain the volume-pressure relationship as an estimate of venous compliance.

So far, the value of forearm venous compliance and blood flow prior to AVF creation has never been evaluated. This thesis presents two studies that focus on this subject.

Preoperative magnetic resonance venography

Preoperative use of magnetic resonance (MR) venography and its advantage over conventional contrast-enhanced venography was documented by Menegazzo et al (59). Although it is considered non-invasive and safe, the quality of the basilic and central veins cannot be assessed, which is a major drawback of the MR venography (60). Furthermore, the cost-effectiveness of MR venography is questionable.

Prevention of vascular access thrombosis

In AVG, most thrombotic events result from one or more progressive stenoses in the venous outflow tract, typically at the venous anastomosis (61-64). These stenoses are caused by intimal

and fibromuscular hyperplasia (65,66). Any obstruction to the outflow from the graft will result in an increase in venous pressure in the dialysis circuit with an accompanying decrease in blood flow (67). Stenoses in AVF tend to occur more centrally at vein bifurcations and venous valves, rather than close to the venous outlet. Stenoses in AVF frequently result in development of collateral veins draining the AVF. As a result, a venous stenosis will cause a reduction in blood flow but often without the increase in venous pressure. Arterial inflow stenoses account for less than 5% of lesions in accesses (67).

Prospective surveillance of vascular accesses for hemodynamically significant stenoses, and subsequent referring for percutaneous transluminal angioplasty (PTA) or surgical revision, improves patency rates and decreases the incidence of thrombosis (Kanterman 1995, Besarab 1995, Beathard 1995, Windus 62,64,68,69). At present, access flow (Qa) and venous pressure measurements are preferred techniques that can be used in surveillance of both AVG and AVF (10).

Access flow

Several methods are available for measuring access flow (Qa). The most widely used and validated method is the ultrasound dilution technique, first introduced by Krivitski (70-73). It is based on the Fick-principle: dilution of blood in the extracorporeal circuit is measured by ultrasound. (70).

Although it is known that low-flow circumstances provoke thrombosis, the optimal threshold level for intervention has not been definitively determined. A limited number of studies using serial access flow measurements, suggest that grafts showing a flow between 500 and 800 ml/min are at risk for thrombosis (74-76). This has led to the general recommendation that intervention should be considered in patients with flows less than 600 ml/min (10). A trend of decreasing

access flow could be more predictive of venous stenosis than a single access flow measurement, however studies on this subject show conflicting results (77,78). Paulson et al. demonstrated that a decrease in flow had a sensitivity of 80%, but had a false-positive rate of 30% (78). This may lead to unnecessary interventions. Still, the NKF-K/DOQI committee recommends referral for angiography in patients with access flows less than 1000 ml/min, who show a decrease of more than 25% over 4 months time (10). Much less evidence is available on the value of flow measurements in AVF. Flow measurement in AVF is unreliable when needles are placed in collateral veins, and the optimal threshold for predicting failure of AVF has not been determined. More important, the incidence or thrombosis in fully matured AVF is very low, which makes it very difficult to evaluate the effect of flow-based monitoring strategies on reducing thrombosis of AVF. However, a flow-based surveillance program with prophylactic PTA of stenoses was shown to effectively reduce thrombosis rates and access-related morbidity in a prospective controlled trial (79).

Venous pressure

Dynamic and static venous pressure measurements are used for access surveillance. Schwab et al. introduced the dynamic venous pressure measurement: venous drip chamber pressure was measured at a pump flow rate of 200-225 mL/min (80). Persistently elevated venous pressure predicted the presence of significant venous stenosis (80). A reduction of thrombotic rate from 0.49 to 0.20 was demonstrated with graft surveillance using dynamic venous pressure monitoring and elective repair when compared to historical controls (80,81). Schwab et el. also included AVF.

However, dynamic venous pressure is importantly influenced by pump flow, needle gauge, blood tubing and blood pressure (82). This problem can be overcome by measuring static venous

pressure. Besarab et al. developed a method to measure venous pressure at zero pump flow, corrected for mean arterial blood pressure (VP0/MAP). Referral for angiography and subsequent intevention of significant stenoses in patients with VP0/MAP ≥ 0.50, resulted in a decrease in thrombosis rate from 57 to 17 per 100 patient years (68). Again, AVF and AVG were included.

An increased thrombotic tendency is an important cause of complications in patients on chronic hemodialysis. Still, the relationship between hypercoagulability and vascular access thrombosis is largely unknown. At present, no evidence-based consensus has been established regarding pharmacological prevention of access prevention. The coagulability abnormalities leading to thrombotic tendency in chronic hemodialysis patients will be discussed in this thesis.

Treatment of vascular access stenosis and thrombosis

Access stenosis and thrombosis are treated either radiologically or surgically. Prior to the introduction of access surveillance programs the most common clinical presentation of access failure was thrombosis. Traditionally, surgical thrombectomy with or without revision was utilized for dialysis access salvation. Surgical therapy has the advantage of elimination of the lesion. However, this has the great disadvantage of loss of potential access puncture sites. Considering the recurrent nature of venous stenosis, this may cause vascular access problems over time. Although literature reports slightly better patency rates after surgical correction of stenosis (83), general opinions are in favour of percutaneous treatment, because of the previously mentioned disadvantage together with the need for hospitalization.

Nowadays, patients often present with access stenosis, which is primarily treated with percutaneous transluminal angioplasty (PTA). Angioplasty is a safe outpatient procedure, which can be successfully repeated if necessary (84). Compared with surgery, PTA has the advantage of

preserving access sites. Also, even centrally located stenoses are accessible. Initial success rates of PTA range from 80 to 94% (62,85,86). The highest rate of technical failure is associated with central lesions (84). Primary patency rates at 6 months after PTA range from 43 to 77% (61,62,84,87), again with poorest long-term success in central lesions (nearly 25% at 6 months, 84). Results after vascular access thrombosis are generally worse, with a reported patency rate of only 19% in one study (88). Additive placement of self-expanding stents should be considered only in a selected group of patients, with central -elastic- lesions not responsive to PTA, or recurrence within 3 months after successful PTA, and patients with vein rupture after PTA (89). Lesions that cannot be dilated with angioplasty should not be treated with stent placement.

References

1. Kolff WJ, Berk HTh: The artificial kidney: a dialyzer with a great area. *Acta Med Scand* 1944; 117:121-34
2. Quinton WE, Dillard D, Scribner BH: Cannulation of blood vessels for prolonged hemodialysis. *Trans Am Soc Artif Intern Organs* 1960; 104-13
3. Brescia MJ, Cimino JE, Appel K, Hurwich BJ: Chronic hemodialysis using venipuncture and surgically created arteriovenous fistula. *N Eng J Med* 1966; 275:1089-92
4. Cimino JE, Brescia MJ: The early development of the arteriovenous fistula needle technique for hemodialysis. *ASAIO J* 1994; 923-7
5. Kapoian T, Sherman RA: A brief history of vascular access for hemodialysis: an unfinished story. *Sem Nephrol* 1997; 17:239-45
6. Dunlop MG, Mackinlay JY, Jenkins AM: Vascular access: experience with the brachiocephalic fistula. *Ann R Coll Surg Engl* 1986; 68:203-6
7. Stonebridge PA, Edington D, Jenkins AM: 'Brachial/basilic vein' transposition for vascular access. *J R Coll Surg Edinb* 1995; 40:219-20
8. Churchill DN, Taylor W, Cook RJ, LaPlante P, Barre P, Cartier P, Fay WP, Goldstein MB, Jindal K, Mandin H, McKenzie JK, Muirhead N, Parfrey PS, Posen GA, Slaughter D, Ulan RA, Werb R: Canadian hemodialysis morbidity study. *Am J Kidney Dis* 1992; 14:214-34
9. Pisoni RL, Young EW, Dykstra DM, Greenwood RN, Hecking E, Gillispie B, Wolfe RA, Goodkin DA, Held PJ: Vascular access use in Europe and the United States: results from the DOPPS. *Kidney Int* 2002; 61:305-16

10. National Kidney Foundation. K/DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis 2001*; 37 (Suppl 1):S137-S181
11. 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* 1998; 32:302-8
12. Sands JJ, Jabyac PA, Miranda CL, Kapsick BJ: Intervention based on monthly monitoring decreases hemodialysis access thrombosis. *ASAIO J* 1999; 45:147-50
13. Powe NR, Jaar B, Furth SL, Hermann J, Briggs W: Septicaemia in dialysis patients: incidence, risk factors and prognosis. *Kidney Int* 1999; 55: 1081-90
14. Schwab SJ, Beathard G: The hemodialysis catheter conundrum: hate living with them, but can't live without them. *Kidney Int* 1999; 56: 1-17
15. 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* 1997; 30 (Suppl.1):S160-S177
16. Feldman HI, Kobrin S, Wasserstein A: Hemodialysis Vascular Access Morbidity. *J Am Soc Nephrol* 1996; 7:523-35
17. Chazan JA, London MR, Pono L: The impact of diagnosis-related groups on the cost of hospitalisation for end-stage renal disease patients at Rhode Island Hospital from 1987 to 1990. *Am J Kidney Dis* 1992; 6:523-5
18. Lee H, Manns B, Taub K, Ghali WA, Dean S, Johnson D, Donaldson C: Cost analysis of ongoing care of patients with end-stage renal disease: the impact of dialysis modality and dialysis access. *Am J Kidney Dis* 2002; 40:611-22
19. National Kidney Foundation. NKF-DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 1997; 30 (Suppl 3): S152-S191

20. Allon M, Ornt DB, Schwab SJ, Rasmussen C, Delmez JA, Greene T, Kusek JW, Martin AA, Minda S: Factors associated with the prevalence of arteriovenous fistulas in hemodialysis patients in the HEMO study. *Kidney Int* 2000; 58:2178-85
21. Hirth RA, Turenne MN, Woods JD, Young EW, Port FK, Pauly MV, Held PJ: Predictors of type of vascular access in hemodialysis patients. *JAMA* 1996; 276:1303-7
22. Young EW, Dykstra DM, Goodkin DA, Mapes DL, Wolfe RA, Held PJ: Hemodialysis vascular access preferences and outcomes in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kidney Int* 2002; 61:2266-71
23. Amann K, Tyralla K, Gross ML, Eifert T, Adamczak M, Ritz E: Special characteristics of atherosclerosis in chronic renal failure. *Clin Nephrol* 2003; 60 (Suppl.1):S13-21
24. Lindner A, Charra B, Sherrard DJ, Scribner BH: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 1974; 28:697-701
25. Rostand SG, Gretes JC, Kirk KA, Rutsky EA, Andreoli TE: Ischemic heart disease in patients with uremia undergoing maintenance hemodialysis. *Kidney Int* 1979; 16:600-11
26. Wever R, Boer P, Hijmering M, Stroes E, Verhaar M, Kastelein J, Versluis K, Lagerwerf F, van Rijn H, Koomans H, Rabelink T: Nitric oxide production is reduced in patients with chronic renal failure. *Arterioscler Thromb Vasc Biol* 1999; 19:1168-72
27. Stroes ES, Joles JA, Chang PC, Koomans HA, Rabelink TJ: Impaired endothelial function in patients with nephrotic range proteinuria. *Kidney Int* 1995; 48:544-50
28. Anderson TJ: Assessment and treatment of endothelial dysfunction in humans. *J Am Coll Cardiology* 1999; 34:631-8
29. Pedrinelli R, Spessot M, Salvetti A: Reactive hyperemia during short-term blood flow and pressure changes in the hypertensive forearm. *J Hypertens* 1990; 8:467-71

30. Pedrinelli R, Dell'omo G, Gimelli A, Di Bello V, Talarico L, Corchia A, Sambuceti G, Neglia D, Parodi O: Myocardial and forearm blood flow reserve in mild-moderate essential hypertensive patients. *J Hypertens 1997*; 15:667-73

31. Taddei S, Virdis A, Mattei P, Arzilli F, Salvetti A: Endothelium-dependent forearm vasodilatation is reduced in normotensive subjects with familial history of hypertension. *J Cardiovasc Pharmocol*1992; 20(s12):s193-s195

32. Panza JA, Quyyumi AA, Brush JE, Epstein SE: Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. *N Eng J Med* 1990; 323:22-7

33. Schulte KL, Braun J, Meyer-Sabellek W, Wegscheider K, Gotzen R, Distler A: Functional versus structural changes of forearm vascular resistance in hypertension. *Hypertension* 1988; 11:320-5

34. Schulte KL, Braun J, Meyer-Sabellek W, Wegscheider K, Gotzen R, Distler A: Effects of reactive hyperemia and nifedipine on forearm vascular resistance in essential hypertension: evidence for functional abnormality. *J Cardiovasc Pharmacol* 1987; 10(s10):s134-s135

35. Rossi M, Taddei S, Fabbri A, Tintori G, Credidio L, Virdis A, Ghiadoni L, Salvetti A, Giusti C: Cutaneous vasodilatation to acetylcholine in patients with essential hypertension. *J Cardiovasc Pharmacol* 1997; 29:406-11

36. Schobel HP, Schmieder RE: Vasodilatory capacity of forearm resistance vessels is augmented in hypercholesterolemic patients after treatment with fluvastatin. *Angiology* 1998; 49(9):743-8

37. Hirooka Y, Imaizumi T, Harada S, Masaki H, Momohara M, Tagawa T, Takeshita A: Endothelium-dependent forearm vasodilatation to acetylcholine but not to substance P is impaired in patients with heart failure. *J Cardiovasc Pharmacol* 1992; 20(s12):s221-s225

38. Morris STW, McMurray JJV, Rodger RSC, Jardine AG:Impaired endothelium-dependent vasodilatation in uraemia. *Nephrol Dial Transplant* 2000; 15:1194-200

39. Pannier B, Guerin AP, Marchais SJ, Metivier F, Safar M, London GM: Postischemic vasodilatation, endothelial activation, and cardiovascular remodeling in end-stage renal disease. *Kidney Int* 2000; 57: 1091-9

40. Widgren BR, Berglund G, Wikstrand J, Andersson OK: Reduced venous compliance in normotensive men with positive family histories of hypertension. *J Hypertens* 1992; 10:459-65

41. Ogilvie R, Nadeau J, Lutterodt A: Vasodilator capacity of forearm vessels in hypertension. *Clin Exp Hypertens* 1982; 4:1391-407

42. Bell D, Collier A, Nicoll JJ, Jackson M, Millar AM, Clarke BF, Muir AL: Reduced venous compliance and increased transcapillary escape of protein in insulin-dependent diabetic patients. *Diabet Med* 1988; 5:454-8

43. Kooman JP, Wijnen JA, Draaijer P, van Bortel LM, Gladziwa U, Peltenburg HG, Struyker-Boudier HA, van Hooff JP, Leunissen KM: Compliance and reactivity of the peripheral venous system in chronic intermittent hemodialysis. *Kidney Int* 1992; 41:1041-8

44. Wali MA, Eid RA, Al-Homrany MA: Smooth muscle changes in the cephalic vein of renal failure patients before use as an arteriovenous fistula (AVF). *J Smooth Muscle Res* 2002; 38: 75-85

45. Wong V, Ward R, Taylor J, Selvakumar S, How TV, Bakran A: Factors associated with early failure of arteriovenous fistulae for haemodialysis access. *Eur J Endovasc Surg* 1996; 12:207-13

46. Malovrh M: Native arteriovenous fistula: preoperative evaluation. *Am J Kidney Dis* 2002; 39: 1218-25

47. Yerdel MA, Kesenci M, Yazicioglu KM, Döşeyen Z, Türkçapar AG, Anadol E: Effect of haemodynamic variables on surgically created arteriovenous fistula flow. *Nephrol Dial Transplant* 1997; 12:1684-88

48. Silva MB, Hobson RW, Pappas PJ, Jamil Z, Araki T, Goldberg MC, Gwertzman G, Padberg FT: A strategy for increasing use of autogenous hemodialysis access procedures: impact of preoperative non-invasive evaluation. *J Vasc Surg* 1998; 27:302-8

49. Mendes RR, Farber MA, Marston WA, Dinwiddie LC, Keagy BA, Burnham SJ: Prediction of wrist arteriovenous fistula maturation with preoperative vein mapping with ultrasonography. *J Vasc Surg* 2002; 36: 460-3

50. Ascher E, Gade P, Hingorani A, Mazzariol F, Gunduz Y, Fodera M, Yorkovich W: Changes in the practice of angioaccess surgery: impact of dialysis outcome and quality initiative recommendations. *J Vasc Surg* 2000; 31:84-92

51. Robbin ML, Gallichio MH, Deierhoi MH, Young CJ, Weber TM, Allon M: US: vascular mapping before hemodialysis access placement. *Radiology* 2000; 217:83-88

52. Malovrh M: Non-invasive evaluation of vessels by duplex sonography prior to construction of arteriovenous fistulas for hemodialysis. *Nephrol Dial Transplant* 1998; 13:125-29

53. Brimble KS, Rabbat CG, Treleaven DJ, Ingram AJ: Utility of ultrasonographic venous assessment prior to forearm arteriovenous fistula creation. *Clin Nephrol* 2002; 58:122-8

54. Parmley MC, Broughan TA, Jennings WC: Vascular ultrasonography prior to dialysis access surgery. *Am J Surg* 2002; 184:568-72

55. Lind L, Sarabi M, Millgård J: Methodological aspects of the evaluation of endothelium-dependent vasodilatation in the human forearm. *Clin Physiol* 1998; 18:81-7

56. Petrie JR, Ueda S, Morris AD, Murray LS, Elliot HL, Connell JMC: How reproducible is bilateral forearm plethysmography? *Br J Clin Pharmocol* 1998; 45:131-9

57. Chang PC, Van Brummelen P: Calibration and variability of forearm blood flow measured by strain gauge plethysmography. *J Cardiovasc Pharmocol* 1987; 10: S123-125

58. Chang PC, Verlinde R, Bruning TA, Van Brummelen P: A micro-computer-based, R-wave triggered system for hemodynamic measurements in the forearm. *Comput Biol Med* 1988; 18: 157-63

59. Menegazzo D, Laissy JP, Durrbach A, Debray MP, Messin B, Delm V, Mignon F, Schouman-Claeys E: Hemodialysis access fistula creation: preoperative assessment with MR venography and comparison with conventional venography. *Radiology* 1998; 209: 723-8

60. Turmel-Rodriques L, Bourquelot P, Paynaud A, Beyssen B, Sapoval M: Hemodialysis fistula: preoperative MR venography – a promising but partial view. *Radiology* 2000; 214:302-3

61. 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* 1996; 199:653-7

62. 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* 1995; 195:135-9

63. 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* 1996; 183:486-92

64. Beathard GA: Thrombolysis versus surgery for the treatment of thrombosed dialysis access grafts. *J Am Soc Nephrol* 1995; 6:1619-24

65. 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* 1989; 80:1726-36

66. Hofstra L: Intimal hyperplasia in human vascular grafts. A study in peripheral bypasses and arteriovenous fistulas. Thesis Rijksuniversiteit Limburg Maastricht 1995, ISBN 90-5278-190-7

67. Sullivan KL, Besarab A, Bonn J, Shapiro MJ, Gardiner GA, Moritz MJ: Hemodynamics of failing dialysis grafts. *Radiology* 1993; 186:867-872

68. 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* 1995; 47:1364-73

69. Windus DW, Audrain J, Vanderson R, Jendrasak MD, Picus D, Delmez JA: Optimalization of high-efficiency hemodialysis by detection and correction of fistula dysfunction. *Kidney Int* 1990;38: 337-41

70. Krivitski NM: Theory and validation of access flow measurement by dilution technique during hemodialysis. *Kidney Int* 1995; 48:244-50

71. Depner TA, Krivitski NM: Clinical measurement of blood flow in hemodialysis access fistulae and grafts by ultrasound dilution. *ASAIO J* 1995; 41: M745-9

72. Sands J, Glidden D, Miranda C: Hemodialysis access flow measurement. Comparison of ultrasound dilution and duplex ultrasonography. *ASAIO J* 1996; 42: M899-901

73. 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* 1996; 7:966-9

74. Shackleton CR, Taylor DC, Buckley AR, Rowley VA, Cooperberg PL, Fry PD: Predicting failure in polytetrafluoroethylene vascular access grafts for hemodialysis: a pilot study. *Can J Surg* 1987; 30:442-4

75. Sands J, Young S, Miranda C: The effect of Doppler flow screening studies and elective revisions on dialysis access failure. *ASAIO J* 1992;38:M524-7

76. Besarab A, Lubkowski T, Frinak S, Ramanathan S, Escobar F: Detecting vascular access dysfunction. *ASAIO J* 1997; 43:M539-43

77. Neyra NR, Ikizler TA, May RA,E, Himmelfarb J, Schulman G, Shyr Y, Hakim RM: Change in access blood flow over time predicts vascular access trombosis. *Kidney Int* 1998; 54:1714-9

78. Paulson WD, Ram SJ, Birk CG, Zapczynski M, Martín SR, Work J: Accuracy of decrease in blood flow in predicting hemodiálisis graft trombosis. *Am J Kidney Dis* 2000; 35:1089-95

79. Tessitore N, Mansueto G, Bedogna V, Lipari G, Poli A, Gammaro L, Baggio E, Morana G, Loschiavo C, Laudon A, Oldrizzi L, Maschio G: A prospective controlled trial on effect of percutaneous transluminal angioplasty on functioning arteriovenous fistulae survival. *J Am Soc Nephrol* 2003; 14:1623-7

80. Schwab SJ, Raymond JR, Saeed M, Newman GE, Dennis PA, Bollinger RR: Prevention of hemodialysis fistula thrombosis. Early detection of venous stenoses. *Kidney Int* 1989; 36: 707-11

81. 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* 1998; 32:302-8

82. Besarab A, Dorrell S, Moritz M: Determinants of measured dialysis venous pressure and its relationship to true intra-access venous pressure. *ASAIO Trans* 1991; 37:M270-M1

83. Dougherty MJ, Caliigaro KD, Schindler N, Raviola CA, Ntoso A: Endovascular versus surgical treatment for thrombosed hemodialysis grafts: a prospective randomized study. *J Vasc Surg* 1999; 30:1016-23

84. Beathard GA: Percutaneous transvenous angioplasty in the treatment of vascular access stenosis. *Kidney Int* 1992; 42: 1390-7

85. Saeed M, Newman GE, McCann RL, Sussman SK, Braun SD, Dunnick ND: Stenoses in dialysis fistulas: treatment with percutanous angioplasty. *Radiology* 1987; 164: 693-7

86. 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* 1997; 26: 382-90

87. Lay LPY, Ashleigh RJ, Tranconi L, Ackrill P: Result of angioplasty of Brescio-Cimino haemodialysis fistulae: medium-term follow-up. *Clinical Radiology* 1998; 53: 608-11

88. Lilly RZ, Carlton D, Barker J, Saddekni S, Hamrick K, Oser R, Westfall AO, Allon M: Predictors of arteriovenous graft patency after radiologic intervention in hemodialysis patients. *Am J Kidney Dis* 2001; 5: 945-53

89. Aruny JE, Lewis CA, Cardella JF, Cole PE, Davis A, Drooz AT, Grassi CJ, Gray RJ, Husted JW, Jones MT, McCowan TC, Meranze SG, Van Moore A, Neithamer CD, Oglevie SB, Omary RA, Patel NH, Rholl KS, Roberts AC, Sacks D, Sanchez O, Silverstein MI, Singh H, Swan TL, Towbin RB: Quality improvement guidelines for percutaneous management of the thrombosed or dysfunctional dialysis access. Standards of Practice Committee of the Society of Cardiovascular & Interventional Radiology. *J Vasc Interv Radiol* 1999; 10:491-8

Chapter 2

AIM AND OUTLINE OF THE THESIS

AIM AND OUTLINE OF THE THESIS

This thesis comprises 5 studies concerning two major hemodialysis vascular access issues:

Preoperative management in patients awaiting vascular surgery

With the recognition of the superiority of the AVF and the increasing comorbidity of the hemodialysis population, efforts are made to evaluate the vasculature of the arm of the patient prior to access surgery. Decision-making on which type of vascular access –AVF or AVG- is best suitable for the individual patient, is notoriously difficult and based on surgeons' personal opinion of the quality of the forearm vasculature or on static anatomical data derived from Duplex ultrasonography. So far, the impact of functional parameters of forearm vasculature prior to surgery on the success of newly created AVF, has never been studied. In chapter 3 and 4 we examine the predictive value of both venous and arterial wall properties in the outcome and maturation of AVF, using the technique of venous occlusion plethysmography.

Chapter 3. Forearm venous distensibility

In this chapter we examine the importance of pre-operative forearm venous distensibility with respect to AVF maturation. I.e. what is the impact of *functional properties*, in addition to anatomy of the forearm venous vasculature on the outcome of newly created AVF? After AVF creation, flow increases as a result of both vasodilatation and vascular remodeling. In several animal models of flow-induced vasodilatation, endothelial cells play an important role in vascular remodeling (1-5). Defective endothelial vasodilator function has been demonstrated in patients with different stages of renal failure (6). Forearm venous distensibility, i.e. the ability to adjust to blood pressure is also impaired in these patients. It is suggested that venous distensibility is also

influenced by endothelial funtion (7). It is not known whether impaired venous distensibility results in AVF failure. Hence, we measured this venous functional parameter in patients with end-stage renal failure awaiting vascular access surgery and investigated its predictive role in AVF failure. Furthermore, the results of plethysmography were compared to the pre-operative Duplex ultrasonography data.

Chapter 4. Forearm blood flow capacity

After creation of an AVF for hemodialysis, blood flow through the radial artery will increase as a result of vasodilatation and vascular remodeling (8). This adaptive response appears to be crucial in reducing wall shear stress to baseline values. Major calcification and stiffening of the radial artery wall will inhibit proper vasodilatation, which will lead to inadequate arterial inflow of the AVF. Vasodilatation after AVF-creation is primarily caused by acute release of nitric oxide by endothelial cells, so-called endothelium-dependent vasodilatation. We hypothesized that the forearm blood flow capacity, i.e. the increase of forearm blood flow as a result of vasodilatation, is an important determinant of failure of newly created AVF in hemodialysis patients. Therefore, in this chapter, we determine whether forearm blood flow capacity in patients with end-stage renal failure awaiting vascular access surgery, is predictive of early failure. To discriminate the influence of the endothelium in early fistula failure, we measure both, endothelium dependent and endothelium independent forearm vasodilatation, using forearm venous occlusion plethysmography.

Prevention of vascular access thrombosis

Once the vascular access, whether AVF or AVG has been placed, another important problem arises: thrombosis. In chapter 5 strategies to identify AVG at risk of thrombosis, i.e. vascular access stenosis, are studied. It has been demonstrated that timely treatment of these stenotic lesions results in less thrombotic events. Chapter 6 will focus on short- and long-term functional effects of percutaneous treatment of stenoses in AVG and AVF. Chapter 7 reviews the hypercoagulable state in hemodialysis patients.

Chapter 5. Graft surveillance

Thrombosis occurs at a rate of 0.5 to 2.5 events per patient-year (9-13). In most cases thrombosis is associated with the presence of stenoses at the venous anastomosis or in the outflow tract (14-18). 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 (19-23). Whereas, VP only reflects outflow resistance, Qa reflects total graft resistance. This raises the following questions: Are Qa measurements superior to VP measurements with regard to prevention of access thrombosis? Are Qa measurements of benefit when *added* to a surveillance protocol using simple VP measurements? In this prospective, randomized study we examine whether referral of patients for corrective interventions based on Qa measurements alone or on the combination of VP and Qa indeed reduces thrombosis rate more than referral based on VP alone.

Chapter 6. Functional effect of percutaneous transluminal angioplasty

Percutaneous transluminal angioplasty (PTA) is an accepted treatment of stenotic lesions (3)24). 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 (17,19,21). 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%(29), patency at 6 months follow-up varies from 38% to 63% (15,20,25,26). 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),15,20,27-29). 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 quantify the short-term functional and angiographic effect of PTA. In addition, we determine the longevity of the functional effect during follow-up. Finally, we addresse the question, whether functional variables are predictive of long-term outcome.

Chapter 7. Coagulation and hemodialysis access thrombosis

In most cases thrombosis is associated with low access blood flow (23,30,31). 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 (14-17). However, not all decreases in access blood flow are related to intimal hyperplasia or stenosis formation. An increased thrombotic tendency is an important cause of complications in patients on chronic hemodialysis leading to complications like ischaemic heart disease or stroke. There has been a growing interest in the role of increased hypercoagulability in access thrombosis. This review will discuss coagulability abnormalities in relation to hemodialysis access thrombosis. 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.

References

1. Tronc F, Wassef M, Esposito B, Henrion D, Glagov S, Tedgui A: Role of NO in flow-induced remodeling of the rabbit common carotid artery. *Arterioscler Thromb Vasc Biol* 1996; 16:1256-62
2. Tronc F, Mallat Z, Lehoux S, Wassef M, Esposito B, Tedgui A: Role of metalloproteinases in blood flow-induced arterial enlargement: interaction with NO. *Arterioscler Thromb Vasc Biol* 2000; 20:120-6
3. Tuttle JL, Nachreiner RD, Bhuller AS, Condict KW, Connors BA, Herring BP, Dalsing MC, Unthank JL: Shear level influences resisance artery remodeling: wall dimensions, cell density, and eNOS expression. *Am J Physiol Heart Physiol* 2001; H1380-9
4. Masuda H, Zhuang YJ, Singh TM, Kawamura K, Murakami M, Zarins CK, Glacov S: Adaptive remodeling of internal elastic lamina and endothelial lining during flow-induced arterial enlargement. *Arteriol Thromb Vasc Biol* 1999; 19:2298-307
5. Guzman RJ, Abe K, Zarins CK. Flow-induced arterial enlargement is inhibited by suppression of nitric oxide synthase activity in vivo. *Surgery* 1997; 122:273-9
6. Kooman JP, Wijnen JA, Draaijer P, van Bortel LM, Gladziwa U, Peltenburg HG, Struyker-Boudier HA, van Hooff JP, Leunissen KM: Compliance and reactivity of the peripheral venous system in chronic intermittent hemodialysis. *Kidney Int* 1992; 41:1041-8
7. London GM, Marchais SJ, Guerin AP, Metivier F, Adda H: Arterial structure and function in end-stage renal disease. *Nephrol Dial Transplant* 2002; 17:1713-24
8. Girerd X, London G, Boutouyrie P, Mourad JJ, Safar M, Laurent S: Remodeling of the radial artery in response to a chronic increase in shear stress. *Hypertension* 1996; 27:799-803

9. National Kidney Foundation. NKF-DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 1997; 30 (Suppl 3):S152-S91

10. Beathard GA: Thrombolysis for the treatment of thrombosed dialysis access grafts: a nephrologist's view. *Semin Dial* 1995; 8:162-5

11. 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* 1998; 32:302-8

12. 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* 1998; 16:126-32

13. Sands JJ, Jabyac PA, Miranda CL, Kapsick BJ: Intervention based on monthly monitoring decreases hemodialysis access thrombosis. *ASAIO J*1999; 45:147-50

14. Bassiouny HS, White S, Glagov S, Choi E, Giddens DP, Zarins CK: Anastomotic intimal hyperplasia: mechanical injury or flow induced. *J Vasc Surg* 1992; 15:708-16

15. 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* 1995; 195:135-9

16. 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* 1996; 183:486-92

17. 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* 1996; 199:653-7

18. 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* 1997; 8:1458-61

19. 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* 1995; 47:1364-73

20. Beathard GA: Percutaneous transvenous angioplasty in the treatment of vascular access stenosis. *Kidney Int* 1992; 42:1390-7

21. Schwab SJ, Raymond JR, Saeed M, Newman GE, Dennis PA, Bollinger RR: Prevention of hemodialysis fistula thrombosis. Early detection of venous stenoses. *Kidney Int* 1989; 36:707-11

22. Sands JJ, Miranda CL: Prolongation of hemodialysis access survival with elective revision. *Clin Nephrol* 1995; 44:329-33

23. Smits JHM, Blankestijn PJ: Haemodialysis access: the case for prospective monitoring. *Curr Opin Nephrol Hypertens* 1999; 8:685-90

24. National Kidney Foundation. K/DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 2001; 37 (Suppl 1):S137-S181

25. Gray RJ: Percutaneous intervention for permanent hemodialysis access: a review. *J Vasc Interv Radiol* 1997; 8:313-27

26. Glanz S, Gordon DH, Butt KM, Hong J, Lipkowitz GS: The role of percutaneous angioplasty in the management of chronic hemodialysis fistulas. *Ann Surg* 1987; 206: 777-81

27. 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* 1997; 26:382-90

28. 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* 1999; 10:389-96

29. 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) 1999; 200A

30. Bosman PJ, Boereboom FTJ, Eikelboom BC, Koomans HA, Blankestijn PJ: Graft flow as a predictor of thrombosis in hemodialysis grafts. *Kidney Int* 1998; 54:1726-30

31. Diskin CJ, Stokes TJJ, Pennell AT: Pharmacologic intervention to prevent hemodialysis vascular access thrombosis. *Nephron* 1993; 64:1-26

Chapter 3

FOREARM VENOUS DISTENSIBILITY PREDICTS SUCCESSFUL ARTERIO-VENOUS FISTULA

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Abstract

Background. The success of a newly created arterio-venous fistula (AVF) depends on sufficient maturation of the forearm vein used. This maturation fails in up to 30%. We hypothesize that impairment of forearm venous distensibility (VD), i.e. the ability of veins to adjust to an increased pressure, is related to AVF failure.

Methods. Forearm VD was measured using strain-gauge plethysmography, in 27 patients with end stage renal failure awaiting vascular access surgery, either AVF or graft (AVG). Ultrasound duplex scanning of the upper extremity circulation was performed 4 weeks prior to surgery. Failure to mature was defined as the inability to use the AVF for hemodialysis within 8 weeks after surgery.

Results. VD in patients receiving AVG (n=10) was 0.44±0.05 mL/mmHg, VD in patients receiving AVF (n=17) was 0.56±0.04 mL/mmHg (p=0.2). VD in patients with an unsuccessful AVF (n=9) was 0.46±0.03 mL/mmHg and 0.66±0.05 mL/mmHg in patients with a successful AVF (n=8)(p=0.003). All 7 patients with VD 0.50 mL/mmHg or less had a non-functional AVF (100%). Whereas only 2 out of 10 patients with VD higher than 0.50 mL/mmHg had a non-functional AVF (20%)(p=0.002). No differences were found in arterial and venous luminal diameters between functional and non-functional AVF.

Conclusions. These preliminary results suggest that forearm VD is a predictor of AVF success, whereas luminal diameters are not. Measurement of VD may be helpful in choosing the most suitable access type for each individual patient, possibly improving access patency.

Introduction

Long-term functioning of a vascular access is of crucial importance in hemodialysis patients. Because of better primary and secondary patency rates and less infectious and thrombotic complications in comparison to prosthetic grafts using polytetrafluoroethylene (AVG), the primary arterio-venous (AVF), i.e. autologous radiocephalic fistula, is considered to be the vascular access of first choice (1,2). Therefore, recent K-DOQI guidelines recommend that at least 50% of new hemodialysis patients should have a primary AVF leading to better patency rates and less access related costs (3).

Adequate maturation of AVF, i.e. sufficient dilatation and arterialization, is a prerequisite for repeated cannulation for haemodialysis treatment. Early successful maturation of an AVF appears to be a strong predictor of long-term function (4,5). However, depending on patient selection, maturation fails in up to 30% of all newly created fistulas, resulting in delayed initiation of dialysis treatment or placement of temporary central venous dialysis catheters, with their related morbidity (6-10). These early failures are frequently regarded as a technical failure, but factors like age, gender, blood pressure and associated illnesses are likely involved in AVF maturation as well (7,11).

Decision-making on which type of vascular access –AVF or AVG- is best suitable for the individual patient, is notoriously difficult and based on surgeons' personal opinion of the quality of the forearm vasculature or on static anatomical data derived from Duplex ultrasonography. Recently, the use of preoperative venous mapping, was shown to not only increase the number of created AVF's, but also to nearly double patency rates and reduce the early failure rate from 36 to 8.3% (8). Several studies demonstrated a relationship between preoperative vessel diameter and AVF success (9,12-14). However, these studies have shown various results and many used AVF

patency, rather than the ability to provide adequate blood flow on hemodialysis as primary outcome.

After AVF creation, flow increases as a result of both vasodilatation and vascular remodeling. In several animal models of flow-induced vasodilatation, endothelial cells play an important role in vascular remodeling, but the mechanism is still unclear (15-19

). In patients with diabetes, hypertension and heart failure endothelial vasodilator function appears to be impaired (20). Also, in patients with different stages of renal failure defective endothelial vasodilator function has been demonstrated (21). Interestingly, venous forearm distensibility (VD), i.e. the ability of veins to adjust to increased pressure is also impaired in these patients (22).

We hypothesized that the dynamic properties of the forearm venous vasculature are an important determinant of the maturation of newly created AVF's in hemodialysis patients. Therefore we determined whether forearm VD in patients with end-stage renal failure awaiting vascular access surgery, was predictive of early successful AVF maturation. Furthermore, the results of plethysmography were compared to the pre-operative Duplex ultrasonography data.

Subjects and methods

Subjects

Patients with advanced renal failure, requiring hemodialysis and awaiting vascular access surgery, were recruited consecutively. The institute's Medical Ethics Committee approved the trial protocol. Written informed consent was obtained from all participating patients. The patients were asked to refrain from smoking and caffeine or alcohol containing beverages for at least 12 hours prior to the study. Vasoactive medication was discontinued 7 days before the study. Within one month after Duplex ultrasonography and forearm strain gauge plethysmography patients underwent vascular access surgery. The vascular surgeon decided the access type -either arterio-venous fistula (AVF) or graft (AVG)- based on physical examination and preoperatively determined duplex parameters. Patients with no visible and/or a tortuous short cephalic vein and/or radial artery diameter less than 1.5 mm received an AVG.

Patients who received an AVF were further evaluated after surgery. The following data were collected: Duplex ultrasound access flow one day after surgery, duration of hospitalization and complications. A non-functional AVF was defined as the inability to use the AVF for two-needle hemodialysis within 8 weeks of surgery, judged by a panel of experienced dialysis nurses, who were unaware of the results of all additional forearm studies. Successful dialysis was defined as the ability to provide at least 250 mL/min dialyzer pump flow.

Duplex ultrasonography

Pre-operative duplex scanning of the upper extremity was performed with the HDI 3000 Ultrasound System (ATL Ultrasound Bothell, USA). A 2-D linear electronic probe, pulse wave

Doppler and color wave Doppler at 5.0 MHz were used. The internal diameters of the cephalic vein and the radial artery at the wrist, and the brachial artery were measured using M-mode technique. A tourniquet to increase vascular size was not used. The flow (mL/min) of the brachial and radial arteries was obtained using the transducer frequency, the Doppler angle and the measured Doppler shift. Blood flow was calculated as the product of time-averaged velocity (TAV: cm × sec^{-1}) and cross sectional area (A; cm^2) of the arteries. The patency of both the proximal cephalic and subclavian vein was examined and their internal diameter was measured. Measurements were performed within one month prior to surgery. One day after AVF creation duplex AVF flow (mL/min) was measured at the venous side of the anastomosis.

Forearm strain-gauge plethysmography

The experiments were performed in the afternoon in quiet air-conditioned room with an ambient temperature of 22ºC. Subjects were studied in supine position with arms supported 10 cm above the level of the right atrium. The arm chosen for vascular access surgery, which was the non-dominant arm in the majority of subjects, was used for measurements. A mercury-in-silastic strain gauge was positioned around the widest part of the forearm. The strain gauge was connected to a plethysmograph (model periflow SU 4, Janssen Scientific Instruments, Beerse, Belgium) with electronic calibration for percentual volume changes and a built-in flow integrator module. To enable off-line data analysis, the plethysmograph was connected to an A/D converter (Dataq Instruments, model DI 420, Akron, OH, USA) for electronic data storage. A cuff was placed around the upper arm. Inflation was achieved using an ECG-triggered rapid cuff inflator (Janssen Scientific Instruments). Blood pressure and heart rate were measured continuously using the Finapress blood pressure monitor (Ohmeda, Inglewood, CO, USA).

Venous distensibility protocol

VD was determined as described by Kooman (22). After a 30-minute rest period, the upper arm cuff was inflated to a cuff pressure of 20 mmHg and was kept inflated during 3 minutes for stabilization of arm volume and venous pressure values. The cuff was deflated for 2 minutes to minimize accumulation of interstitial fluid due to capillary filtration. The changes in volume (dV, $mL/100ml^{-1}$ forearm) during each cuff pressure step (dP, in mmHg) were obtained from the values measured just before and after deflation of the cuff. The dV was corrected for forearm volume, which was measured using a column filled with water to a fixed level (dV, mL). Cuff pressure was used (23,24) as an estimate of venous pressure (VPc). Subsequently, the same procedures were followed to obtain volume/pressure ratios during cuff pressures of 30, 40, 50 and 60 mmHg. The ratios of dV and VPc were used in a linear regression analysis to obtain the volume-pressure relationship as an estimate for VD (mL/mmHg).

Statistics

For comparison of individual data between groups 2-sided t-test analysis was used. Linear regression analysis was used to calculate correlations between datasets. A *p*-value of less than 0.05 was considered significant.

Results

Twenty-seven patients with end stage renal disease awaiting vascular access surgery either for AVF or AVG participated in the study. In seventeen patients an AVF was created, the remaining 10 patients received an AVG. Patient characteristics are summarized in table 1.

Table 1. Patient characteristics

	Arterio-venous fistula		Arterio-venous graft
	Functional n=8	Non-functional n=9	n=10
age (years)*	56 (32-83)	59 (35-78)	62 (30-81)
gender (m/f)	8/0	6/3	2/8
serum creatinine (mg/dl)*	7.7 (5.2-9.9)	8.4 (5.3-11.3)	7.5 (5.8-12.2)
diabetes (n)	0	1	2
hypertension (n)	7	8	7
smoking (n)	2	3	0
peripheral vascular disease (n)	0	3	2

NOTE. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4.

* data are presented as mean and range

Venous distensibility

VD of patients receiving AVG (n=10) was 0.44±0.05 mL/mmHg and 0.56±0.04 mL/mmHg in patients receiving AVF (n=17)(p=0.2). VD in patients with an unsuccessful AVF eight weeks after surgery (AVF-, n=9) was 0.46±0.03 mL/mmHg, while in patients with a successful AVF (AVF+, n=8) VD was 0.66±0.05 mL/mmHg (p=0.003, Figure 1). The mean duration of hospitalization was 5.3 days (range 1-21 days) in AVF- and 3.6 days (1-8 days) in AVF+ (p=0.53).

Figure 1 shows that all 7 patients with VD of 0.50 mL/mmHg or lower had a non-functional AVF (100%). Only 2 out of 10 patients with VD higher than 0.50 mL/mmHg had a non-functional AVF (20%). This difference was statistically significant by Fisher's exact test (p=0.002). Application of this criterion yielded a sensitivity of 100% (8/8), a specificity of 78% (7/9), a positive predictive value of 80% (8/10) and a negative predictive value of 100% (7/7). The outcome of 15 patients was correctly predicted by VD (88%).

Two patients with non-functional AVF had VD above 0.50 mL/mmHg. Angiography showed a severe venous stenosis a few centimeters from the anastomosis in both AVF. A pseudoaneurysm was seen at the stenotic region in one AVF. Both AVF's were surgically revised 3 months after the first operation. One AVF could be used for hemodialysis after revision, the other occluded. Of the other 7 non-functional AVF 3 never matured: these patients went for secondary access surgery. Four AVF's could be cannulated for hemodialysis only after 100 days (range 84-132 days). Angiography showed an arterial stenosis in one patient and a venous stenosis and with extended collateral circulation in another. After 3 percutaneous transluminal angioplasty (PTA) procedures these AVF could be used for dialysis. The remaining 2 AVF showed no significant stenoses at angiography and finally matured.

No differences were found in the brachial and radial artery and cephalic vein luminal diameters between AVF+ and AVF- . No significant correlation was found between VD and cephalic vein diameter. Results of preoperative duplex ultrasonography are depicted in more detail in table 2.

Table 2. Duplex ultrasonography data of patients with AVF

	Functional AVF n=8	Non-functional AVF n=9	
Luminal diameter (mm)*			
• Radial artery	2.1±0.1	2.0±0.2	Ns
• Brachial artery	4.3±0.4	4.1±0.3	Ns
• Cephalic vein	1.9±0.4	1.9±0.2	Ns
• Subclavian vein	8.0±1.3	8.5±0.7	Ns
Brachial artery flow (mL/min)*	44.1±13.8	34.3±8.0	Ns

* data are presented as mean±sd

Discussion

This prospective study evaluates venous forearm function rather than anatomy prior to AVF creation for the first time. The results of this study support our hypothesis that apart from structural changes, the functional properties of forearm veins are important in the adaptive response to increased blood flow after AVF creation. Furthermore, functional data of forearm venous vasculature do not correspond with anatomical data. Our data suggest that VD predicts successful AVF maturation, whereas venous and arterial diameters do not.

Previous studies found that in patients with end-stage renal failure forearm veins are less distensible in comparison to healthy controls (22,25). Several authors reported increased venous intimal and media thickness in renal failure (26,27). Wali et al. showed accumulation of collagen fibers in the vein wall (27). Also, venous wall edema may account for decreased venous distensibility (28). The importance of endothelial function in arterial vasodilatation after AVF creation is demonstrated by several authors (15-19). In addition, Tronc et al. (15) demonstrated less venous dilatation in response to increased blood flow in L-NAME treated rabbits, suggesting a critical role of the endothelial cells in venous remodeling as well. However, the influence of the endothelium on VD remains to be elucidated.

Studies on the use of ultrasound prior to AVF creation have shown varying results and many have used AVF patency as primary outcome rather than the ability to provide adequate blood flow for hemodialysis (13,14). Our study could not demonstrate differences in success rates at any cut-off point for radial artery or cephalic vein diameter. This is in contrast with the a post hoc analysis of Wong et al., who showed that luminal radial artery or cephalic vein diameter of less than 1.6 mm was associated with AVF failure (14). Actually, only 6 out of 60 patients had vessel diameters this small. Malovr et al described a significant difference in success rate of patients

with a radial artery diameter of 1.5 mm or less (45%) and patients with a radial artery diameter above 1.5 mm (92%)(13). However, definition of AVF failure was not provided in this study. This difference in study results can, at least in part, be explained by our study design, which selected patients with a radial artery diameter under 1.5 mm for AVG. The question whether these patients can undergo AVF creation successfully, cannot be answered definitively.

Numerous studies have evaluated the utility of Doppler ultrasound access flow in the immediate postoperative period subsequent to AVF creation (6,14,29-31). Although several authors (6,29,30) demonstrated higher intraoperative access flow in successful AVF, others failed to show any correlation between intraoperative access flow and outcome (14,31). This difference is frequently attributed to vessel spasm during operation, resulting in poor fistula flow. This would explain the better correlation between 1-day postoperative access flow and AVF outcome as demonstrated by Wong et al. (14). In our study, day one postoperative duplex flow was measured in 12 patients, and was also found to be higher in functional AVF (n=6) when compared to non-functional AVF (n=6), however large variations were found within both groups, limiting its predictive value in clinical practice (data not shown).

The majority of female patients received AVG in our study. Several studies have reported that female patients are much less likely to dialyze with a fistula (2,32,33). VD was significantly higher in males (p=0.0002). Also, female patients were found to have smaller radial arteries and cephalic veins (data not shown). Thus, both functional and anatomical differences must be responsible for this observation.

Our study has certain limitations. Because of the limited number of patients, the effect of confounding factors on our results could not be evaluated. Indeed, factors like peripheral vascular disease, female gender and diabetes may have influenced VD in a negative way in the group of patients with non-functional AVF's. However, currently these factors are never used to select

access type in daily clinical practice. VD, on the other hand, possibly reflects endothelial dysfunction in these patients, and may be used as a practical tool to estimate the risk of AVF failure in the individual patient.

The time required for fistula maturation varies among patients. We have chosen an arbitrary time period of 8 weeks in our study, which is in agreement with DOQI guidelines (3). The Work Group does not advise use of the fistula within the first month after construction because premature cannulation of a fistula may result in a higher incidence of infiltration with associated compression of the vessel by hematoma and permanent loss of the fistula. Allowing the fistula to mature for 3 months before use may be ideal. However, the Work Group did not reach consensus on this topic. In fact, allowing 3-month maturation would not have changed our results, since final cannulation in the 5 patients in the non-functional AVF group, was only possible after 100 days, usually after PTA or surgical revision. Furthermore, patients with functional AVF's were cannulated after 41 days.

Considering our data provided proof of the principle that functional vessel wall characteristics predict fistula maturation, the preoperative evaluation of the forearm vasculature should not only focus on resting static diameters. In view of the large potential benefits of optimization of the matching of patients and access type, further and larger studies of novel techniques are urgently needed.

References

1. Churchill DN, Taylor W, Cook RJ, LaPlante P, Barre P, Cartier P, Fay WP, Goldstein MB, Jindal K, Mandin H, McKenzie JK, Muirhead N, Parfrey PS, Posen GA, Slaughter D, Ulan RA, Werb R.: Canadian hemodialysis morbidity study. *Am J Kidney Dis* 1992;14:214-34
2. Pisoni RL, Young EW, Dykstra DM, Greenwood RN, Hecking E, Gillispie B, Wolfe RA, Goodkin DA, Held PJ: Vascular access use in Europe and the United States: results from the DOPPS. *Kidney Int* 2002; 61:305-16
3. National Kidney Foundation: K/DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 2001; 37(Suppl 1): S137-S181
4. Kinnaert P, Vereerstraeten P, Toussaint C, Van Geertruyden J: Nine years' experience with internal arteriovenous fistulas for haemodialysis: a study of some factors influencing the results. *Br J Surg* 1977; 64:242-6
5. Windus DW: Permanent vascular access: a nephrologist's view. *Am J Kidney Dis* 1993; 21:457-71
6. Elfström J, Thomsen M: The prognostic value of blood-flow measurements during construction of arteriovenous fistulae. *Scand J Urol Nephrol* 1981; 15(3):323-26
7. Kalman PG, Pope M, Bhola C, Richardson R: A practical approach to vascular access for hemodialysis and predictors of success. *J Vasc Surg* 1999; 30:727-33
8. Silva MB, Hobson RW, Pappas PJ, Jamil Z, Araki T, Goldberg MC, Gwertzman G, Padberg FT: A strategy for increasing use of autogenous hemodialysis access procedures: impact of preoperative non-invasive evaluation. *J Vasc Surg* 1998; 27:302-8

9. Yerdel MA, Kesenci M, Yazicioglu KM, Döşeyen Z, Türkçapar AG, Anadol E: Effect of haemodynamic variables on surgically created arteriovenous fistula flow. *Nephrol Dial Transplant* 1997; 12:1684-88

10. Lin SL, Huang CH, Chen HS, Hsu WA, Yen CJ, Yen TS: Effects of age and diabetes on blood flow rate and primary outcome of newly created hemodialysis arteriovenous fistulas. *Am J Nephrol* 1998; 18:96-100

11. Lazarides MK, Iatrou CE, Karanikas ID, Kaperonis NM, Petras DI, Zirogiannis PN, Dayantas JN: Factors affecting the lifespan of autologous and synthetic arteriovenous access routes for haemodialysis. *Eur J Surg* 1996; 162:297-301

12. Malovrh M: Native arteriovenous fistula: preoperative evaluation. *Am J Kidney Dis* 2002; 39:1218-25

13. Malovrh M: Non-invasive evaluation of vessels by duplex sonography prior to construction of arteriovenous fistulas for hemodialysis. *Nephrol Dial Transplant* 1998; 13:125-9

14. Wong V, Ward R, Taylor J, Selvakumar S, How TV, Bakran A: Factors associated with early failure of arteriovenous fistulae for haemodialysis access. *Eur J Endovasc Surg* 1996; 12:207-13

15. Tronc F, Wassef M, Esposito B, Henrion D, Glagov S, Tedgui A: Role of NO in flow-induced remodeling of the rabbit common carotid artery. *Arterioscler Thromb Vasc Biol* 1996; 16:1256-62

16. Tronc F, Mallat Z, Lehoux S, Wassef M, Esposito B, Tedgui A: Role of metalloproteinases in blood flow-induced arterial enlargement: interaction with NO. *Arterioscler Thromb Vasc Biol* 2000; 20:120-6

17. Tuttle JL, Nachreiner RD, Bhuller AS, Condict KW, Connors BA, Herring BP, Dalsing MC,

Unthank JL: Shear level influences resisance artery remodeling: wall dimensions, cell density, and eNOS expression. *Am J Physiol Heart Physiol* 2001; H1380-9

18. Masuda H, Zhuang YJ, Singh TM, Kawamura K, Murakami M, Zarins CK, Glacov S: Adaptive remodeling of internal elastic lamina and endothelial lining during flow-induced arterial enlargement. *Arteriol Thromb Vasc Biol* 1999; 19:2298-307
19. Guzman RJ, Abe K, Zarins CK: Flow-induced arterial enlargement is inhibited by suppression of nitric oxide synthase activity in vivo. *Surgery* 1997; 122: 273-9
20. Anderson TJ: Assessment and treatment of endothelial dysfunction in humans. *J Am Coll Cardiology* 1999; 34:631-8
21. London GM, Marchais SJ, Guerin AP, Metivier F, Adda H: Arterial structure and function in end-stage renal disease. *Nephrol Dial Transplant* 2002; 17:1713-24
22. Kooman JP, Wijnen JA, Draaijer P, van Bortel LM, Gladziwa U, Peltenburg HG, Struyker-Boudier HA, van Hooff JP, Leunissen KM: Compliance and reactivity of the peripheral venous system in chronic intermittent hemodialysis. *Kidney Int* 1992; 41:1041-8
23. Christ F, Gamble J, Baschnegger H, Gartside IB: Relationship between venous pressure and tissue volume during venous congestion plethysmography in man. *J Physiol* 1997; 503:463-7
24. Halliwill JR, Minson CT, Joyner MJ: Measurement of limb venous compliance in humans: technical considerations and physiological findings. *J Appl Physiol* 1999; 87:1555-63
25. Bradley JR, Evans DB, Cowley AJ: Abnormalities of the peripheral circulation in patients with chronic renal failure. *Nephrol Dial Transplant* 1988; 3:412-6
26. Kooman JP, Daemen MJ, Wijnen R, Verluyten-Goessens MJ, van Hooff JP, Leunissen KM: Morphological changes of the venous system in uremic patients. A histopathologic study. *Nephron* 1995; 69:454-8
27. Wali MA, Eid RA, Al-Homrany MA: Smooth muscle changes in the cephalic vein of renal

failure patients before use as an arteriovenous fistula (AVF). *J Smooth Muscle Res* 2002; 38:75-85

28. Simon G, Pamnani MB, Overbeck HW: Decreased venous compliance in dogs with chronic renal hypertension. *Proc Soc Exp Biol Med* 1976; 152:122-5
29. Johnson CP, Zhu Y, Matt C, Pelz C, Roza AM, Adams MB: Prognostic value of intraoperative blood flow measurements in vascular access surgery. *Surgery* 1998; 124:729-38
30. Won T, Jang JW, Lee S, Han JJ, Park YS, Ahn JH: Effects of intraoperative blood flow on the early patency of radiocephalic fistulas. *Ann Vasc Surg* 2000; 14:468-72
31. Anderson CB, Etheredge EE, Harter HR, Graft RJ, Codd JE, Newton WT: Local blood flow characteristics of arteriovenous fistulas in the forearm for dialysis. *Surg Gynaecol Obstet* 1977; 144:531-3
32. Ifudu O, Macey LJ, Homel P, Hyppolite JC, Hong J, Sumrani N, Distant D, Sommer BG, Friedman EA: Determinants of type of initial hemodialysis vascular access. *Am J Nephrol* 1997; 17:425-7
33. Allon M, Ornt DB, Schwab SJ, Rasmussen C, Delmez JA, Greene T, Kusek JW, Martin AA, Minda S: Factors associated with the prevalence of arteriovenous fistulas in hemodialysis patients in the HEMO study. Hemodialysis (HEMO) Study Group. *Kidney Int* 2000; 58:2178-85

Chapter 4

ROLE OF FOREARM BLOOD FLOW RESERVE IN EARLY FAILURE OF NEWLY CREATED ARTERIO-VENOUS HEMODIALYSIS FISTULAE

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Abstract

Background. The autologous AV-fistula is the vascular access of choice in hemodialysis patients because of superior long-term survival due to a lower risk for thrombosis and infection. Access surgery should be followed by adequate fistula maturation, i.e., a gradual increase of vessel diameter, and thus increase in access flow. We hypothesized that preoperative measurement of the arterial forearm blood flow (FBF) reserve predicts successful fistula development.

Methods and patients. Prior to surgery, we measured FBF during incremental infusion of both an endothelium-dependent vasodilator, metacholine (MCh), and an endothelium-independent vasodilator, sodium nitroprusside (SNP), using venous occlusion plethysmography. Twenty-one patients (age 62±3, (mean ±sem), 10M /11F) with end-stage renal failure awaiting access surgery were studied.

Results. In patients with successful AVF maturation (n=17) the AUC of both vasodilators was higher than in patients with AVF failure (n=4)(MCh: 122.2±9.8 U vs. 79.1±5.8, $p<0.05$; SNP: 255.9±19.4 vs. 127.8±29.4, $p<0.01$). The absolute FBF increase was also significantly different between both groups (MCh:10.3±0.9 vs. 6.2±1.0 mL/100mL/min, $p=0.03$; SNP: 11.8±1.1 vs. 5.4± 1.4 mL/100mL/min, $p<0.01$). No AVF failure was observed when AUC was above 100 U after MCh (n=11) ($p<0.05$), or when AUC was above 200 U after SNP (n=13) ($p<0.01$). Baseline MAP and FBF was not different (107±4 vs. 109±5 mmHg, N.S.; 3.4±0.7 vs.4.6±0.4, N.S.). Duplex radial artery diameter did not differ between patients with successful or unsuccessful AVF maturation (2.4±0.2 vs. 2.8±0.3, N.S.).

Conclusions. We conclude that with measurement of FBF reserve, successful or unsuccessful AVF maturation can be predicted accurately. Endothelial function does not seem to play a role, as

endothelium-dependent and -independent vasodilators had similar effects. In addition to anatomical mapping, functional preoperative evaluation may improve AVF outcome.

Introduction

Adequate blood flow through an arterio-venous access is mandatory for successful hemodialysis in patients with end-stage renal disease (ESRD). According to DOQI-guidelines, the native radiocephalic arterio-venous fistula (AVF) as described by Brescia and Cimino, is the access of first choice (1). Patency rates of AVF are clearly superior when compared to the outcome of arterio-venous grafts (AVG), which is the result of much less thrombotic and infectious events in AVF. However, it is known that up to 15% of all newly created AVF fail shortly after surgery as a result of thrombosis. These so called early failures are frequently regarded as technical errors, although several hemodynamic parameters may also play a role.

After creation of an AVF for hemodialysis, blood flow through the radial artery will increase as a result of vasodilatation and vascular remodeling. Girerd et al. found a 1.4 fold increase in arterial diameter while the intima media thickness remained unchanged, clearly suggesting a remodeling of the arterial wall (2). This adaptive response appears to be crucial in reducing wall shear stress to baseline values. Major calcification and stiffening of the radial artery wall will inhibit proper vasodilatation, which will lead to inadequate arterial inflow of the AVF. Vasodilatation after AVF-creation is primarily caused by acute release of nitric oxide by endothelial cells, so-called endothelium-dependent vasodilatation. Also, endothelial cells play a central role in vascular remodeling. This is illustrated by the observation that endothelial denudation and inhibition of NO by L-NAME abolish arterial enlargement in animal models of arterio-venous fistula (3-5).

Endothelium-dependent vasodilatation of forearm capacitance vessels is affected by many diseases, among which several are known to cause renal failure, like diabetes and hypertension (6). Also, in patients with different stages of renal failure defective endothelial vasodilator function has been demonstrated (7).

We hypothesized that the forearm blood flow reserve, i.e. the increase of forearm blood flow as a result of vasodilatation, is an important determinant of failure of newly created AVF in hemodialysis patients. Therefore, we determined whether forearm blood flow reserve in patients with end-stage renal failure awaiting vascular access surgery, was predictive of early failure. To discriminate the influence of the endothelium in early fistula failure, we measured both, endothelium dependent and endothelium independent forearm vasodilatation, using forearm venous occlusion plethysmography. Duplex radial artery diameter will be evaluated in order to find any relationship between functional and anatomical data. Furthermore, the number of surgical or percutaneous procedures needed to obtain a functional AVF was determined.

Subjects and methods

Subjects

Patients with end-stage renal disease (ESRD) requiring hemodialysis and awaiting AVF creation were included after written informed consent. The trial protocol was approved by the institute's Medical Ethics Committee. Based on physical examination and preoperatively determined duplex parameters, the vascular surgeon decided the feasibility of creating an AVF in the individual patient. Patients with no visible and/or a tortuous short cephalic vein and/or radial artery diameter less than 1.5 mm received an AVG and did not participate in the study. The patients were asked to refrain from smoking and caffeine or alcohol containing beverages for at least 12 hours prior to the study. All vasoactive medication was discontinued 7 days before the study. Within one month after Duplex ultrasonography and forearm strain gauge plethysmography patients underwent vascular access surgery.

AVF which could be used for successful two needle hemodialysis, judged by a panel of experienced dialysis nurses who were unaware of the results of all additional forearm studies, were defined as functional AVF. Successful dialysis was defined as the ability to provide at least 250 mL/min dialyzer pump flow. After surgery, all patients received anticoagulant therapy (acenocoumarol) for six months.

Methods

Duplex ultrasonography

Pre-operative duplex scanning of the upper extremity was performed with the HDI 3000 Ultrasound System (ATL Ultrasound Bothell, USA). A 2-D linear electronic probe, pulse wave Doppler and color wave Doppler at 5.0 MHz were used. The internal diameter of the radial artery

at the wrist was measured using M-mode technique. A tourniquet to increase vascular size was not used. The patency of both the proximal cephalic and subclavian vein was examined.

Four weeks after surgery Duplex ultrasonography was performed to examine the AVF for development of stenotic lesions. Patients with significant stenotic lesions (>50% of the luminal diameter) were referred for percutaneous transluminal angioplasty within 2 weeks.

Forearm strain-gauge plethysmography

Venous occlusion strain-gauge plethysmography is a frequently used technique for measurement of forearm blood flow and venous compliance (8). Throughout the years the method has been standardized and computerized, resulting in a reasonably simple and reliable technique (9-11). It works on the principle that during short-term occlusion of venous return, the rate of distension of the forearm is proportional to the rate of arterial inflow into the forearm. Provided that the arterial blood pressure remains constant, changes in flow reflect changes in smooth muscle tone in small arteries and arterioles.

The experiments were performed in the afternoon in quiet air-conditioned room at constant temperature (20-24ºC). Subjects were studied in supine position with arms supported 10 cm above the level of the right atrium. The arm chosen for vascular access surgery, which was the non-dominant arm in the majority of subjects, was used for measurements. Forearm volume was measured by water displacement. The brachial artery was cannulated (cannula of 1.0 × 45 mm) after local anesthesia with lidocaine (1%). A mercury-in-silastic strain gauge was positioned around the widest part of the forearm. The strain gauge was connected to a plethysmograph (model periflow SU 4, Janssen Scientific Instruments, Beerse, Belgium) with electronic calibration for percentual volume changes and a built-in flow integrator module. To enable off-

line data analysis, the plethysmograph was connected to an A/D converter (Dataq Instruments, model DI 420, Akron, OH, USA) for electronic data storage. A venous occlusion cuff was placed around the upper arm. Inflation was achieved using an ECG-triggered rapid cuff inflator (Janssen Scientific Instruments), inflating the cuff to 60 mmHg during 4 heartbeats and deflating it during the next 3 heartbeats.

Baseline FBF (mL /100ml forearm/min) (FBF_{BL}) was measured after a resting period of at least 30 minutes after intra-arterial cannulation of the brachial artery. During this measurement saline was infused at 1 mL/min. Then, FBF was measured during incremental infusions (dose range 0.1-10 μg/kg/min) of metacholine (MCh), to examine endothelium-dependent vasodilatation. Each dosing step lasted 4 minutes. Sodium nitroprusside (SNP) was used (dose range 1-20 μg/kg/min) at 4-minute dosing steps to examine endothelium-independent vasodilatation. Between the various experiments sufficient time was allowed for FBF to return to baseline levels. Mean arterial blood pressure (MAP) and heart rate were measured continuously using the Finapress blood pressure monitor (Ohmeda, Inglewood, CO, USA).

Statistical analysis

Results are given as means±S.E.M. Dose-response curves were constructed for the vasodilator effects of MCh and SNP. Absolute change in FBF ($dFBF_{ABS}$), area under curve (AUC) for MCh and SNP and Duplex radial artery diameter were compared in patients with and without functional AVF, using Students' t-tests. P-values below 0.05 were considered statistically significant.

Results

Twenty-one consecutive patients with ESRD awaiting AVF creation were included into the study. All patients received an brachio-cephalic forearm fistula. In 4 patients the AVF occluded (AVF-NF), 3 of which in the first week after surgery. The remaining 17 AVF matured enough to enable 2-needle dialysis, and were functional after 78±11 days (range 43-157, AVF-F). Six AVF developed one or more significant stenotic lesions. Most lesions (6/11) were found in the venous outflow tract of the AVF, 3 were located at the anastomosis and the other 2 were arterial stenoses. After percutaneous transluminal angioplasty these AVF matured and were successfully cannulated for hemodialysis. The remaining 11 patients had a functional AVF within eight weeks. Duplex ultrasonography 4 weeks after surgery could not demonstrate any significant stenoses. Patient characteristics are depicted in Table 1.

Table 1. Patient characteristics

	AVF (n=21)	
	AVF-F n=17	AVF-NF n=4
Age	63±3	57±5
Gender (m/f)	8/9	2/2
Creatinin (μmol/L)	658±53	563±47
Diabetes (n)	8	0
Hypertension (n)	16	3
Smoking (n)	4	1
Cardiovascular disease (n)*	6	2

** stroke, peripheral vascular disease and/or myocardial infarction*

FBF venous occlusion plethysmography

Baseline mean arterial blood pressure (MAP_{BL}) -measured 30 minutes after intra-arterial cannulation- was 107±4 mmHg, and remained stable throughout both infusion protocols (MAP_{MCh} 109±5 mmHg and MAP_{NP} 107±4 mmHg, N.s, paired t-test.). Considering all patients (n=21), AUC after MCh infusion was significantly lower than AUC after NP infusion (114.0±8.8 and 231.5±19.9 resp., $p<0.0001$, paired t-test). Also, the absolute increase in FBF differed between both infusion protocols: dFBF MCh was 9.1±0.8 mL/100mL/min and dFBF NP was 10.5±1.1 mL/100mL/min, p=0.04, paired t-test).

FBF_{BL} was 4.4±0.4 mL/100mL/min and did not differ between AVF-F and AVF-NF (4.6±0.4 mL/100mL/min and 3.4±0.7, p=0.2).

MCh

In patients with non-functional AVF (AVF-NF) the absolute change in FBF ($dFBF_{ABS}$) during MCh infusion was 6.2±1.0 mL/100mL/min. In patients with functional AVF (AVF-F) $dFBF_{ABS}$ was more prominent: 10.3±0.9 mL/100mL/min (p=0.03). The AUC was 122.2±9.8 in AVF-F

patients and 79.1±5.8 in AVF-NF patients (p=0.045). Furthermore, all 4 failures had $dFBF_{ABS}$ and AUC values lower than the average $dFBF_{ABS}$ and AUC values of the whole series (9.1 mL/100mL/min and 114 respectively, Figure 1.). No fistula failure was seen in patients with $dFBF_{ABS} \geq 10$ mL/100mL/min (0/9). Four failures occurred in 12 patients with $dFBF_{ABS} < 10$ mL/100mL/min. This difference was insignificant by Fisher's exact test (p=0.1). It is noteworthy that all 4 fistula failures occurred in 10 patients with AUC < 100, while no failures were seen in 11 patients with AUC ≥ 100. This difference was statistically significant by Fisher's exact test (p=0.04).

NP

The $dFBF_{ABS}$ during NP infusion was significantly higher in AVF-F than in AVF-NF patients (11.8±1.1 mL/100mL/min and 5.4±1.4, respectively, p=0.01). The AUC was 255.9±19.4 in AVF-F and 127.8±29.4 in AVF-NF patients (p=0.008). Again, all non-functional AVF had lower $dFBF_{ABS}$ and AUC than the averages of the total group (10.5 mL/100mL/min and 231.5, Figure 1.). No differences in the risk of fistula failure were found between patients with $dFBF_{ABS}$ <10 and patients with $dFBF_{ABS}$ ≥10 mL/100mL/min. Of 8 patients with AUC <200, 50% of AVF failed, while none of the AVF of patients with AUC ≥200 failed (13/13), which was a significant difference (p=0.01, Fisher's exact test).

Duplex radial artery diameter

No significant differences were found between radial artery diameter of patients with AVF-F and AVF-NF (2.4±0.2 and 2.8±0.3 mm, respectively, p=0.2). Interestingly, all 4 non-functional fistulae had radial artery diameters of at least 2.2 mm.

Discussion

Under ideal circumstances, in which a group of skilled vascular surgeons is responsible for vascular access surgery, the success of a newly constructed AVF must depend on several hemodynamic variables affecting the in- and outflow of the AVF. Since AVF construction is directly followed by increased arterial blood flow, hypothetically, higher forearm blood flow capacitance, should be associated with better outcome of AVF. To provide evidence for this hypothesis, we measured forearm blood flow changes after infusion of the vasodilatant substances MCh and SNP, using venous occlusion plethysmography. To our knowledge, this is the first time invasively measured forearm blood flow capacity is related to outcome of AVF. This study shows that pre-operative forearm blood flow capacity is predictive of early AVF failure. Furthermore, our data indicate that AVF failure is not the result of pure endothelial dysfunction, because endothelial-independent forearm blood flow capacity is also diminished in patients with AVF failure. Finally, we showed that arterial diameter is not predictive of early AVF failure.

We demonstrated that patients with insufficient forearm blood flow capacity are likely to encounter primary AVF failure. Especially, the AUC of dose response curves seems predictive of AVF outcome. An AUC of 100 in MCh and 200 in NP seems a prerequisite of short term success of the AVF. To our knowledge forearm blood flow capacity using venous occlusion plethysmography was never examined as a determinant of fistula failure. However, Malovr et al. demonstrated a significantly lower arterial blood flow increase and higher vascular resistance after reactive hyperemia after reopening a clenched fist in patients with nonfunctional AVF in compare to patients with functional AVF (12,13). In agreement with Yerdel et al., baseline forearm blood (14) did not differ between patients with functional and not-functional AVF.

Therefore, differences in concentration of drug reaching the tissues, influencing the response to it, can be neglected.

We also hypothesized that the endothelium, responsible for direct nitric oxide release after AVF construction, is of importance in immediate AVF failure. Our data indeed demonstrate disturbance of MCh induced vasodilatation with relative preservation of NP induced vasodilatation, indicating endothelial dysfunction in ESRD. However, both determinants (AUC MCh and AUC NP) were found to be predictive of immediate AVF failure, suggesting structural arterial wall changes besides endothelial dysfunction. Indeed, in a recent study preoperative Duplex evaluation demonstrated severe arterial wall changes – wall thickening and calcification- in almost 40% of all patients awaiting vascular access surgery (13). Since our patients are comparable with respect to severity of renal dysfunction, it is reasonable to believe that these structural changes are also of importance in our study population.

In the past, several studies demonstrated worse AVF outcome in women and elderly (15-17). Because of small numbers, our data do not allow multivariate analysis of these clinical variables, but we found no differences in age and gender between patients with functional and non-functional AVF. It is possible that our study design, which selected patients with a radial artery diameter less than 1.5 mm for AVG, has eliminated mostly women and elderly from the study. However, within the group with functional AVF, almost 90% of interventions for stenotic lesions took place in women older than 65 years.

With the advent of mercury-in- rubber strain gauges, the technique of forearm venous occlusion plethysmography is accurate and widely used to probe mechanisms of human vascular control Venous occlusion plethysmography has the advantage of measurement of *total* forearm blood flow. However, clinical implementation of venous occlusion plethysmography, prior to access surgery, is not simple. First, this technique is very time-consuming and requires expensive hard-

and software. Second, and even more important, it is an invasive measurement. Although we didn't encounter any complications in our study, theoretically, formation of haematoma could interfere with arterial inflow. In vessels with relatively small diameter, such as the radial artery, estimation of volume flow by duplex sonography, using cross-sectional area, is inherently inaccurate. However, Malovr et al. described an alternative approach to measure blood flow capacitance in the radial artery (12). After releasing a fist the triphasic Doppler waveform in the radial artery should normally change to a low-resistance biphasic waveform, caused by post-ischemic dilatation of peripheral arterioles and consecutive reduction of peripheral resistance. Patients who lacked this conversion showed significantly more AVF failure. It would be of interest to study both techniques within one patient to determine the correlation of both modalities.

Although the number of patients is small, necessitating further prospective trials, our study provides valuable information on the influence of arterial inflow capacitance on fistula failure. Of course, arterial inflow is not the only factor in fistula maturation, and always depends on sufficient outflow as well. Considering the amount of stenoses found in the outflow tract at post-operative Duplex-examination, it is possible that inappropriate *venous* distensibility is of importance in the maturation of AVF that survive the first period after surgery. Ideally, the measurement of pre-operative forearm blood flow capacitance may direct the operation to be performed under more suitable conditions, or may result in primary placement of graft material, in order to overcome fistula failure in patients with unsuitable vascular anatomy. In order to use our findings in daily clinical practice, future studies should focus on easier, non-invasive ways to examine the role of forearm blood flow capacity in early fistula failure.

References

1. National Kidney Foundation. K/DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 2001; 37 (Suppl 1):S137-S181
2. Girerd X, London G, Boutouyrie P, Mourad JJ, Safar M, Laurent S: Remodeling of the radial artery in response to a chronic increase in shear stress. *Hypertension* 1996; 27:799-803
3. Tohda K, Masuda H, Kawamura K, Shozawa T: Difference in dilatation between endothelium-preserved and –desquamated segments in the flow-loaded rat common carotid artery. *Arterioscler Thromb* 1992; 12:519-28
4. Guzman RJ, Abe K, Zarins CK: Flow-induced arterial enlargement is inhibited by suppression of nitric oxide synthase activity in vivo. *Surgery* 1997; 122:273-80
5. Tronc F, Wassef M, Esposito B, Henrion D, Glagov S, Tedgui A: Role of NO in flow-induced remodeling of the rabbit common carotid artery. *Arterioscler Thromb Vasc Biol* 1996; 16:1256-62
6. Anderson TJ: Assessment and treatment of endothelial dysfunction in humans. *J Am Coll Cardiology* 1999; 34:631-8
7. London GM, Marchais SJ, Guerin AP, Metivier F, Adda H: Arterial structure and function in end-stage renal disease. *Nephrol Dial Transplant* 2002; 17: 1713-24
8. Lind L, Sarabi M, Millgård J: Methodological aspects of the evaluation of endothelium-dependent vasodilatation in the human forearm. *Clin Physiol* 1998; 18(2):81-7
9. Petrie JR, Ueda S, Morris AD, Murray LS, Elliot HL, Connell JMC: How reproducible is bilateral forearm plethysmography? *Br J Clin Pharmocol* 1998; 45:131-9
10. Chang PC, Van Brummelen P: Calibration and variability of forearm blood flow measured by strain gauge plethysmography. *J Cardiovasc Pharmocol* 1987; 10: S123-5

11. Chang PC, Verlinde R, Bruning TA, Van Brummelen P: A micro-computer-based, R-wave triggered system for hemodynamic measurements in the forearm. *Comput Biol Med* 1988; 18:157-63

12. Malovrh M: Non-invasive evaluation of vessels by duplex sonography prior to construction of arteriovenous fistulas for hemodialysis. *Nephrol Dial Transplant* 1998; 13:125-29.

13. Malovrh M: Native arteriovenous fistula: preoperative evaluation. *Am J Kidney Dis* 2002; 39:1218-25

14. Yerdel MA, Kesenci M, Yazicioglu KM, Döşeyen Z, Türkçapar AG, Anadol E: Effect of haemodynamic variables on surgically created arteriovenous fistula flow. *Nephrol Dial Transplant* 1997; 12: 1684-8

15. Miller CD, Robbin ML, Allon M: Gender differences in outcomes of arteriovenous fistulas in hemodialysis patients. *Kidney Int* 2003; 63:346-52

16. Wong V, Ward R, Taylor J, Selvakumar S, How TV, Bakran A: Factors associated with early failure of arteriovenous fistulae for haemodialysis access. *Eur J Endovasc Surg* 1996; 12:207-13

17. Tordoir JHM, Hoeneveld H, Eikelboom BC, Kitslaar PJEHM: The correlation between clinical and Duplex ultrasound parameters and the development of complications in arterio-venous fistulae for haemodialysis. *Eur J Vasc Surg* 1990; 4:179-84

Chapter 5

GRAFT SURVEILLANCE: VENOUS PRESSURE, ACCESS FLOW, OR THE COMBINATION?

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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.

Methods

Patients

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).

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.

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)	

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 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

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 *months* (range)	6.7 (1.0-49.7)	4.6 (1.2-28.4)	NS	11.6 (0.0-73.6)	6.0 (0.0-100.0)	NS
Mean age graft *months* (SD)	12.8 (13.8)	8.3 (7.6)		18.1 (20.9)	16.4 (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* (range)	11.2(0.9-15.5)	5.8(1.1-15.2)	0.016	5.9(1.7-20.4) 8.4 (5.7)	5.1(0.4-20.4) 6.2 (4.9)	NS
mean *months* (SD)	10.4 (4.4)	7.2 (4.9)				

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.

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).

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

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 various 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**).**

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 difference 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.

References

1 Feldman HI, Kobrin S, Wasserstein A: Hemodialysis vascular access morbidity. *J Am Soc Nephrol* 1996; 7:523-35

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* 1997; 30 (Suppl 1):S160-S177

3 Feldman HI, Held PJ, Hutchinson JT, Stoiber E, Hartigan MF, Berlin JA: Hemodialysis vascular access morbidity in the United States. *Kidney Int* 1993; 43:1091-6

4 National Kidney Foundation. NKF-DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 1997; 30 (Suppl 3):S152-S191

5 Beathard GA: Thrombolysis for the treatment of thrombosed dialysis access grafts: a nephrologist's view. *Semin Dial* 1995; 8:162-5

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* 1998; 32:302-8

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* 1998; 16:126-32

8 Sands JJ, Jabyac PA, Miranda CL, Kapsick BJ: Intervention based on monthly monitoring decreases hemodialysis access thrombosis. *ASAIO J* 1999; 45:147-50

9 Bassiouny HS, White S, Glagov S, Choi E, Giddens DP, Zarins CK: Anastomotic intimal hyperplasia: mechanical injury or flow induced. *J Vasc Surg* 1992; 15:708-16

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* 1995; 195:135-9

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* 1996; 183:486-92

12 Safa AA, Valji K, Roberts AC, Zieglet 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* 1996; 199:653-7

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* 1997; 8:1458-61

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* 1995; 47:1364-73

15 Beathard GA: Percutaneous transvenous angioplasty in the treatment of vascular access stenosis. *Kidney Int* 1992; 42:1390-7

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* 1989; 36:707-11

17 Sands JJ, Miranda CL: Prolongation of hemodialysis access survival with elective revision. *Clin Nephrol* 1995; 44:329-33

18 Smits JHM, Blankestijn PJ: Haemodialysis access: the case for prospective monitoring. *Curr Opin Nephrol Hypertens* 1999; 8:685-90

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* 1997; 52:1084-8.

20 Beathard GA: Mechanical versus pharmacomechanical thrombolysis for the treatment of thrombosed dialysis access grafts. *Kidney Int* 1994; 45:1401-6

21 Roberts AC, Valji K, Bookstein JJ, Hye RJ: Pulse-spray pharmacomechanical thrombolysis for treatment of thrombosed dialysis access grafts. *Am J Surg* 1993; 166:221-5

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* 1995; 164:1495-1500

23 Swan TL, Smyth SH, Ruffenach SJ, Berman SS, Pond GD: Pulmonary embolism following hemodialysis access thrombolysis/thrombectomy. *J Vasc Interv Radiol* 1995; 6:683-6

24 Krivitski NM: Theory and validation of access flow measurement by dilution technique during hemodialysis. *Kidney Int* 1995; 48:244-50

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* 1996; 7:966-9

26 Blankestijn PJ, Smits JH: How to identify the haemodialysis access at risk of thrombosis? Are flow measurements the answer? *Nephrol Dial Transplant* 1999; 14:1068-71

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* 1999; 10 (Suppl 13):S297-S305

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* 1997; 52:1656-62

29 Neyra NR, Ikizler TA, May RE, Himmelfarb J, Shulman G, Shyr Y, Hakim RM: Change in access blood flow over time predicts vascular access thrombosis. *Kidney Int* 1998; 54:1714-9

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* 1998; 44:M555-M8

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* 1998; 9:284-9

32 Allon M, Bailey R, Ballard R, Deierhoi MH, Hamrick K, Oser R, Rhynes VK, Robbins ML, Saddekni S, Zeigler ST: A multidisciplinary approach to hemodialysis access: prospective evaluation. *Kidney Int* 1998; 53:473-9

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* 1991; 37:M270-M1

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* 1994; 9:1616-21

35 Bosman PJ, Boereboom FTJ, Eikelboom BC, Koomans HA, Blankestijn PJ: Graft flow as a predictor of thrombosis in hemodialysis grafts. *Kidney Int* 1998; 54:1726-30

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* 1999; 34:478-85

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* 2000; 35:1089-95

Chapter 6

SHORT- AND LONG-TERM FUNCTIONAL EFFECT OF PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY IN HEMODIALYSIS VASCULAR ACCESS

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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

Patients

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.

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

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.

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 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 ($P = 0.09$).

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)

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 (= 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.

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* 1992; 19:214-34

2. Feldman HI, Held PJ, Hutchinson JT, Stoiber E, Hartigan MF, Berlin JA: Hemodialysis vascular access morbidity in the United States. *Kidney Int* 1993; 43:1091-6

3. National Kidney Foundation. K/DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 2001; 37 (Suppl 1):S137-S181

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* 1989; 36: 707-11

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* 1995; 47: 1364-73

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* 1996; 199:653-7

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* 2001; 59:1551-8

8. Gray RJ: Percutaneous intervention for permanent hemodialysis access: a review. *J Vasc Interv Radiol* 1997; 8:313-27

9. Beathard GA: Percutaneous transvenous angioplasty in the treatment of vascular access stenosis. *Kidney Int* 1992; 42:1390-7

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* 1987; 206:777-81

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* 1995; 195:135-9

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* 1997; 26:382-90

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* 1999; 10:389-96

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* 1999; 10 (ASN Program and Abstracts): 200A

15. Gray RJ, Sacks D, Martin LG, Trerotola SO: Reporting standards for percutaneous interventions in dialysis access. Technology Assessment Committee. *J Vasc Interv Radiol* 1999; 10:1405-15

16. Krivitski NM: Theory and validation of access flow measurement by dilution technique during hemodialysis. *Kidney Int* 1995; 48:244-50

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* 1996; 7:966-9

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* 2001; 59:358-62

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* 2000; 15:2029-36

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* 1997; 52: 1084-8

21. Blankestijn PJ, Smits JH: How to identify the haemodialysis access at risk of thrombosis? Are flow measurements the answer? *Nephrol Dial Transplant* 1999; 14:1068-71

22. Smits JHM, Blankestijn PJ: Thrombosis-free hemodialysis grafts: a possibility for the next century? *Semin Dial* 1999; 12:44-9

23. Smits JHM, Blankestijn PJ: Haemodialysis access: the case for prospective monitoring. *Curr Opin Nephrol Hypertens* 1999; 8:685-90

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* 1999; 10 (ASN Program and Abstracts): 221A

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* 1991; 40:91-5

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* 1998; 54:1714-9

27. Sands JJ, Jabyac PA, Miranda CL, Kapsick BJ: Intervention based on monthly monitoring decreases hemodialysis access thrombosis. *ASAIO J* 1999; 45:147-50

Chapter 7

COAGULATION AND HAEMODIALYSIS ACCESS THROMBOSIS

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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.

Table 1. Possible causes of vascular access thrombosis

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

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 hemostasis and fibrinolysis

Normal hemostatic 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 hemostatic response involves platelet adherence to the 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 hemostasis 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 hemostatic responses require both coagulation and platelet-dependent processes.

In hemodialysis 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 hemodialysis patients contributing to thrombotic tendency

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

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

Platelet abnormalities

Platelet abnormalities are common in patients on hemodialysis. 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 hemodialysis? 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 hemodialysis patients, adheres to glycoprotein IIb/IIIa on the surface of the platelet. Once attached to the surface (solid 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 hemodialysis 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 hemodialysis 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 prospective 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 1μmol/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 hemodialysis 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 frequency 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 hemodialysis 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* 1974; 290:697-701

2. Feldman HI, Kobrin S, Wasserstein A: Hemodialysis vascular access morbidity. *J Am Soc Nephrol* 1996; 7:523-35

3. 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* 1997; 30 (Suppl 1):S160-S77

4. Feldman HI, Held PJ, Hutchinson JT, Stoiber E, Hartigan MF, Berlin JA: Hemodialysis vascular access morbidity in the United States. *Kidney Int* 1993; 43:1091-6

5. Bosman PJ, Boereboom FTJ, Eikelboom BC, Koomans HA, Blankestijn PJ: Graft flow as a predictor of thrombosis in hemodialysis grafts. *Kidney Int* 1998; 54:1726-30

6. Smits JHM, Blankestijn PJ: Haemodialysis access: the case for prospective monitoring. *Curr Opin Nephrol Hypertens* 1999; 8:685-90

7. Diskin CJ, Stokes TJJ, Pennell AT: Pharmacologic intervention to prevent hemodialysis vascular access thrombosis. *Nephron* 1993; 64:1-26

8. Bassiouny HS, White S, Glagov S, Choi E, Giddens DP, Zarins CK: Anastomotic intimal hyperplasia: mechanical injury or flow induced. *J Vasc Surg* 1992; 15:708-16

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* 1995; 195:135-9

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* 1996; 183:486-92

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* 1996; 199:653-7

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* 1997; 8:1458-61

13. Smits JHM, Blankestijn PJ: Thrombosis-free hemodialysis grafts: a possibility for the next century? *Semin Dial* 1999; 12:44-9

14. Windus DW: Permanent vascular access: a nephrologist's view. *Am J Kidney Dis* 1993; 21:457-71

15. Sakariassen KS, Bolhuis PA, Sixma JJ: Platelet adherence to subendothelium of human arteries in pulsatile and steady flow. *Thromb Res* 1980; 19:547-59

16. Baumgartner HR: The role of blood flow in platelet adhesion, fibrin deposition, and formation of mural thrombi. *Microvasc Res* 1973; 5:167-79

17. Turitto VT, Weiss HJ, Baumgartner HR: Rheological factors influencing platelet interaction with vessel wall surfaces. *J Rheol* 1979; 23:735-49

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* 1983; 62:214-7

19. Aarts PA, Heethaar RM, Sixma JJ: Red blood cell deformability influences platelets-vessel wall interaction in flowing blood. *Blood* 1984; 64:1228-33

20. Stel HV, Sakariassen KS, de Groot PG, van Mourik JA, Sixma JJ: Von Willebrand factor in the vessel wall mediates platelet adherence. *Blood* 1985; 65:85-90

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* 1983; 61:99-110

22. Sixma JJ, Wester J: The hemostatic plug. *Semin Hematol* 1977; 14:265-99

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* 1987; 70:475-83

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* 1983; 72:1-12

25. Solum NO: Procoagulant expression in platelets and defects leading to clinical disorders. *Arterioscler Thromb Vasc Biol* 1999; 19:2841-6

26. Furie B, Furie BC: Molecular and cellular biology of blood coagulation. *N Engl J Med* 1992; 326:800-6

27. Eberst ME, Berkowitz LR: Hemostasis in renal disease: pathophysiology and management. *Am J Med* 1994; 96:168-79

28. Castillo R, Lozano T, Escolar G, Revert L, Lopez J, Ordinas A: Defective platelet adhesion on vessel subendothelium in uremic patients. *Blood* 1986; 68:337-42

29. Escolar G, Cases A, Bastida E Garrido M, Jopez 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* 1990; 76:1336-40

30. Sloand JA, Sloand EM: Studies on platelet membrane glycoproteins and platelet function during hemodialysis. *J Am Soc Nephrol* 1997; 8:799-803

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* 1993; 22:668-76

32. Liani M, Salvati F, Tresca E Di Paolo G, Vitacollona L, Golado 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* 1996; 19:451-4

33. Hakim RM, Schafer AI: Hemodialysis-associated platelet activation and thrombocytopenia. *Am J Med* 1985; 78:575-80

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* 1993; 43 (Suppl 41): S217-S20

35. Turitto VT, Hall CL: Mechanical factors affecting hemostasis and thrombosis. *Thromb Res* 1998; 92:S25-S31

36. Viener A, Aviram M, Better OS, Brook JG: Enhanced in vitro platelet aggregation in hemodialysis patients. *Nephron* 1986; 43:139-43

37. Savage B, Ruggeri ZM: Selective recognition of adhesive sites in surface-bound fibrinogen by glycoprotein IIb-IIIa on nonactivated platelets. *J Biol Chem* 1991; 266:11227-33

38. Salzman EW, Lindon J, McManama G, Ware JA: Role of fibrinogen in activation of platelets by artificial surfaces. *Ann N Y Acad Sci* 1987; 516:184-95

39. Windus DW, Santoro S, Royal HD: The effects of hemodialysis on platelet deposition in prosthetic graft fistulas. *Am J Kidney Dis* 1995; 26:614-21

40. Colman RW, Scott CF, Schmaier AH, Wachtfogel YT, Pixley RA, Edmunds LHJ: Initiation of blood coagulation at artificial surfaces. *Ann N Y Acad Sc.* 1987; 516:253-67

41. Sagripanti A, Cupisti A, Baicchi U, Ferdeghini M, Morelli E, Barsotti G: Plasma parameters of the prothrombotic state in chronic uremia. *Nephron* 1993; 63:273-8

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* 1991; 64:81-90

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* 1999; 14:137-41

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* 1991; 17:38-42

45. LeSar CJ, Merrick HW, Smith MR: Thrombotic complications resulting from hypercoagulable states in chronic hemodialysis vascular access. *J Am Coll Surg* 1999; 189:73-9

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* 1996; 11:1299-1305

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* 1995; 26:347-52

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* 1995; 48:794-800

49. Prieto LN, Suki WN: Frequent hemodialysis graft thrombosis: association with antiphospholipid antibodies. *Am J Kidney Dis* 1994; 23:587-90

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* 1991; 6:543-7

51. Sitter T, Schiffl H: Anticardiolipin antibodies in patients on regular hemodialysis: an epiphenomenon? *Nephron* 1993; 64:655-6

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* 1999; 55:315-20

53. Valeri A, Joseph R, Radhakrishnan J: A large prospective survey of anti-cardiolipin antibodies in chronic hemodialysis patients. *Clin Nephrol* 1999; 51:116-21

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* 1999; 9:125-31

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* 1995; 274:1049-57

56. Den Heijer M, Blom HJ, Gerrits WB, Rosendaal FR, Haak HL, WijermansPW, Bos GM: Is hyperhomocysteinaemia a risk factor for recurrent venous thrombosis? *Lancet* 1995; 345:882-5

57. Selhub J, D'Angelo A: Relationship between homocysteine and thrombotic disease. *Am J Med Sci* 1998; 316:129-41

58. Bostom AG, Lathrop L: Hyperhomocysteinemia in end-stage renal disease: prevalence, etiology, and potential relationship to arteriosclerotic outcomes. *Kidney Int* 1997; 52:10-20

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* 1997; 17:2554-8

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* 1998; 97: 138-41

61. McCully KS, Carvalho AC: Homocysteine thiolactone, N-homocysteine thiolactonyl retinamide, and platelet aggregation. *Res Commun Chem Pathol Pharmacol* 1987; 56:349-60

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* 1982; 16:490-3

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* 1999; 10:1095-9

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* 1997; 12:2037-8

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* 1999; 14:738-43

66. Collaborative overview of randomised trials of antiplatelet therapy- II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. Antiplatelet Trialists' Collaboration. *BMJ* 1994; 308:159-68

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* 1994; 45:1477-83

68. Harvey R, Bredenberg CE, Couper L, Himmelfarb J: Aspirin enhances platelet-derived growth factor-induced vascular smooth muscle cell proliferation. *J Vasc Surg* 1997; 25:689-95

69. Himmelfarb J, Couper L: Dipyridamole inhibits PDGF- and bFGF-induced vascular smooth muscle cell proliferation. *Kidney Int* 1997; 52:1671-7

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* 1997; 29:560-4

71. Wing AJ, Curtis JR, De Wardener HE: Reduction of clotting in Scribner shunts by long-term anticoagulation. *Br Med J* 1967; 3:143-5

72. Boyd SJJ, Dennis MB, Nogami RT, Cole JJ, Scribner BH: Prophylactic coumadin and A-V cannula function. *J Appl Physiol* 1974; 37:6-7

73. Ambühl PM, Wüthrich RP, Korte W, Schmid L, Krapf R:. Plasma hypercoagulability in haemodialysis patients: impact of dialysis and anticoagulation. *Nephrol Dial Transplant* 1997; 12:2355-64

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* 1999; 22:14-7

75. Tevlin MT, Portner ME, Kraus MG, Dulaney JT: Clotting frequency of hemodialysis accesses before and after systemic anticoagulation with coumadin. *J Am Soc Nephrol* 1996; 7:1421 (Abstract)

76. Blankestijn PJ, Smits JH: How to identify the haemodialysis access at risk of thrombosis? Are flow measurements the answer? *Nephrol Dial Transplant* 1999; 14:1068-71

Chapter 8

SUMMARY AND GENERAL DISCUSSION

Summary and general discussion

Since the introduction of the AV fistula and the use of interposition graft little improvement has been made in the vascular access field. Still, vascular access related complications, are one of the most important reasons for patient hospitalization, morbidity and even mortality (1,2). Interestingly, the costs of vascular access related care was found to be more than fivefold higher for patients with AVG compared with patients with a functioning AVF (3). In an attempt to improve overall patency rates and reduce access related costs, the NFK-DOQI committee currently recommends that in any dialysis center the majority of new dialysis patients should have a primary AVF constructed (4,5). Unfortunately, creation of an AVF is not always possible as a consequence of prior vascular access surgery, insufficient caliber of forearm vessels or sclerosis caused by prior venipunctures. Although less thrombotic and infectious complications occur in AVF, the AVF is not ideal, i.e. 100% successful. Adequate maturation of AVF, i.e. sufficient dilatation and arterialization, fails in up to 30% of all newly created fistulae, resulting in delayed initiation of dialysis treatment or placement of temporary central venous dialysis catheters, and related morbidity (6-10). Optimalization of patient selection could improve AVF patency rates and access related morbidity. Considering the increasing age of hemodialysis patients, prolongation of the dialysis therapy, and the worldwide increase of the number of patients requiring hemodialysis, the number of AV grafts will probably increase rather than decrease. As a consequence, vascular access complications, particularly thrombosis, will continue to challenge vascular access care in the future.

In **chapter 3** we examined the importance of pre-operative **forearm venous distensibility** with respect to AVF maturation. With the recognition of the superiority of the AVF and the increasing

comorbidity of the hemodialysis population, efforts are made to evaluate the vasculature of the arm of the patient prior to access surgery. This prospective study evaluates forearm venous function rather than anatomy prior to AVF creation for the first time. The results of this study confirm our hypothesis that apart from structural changes, the functional properties of forearm veins are important in the adaptive response to increased blood flow after AVF creation. Furthermore, functional data of forearm vasculature do not correspond with anatomical data. Importantly, we demonstrate that venous distensibility is predictive of the potential success of AVF construction and adequate maturation, whereas venous and arterial diameters are not. Finally, our study confirms recent data indicating that AVF flow measured one day after surgery is higher in AVF with successful maturation in compare to AVF that fail to mature (11). Considering our data support the hypothesis that functional vessel wall characteristics predict fistula maturation, the preoperative evaluation of the forearm vasculature should not only focus on resting static diameters. In view of the large potential benefits of optimization of the matching of patients and access type, further and larger studies of novel techniques are urgently needed.

In **chapter 4**, we determined whether **forearm blood flow capacity** in patients with end-stage renal failure awaiting vascular access surgery, is predictive of early failure of AVF. We hypothesized that forearm blood flow capacity, i.e. the increase of forearm blood flow as a result of vasodilatation, is an important determinant of failure of newly created AVF in hemodialysis patients. To discriminate the influence of the endothelium in early fistula failure, we measured both endothelium dependent (i.e. metacholine-induced) and endothelium independent (i.e. sodium nitroprusside-induced) forearm vasodilatation, using forearm venous occlusion plethysmography. To our knowledge, this is the first time invasively measured forearm blood flow capacity is related to outcome of AVF. This study shows that pre-operative forearm blood

flow capacity is predictive of early AVF failure. Especially, the AUC of dose response curves seems predictive of AVF outcome. An AUC of 100 in MCh and 200 in NP seems a prerequisite of short term success of the AVF. Furthermore, our data indicate that AVF failure is not the result of pure endothelial dysfunction, because endothelial-independent forearm blood flow capacity is also diminished in patients with AVF failure. Structural arterial wall changes can be responsible for this finding (12). Finally, we showed that arterial diameter is not predictive of early AVF failure. Venous occlusion plethysmography has the advantage of measurement of *total* forearm blood flow. However, clinical implementation of venous occlusion plethysmography prior to access surgery is not simple. First, this technique is very time-consuming and expensive devices are needed. Second, and even more important, it is an invasive measurement. Future research should focus on easier and non-invasive methods to measure pre-operative arterial flow reserve.

Chapter 5 explored the effect of monitoring and selection for corrective interventions based on VP and/or Qa, on thrombosis rates of AVG. This study confirms the usefulness of VP and Qa measurements as **access surveillance** variables: thrombosis rates in our patients can be maintained below the quality of care standards formulated by the NKF-DOQI committee (13). Based on the hypothesis that stenoses located in the flow tract upstream the venous needle would not by picked up by VP measurements, we expected Qa measurements, or combined measurement of Qa and VP, to be superior as a monitoring tool, in compare to VP measurements alone (14). This hypothesis is not confirmed in our study: thrombosis rates in groups monitored by VP or Qa alone or by the combination of tests do not differ. We found a strong predominance of venous lesions in the patients referred for angiography or thrombectomy. In less than 5% of patients referred for angioplasty arterial lesions were found. It is possible that in patients who develop more arterial lesions, surveillance using Qa would result in lower thrombosis rates than

using VP measurements. Our study confirms previous evidence that dynamic VP does not accurately reflect resistance caused by stenosis formation, since most referrals for intervention in patients monitored by VP measurements alone were based on static VP measurements (15). Dynamic VP is highly biased by pump flow, blood tubing, needle size, and blood pressure (16). Static VP measurements, on the other hand, particularly when corrected for mean arterial pressure, avoid these potential confounders.

Our study results indicate that the decision which method to use, (static) VP or Qa, can in fact be based on the preferences of those involved in the access care. There is no rationale in combining VP and Qa monitoring. It is important to bear in mind that a monitoring strategy can only be successful when abnormal tests are followed by diagnostic and interventional procedures on short notice. This is illustrated by the fact that almost one third of all thrombotic events in this study occurred in patients awaiting angiography.

In **chapter 6** we assessed hemodialysis access function in patients undergoing PTA. To our knowledge this is the first study in AVG and AVF reporting both angiographic and **functional results of PTA**. This study confirms earlier data that PTA results in an immediate access flow increase of about 250 mL/min (17). Although post-PTA stenosis poorly predicts patency after PTA, the post-PTA stenosis is frequently used to express the efficiency of the procedure (18). We demonstrated that adequate angiographic improvement, i.e. 25% or less post-PTA stenosis, does not necessarily correspond with adequate functional improvement, i.e. access flow above 600 mL/min. More important, we found functional parameters are predictive for long-term outcome, whereas angiographic results are not. Whereas almost all PTA procedures were angiographically successful, only 66% of AVG and 50% of AVF obtained adequate access flow. This may be caused by rapid elastic recoil of the stenotic lesion or may reflect other unidentified and thus

untreated stenoses. Access flow measurements during, or just after the intervention could be helpful to overcome this problem and optimize PTA results (22-24). Finally, time to repeat PTA in our study is substantially shorter than in other studies (19-21,25). This suggests a more rapid recurrence of stenosis in the present study. This difference may reflect differences in stenosis severity prior to PTA, as a result of more strict selection criteria for referral for angiography. The combined data of these studies suggest there is an optimal moment of PTA.

Chapter 7 reviews **coagulability** abnormalities in relation to hemodialysis **access thrombosis**. An increased thrombotic tendency is an important cause of ischaemic heart disease, stroke, and vascular access thrombosis in chronic hemodialysis patients (26). Although most cases of access thrombosis are associated with low access blood flow, caused by intimal hyperplasia in the venous outflow tract, in a number of cases, thrombosis is not preceded by low access flow measured during hemodialysis. Hypotension, hypovolemia and external compression during the interdialytic period are proposed mechanisms of these non-stenotic thrombotic events (27). However, several coagulability abnormalities may attribute to access thrombosis. Platelet abnormalities are common in patients on hemodialysis. Obviously, dysfunctional platelets favor a bleeding tendency. However, other circumstances may create a favorable situation for thrombotic complications. Adherence of platelets to the extracorporal circuit, high shear stress and turbulence in the vascular access may be responsible for exaggerated platelet activation (28-31). The artificial surface of the polytetrafluoroethylene material of AVG promotes adhesion of fibrinogen on platelet receptors, thereby activating them, and adhancing platelet deposition on the surface (32). High plasma fibrinogen and elevated titers of antiphospholipide antibodies are shown to increase the risk of access failure (33-38). Hyperhomocysteinemia has also been proposed as potential risk factor of access thrombosis (39,40). However, studies on this subject

are limited and the results are controversial. Obviously, long-term prospective studies with serial, instead of occasional determinations of plasma homocysteine are needed to address this problem. What are the clinical implications of these findings? 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. Furthermore, it remains questionable whether the benefits of antithrombotic therapy outweigh the risk of bleeding complications. In the meantime it seems reasonable to give some form of anticoagulant therapy based on pathophysiological considerations and the high risk of thrombotic complications. Future research on hemodynamic factors affecting the lifespan of vascular accesses should also take into account plasma markers of hypercoagulability. Because personal belief is an important factor in prescribing anticoagulant therapy, it seems unlikely that long-term placebo-controlled trials will be started in the near future.

Future perspectives

The nephrologist is primarily responsible for the management of patients with renal failure, both before and after initiation of dialysis treatment. Together with the patient he makes the decision as to when hemodialysis should begin. According to the National Kidney Foundation's recent Clinical Practice Guidelines, patients with ESRD should be prepared for dialysis when their glomerular filtration rate is less than 25 mL/min. This provides sufficient time for maturation and incorporation of the access. More accurate coordination between the placement of a fistula or graft and the initiation of dialysis may avoid the need of central venous catheters. Furthermore, timely referral to a nephrologist is associated with a higher proportion of patients starting hemodialysis on a functioning AVF and a lower overall mortality. Planning a vascular access

strategy for the individual patient well in advance of dialysis however, is best accomplished in a multidisciplinary setting, in which all efforts are made to create native AVF if possible.

Doppler ultrasound has been the most extensively studied and widely used test to guide access creation. However, we have demonstrated that seemingly adequate vessel diameter alone does not guarantee successful outcome of AVF. The influence of functional variables like forearm blood flow reserve and venous distensibility on the outcome of AVF has never been studied before and should be addressed extensively in future studies. Pre-existing endothelial dysfunction and structural wall changes are proposed mechanisms of forearm vessel dysfunction in patients with ESRD. Once the role of endothelial dysfunction on outcome of AVF is clarified, it would be very interesting to explore the effects of medications that could prevent endothelial cell injury prior to access surgery, like statins or angiotensin converting enzyme inhibitors. Intimal hyperplasia is a well-known cause of access thrombosis. However, it has become clear that these intimal changes can be demonstrated in most of the apparently normal cephalic veins in ESRD patients at the time of AVF construction (41). Although several efforts are made to decrease intimal hyperplasia after access creation, it would be of interest to study the effect of pharmacological inhibition of intimal hyperplasia *in advance* of access creation.

Patients aged 65 or more undergoing dialysis, have a life-expectancy of approximately 3 years, and life-expectancy in the oldest age groups is very limited. Therefore, dialysis in the elderly remains a challenge and raises the question whether it is proper to offer expensive and complicated treatment to a growing worldwide population of older patients with renal failure. Although DOQI Vascular Access Guidelines strongly recommand the contruction of AVF in elderly, it seems reasonable to consider other options in elderly patients with short life expectancy from other comorbidities or chronic hypotension. Recently, the Dialock system, a device totally implanted under the pectoral skin and inserted in the subclavian vein, was

demonstrated to be safe and effective in “complex” hemodialysis patients. Infection and complication rates of this device were even lower in compare to permanent central venous catheters and AVG (42,43). It remains to be elucidated whether this device is useful in the elderly. Also, the cost-effectiveness of this approach needs to be addressed.

Over the past years the effectiveness of access surveillance has been demonstrated. Prospective surveillance of vascular accesses for hemodynamically significant stenoses, and subsequent referring for percutaneous transluminal angioplasty or surgical revision, improves patency rates and decreases the incidence of thrombosis. At present, access flow (Qa) and venous pressure measurements are preferred techniques that can be used in surveillance of both AVG and AVF. However, structural access surveillance still needs to be introduced in many dialysis centers. An adequate surveillance strategy can only succeed in an enthusiastic team with affinity for the vascular access, consisting of a nephrologist, vascular surgeon, radiologist and nursing staff.

References

1. Powe NR, Jaar B, Furth SL, Hermann J, Briggs W: Septicaemia in dialysis patients: incidence, risk factors and prognosis. *Kidney Int* 1999; 55: 1081-90
2. Schwab SJ, Beathard G: The hemodialysis catheter conundrum: hate living with them, but can't live without them. *Kidney Int* 1999; 56: 1-17
3. Lee H, Manns B, Taub K, Ghali WA, Dean S, Johnson D, Donaldson C: Cost analysis of ongoing care of patients with end-stage renal disease: the impact of dialysis modality and dialysis access. *Am J Kidney Dis* 2002; 40:611-22
4. National Kidney Foundation. NKF-DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 1997; 30 (Suppl 3): S152-S191
5. National Kidney Foundation. K/DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis 2001*; 37 (Suppl 1): S137-S181
6. Elfström J, Thomsen M: The prognostic value of blood-flow measurements during construction of arteriovenous fistulae. *Scand J Urol Nephrol* 1981;15(3):323-6
7. Kalman PG, Pope M, Bhola C, Richardson R, Sniderman KW: A practical approach to vascular access for hemodialysis and predictors of success. *J Vasc Surg* 1999; 30:727-33
8. Silva MB, Hobson RW, Pappas PJ, Jamil Z, Araki T, Goldberg MC, Gwertzman G, Padberg FT: A strategy for increasing use of autogenous hemodialysis access procedures: impact of preoperative non-invasive evaluation. *J Vasc Surg* 1998; 27:302-8
9. Yerdel MA, Kesenci M, Yazicioglu KM, Döşeyen Z, Türkçapar AG, Anadol E: Effect of haemodynamic variables on surgically created arteriovenous fistula flow. *Nephrol Dial Transplant* 1997; 12:1684-88

10. Lin SL, Huang CH, Chen HS, Hsu WA, Yen CJ, Yen TS: Effects of age and diabetes on blood flow rate and primary outcome of newly created hemodialysis arteriovenous fistulas. *Am J Nephrol* 1998; 18:96-100

11. Wong V, Ward R, Taylor J, Selvakumar S, How TV, Bakran A: Factors associated with early failure of arteriovenous fistulae for haemodialysis access. *Eur J Endovasc Surg* 1996; 12:207-13

12. Malovrh M: Native arteriovenous fistula: preoperative evaluation. *Am J Kidney Dis* 2002; 39:1218-25

13. National Kidney Foundation. NKF-DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 1997; 30 (Suppl 3):S152-S91

14. Blankestijn PJ, Smits JH: How to identify the haemodialysis access at risk of thrombosis? Are flow measurements the answer? *Nephrol Dial Transplant* 1999; 14:1068-71

15. 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* 1995; 47:1364-73

16. 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* 1991; 37:M270-M271

17. 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* 2001; 59:358-62

18. Beathard GA: Percutaneous transvenous angioplasty in the treatment of vascular access stenosis. *Kidney Int* 1992; 42:1390-7

19. 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* 1995; 195:135-9

20. 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* 1997; 26:382-90

21. 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* 1999; 10:389-96

22. 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): 1999; 200A

23. 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* 1991; 40:91-5

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): 1999; 221A

25. 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* 2000; 15:2029-36

26. Lindner A, Charra B, Sherrard DJ, Scribner BH: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 1974; 290: 697-701

27. Windus DW: Permanent vascular access: a nephrologist's view. *Am J Kidney Dis* 1993; 21: 457-71

28. Hakim RM, Schafer AI: Hemodialysis-associated platelet activation and thrombocytopenia. *Am J Med* 1985; 78:575-80

29. 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* 1993; 43 (Suppl 41): S217-S220

30. Turitto VT, Hall CL: Mechanical factors affecting hemostasis and thrombosis. *Thromb Res* 1998; 92:S25-S31

31. Viener A, Aviram M, Better OS, Brook JG: Enhanced in vitro platelet aggregation in hemodialysis patients. *Nephron* 1986; 43:139-43

32. Savage B, Ruggeri ZM: Selective recognition of adhesive sites in surface-bound fibrinogen by glycoprotein IIb-IIIa on nonactivated platelets. *J Biol Chem* 1991; 266: 11227-33

33. Salzman EW, Lindon J, McManama G, Ware JA: Role of fibrinogen in activation of platelets by artificial surfaces. *Ann N Y Acad Sci* 1987; 516:184-95

34. 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* 1999; 14:137-41

35. LeSar CJ, Merrick HW, Smith MR: Thrombotic complications resulting from hypercoagulable states in chronic hemodialysis vascular access. *J Am Coll Surg* 1999; 189:73-9

36. 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* 1995; 26:347-52

37. 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* 1995; 48:794-800

38. Prieto LN, Suki WN: Frequent hemodialysis graft thrombosis: association with antiphospholipid antibodies. *Am J Kidney Dis* 1994; 23:587-90

39. 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* 1999; 10:1095-9

40. 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* 1997; 12:2037-8

41. Wali MA, Eid RA, Dewan M, Al-Homrany MA: Intimal changes in the cephalic vein of renal failure patients before arterio-venous fistula (AVF) construction. *J Smooth Muscle Res* 2003; 39:95-105

42. Canaud B, Morena M, Leray-Moragues H: Dialock. results of a French multicenter study. *Nephrology* 2001; 22:391-7

43. Hessinger M, Zitta S, Holzer H, Tiesenhausen K: Dialock - an alternative to Permcath and access graft. *Zentralbl Chir* 2003; 128:753-6

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Lieve X., zonder sentimenteel te worden, hoop ik met heel mijn hart, dat everlasting eeuwig duurt!

Allerliefste Boris, mijn o zo grote maar nog kleine man, mama is er klaar mee! Het wordt weer eens tijd voor een vliegreisje dacht ik zo...

Curriculum Vitae

Joke van der Linden werd op 21 maart 1972 geboren te Dordrecht en is getogen in Zwijndrecht. Zij behaalde in 1990 haar Atheneum diploma op Openbare Scholen Gemeenschap Walburg. In datzelfde jaar startte zij met haar studie Geneeskunde aan de Erasmus Universiteit Rotterdam, alwaar zij in 1994 het doctoraal Geneeskunde behaalde. In afwachting van haar co-schappen liep zij enkele maanden stage op de afdeling Chirurgie in het Tyks Ziekenhuis in Türku, Finland. In november 1996 legde zij haar artsexamen af. Daarna startte zij als arts-assistent bij de afdeling Interne Geneeskunde in het St. Clara Ziekenhuis te Rotterdam (Dr. A.F. Grootendorst). In afwachting van een opleidingsplaats, heeft zij gedurende twee jaar onderzoek verricht bij de afdeling Nefrologie binnen dit ziekenhuis. Hier werd het idee opgevat te gaan promoveren in het veld van de shuntzorg. In december 2000 is zij begonnen met de opleiding tot internist in het Erasmus M.C. te Rotterdam (opleiders Prof. Dr. H.A.P. Pols en Dr. J.C.L.M. van Saase). Aan het einde van haar eerste opleidingsjaar beviel zij van haar zoon Boris. Na haar zwangerschapsverlof keerde zij gedurende drie jaar terug naar het M.C.R.Z. locatie Clara (voorheen St. Clara Ziekenhuis) te Rotterdam. Het promotie onderzoek werd in die tijd voortgezet. In januari 2005 is zij inmiddels gestart aan het aandachtsgebied Endocrinologie in het Erasmus M.C. (Dr. A.J. van der Lely).

Bibliography

Van der Linden J, Sinnige HAW, van den Dorpel MA. Gustatory sweating and diabetes. *Neth J Med* 2000; 56(4):159-62

Smits JH, **van der Linden J**, Blankestijn PJ, Rabelink TJ. Coagulation and haemodialysis access thrombosis. *Nephrol Dial Transplant* 2000; 15(11):1755-60

Smits JH, **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* 2001; 59(4):1551-8

De Rave S, Tilanus HW, **van der Linden J**, de Man RA, vd Berg B, Hop W, IJzermans JNM, Metselaar HJ.The importance of orthotopic liver transplantation in acute hepatic failure. *Transpl Int* 2002;15(1):29-33

Van der Linden J, Smits JH, Assink JH, Wolterbeek DW, Zijlstra JJ, de Jong GH, van den Dorpel MA, Blankestijn PJ. Short- and long-term functional effects of percutaneous transluminal angioplasty in hemodialysis vascular access. *J Am Soc Nephrol* 2002; 13(3):715-20

Van der Linden J, Lameris TW, van den Meiracker AH, André A.E.A de Smet AAEA, Blankestijn PJ, van den Dorpel MA. Forearm venous distensibility predicts successful arterio-venous fistula. *Submitted*

Van der Linden J, Lameris TW, van den Meiracker AH, de Smet AAEA, Blankestijn PJ, van den Dorpel MA. Role of forearm blood flow reserve in early failure of newly created arterio-venous hemodialysis fistulae. *Submitted*

Van der Linden J, van den Dorpel MA. Percutaneous transluminal angioplasty of failing hemodialysis grafts and fistulae. *Saudi J Kidney Dis Transplant* 2004