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SURVEILLANCE FOR INFRAINGUINAL VEIN GRAFT STENOSIS

Leo Ihlberg

Academic dissertation

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"When the truth is discovered by someone else, it loses its attractiveness"

–Alexander Solzenitzyn: Candle in the wind iii–

Contents

List of original articles

This thesis is based on the following publications, which are referred to in the text by their Roman numerals

I Ihlberg LHM, Albäck NA, Lassila R and Lepäntalo M. Intraoperative flow predicts the development of stenosis in infrainguinal vein grafts. J Vasc Surg (Accepted for publication)

II Ihlberg L, Albäck A, Roth W-D, Edgren J and Lepäntalo M. Interobserver agreement of duplex scanning for vein grafts. Eur J Vasc Endovasc Surg 2000;19:504-508

III Ihlberg LHM**,** Mätzke S, Albäck NA, Roth W-D, Sovijärvi ARA and Lepäntalo M. Transfer function index of pulse volume recordings – a new method for vein graft surveillance. J Vasc Surg 2001 (In press)

IV Ihlberg L**,** Luther M, Tierala E and Lepäntalo M. The utility of duplex scanning in infrainguinal vein graft surveillance as a part of clinical practice: results from a randomised controlled study. Eur J Vasc Endovasc Surg 1998;16:19-27

V Ihlberg L**,** Luther M, Albäck A, Kantonen I and Lepäntalo M. Does a completely accomplished duplex-based surveillance reverse vein graft failure? Eur J Vasc Endovasc Surg 1999;18:395-400

Abbreviations

ABI	Ankle brachial pressure index
AVF	Arteriovenous fistula
CAD	Coronary artery disease
COPD	Chronic obstructive pulmonary disease
CVD	Cerebrovascular disease
CLI	Critical leg ischaemia
DA	Directional atherectomy
DD	Duplex Doppler
DSA	Digital subtraction angiography
EDV	End-diastolic velocity
LSV	Long saphenous vein
MFC	Maximal flow capacity
MIH	Myointimal hyperplasia
MRA	Magnetic resonance angiography
PAOD	Peripheral arterial occlusive disease
PSV	Peak systolic velocity
PVR	Pulse volume recordings
PTA	Percutaneous transluminal angioplasty
RR	Relative risk
SEM	Standard error of mean
SSV	Short saphenous vein
TAMV	Time-average mean velocity
TFI	Transfer function index
VPA	Vein patch angioplasty

Introduction

Following the developments in modern surgery over the last few decades, vascular surgery has evolved as a discipline in which huge leaps have been made not only in the adoption of new treatment techniques, but also in the areas of biomedical basis for vascular diseases, clinical physiology, internal medicine, vascular imaging and interventional radiology. The vascular surgeon is no longer just a master of surgical techniques. His field of knowledge must cover the essentials of all the aforementioned areas if he is to be of maximum benefit to the patient.

Chronic leg ischaemia is a gradually developing process caused by a constantly insufficient blood flow. The leading symptom of milder peripheral arterial occlusive disease (PAOD) is intermittent claudication, where the insufficient circulation manifests itself only during exercise. Critical leg ischaemia (CLI) is the result of a more serious impairment in blood flow in which the vitality of the leg is endangered. The development of CLI is a harbinger of a particularly poor prognosis in terms of decreased life expectancy and a high risk of major lower limb amputation. (Beard, JD 1992; Lepäntalo, M and Mätzke, S 1996; Bertele,V et al. 1999) The clinical, epidemiological and public health importance of PAOD has increasingly been recognised. (Golledge, J 1997) Furthermore, the problem is growing over time. In Finland, it was predicted at the beginning of the 1990's that a 50% increase in the incidence of major amputations could be expected within the next 20-30 years. (Pohjolainen, T 1991)

Most of the arterial changes are at multiple levels in the infrainguinal region, which is the main challenge for vascular surgeons treating CLI. The treatment of CLI has undergone profound evolution over the past 20 years. The expectations of surgeons and patients have been elevated as infrainguinal bypass procedures and the resultant limb salvage have become increasingly successful. In particular, this improvement has been achieved through an appreciation of the superiority of the autogenous vein as a bypass conduit. (Hall, KV 1964; Shah, DM et al. 1995; TASC 2000) Despite advances in the diagnosis of CLI and technical refinements in infrainguinal bypass surgery, the high failure rate of the reconstructions is still a matter of concern. Also after the immediate postoperative period the survival rates achieved with these grafts show steady attrition as a result of late graft thrombosis. The published long-term results show a large variation in graft patency from 80 percent at 5 years to 30 percent at 12 months. (Hobson, RWd et al. 1980; Leather, RP et al. 1988) The durability of good initial success rates is most commonly threatened by the development of intrinsic vein graft stenosis, accounting for approximately 60% of all graft thromboses. (Szilagyi, DE et al. 1973; Mills, JL 1993) The greatest potential for further improvement of infrainguinal revascularisation lies is in the prevention and management of these lesions. It has been established, that the stenoses developing within the vein conduit or at the anastomotic areas are due to

progressive neointimal hyperplasia. (Davies, MG and Hagen, PO 1995) As the pathophysiology of neointimal hyperplasia is unknown, no effective clinical regimen to limit its development is available. (Davies, MG and Hagen, PO 1995) Thus, the treatment strategy has been surgical or endovascular correction of already established stenoses. (Veith, FJ et al. 1984; Nehler, MR et al. 1994)

The aim of this study is to identify the risk factors for the development of graft stenosis, improve the accuracy of the methods used for the detection of the stenosis and analyse the potential benefits for the outcome of infrainguinal bypass surgery of a treatment policy, that consists of intensive surveillance and prophylactic correction of asymptomatic stenoses. This might result in better patient selection and an improved focusing in postoperative follow-up and reinterventions.

Review of the literature

1. Infrainguinal vein bypass reconstruction

1.1. Indications for revascularisation

It is quite rare, technically speaking, not to be able to perform some kind of arterial reconstruction in the lower extremities, if only anatomic considerations are taken into account. A distal tibial or pedal artery suitable for reconstruction can almost always be found. An adequate perfusion to limb can be achieved to allow a distal foot or toe amputation to heal. However, the identification of patients who will fare well after reconstruction and benefits from the operation may be difficult and may demand exquisite judgement. As a rule, arterial reconstruction should be advised in all patients who are mobile and lead independent lives; in contrast, it makes little sense in the case of nonambulatory nursing-home patients. (Luther, M 1997) During the decision-making process the degree of leg ischaemia and other possible comorbidities must be considered. Severe distal tibial and pedal arterial disease, (Albäck, A and Lepäntalo, M 1998) the presence of end-stage renal disease (Whittemore, AD et al. 1993; Peltonen, S et al. 1998) and a previously failed arterial reconstruction (Belkin, M et al. 1995; Robinson, KD et al. 1997) are factors which speak against durable patency of the graft and limb salvage. The two proven factors which determine the technical success of distal grafts are patency of the pedal outflow vessels and the use of vein grafts. (Londrey, GL et al. 1991; Lundell, A et al. 1993; Seeger, JM et al. 1999).

1.2. Definition of outcome parameters commonly used in vascular surgery

The first-line measure of outcome in vascular surgery is whether the reconstruction is technically successful. This is reported as graft patency rates. *Primary patency* usually refers to grafts that have uninterrupted patency. This means that no future intervention after initial surgery neither to open an occluded graft nor to perform dilatations or revision procedures to prevent eventual graft failure while the graft is still patent, has been necessary. *Assisted primary patency* is applied in situations where patency was never lost but maintained by prophylactic intervention. *Secondary patency* refers to all grafts that remain primarily patent, as well as those which had occluded and whose patency regained by means of lysis or thrombectomy with revision. These rates should not be confused with patency achieved across the same limb segment by means of secondary or tertiary reconstruction i.e redo bypasses, where most of the original graft and at least one anastomosis is omitted. (Rutherford, RB et al. 1997)

Limb salvage is the ultimate goal of reconstructive surgery for CLI. This is successfully achieved in limbs requiring only

minor amputations to the metatarsal level. Even though limb salvage is quite soundly defined, some critical remarks should be made when assessing the results of infrainguinal bypass surgery. Firstly, the limb salvage rates are enhanced when a large proportion of claudicants is included in the study material. Secondly, not all legs with CLI will necessarily undergo a major amputation when not reconstructed (Lepäntalo, M and Mätzke, S 1996).

1.3. Outcome of infrainguinal vein bypasses

The published studies on the outcome of infrainguinal arterial reconstruction with a vein graft show a large variation due to several confounding factors. Usually retrospective historical series of a single unit are reported that represent different clinical practices. The reports are not adjusted for known risk factors, indication for procedure, or bypass anatomy. The completeness of postoperative follow-up also varies. In a survey of published clinical follow-up papers of 2 years time in European Journal of Vascular and Endovascular Surgery, 51% of the articles did not contain sufficient information to permit assessment of the completeness of the follow-up. (Jensen, LP and Schroeder, TV 1999) If a significant proportion of the patients are lost to follow-up, reliability of the reported results can be unacceptably poor. (Jensen, LP et al. 1996) A fact which further precludes statistically valid comparisons is that standardised methods of reporting, proposed by the ISCVS/SVSD, are not uniformly adopted. (Rutherford, RB et al. 1997) These facts make a comprehensive assessment of the efficacy of infrainguinal reconstructions difficult.

Table I shows the outcome of unselected consecutive clinical series of infrainguinal vein bypasses according to the type of conduit used. As indicated, the 5-year cumulative secondary patency exceeds 70% in reported series utilising single long saphenous vein (LSV) as a graft material. It is also shown, that, armed with a reliable venous conduit, more distal outflow tracts can be revascularised in selected patients with impunity. (Hickey, NC et al. 1991; Davidson, JTd and Callis, JT 1993) If an adequate long saphenous vein is not available, the options are to use prosthetic grafts, composite grafts of prosthetic and autogenous vein or alternative vein grafts (arm vein, short saphenous vein (SSV) or remnants of LSV). In reported series, the patency of alternative vein grafts is inferior to the best reported patency rates for LSV grafts. However, the reported series using alternative veins have a significant proportion of secondary or tertiary procedures. (Harward, TR et al. 1992; Londrey, GL et al. 1994; Tisi, PV et al. 1996) Despite this excellent long-term results have been published. (Edwards, JE et al. 1990; Taylor, LM, Jr. et al. 1990) This was affirmed recently, when results of 520 infrainguinal reconstructions using arm vein were reported. (Faries, PL et al. 2000) The 5-year overall primary patency, secondary patency and limb salvage rates were 55%, 58% and 72%, respectively. In addition, a sample of 246 primary procedures was subanalysed. They showed respective primary and secondary patency rates at the same point in time of 68% and 70%. These results, which approaches those achieved with a single long vein conduit for infrainguinal revascularisation, are clearly superior when compared to prosthetic graft materials. (Londrey, GL et al. 1991; Sayers, RD et al. 1998) As morbidity in harvesting vein grafts from alternative sources appears to be low, (Faries, PL et al. 2000) an all-autogenous policy for infrainguinal arterial reconstruction seems to be justified. The

Table I. Results of primary infrainguinal bypass surgery according to the type of vein conduit.

Long saphenous vein										
			Primary patency (%)				Secondary patency (%)			
Author	Year	No. of reconstructions	1m	1y	2y	5y	1m	1y	2y	5y
Bergamini	1991	361	93	78	71	63	97	92	89	81
Donaldson	1991	440	89	81	79	72	93	87	85	83
Taylor	1990	285		89	86	80		90	88	84
Quinones-Baldrich[6]	1993	46			72					
Shah	1995	2058	93	84	80	71	96	91	88	81
Davidson[1,7]	1993	75	96	83	79	68	96	88	82	70
Alternative conduits*										
			Primary patency (%)				Secondary patency (%)			
Author	Year	No. of reconstructions	1m	1y	2y	5y	1m	1y	2y	5y
Taylor	1990	231		84	78	68		89	86	77
Tisi[2]	1996	42			36				60	
Chang	1995	184	85	72	64	45[3]	88	79	73	61
Londrey[4]	1994	257		68	50	39		70	52	43
Hölzenbein	1996	85			52[5]					
Harward[2]	1992	43		67	58			74	64	
Calligaro	1997	45			33				46	
Faries	2000	246				68[3]				70[3]

*Alternative conduits include the use of arm and lesser saphenous veins or vein segment splicing

[1]Only reconstructions to single patent crural or pedal vessel

[2] Only arm veins, 52% secondary or tertiary procedures

[3]4-year patency rate

[4]70% secondary or tertiary reconstructions

[5]3-year patency rate

[6]Only pedal bypasses

[7]5 bypasses with arm vein

Table 2. Mechanisms of vein graft failure

Intrinsic	**Extrinsic**
Poor vein quality	Compromised outflow
Missed valve/branch	Compromised inflow
Branch ligature placement	Thromboembolism
Intimal flaps	Hypotension
Focal vein stenosis (anastomotic or intra-graft)	Hypercoagulability
Accelerated atherosclerosis	Graft sepsis
Aneurysmal degeneration	Graft entrapment or kinking

weight of evidence in support of this attitude was further increased by a recent multicenter clinical trial, in which above knee-bypasses with vein grafts also had a significantly lower risk of occlusion than non-venous bypass grafts. (Tangelder, MJ et al. 2000)

2. Reasons for postoperative graft failure

2.1. Classification of the postoperative period

Generically the reasons for graft failure can be divided into intrinsic and extrinsic lesions (**Table 2**). In a study by Donaldson et al. (1992) of 104 causes contributing to primary graft failure of in situ bypasses, 63% were judged to have an intrinsic cause. (Donaldson, MC et al. 1992) Because the reasons for vein graft failure vary as a function of the time elapsed since the operation (**Figure 1**), it is practical to classify the postoperative period into several phases.

The most widely used classification of graft failures divides the postoperative period into three temporal categories: early or immediate (0 to 30 days), intermediate (30 days to 2 years) and late (greater than 2 years). (Whittemore, AD et al. 1981) It is an accepted concept that immediate failures are predominantly caused by physician-determined judgemental or technical error. Intermediate-term failures are attributed largely to the development of myointimal hyperplasia in the graft both within the conduit and at the anastomotic areas. Finally, late failures appear to be associated with the progression of the underlying atherosclerotic process involving compromise of outflow and inflow arteries. (Whittemore, AD et al. 1981; Berkowitz, HD et al. 1989; Mills, JL 1993) Many authors have, however, extended the early postoperative period to 3 to 6

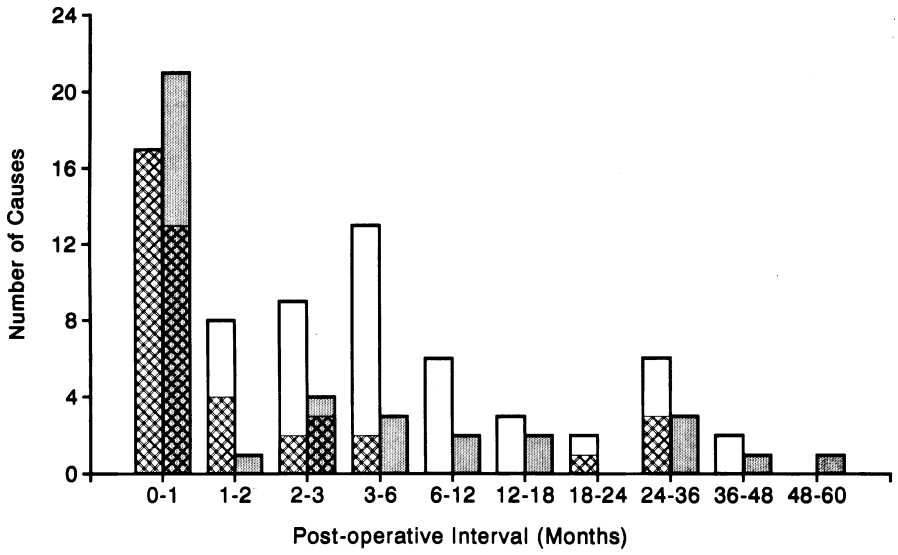


Fig. 1. The temporal occurence of graft failures by postoperative interval grouped into intrinsic (white) and extrinsic (grey) categories. The proportion of causes amenable to physician control is cross-hatched. (From Donaldson et al., J Vasc Surg 1992, with permission)

months. (O' Mara, CS et al. 1981; Lundell, A and Bergqvist, D 1993; Ihnat, DM et al. 1999)

It is established, that of all graft failures, 15% will take place within the first month, almost 80% during the first 2 years and the remainder will fail after this time. (Brewster, DC et al. 1983).

However, the causes contributing to graft failure are multiple and complex, sometimes with simultaneous interaction. In that sense classifications are always somewhat arbitrary.

2.2. Technical and judgement errors

Technical errors and errors of judgement are the main cause of immediate thrombosis of the arterial bypasses. In the literature, the reported incidence of immediate failure of in situ grafts varies from 5 to 34%. (Miller, A et al. 1993; Sayers, RD et al. 1993) This large variation indicates that several preoperative and intraoperative factors determine the immediate success of the reconstruction. These factors include patient selection, pre-implantation quality of the vein graft, vein preparation, construction of the anastomosis and quality of the intraoperative assessment.

2.2.1. The impact of inflow and outflow arteries

As far as technical success is concerned, the first critical step is the proper selection of the inflow and outflow sites of the bypass. The aortoiliac segment is usually not diseased and the selection of inflow site does not pose a clinical problem. If there is evidence of inflow occlusive disease, it is generally believed that it should be treated meticulously prior to or at the time of infrainguinal bypass reconstruction. There is evidence showing that when femoral outflow increases as a result of the bypass, iliac flow may be greatly enhanced and a functionally important inflow pressure gradient generated. (Gupta, SK et al. 1990) However, no data exists to show whether hemodynamically compromised inflow has an impact on bypass patency. Also in dispute is whether inflow stenoses and occlusions developing during follow-up are a cause of reconstruction failure. (Mills, JL et al. 1993; Taylor, SM et al. 1994)

The level of outflow arteries and the condition of runoff vessels influence the patency rates. The longer the bypass, the higher the risk of early thrombosis, (Luther, M and Lepäntalo, M 1997) although there are studies in which the patency rates were not influenced by the site of the distal anastomosis. (Sayers, RD et al. 1993; Tordoir, JH et al. 1993) This might not relate only to the more limited runoff, because the length of the conduit as such seems to be a predictive factor for immediate failure. (Ascer, E et al. 1988) In clinical retrospective series compromised runoff due to occlusive disease of outflow vessels is reported to be the cause of early graft occlusion in 25 to 42% of cases. (Miller, J et al. 1990; Sayers, RD et al. 1993; Varty, K et al. 1993; Albäck, A et al. 1998) However, when the impact of runoff on bypass patency has been prospectively tested with a scoring system, (Rutherford, RB et al. 1986) the results have been contradictory. (Okadome, K et al. 1991; Tordoir, JH et al. 1993; Takolander, R et al. 1995; Albäck, A et al. 1998)

2.2.2. The quality of the vein graft

A good-quality vein graft has a sufficient transverse diameter and shows no signs of pre-existing vein disease. Generally, the minimum vein diameter should exceed 3 mm, as the risk of occlusion is markedly increased for small-calibre (< 3mm) grafts.

(Buxton, B et al. 1980; Wengerter, KR et al. 1990) Some reports claim that with the in situ technique small calibre veins fare better than with the reversed vein technique; veins as small as 2.5 mm can be utilised with good results. (Corson, JD et al. 1984; Qvarfordt, P et al. 1988; Bergamini, TM et al. 1991) Comparison of studies on vein size is difficult because internal and external measurements may be quoted, and especially because the vein wall thickness is extremely variable. One further explanation of contradictory results is that the location and intraoperative timing of the diameter measurement is probably variable. Vein diameter is probably a risk factor for early graft failure with no great effect on long-term outcome. (Towne, JB et al. 1991) Indeed, there is data to suggest that vein grafts tend to go through adaptive changes over time in response to chronic alterations in blood flow. It is argued that one year after the operation the vein diameter has stabilized to a uniform values regardless of the initial diameter. (Fillinger, MF et al. 1994)

Frequently encountered pathologic conditions affecting the LSV include varicosities, phlebothrombosis and thrombophlebitis. It is estimated that pre-existing vein disease is present in 12% of veins considered for bypass grafting and that bypass performed using a saphenous vein with pre-existing disease has a 30 month patency of 32% compared with 73% for a normal saphenous vein. (Panetta, TF et al. 1992) Perhaps the poorer long-term results obtained with the use of arm veins are associated with vein quality, as arm veins have webs and strands not often seen in the saphenous system. (Marcaccio, EJ et al. 1993) Their recognizition by means of intraoperative assessment is desirable. At present, intraoperative angioscopy for identification and correction of these imperfections is perhaps the most effective method for upgrading the quality of the vein and thereby possibly improving the patency rates. (Stonebridge, PA et al. 1991; Marcaccio, EJ et al. 1993)

2.2.3. Vein preparation and construction of anastomoses

About 50% of the early graft failures can be related to technical defects. (Beard, JD et al. 1989; Miller, A et al. 1990; Varty, K et al. 1993) It is clear that infrainguinal bypass surgery demands meticulous surgical technique when preparing the vein for grafting and constructing the anastomoses. In the immediate postoperative period residual anatomical lesions such as valvulotome scrapes, kinking, torsion and entrapment of the graft, and retained valve leaflets appear to play a dominant role. (Donaldson, MC et al. 1992; Mills, JL et al. 1993) With in situ technique, unligated side branches with residual AVF have been suspected of leading to distal graft thrombosis. (Donaldson, MC et al. 1992) However, in a recent study, residual AVF did not compromise patency and thrombosed spontaneously on condition that they did not alter the hemodynamics of the graft distal to the AVF (Lundell, A and Nyborg, K 1999) Mechanical valve lysis is mandatory for in situ grafts, and it is documented that with the current valvulotomes this is often done imperfectly (Blankensteijn, JD et al. 1995; Albäck, A et al. 1999) or a valvulotome injury to the graft might take place. (Donaldson, MC et al. 1992) This may be the cause of graft failure in over 10% of cases. (Donaldson, MC et al. 1992)

2.3. Progression of atherosclerotic disease

The impact of atherosclerotic disease on infrainguinal bypass failure might be spread broadly over the postoperative period. When the revascularisation policy is aggressive, immediate failures are evident in patients, where the outflow tract was already highly compromised at the time of the implantation. Late failures are due to progression of the atherosclerotic disease. However, little is known about the rate of progression and how it relates to graft failure after lower extremity revascularisation. When follow-up studies (20% angiography and 80% duplex scans) were compared with a presurgical angiography, it was found out that at a mean follow-up of 4.8 years 18% of native arteries demonstrated disease progression. (McLafferty, RB et al. 1995) It could not be demonstrated that revascularisation would had adverse influenced the progression of atherosclerotic disease. Apart from this publication, postoperative studies have focused almost exclusively on graft patency. After the first postoperative year, the long-term outcome studies of infrainguinal vein bypass grafts show a steady failure rate of 1–2% annually. (Berkowitz, HD et al. 1989; Donaldson, MC et al. 1991; Shah, DM et al. 1995) These failures have been categorically attributed to atherosclerotic disease progression, but this has not been proved.

2.4. Hypercoagulability

Systemic hypercoagulable states may cause a graft thrombosis alone or contribute in the presence of other coincident factors – likely more often than previously assumed. In a preoperative screening program of 272 vascular surgical patients, 13.6% had a blood clotting abnormality, the most common being antiphospholipid syndrome (APS). (Donaldson, MC et al. 1990) Other screened and detected hypercoagulable states were protein C deficiency, protein S deficiency, antithrombin III deficiency, heparin-induced thrombocytopenia (HIT) and plasminogen abnormality. In a prospective study, lupus anticoagulant was found in 26 out of 60 vascular patients compared with none amongst the general surgical controls. (Fligelstone, LJ et al. 1995) The incidence of clotting disorders might be even higher among young adults with lower limb ischaemia. (Eldrup-Jorgensen, J et al. 1989) Hypercoagulable states have been shown to be an independent risk factor for post-operative bypass failure. (Ray, SA et al. 1997) Of the known clotting abnormalities, lupus anticoagulant and heparin-induced platelet activation appear to be the most important with regard to early infrainguinal graft patency. (Donaldson, MC et al. 1990)

Recently, two thrombogenic mutations have been discovered. The first is in factor V (FV Leiden), causing resistance to activated protein C and leading to uncontrolled coagulation activity (Ouriel, K et al. 1996). The second is prothrombin G20210A mutation which leads to increased prothrombin levels, but it is still unsettled whether this mutation increases the risk of arterial thrombosis. (Franco, RF et al. 1999; Ridker, PM et al. 1999)

It is not clear how actively patients should be screened for hypercoagulable states and, furthermore, what action should be taken if an abnormality is detected. Laboratory screening is costly, and, when occasionally fruitful, is likely to result in the institution of the same preventive measures that would have been used in the first place. However, there are recommendations for screening certain risk groups, including those with: a

history of previous unexplained thrombosis, a known hereditary condition, a predisposing illness (malnutrition, nephrotic syndrome, malignancy, pregnancy, oral contraceptives, myeloproliferative disorders), age less than 45 years and elevated PT, PTT, platelets or hematocrit. (Donaldson, MC 1996; Ray, SA et al. 1997) If an abnormality is detected, some advise avoidance of surgical re-vascularisation wherever possible. (Nitecki, S et al. 1993) Although there is no data supporting it, careful combined anti-coagulation and platelet inhibition is generally recommended. (Khamashta, MA et al. 1995) Specifically, deficiencies in antithrombin III and proteins C and S can be treated with fresh frozen plasma. If intervention can be postponed, most patients with HIT will revert to normal within a few months provided they are not re-exposed to heparin in the interim. (Laster, J et al. 1987; Donaldson, MC 1996)

Aspirin is universally instituted as a long-term therapy for all patients being treated for lower limb ischaemia if no contraindications exist. There is only little evidence that aspirin enhances infrainguinal graft patency, but patients taking aspirin have a significantly better chance of survival. (McCollum, C et al. 1991; Olojugba, DH et al. 1999; Tangelder, MJ et al. 1999) However, evidence for the beneficial effects of antiplatelet therapy in patients with PAOD is based on a small number of trials only, and can be regarded at present as indicative.

3. Graft and anastomotic stenoses

During the intermediate period, bypass failure is associated predominantly with the development of intrinsic graft and anastomotic stenoses due to myointimal hyperplasia or, occasionally, fibrosis at the valve cusps. This group constitutes the largest proportion of potentially identifiable and treatable graft lesions. The nature, aetiology and management of vein graft stenoses will be discussed in more detail in the following chapters.

3.1. Pathophysiology of stenosis development

3.1.1. Anatomy and physiology of the veins

The wall of a vein is traditionally divided into three anatomic layers: the intima, the media and the adventitia. The intima is composed of a thin layer of endothelial cells beneath which is a fenestrated basement membrane, a subendothelial matrix of glycoproteins and connective tissue elements. In the media, the smooth muscle cells are arranged in an inner longitudinal and an outer circumferential pattern with collagen and elastic fibrils interlaced. The adventitia forms the outer layer of vein wall and is often thicker than the media and consists of a loose network of longitudinally orientated collagen bundles and scattered fibroblasts through which the vasa vasorum pass.

Veins are highly compliant over the range of venous pressures and are relatively non-compliant at arterial pressures. (Wesly, RL et al. 1975) They appear to have a different metabolic profile and tissue content compared to arteries which may in part account for the distinct patterns of lipid accumulation found between veins and arteries. (Sisto, T et al. 1990) The total protein content does not differ, but the amount of collagen appears to be greater in the saphenous veins. The endothelium releases factors that control vascular relaxation and

contraction, thrombo-genesis and fibrinolysis, and platelet activation and inhibition. Nitric oxide and prostacyclin mediated relaxation responses of saphenous veins are much smaller, and the maximal contractile forces much greater, than those of the internal mammary artery. (Luscher, TF and Barton, M 1997)

3.1.2. Myointimal hyperplasia

Myointimal hyperplasia (MIH) is the universal response of a vein graft to insertion into the arterial circulation and is considered to result from both the migration of smooth muscle cells out of the media and into the intima and the proliferation of these smooth muscle cells. Macroscopically, intimal hyperplastic lesions appear pale, smooth, firm and homogenous; they are uniformly located between the endothelium and the medial smooth muscle layer of the vein graft. (Chervu, A and Moore, WS 1990)

Although not fully defined, it seems that the origin of the initiating factors goes back to the time of surgery. The vein suffers from implantation injury, which leads to endothelial dysfunction, endothelial cell injury, endothelial denudation and smooth muscle cell injury. Several mediators, such as fibroblast growth factors and either endogenous or exogenous platelet derived growth factors, are activated which contribute to the medial proliferation and to the migration of smooth muscle cells from the media to the intima. Several other mediators of both the tyrosine kinase (IGF-1, TGF-α, α-thrombin and inter-leukin-1β) and G-protein (angiotensin II, endothelin-1, serotonin) coupled membrane receptors have been known to participate in these initial events. (Davies, MG and Hagen, PO 1995) In addition to the increased number of vascular smooth muscle cells, stenotic lesions contain an abundance of extracellular matrix. Recent studies have suggested that the proliferation and migration of smooth muscle cells requires degradation of the surrounding matrix proteins, and that up regulation of matrix metalloproteases, the principal physiological mediators, may play a central role in the formation of MIH. (Porter, KE et al. 1999)

In general, MIH is a self-limiting process which does not produce luminal compromise and which usually calms down within 2 years of implantation. However, in focal areas, the intimal hyperplastic process can proceed to significant stenosis. Primary cultures from these lesions have suggested that the smooth muscle cell phenotype present is more resistant to the action of growth inhibitors such as heparin than other areas of the graft. (Chan, P et al. 1993)

Considerable efforts has been put into finding therapeutic agents to limit the development of MIH. However, the various classes of compounds which have shown promise in experimental models have, by and large, been ineffective in the clinical setting. (Davies, MG and Hagen, PO 1995) Apart from attempting to minimise the degree of injury at the time of implantation by using minimum manual and instrumental contact, no effective strategy has been developed to prevent the development of MIH following vascular reconstruction.

3.1.3. Systemic risk factors

As it is likely that some individual grafts are at a greater risk of stenosis development than others, the association between the development of vein graft stenoses and several risk factors has been studied. Hyperlipidemia has been shown to correlate with a progressive narrowing of aortocoronary vein grafts, but its role in infrainguinal vein bypass stenoses is unclear. (Lytle, BW et al. 1985)

Other systemic variables which might be associated with graft stenosis are lipoprotein (a), smoking and plasma fibrinogen (Cheshire, NJ et al. 1996), hyperhomocystinaemia (Irvine, C et al. 1996; Beattie, DK et al. 1999) and antibodies to cardiolipin. (Nielsen, TG et al. 1997) Recently, the female gender was found to have a higher risk for graft stenosis. (Watson, HR et al. 2000) No association has been found with patient age, presenting symptoms, hypertension, diabetes or the condition of the outflow vessel. Interestingly, it has been found that patients who develop vein graft stenosis in one limb are at a greater risk of developing a contralateral vein graft stenosis if that limb is grafted. (McCarthy, MJ et al. 1998) Whether this is due to unidentified systemic factors or individual vein morphology is unknown.

3.1.4. Local graft-related factors

Stenotic lesions have a localized nature. This has prompted theories that local factors related to the type, quality, and operative technique form a "nidus" for later development of stenosis. The possible predisposing factors are pre-existing morphological changes, vein size, compliance, tributaries, valves and operative trauma.

As already mentioned, pre-existing morphological changes at gross inspection are a very common finding in patients undergoing peripheral vein bypass surgery. Further evidence exists showing that microscopically marked changes of muscle hypertrophy and intimal hyperplasia are also present in the vein prior to grafting. (Davies, AH et al. 1993) Marin et al. (1993) studied microscopic abnormalities in vein biopsies taken at the time of surgery. They found that intimomedial thickening and cellularity were strongly associated with failed or failing grafts at 18–30 months. (Marin, ML et al. 1993) Their findings were supported by studies in which a link between poor-compliance veins, usually due to moderate or severe intimal hyperplasia, and subsequent graft stenosis was demonstrated. (Davies, AH et al. 1993; Davies, AH et al. 1994) Furthermore, the presence of a macrophage or lymphocyte infiltrate in the prebypass vein increased the likelihood of the subsequent stenosis development. These results were, however, contradicted by Varty et al. (1996), who neither in vitro nor in vivo could reveal a correlation between intimal or medial thickness and grafts that subsequently stenosed and those that did not. (Varty, K et al. 1996) The different results may be partly explained by the different methods used for assessing vein wall morphology in these studies. It seems that vein morphology, with present methods, is unlikely to be a clinically useful indicator of the risk of graft stenosis.

It has been documented that a small diameter vein graft has an unfavourable effect on durable patency. It has been studied whether this is due to a higher incidence of MIH in a small-calibre graft. (Davies, AH et al. 1994; Idu, MM et al. 1999) Davies et al. (1994) showed, in a cohort of 88 patients, that the mean diameter of the vein grafts that developed stenosis was 3.7 mm compared to 4.7 mm in those that did not ($p = 0.006$), but there was no clear size discriminator. In the study by Idu et al., 300 vein grafts were grouped in accordance with their intra-operatively measured minimum graft diameter into those < 3.5 mm, those between 3.5 and 4.5 mm, and those ≥ 4.5 mm. (Idu, MM et al. 1999) At 1 year, the respective free-of-stenosis rates were 40%, 58%, and 75%. In a multivariate analysis the minimum graft diameter was the single independent factor which correlated with the development of an event-causing stenosis. They postulated that this might be

due to increased vulnerability of a small calibre graft during harvesting and valve lysis which may initiate a local myointimal hyperplastic response.

Early work suggested that stenoses in reversed vein grafts occurred at the sites of valves. (Whitney, DG et al. 1976) This has been supported by Mills et al (1993), who found that all midgraft stenoses occurred at fibrotic valve sites. (Mills, JL et al. 1993) However, this theory has been tested in more detailed studies, in which a relationship between the site of the stenosis and that of either a tributary or valve cusp could not be confirmed. (Moody, AP et al. 1992; Davies, AH et al. 1994) The role of local injury response resulting from instrumentation and manipulation in the initiation of neointimal hyperplasia is also disputed. Mills et al. (1993) observed that the most common site for intrinsic lesions was in the juxta-anastomotic position in the vein graft segment immediately adjacent to both anastomoses. (Mills, JL et al. 1993) They discussed whether the manipulation of the vein graft heel during the performance of the anastomosis perhaps sets the stage for intimal hyperplasia. However, in an elegant study by Moody et al. (1992) in which the residual valve sites, clipped tributary veins, venotomy sites, and areas of clamp application were marked intraoperatively, no correlation between these sites and the sites where stenoses ultimately developed was found. (Moody, AP et al. 1992) In addition, when the degree of endothelial injury caused by stripping was assessed by means of endothelial cell markers, no relationship with respect to the development of graft stenoses was observed. (Davies, AH et al. 1994) Regarding the influence of grafting techniques on the stenosis development, results have been published in which the reversed vein and alternative vein conduits had an incidence of stenosis and a need for revision twice as high as those of in situ bypasses. (Gupta, AK et al. 1997) These results should, however, be viewed with some caution, as the series are prone to the pitfalls of a retrospective study. Firstly, the grafting technique varied with the surgeon's preference as well as with the sites selected for the proximal and distal anastomosis. Secondly, the number of redo-bypasses varied among the groups. Thirdly, a significant difference in primary patency at 3 years in favour of in situ bypasses was also seen among those grafts for which the intraoperative duplex scan was normal.

Attempts to identify promoters of a subsequent development of graft stenosis during the operation or in the immediate postoperative period using duplex scanning have been made with varying success. Bandyk et al. (1996) studied the fate of borderline duplex abnormalities that were encountered intraoperatively but left untreated. (Bandyk, DF et al. 1996) A revision was needed in 18 of 40 such grafts (45%). The follow-up, however, was only 3 months and the study was not blinded. In the most recent report by the same group further data on intraoperative duplex scanning on 626 vein grafts was provided, in which the 90-day combined failure and revision rate for those grafts that had a normal duplex scan was 2.5%, whereas for grafts that had a residual stenosis or an unrepaired defect the respective figure was 40%. (Johnson, BL et al. 2000) The conclusion was, that the borderline abnormalities had a tendency to progress to a level where intervention was necessary. However, the short follow-up time hindered a more thorough analysis of it was a question of developing graft stenoses due to MIH. In contradiction to this study, Passman et al. (1995) found that duplex scanning within 2

weeks of surgery could identify only 14 % of grafts that eventually developed stenoses. (Passman, MA et al. 1995) The predictive value of predischarge duplex scanning for subsequent stenosis development has been studied with conflicting results. (Wilson, YG et al. 1995; Olojugba, DH et al. 1998)

In summary, efforts to divide grafts into high- and low-risk categories with regard to stenosis development have not been successful, and as yet no recommendation can be given with respect to reviewed risk factors for planning the postoperative follow-up. The potential of intraoperative assessment using duplex scanning has recently shown promise, but these singe-unit experiences have not yet been confirmed by others.

3.1.5. Biomechanical factors

It has increasingly been recognised that the vascular endothelium is a living organ in which metabolism and the synthetic activities of different vasoactive factors are altered in response to biomechanical forces generated by the blood flow. (Gimbrone, MA, Jr. et al. 1999) The mechanisms underlying arterial wall adaptation to biomechanical forces have been shown to be closely related to a complex interaction of molecular and cellular events. Physical forces sensed at the blood-wall interface trigger a series of immediate responses such as platelet activation and the activation of immediate early genes, as well as later responses, which include the production of several growth factors.

Wall shear stress is a direct function of blood flow and viscosity and inversely proportional to the the third cube of the radius of the vessel wall curvature. Shear stress (t) can be calculated according to Poiseuille's law: $\tau = 4\eta Q/\pi r^3$, where η= viscosity, Q = volume flow and r = internal vessel radius.

In normal arteries, flow-induced remodelling results in changes in arterial diameter which have the negative-feedback effect of returning the wall shear stress towards normal. (Langille, BL 1996) In addition, it has been demonstrated that the same phenomenon also takes place in vein grafts; as a response to changes in shear stress small-diameter veins had, one year on from surgery, remodelled to a final diameter that was not significantly different from that of larger veins. (Fillinger, MF et al. 1994)

This remodelling might contribute to the pathophysiology of neointimal hyperplasia as it has been shown that shear stress can regulate endothelial smooth muscle cell migration and proliferation. (Mattsson, EJ et al. 1997) Already in early studies it had been reported that intimal hyperplasia correlates with low graft flow. (Faulkner, SL et al. 1975; Berguer, R et al. 1980) This was verified in a detailed study by Dobrin et al. (Dobrin, PB et al. 1989) Their study using a canine model showed that of nine different mechanical factors blood flow is best associated with the formation of neointimal hyperplasia independently of deformations and stresses in the circumferential, longitudinal and radial directions and independent of pulsatile deformation. Similarly, it was reported that accelerated intimal thickening develops in vein grafts under low flow conditions and the process is reversed when the grafts are re-implanted into a system with normal flow parameters. (Morinaga, K et al. 1987) As there is evidence that endothelial cells play a pivotal role in modulating the neointimal hyperplastic response, it has been hypothesized that the endothelium is dysfunctional in the low-flow state. Indeed, it has been demonstrated that the receptor-mediated release of endothelium-derived relaxing factors is regulated downwards

when blood flow is diminished. (Cambria, RA et al. 1994; Komori, K et al. 1995) It is probable that release of nitric oxide (NO) accounts for the biological activity of endothelium-derived relaxing factor. NO has been shown to be a very potent vasodilator and to efficiently inhibit smooth muscle cell proliferation. In an experimental in vivo model, endothelial nitric oxide synthase was induced in high-flow graft intima. (Mattsson, EJ et al. 1998)

The evidence gathered so far is based on experimental data, and the clinical relevance of these findings is still unproven. Furthermore, it seems evident that this theory alone does not provide the ultimate solution and that there are also other mechanical factors that play a role. Otherwise it would be difficult to understand how veins survive in their usual state as low-flow and low-pressure conduits.

3.2. Diagnosis of vein graft stenosis

3.2.1. Clinical assessment

When assessing infrainguinal vein grafts clinically, one looks for symptoms and signs of deterioration in the hemodynamic condition of the limb. Sudden onset of disabling claudication, ischaemic pain or ischaemic ulcers is a sign of a failing or failed bypass graft. Clinical signs include changes in the colour, temperature and capillary circulation of the limb or loss of previously palpable graft and distal pulses. However, the majority of hemodynamically significant graft stenoses are asymptomatic, and only 11% to 38% can be diagnosed by the return of ischaemic symptoms or decreased pulses on the physical examination. (Disselhoff, B et al. 1989; Moody, P et al. 1990)

3.2.2. Ankle brachial pressure index (ABI)

Thanks to the introduction of Doppler, the measurement of lower limb blood pressure has been possible using non-invasive techniques for the past 30 years. (Yao, ST et al. 1969) The measurement is quick and easy to perform, and can be regarded as a standard noninvasive test in PAOD. (Dormandy, JA and Murray, GD 1991) Determination of the ankle brachial systolic pressure index (ABI) is a simple test for peripheral arterial disease, and it eliminates the influence of temporal variations in absolute systolic blood pressure on the results. (Yao, ST et al. 1969)

In general, a drop in ABI of more than 0.15 compared to the immediate post-operative value was found to be a more sensitive indicator than clinical symptoms in the diagnosis of significant hemodynamic deterioration in the bypass graft. (Berkowitz, HD et al. 1981; O' Mara, CS et al. 1981) Nevertheless, ABI measurement is not free from variation, and a cut-off level of 0.15 falls within the biological and measurement variations of the test, while a decrease greater than 0.20 is often associated with a bypass which has already occluded. (Fowkes, FG et al. 1988; Ray, SA et al. 1994) In the most recent study, the 95% confidence limits for the difference were $\pm$ 0.21. (Fisher, CM et al. 1996) The variation in ABI could arise from several different sources, such as differences in technique and experience (interobserver variation), non-compressible arteries in the presence of medial calcification or non-standardized conditions of measurement. (Carter, SA 1992; Kaiser, V et al. 1999)

The ABI has been extensively evaluated as a screening method for vein graft stenosis, but has been found to be of limited value. Furthermore, pressure measurements in respect of paramalleolar and pedal grafts are

meaningless because the cuff is applied over the graft; stump pressure is obtained reflecting only the inflow pressure of the bypass. (Sumner, DS and Mattos, MA 1995) As ABI measurements are used routinely in the assessment of both patients who have undergone surgery and those who have not, their use could be justified as a first-line method, potentially as an adjunct to another non-invasive method. A pre-requisite for usefulness should be good sensitivity i.e. having a minimal risk of false-negative results. Aggregate data from several studies show that when cut-off values of 0.1, 0.15, and 0.2 are used, the respective sensitivity figures are 75%, 45%, and 35%. (Lepäntalo, M et al. 1996) Even with the lowest cut-off value of 0.1 only one or two authors have proposed the use of ABI as the sole tool for detecting graft stenosis. (Brennan, JA et al. 1991; Stierli, P et al. 1992) Stierli et al. (1992), using the above-mentioned discriminator found all stenosed grafts (12/41) and recommended its use as a primary examination for selecting patients for colour flow duplex scanning on the following conditions: the ABI is below 1.3 indicating of compressible distal vessels; the ABI changes are less than 0.1 on serial testing; the distal anastomosis is well above the ankle joint. (Stierli, P et al. 1992) It can be anticipated that the difference of 0.1 is associated with an unacceptably poor specificity due to variations in reproducibility. This means there is likely to be a large number of false positive studies, and a large number of people may therefore be given unnecessary angiograms. It is questionable whether a surveillance programme based on ABI is likely to be any better than no surveillance at all. Nevertheless, Stierli et al. calculated that 50% of bypasses would not have needed any other type of surveillance method. (Stierli, P et al. 1992)

Even though it is has been proved that stenosed grafts are three times more likely to occlude, (Moody, P et al. 1989) the majority of them do not fail. Similarly, some grafts that have previously undergone invasive and non-invasive studies occlude suddenly without warning. (Green, RM et al. 1990) Thus, while a stenotic graft can be identified with some accuracy, the one that is likely to occlude is more difficult to define. On the basis of this some have advocated that grafts with diagnosed stenosis should be corrected only in the presence of a hemodynamically significant drop in the ABI. (Green, RM et al. 1990; Dalsing, MC et al. 1995; Nielsen, TG 1996) According to Green et al. (1990), in cases where the outcome of the duplex scan was abnormal but the ABI normal, the incidence of sudden graft occlusion was only 4% over the next 3 months. (Green, RM et al. 1990) In contrast, when both the duplex scan and the ABI were abnormal, the risk of a graft occlusion was 66%. A similar result was observed in a small prospective series of grafts with duplex-verified stenoses that were not corrected. (Nielsen, TG 1996) The cumulative patency at 12 months was significantly lower for bypasses with hemodynamically significant stenoses, defined as an ABI-reduction of more than 0.15 (68% vs. 33%). In contrast, when the long-term fate of 235 infrainguinal bypasses was studied, a decrease in the ABI of more than 0.2 during one or more intervals after surgery was not predictive of graft failure. (Barnes, RW et al. 1989) Such disparate observations have led to equally contradictory recommendations on whether duplex abnormality alone is a sufficient indication of the need for further invasive imaging and/or treatment.

As it is evident that measuring the resting ABI alone is not a sufficient method of

screening grafts, and since it is disputed whether this improves the accuracy of screening as an adjunct to other methods, attempts to improve the sensitivity of ABI by adding of a standard treadmill exercise have been made. (Wolfe, JH et al. 1987; Benveniste, GL et al. 1988; Brennan, JA et al. 1991) Even though this might unmask some stenoses, it seems likely that the overall sensitivity will not be markedly increased. Another drawback of this test is that, typically, older patient population often cannot perform the treadmill exercise adequately. Hyperaemia using cuff occlusion may overcome this problem, but no reports of its utility in diagnosis of vein graft stenosis has been published.

3.2.3. Arteriography

Since the report by Szilagyi et al. in 1973, intra-arterial arteriography has been referred to as the "gold standard" for delineating and grading the degree of stenoses against which other methods should be compared. (Szilagyi, DE et al. 1973) It provides fine anatomical detail (**Figure 2**) but is, however, cumbersome, and includes risks that are related both to the puncture site and contrast agents used. In addition, it is too expensive for serial imaging. With the advent of digital techniques in the 1980's, intravenous digital subtraction angiography (IV DSA) was proposed as a means of detecting stenosed grafts. (Turnipseed, WD and Acher, CW 1985; Wolfe, JH et al. 1987; Moody, P et al. 1989) Because of a lack of spatial resolution, IV DSA is not necessarily adequate for visualising the whole bypass, which, in particular, makes an adequate assessment of the reduction in diameter difficult. (Sumner, DS et al. 1985) In addition, the risks of repeated radiation raises the threshold to its widespread use as a serial diagnostic procedure.

Consequently, in later studies the use of angiography has been confined to determining the localisation and severity of a stenotic lesion after its presence has been indicated by other methods. Angiographic confirmation is usually requested before a decision on corrective measures can be made.

The technology and quality of magnetic resonance angiography (MRA) has developed rapidly over the last decade and there is potential for overcoming the inherent limitations of conventional angiography. However, the data on the utility of the

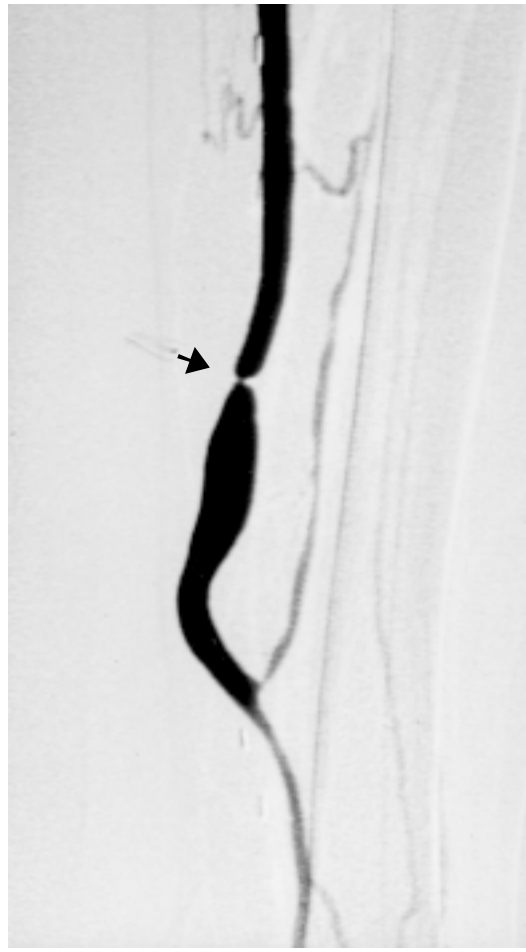


Figure 2. Angiographic visualisation of a vein graft stenosis (arrow) in an infrainguinal bypass graft close to the distal anastomosis.

MRA in detecting a vein graft stenosis is scant. In the only published study on the subject, the MRA demonstrated a satisfactory correlation with conventional angiography, but with a tendency towards overdiagnosis in the presence of turbulent flow. (Turnipseed, WD and Sproat, IA 1992) At present, the MRA is still far too expensive for routine use as a surveillance instrument.

3.2.4. Duplex scanning

Duplex scanning provides both anatomic and hemodynamic information, as it embodies both B-mode imaging and Doppler ultrasound. The diameter changes of the bypass can be measured both in longitudinal and transverse projections. Quantitative pulsed Doppler waveform analysis of blood flow velocity can be performed. Flow within the graft can be calculated at any point as the product of the average velocity and the cross-sectional area.

Monochrome duplex scanning first became available for non-invasive vascular diagnosis about 20 years ago. With that technique, scanning of the entire bypass was a long and tedious process, requiring many Doppler samples to be taken down the length of the graft. There are studies dating back to that time in which efforts to simplify duplex scanning were made. It was proposed that a single point measurement of peak systolic velocity (PSV) usually made in the normal midgraft portion can act as a reliable screening method for failing grafts. Bandyk et al (1985), using a PSV < 45 cm/sec as a criterion, identified 96% of failing grafts and, furthermore, found an association with high incidence of graft occlusion during follow-up. (Bandyk, DF et al. 1985) This was supported by later studies. (Green, RM et al. 1990; Mills, JL et al. 1990; Schmitt, DD et al. 1990) Nevertheless, it became evident that low PSV identifies only a minority of significant graft stenoses (Buth, J et al. 1991; Robison, JG and Elliott, BM 1991; Belkin, M et al. 1992; Taylor, PR et al. 1992) Moreover, it was recognized that low PSV-values may occur in normal grafts of large diameter as well as frequently being caused by run-off or inflow disease (Belkin, M et al. 1992; Belkin, M et al. 1994; Treiman, GS et al. 1999) Further attempts aimed at achieving simplified identification of failing grafts have been made. (Chang, BB et al. 1990; Nielsen, TG et al. 1995) Nielsen et al. (1995) correlated midgraft PSV, pulsatility index and the ratio of hyperaemic and resting time-average mean velocities (TAMV) with the presence and severity of stenoses. (Nielsen, TG et al. 1995) They found that impaired hyperaemic response (TAMV ratio ≤ 2.0) was observed in 88% of stenosed grafts and concluded that it might be of use as a simple screening procedure for those grafts that require a more detailed duplex scanning. In their study, the accuracy of pulsatility index was poor, whereas others have achieved better sensitivity and specificity compared to other duplex parameters with a one-point measurement of pulsatility index. (Inoue, Y et al. 1997) Other single-point measurements used as indicators of a failing graft include a change in graft flow waveform from a triphasic to bi- or monophasic pattern, a decrease in PSV of more than 30 cm/sec relative to a previous test and a distal graft flow lower than 25 ml/min (Bandyk, DF et al. 1988; Chang, BB et al. 1990), but these criteria have not gained wider acceptance. Duplex-derived graft volume measurements have been shown to be unreliable, as they are poorly reproducible. (Grigg, MJ et al. 1988) Flow measurements rely on a detailed estimation of luminal diameter so a small inaccuracy in the diameter measurement

dramatically alters the flow measurement.

The addition of a colour coding facility to the duplex scanner made scanning of the whole graft simpler and quicker. Changes in velocity and poststenotic turbulence are indicated by alterations in colour-coded images, and can be interrogated more carefully with quantitative pulsed Doppler velocity measurements. Maximum PSV has been proposed for grading graft stenosis, but the recommended cut-off value varies from 110 to 300 cm/sec. (Cullen, PJ et al. 1986; Sladen, JG et al. 1989; Green, RM et al. 1990; Buth, J et al. 1991) An increase in the end-diastolic velocity (EDV) of greater than 20 cm/sec has also been considered as a reliable predictor of severe stenosis, with the optimal measurement taken very close to the site of maximal diameter reduction. (Nicholls, SC et al. 1986; Buth, J et al. 1991)

Because graft flow at one point equals flow at any other point in the graft, provided no branches lie in between, any change in luminal area will be associated with a proportional shift in velocity. (**Figure 3**). The V2/V1 ratio (V2: PSV at the site of maximal stenosis, V1: PSV in a normal graft segment within 2 cm of the stenotic segment) has been shown to provide an accurate estimation of the degree of the stenosis. (Leopold, PW et al. 1989; Landwehr, P et al. 1991) The use of a ratio is beneficial, since changes in graft flow due to variation in cardiac output and peripheral resistance are eliminated, and accurate comparisons over a period of time are possible. The correlation between velocity shift and percentage diameter reduction of the stenosis is denoted by the equation: **% diameter reduction = 100 x (1-√v1/v2)** (Grigg, MJ et al. 1988). Using this equation, a doubling of PSV at the site of the stenosis denotes a 30% diameter reduction, a six fold increase a stenosis of 60% and a ten fold increase a stenosis of 70%. However, in practice it is noted that this equation underestimates the degree of the stenosis, and a V2/V1 ratio = 2 is usually considered equivalent to 50% stenosis. (Jager, KA et al. 1985)

The V2/V1 ratio has become the most accepted criterion for diagnosis of a stenosis within the vein graft. (Grigg, MJ et al. 1988; Giannoukas, AD et al. 1996) Using this as the sole criterion, a sensitivity of 100% with IV-DSA as the diagnostic standard was achieved when screening a total of 412 infrainguinal grafts (Taylor, PR et al. 1990) Likewise, in a series of 76 grafts, only two grafts that were not detected by duplex scanning later occluded during the follow-up. (Sladen, JG and Gilmour, JL 1981) In a detailed study of different colour-flow duplex criteria for grading stenoses, the midgraft PSV, maximum PSV, V2/V1 ratio, end-diastolic velocity (EDV) at a stenosis or from narrowest graft segment and colour-flow image diameter measurements were compared for normal appearing grafts using IV-DSA and for those with suspected stenosis using IA-DSA. (Buth, J et al. 1991) The V2/V1 ratio proved to be the optimal identification of stenoses with more than 49% of diameter reduction (sensitivity 89% and specificity 92%), whereas severe stenoses

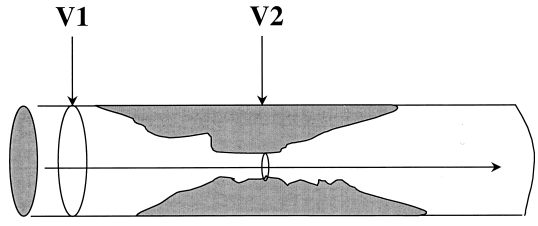


Figure 3. Velocity ratio V2/V1 is calculated from the stenosis and from the adjacent normal graft segment within 2 cm of the stenosis

(70% to 99% diameter reduction were most associated with an EDV > 20 cm/sec.

Colour-flow duplex scanning, as described above, permits efficient tracing of the entire graft. It also improves the identification of the graft when assessing difficult areas such as distal or proximal anastomosis at the popliteal fossa. (Sladen, JG et al. 1989;Taylor, PR et al. 1992) Despite this difficulties may arise: Sladen et al. could not visualize the lower anastomosis in 17% of the studies. (Sladen, JG et al. 1989) It seems that when both the high- and low velocity criteria are combined, they are complementary, and nearly optimal accuracy can be achieved (Sladen, JG et al. 1989; Laborde, AL et al. 1992; Taylor, PR et al. 1992). Sladen et al. scanned 114 grafts using duplex criteria suggestive of stenosis PSV < 45 cm/sec, maximum PSV > 300 cm/sec, or V2/V1 ratio greater than three, which were compared with concurrent angiograms. (Sladen, JG et al. 1989) Only one false-negative finding was observed, leading to a sensitivity of 98% and specificity of 87%. Nevertheless this was a non-systematic retrospective study, and the group of patients represented a data set rather than a consecutive series where not all patients during the study period were referred for angiography. The findings of Taylor et al. were in accord with the previous ones. (Taylor, PR et al. 1992) A total of 74 grafts were studied using duplex scanning, where a PSV < 45 cm/sec andV2/V1 ratio > 2 were regarded to sign a significant stenosis. Subsequent blind IV-DSA was used as an arbiter for normal and stenosed grafts. With these two criteria combined, all stenosed grafts were detected, with only one false-positive study (**Figure 4)**.

As indicated above, methodological testing of the accuracy and reproducibility of colour-flow duplex scanning against the "gold standard", which, historically, is multiplanar intra-arterial angiography, is difficult to accomplish and has not yet been properly performed. In practice, a study of that kind is difficult to design and also gives rise to ethical considerations. However, with present knowledge, it seems that duplex scanning is a very effective non-invasive tool with an accuracy close to, or even superior to, that of other vascular imaging studies in the detection of hemodynamically significant lesions in vein grafts. (Lewis, DR et al. 1998) The main arguments against universal acceptance of duplex scanning are the relatively high initial cost of the machines and the requirement of a well-trained operator for high-quality studies. In a U.K. survey encompassing 112 vascular consultants 22% of teaching hospitals and 44% of district general hospitals did not use duplex for

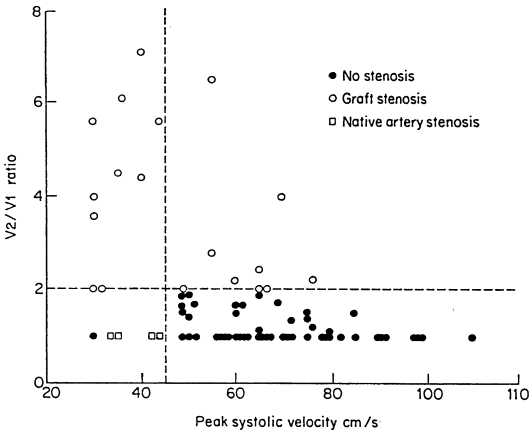


Figure 4. In a comparison to subsequent angiographic findings, combining both the V2/V1 ratio and a peak systolic velocity < 45 cm/sec, nearly perfect accuracy is achieved with duplex scanning in detecting vein graft stenoses (Taylor et al. 1992, reproduced with permission of Eur J Vasc Surg)

screening vein grafts. The reasons stated for the negative attitude were either insufficient resources or a lack of belief in its efficacy. (Gibbs, RGJ et al. 1997)

3.2.5. Other non-invasive studies

Non-invasive impedance analysis is the most extensively studied alternative to other non-invasive studies. (Wyatt, MG et al. 1991; Davies, AH et al. 1993; Arora, S et al. 1995; Woodburn, KR et al. 1995; Zhang, Q et al. 1995) Impedance can be defined as an opposition to pulsatile flow, and for the calculation pulsatile pressure and flow need to be assessed. Noninvasive surrogates utilised for impedance calculations are pletysmographic pulse volume recordings and Doppler waveforms. These measurements can be regarded as rough non-invasive estimates of impedance rather than true empirical measurement of impedance. (Wyatt, MG et al. 1991) Yet good results have been achieved. Wyatt et al. were the first to report on impedance analysis as a method for screening vein grafts. (Wyatt, MG et al. 1991) Their method involved Doppler waveforms and pulse volume recordings from the upper and lower ends of the graft, and the higher of the two impedance scores was used for subsequent analysis. An impedance score > 0.45 was able to detect 20 of 22 grafts determined to be at risk by arteriography. Similar results were obtained by Arora et al., who, with a threshold value of 0.5 achieved a sensitivity of 91% and a specificity of 94%. (Arora, S et al. 1995) Woodburn et al. combined direct Doppler insonation with an impedance value over 0.55 and were able to identify all at-risk grafts. (Woodburn, KR et al. 1995) In the study by Davies et al., impedance analysis was a better screening method than single-point PSV measurement or ABI, but the accuracy was inferior to that provided by duplex scanning of the entire graft. (Davies, AH et al. 1993) However, these results on the accuracy of impedance analysis were not confirmed by Zhang et al., (Zhang, Q et al. 1995) who could not recommend the use of impedance analysis for screening grafts.

Even though equipment is commercially available, impedance analysis has not gained wider popularity. The method per se is cheap, simple and quick to perform and it may offer improved accuracy in the detection of run-off disease over duplex scanning. It does not, however, grade the stenosis nor does it give any anatomical information; thus, further imaging is always necessary if significant hemodynamic lesions in the bypass are suspected. It may also be that the practical difficulties involved in obtaining reliable graft waveform signals with a hand-held Doppler, in particular for deeply routed grafts, are an obstacle to the widespread use of this method.

3.3. The incidence of vein graft stenoses

The true incidence and time of onset of vein graft stenoses is somewhat difficult to establish, as the definition of vein graft stenosis depends on the imaging modality utilised and the variable intensity of serial imaging studies in published series.

In a landmark study by Szilagyi et al. (1973), the results of long-term angiographic follow-up in a large series of lower limb autogenous vein bypasses performed over the period 1962 to 1972 were published. (Szilagyi, DE et al. 1973) In a series of 260 autogenous vein grafts, on the basis of angiographic appearance, he recognized six different types of morphological alterations along the course of the graft or at the

anastomoses. The most common change was a wavy narrowing of the lumen (myointimal hyperplasia?), followed by arteriosclerosis, fibrotic valve, traumatic stenosis, suture stenosis and aneurysmal dilatation. Altogether, these alterations were detected in almost one-third of grafts. Furthermore, all the angiographic lesions showed progression in serial angiographic studies, albeit with some variations in the rate of progression. The mean time of onset for stenotic lesions was over 12 months apart from suture stenosis (9 months). The rather late onset is more a reflection of the study design, where angiograms where obtained before discharge, at 1 year postoperatively and at intervals of 1–3 years thereafter. To date the Szilagyi's series is the only follow-up study with serial angiographic data.

The more modern series on incidence of stenosis are based on data from vein graft surveillance programmes using duplex scanning. According to these studies, the incidence of vein graft stenoses following bypass remains uncertain ranging from 6 to 36% (**Table 3**). There are several potential reasons for the large variation. The follow-up time in these series is variable, but, the peak incidence is frequently between 6-9 months, however, and the number of detected stenoses after one year is only 0 to 20% of all stenoses. In some series it is not indicated, how many extrinsic lesions are included. In addition, even though the stenoses were usually confirmed with angiography, the duplex criteria are variable and, furthermore, in some studies only those stenoses which were revised are reported. However, it is justifiable to estimate from this aggregated data that the "true" incidence of stenosis of more than 50% reduction in diameter is at least 20% and the majority of stenoses develop within the first postoperative year.

Table 3. Incidence of vein graft stenosis following infrainguinal arterial revascularisation (at least 1-year duplex scanning follow-up)

Author (Year)	No of grafts	Stenosed (%)
Grigg (1988)	80	19 (24)
Mills (1990)	379	24 (6)
Moody (1990)	63	15 (24)
Taylor (1990)	301	57 (19)
Bandyk (1991)	394	83 (21)
Stierli (1991)	41	10 (23)
Wyatt (1991)	50	12 (24)
Laborde (1992)	124	38 (31)
Idu (1993)	187	58 (31)
Mattos (1993)	170	62 (36)
Bergamini (1995)	317	56 (18)
Caps (1995)	61	21 (34)
Lundell (1995)	56	9 (16)
Mohan (1995)	171	56 (33)
Passman (1995)	447	36 (8)
Wilson (1996)	275	85 (22)
Olojugba (1998)	44	15 (34)
Avino (1999)	528	87 (16)
Watson (2000)	277	75 (27)
Total	**3695**	**818 (22)**

3.4. The natural history of untreated vein graft stenoses

To understand the nature and behaviour of vein graft stenosis is of crucial importance in providing the theoretical rationale for clinical decision making. On the whole, there are few comparative studies concentrating on the natural course of a stenosed graft left untreated, and their results are contradictory. In the original study by Moody et al. (1989), 22 asymptomatic graft stenoses of variable degree diagnosed with IV-DSA were followed up by a second IV-DSA for a median of 13 months (Moody, P et al. 1989). It found that five of these (23%) were occluded compared to 4 out of 58 non-strictured grafts (6,9%). In studies by Mattos et al. (1993) and

Wilson et al. (1996) the patency rates were lower for subgroups of untreated patients known to have stenosis detected by duplex scanning (Mattos, MA et al. 1993; Wilson, YG et al. 1996). However, discordant experiences have been reported by Dougherty et al. (Dougherty, MJ et al. 1998) They divided a cohort of 85 stenosed grafts into three groups: 25 grafts revised early, 20 grafts revised more than 2 months after the detection of stenosis and 40 grafts not revised at any time. No difference in any outcome criteria was observed between the three groups.

These studies imply that vein graft stenosis does not inevitably lead to graft occlusion and the natural course for an individual lesion can be quite variable. When 158 graft lesions of variable degree in 61 grafts were followed, regression was in general more common than progression and was dependent on the severity of the stenosis. (Caps, MT et al. 1995) In that study it was also observed that lesion progression in vein grafts with multiple lesions tend to occur in an all-or-none fashion; progression and the requirement for revision procedures in these conduits were usually either not seen at all or were seen at multiple sites. Dougherty et al. studied the fate of 42 grafts of high-degree stenoses, which, for various reasons, were not revised. (Dougherty, MJ et al. 1998) Abnormalities regressed in 10 grafts (21.7%), progressed in 5 (10.9%), and were stable in the remainder. Fourteen grafts (30.4%) were ultimately revised. However, 38% of their series were prosthetic grafts and the results were not subanalysed for different graft materials. In a study of 63 duplex-verified stenoses with over 50% of diameter reduction, 42 stenoses were treated conservatively mainly because they did not cause hemodynamically significant ABI-reduction. (Nielsen, TG 1996) It was found that 16 lesions (38%) regressed or remained stable, eight (19%) progressed and another 18 (43%) resulted in bypass thrombosis during a median follow-up of 8 months. Furthermore, this study showed that patients who developed stenoses within 3 months of surgery had a significantly higher risk of bypass thrombosis than patients in whom the stenosis development occurred at a later stage (12 month patency 40% vs. 83%). Accordingly, Ho et al. (1995) found that the risk of thrombosis was twice as high in patients with stenoses detected within three months. (Ho, GH et al. 1995) The severity of stenosis at the time of detection seems to predict the course of further progression. In an angiographic study of 18 stenosed grafts, no occlusions were found when stenoses of less than 50% (0/8) were treated conservatively. In lesions of 50 to 69% and ≥ 70% of diameter reduction 57% (4/7) and 100% (3/3) respectively occluded. (Idu, MM et al. 1993) Others have also verified the significance of the degree of stenosis for stenosis progression. (Moody, P et al. 1989; Caps, MT et al. 1995; Ho, GH et al. 1995)

In all modern series, stenoses thought to threaten graft patency have undergone prophylactic revisions, and subsequent studies on the natural history of vein graft stenoses comprise only subgroups of patients, who, for various reasons, did not undergo revision. These selected patient populations may not be fully representative. Even though evidence is provided that stenoses increase the risk of graft occlusion, to date, the natural course of stenotic lesions has not been completely clarified and the proportion of untreated grafts that become occluded is unknown.

4. Treatment of vein graft stenosis

4.1. Criteria for intervention

It is crucial for the whole concept of managing stenosed vein grafts that the criteria for intervention are as optimum as possible in order to minimise the number of unnecessary procedures introducing extra risk for the patient and the patency of the graft. As the natural history and the proportion of vein grafts that eventually occlude is not known, there has been a tendency to apply the same criteria stenosis that are used when treating symptomatic stenoses in native arterial tree. The treatment decision has been based on angiographic confirmation of a stenosis. A threshold value of 50% (corresponding V2/V1 ratio of 2.0) has been used in many centres as an intervention point. (Mills, JL et al. 1990; Taylor, PR et al. 1992; Idu, MM et al. 1993; Mattos, MA et al. 1993; Wilson, YG et al. 1996) However, more recent studies have suggested that the cut-off value is perhaps too low, and intervention is necessary only for those lesions with a V2/V1 ratio above 3.0 or 3.5. (Sladen, JG et al. 1989; Papanicolaou, G et al. 1995; Westerband, A et al. 1997; Olojugba, DH et al. 1998) In a small retrospective series by Papanicolau et al. (1995), no grafts with a velocity ratio less than 3.4 occluded or required revision. Westerband et al. (1997) completed a prospective study in which the fate of 43 stenosed grafts (V2/V1 > 1.5) was studied. When applying V2/V1 ratio > 3.5 as the criteria for further evaluation and intervention, they found that 46% of stenoses remained stable or regressed, whereas the remaining 54% progressed and were revised. However, three stenosed grafts occluded prior to intervention. Olojugba et al. prospectively scanned monthly 38 primary stenoses with V2/V1 ratio between 2.0 and 2.9. (Olojugba, DH et al. 1998) Overall, 42% of them regressed spontaneously, 29% remained stable and 29% progressed to a V2/V1 ratio ≥ 3.0 and underwent correction. No grafts with V2/V1 ratio between 2.0 and 2.9 occluded under this policy. It seems probable that 'watchful anticipation' is appropriate treatment for a stenosis with a V2/V1 ratio < 3.0. This would markedly reduce the number of interventions without impairing graft patency.

With the increasing confidence in the quality of duplex scanning, the mandatory requirement for angiographic confirmation before making a treatment decision has been questioned. (Caps, MT et al. 1995; Treiman, GS et al. 1997; Calligaro, KD et al. 1998; Idu, MM et al. 1998) In the data reported by Caps et al. (1995), preoperative angiography did not alter the management plan in any of their cases. Treiman et al. (1997) surgically revised 31 grafts on the basis of duplex scans alone, and only two of them occluded within 30 months. Others have suggested that duplex scanning can replace preoperative angiography, provided that the stenosis is well-defined within the conduit or at the inflow and outflow arteries (Calligaro, KD et al. 1998) Idu et al. (1998) proposed an algorithm, which dictates that stenosed grafts with V2/V1 ratio < 2.5 be subjected to intensified surveillance, those with a V2/V1 ratio between 2.5 and 4.0 undergo confirmatory angiography of the severity of the lesion and those with a V2/V1 ratio above 4.0 be prescribed corrective measures solely on the basis of duplex findings. This policy has, however, encountered some criticism. Landry et al. calculated that angiography had significantly contributed to the preprocedural planning in 42% of

cases where non-invasive studies signalled a failing graft. (Landry, GJ et al. 1999)

4.2. Treatment options

4.2.1. Nonoperative management

Many different pharmacological interventions have shown promise in animal studies. The combination of aspirin and dipyridamole significantly reduced the formation of MIH in femoral vein bypass grafts in dogs compared to controls (Dobrin, PB et al. 1988). Several types of ACE-inhibitors have been studied with conflicting results (Daemen, MJ and De Mey, JG 1995). Low molecular heparin suppressed the formation of MIH in a sheep model (Ao, PY et al. 1999). However, in humans all pharmacologic regimens have produced little or no benefit (Davies, MG and Hagen, PO 1995).

Irradiation therapy has been demonstrated to attenuate the formation of MIH in experimental studies. Endovascular brachytherapy has been introduced to clinical work as an adjunct to PTA in coronary arteries, but whether it will provide benefits of clinical value is still unproven (Liermann, DD et al. 1997; Illig, KA et al. 2000).

The expectations of gene therapy have been raised in the last decade as a means of finding solution to several medical conditions, but to date no real clinical breakthroughs have been achieved. In experimental models some evidence has been gathered of successful gene transfer to vessel wall and anti-proliferative effect of gene therapy to reduce the formation of MIH (Cable, DG et al. 1999; Fortunato, JE et al. 2000).

Whilst no effective clinical treatment regimen combatting the development of vein graft stenosis exists, the treatment options are invasive modalities for correcting lesions that have already become established. In practice, the alternatives available are surgical correction or radiological intervention. The different factors that are taken into account, in addition to the general medical condition and willingness of the patient, are the length and location of the stenosis, the type of conduit and the time of occurrence.

4.2.2. Surgery

There are not many large series available on the outcome for stenosed grafts which have undergone surgical correction. Nevertheless, the reported patency rates are impressive, reaching levels that are comparable with patency rates of undiseased bypasses (**Table 4**). In addition, the need for repeat procedures after primary revision seems to be quite limited, as the reported stenosis-free patency rates within 2 years of surgical correction vary from 65% to 95%. (Stierli, P and Aeberhard, P 1993; Sanchez, LA et al. 1994; Avino, AJ et al. 1999)

Surgical techniques for graft revision involves patch angioplasty (VPA) with autogenous vein and interposition grafts or extension ”jump” grafts, particularly if the lesion is at the distal anastomosis. For stenoses within the graft, the choice is between VPA and interposition graft, whereas for anastomotic or juxta-anastomotic lesions it is between VPA and extension graft. It is generally believed that VPA will give less durable results as the diseased segment is not excluded, resulting in higher restenosis rate (Bandyk, DF et al. 1991). The studies comparing different surgical techniques have contradictory results. Bandyk et al. achieved inferior primary assisted patency rates at 5 years for extension grafts whereas for Avino et al., VPA was significantly superior to both of the other techniques. (Bandyk, DF et al. 1991; Avino, AJ et al. 1999) In contrast,

Sullivan et al. found them all equally effective. (Sullivan, TR, Jr. et al. 1996) All these studies involve a small number of patients and describe different clinical philosophies and practices. Typically, VPA is used primarily for very focal stenoses, while interposition and extension grafts are reserved for more diffuse strictures. (Sullivan, TR, Jr. et al. 1996)

The obvious advantages of surgical intervention are an established long-term durability with a low incidence of recurrent stenoses. In addition, stenosing due to external compression can be detected and corrected reliably. Nevertheless, surgery has considerable perioperative morbidity and is not free from complications. (Sullivan, TR, Jr. et al. 1996) Furthermore, repeat surgery in scarred tissues is at times very difficult, especially when the lesion occurs at an anastomosis or is located in a deeply tunnelled graft. In addition, the occasionally very limited autogenous vein material resources are consumed.

4.2.3. Endovascular treatment modalities

Endovascular techniques include percutaneous transluminal angioplasty (PTA), stenting and directional atherectomy. Of these, PTA has been most extensively studied as an alternative to surgical intervention. The studies with a sample size large enough to permit survival analysis show a quite acceptable long-term assisted primary patency (**Table 4**). However, although many grafts can be treated successfully, the restenosis rate is high. There is a large variation in reported incidence of recurrence, as the stenosis-free patency rates vary from 0% at 6 months to 100% at 1 year (**Table 5**). While some authors claim that recurrent stenoses can be successfully treated

Table 4. Cumulative assisted primary patency rates of grafts where either surgical or radiological intervention has been performed for maintenance of graft patency

Open surgical correction							
Author (Year)	No. of grafts	Assisted primary patency					
		3 Mo	6 Mo	1 Year	2 Years	3 Years	5 Years
Sladen (1981)	34				80%		76%
Bandyk (1991)	80	97%	96%	96%	92%	92%	85%
Stierli (1993)	22			95%	95%		
Nehler (1994)[1]	100		99%	99%	98%	96%	92%
Sullivan (1996)	67	98%	98%	97%	97%	87%	72%
Landry (1999)[1]	168	99%	96%	95%	94%	91%	91%

Percutaneous transluminal angioplasty							
Author (Year)	No. of grafts	Assisted primary patency					
		3 Mo	6 Mo	1 Year	2 Years	3 Years	5 Years
Sanchez (1991)[2]	71	100%	94%	89%	74%	68%	58%
Berkowitz (1992)	58		95%	87%	82%	80%	80%
Houghton (1997)[3]	42			84%			
Tonnessen (1998)	50			74%			

[1]The reports by Nehler et al. (1994) and Landry et al. (1999) comes from the same institute. The former comprises grafts revised from 1987 to 1993 and the latter grafts revised between 1990 and 1997; it is likely that these reports include partly same patients.
[2]Secondary patency, includes a minority of prosthetic bypasses
[3]Technical failures are excluded

with a repeat PTA, and recommend it as a primary therapy for graft stenoses, (Berkowitz, HD et al. 1992; London, NJ et al. 1993; Tonnesen, KH et al. 1998) studies with less favourable long-term data have been reported. (Perler, BA et al. 1990; Whittemore, AD et al. 1991) No case-matched comparative studies exist. Open surgical and endovascular techniques used to repair stenotic segments are variable with regard to anatomic site, lesion length, conduit diameter, and time of appearance after the primary grafting procedure. The largest published series in which both treatment modalities were equally used showed identical stenosis-free patency rates of 63% at 2 years both for both surgical and for endovascular intervention. (Avino, AJ et al. 1999) Typically, PTA was also used in their study in selected patients to treat focal (< 4 cm) lesions, whereas more extensive and diffuse longer lesions were treated surgically. Nevertheless, they found a similar outcome regardless of the graft type, treatment of primary versus recurrent stenosis and site of the stenosis.

Attempts to refine the indications of PTA have been made with regard to location of the stenosis, time of occurrence and its length. Berkowitz et al. advocated PTA for proximal graft lesions and surgical revision for mid-graft and distal anastomotic lesions because they did much worse with balloon angioplasty. (Berkowitz, HD et al. 1992) Accordingly, others have also found a high restenosis rate for lesions at distal third of the graft. (Dunlop, P et al. 1995) Somewhat conflicting results were obtained in a recent study in which graft body stenoses showed a better 2-year cumulative primary patency than proximal or distal juxta-anastomotic lesions (86%, 45% and 62%, respectively). (Hoksbergen, AW et al. 1999) Tonnessen et al. suggested that early lesions can be successfully treated with PTA, while late treatment is of less benefit. (Tonnesen, KH et al. 1998) In their study, the length of stenosis did not affect the results of PTA. In contrast, Avino et al. achieved best results for focal (< 2 cm) and late-appearing (> 3 months) stenoses; the stenosis-free patency at 1 year was 89% for those lesions. (Avino, AJ et al. 1999)

Only anecdotal evidence exists on the suitability of stenting for vein graft stenoses

Table 5. Recurrence rates of stenotic lesions after PTA

Author (Year)	Nr of grafts	Primary patency					
		3 Mo	6 Mo	1 Year	2 Years	3 Years	5 Years
Alpert (1979)	12	83%					
Greenspan (1985)	6		66%				
Thompson (1989)	14		0%				
Moody (1990)	8			100%			
Taylor (1990)	13			46%			
Perler (1991)	19			69%	29%		22%
Whittemore (1991)	54		70%	59%	42%	36%	18%
Sanchez (1994)	95				42%		
Spijkerboer (1997)	43			44%			
Avino (1999)	56				66%	63%	
Hoksbergen (1999)*	58				60%	55%	

* Number of stenoses

(Davies, AH et al. 1993) and its role has not been addressed. Experiences with stenting for infrainguinal native arteries do not speak in favour of durable long-term results.

Directional atherectomy (DA) is an endovascular technique, in which, under fluoroscopic control, the lesion is resected step-by-step around the entire circumference of the vein lumen. It is postulated that the actual removal of the atheroma might result in a lower restenosis rate compared with the more traumatic remodelling of the atheroma and arterial wall during PTA. Only one report of the use of DA in vein graft stenosis exists. (Porter, DH et al. 1996) In this study, technical success was achieved in 49 of 52 procedures (94%) and at 3 years the primary patency rate was 79%, approaching long-term patency rates of surgical vein patch angioplasty. A disadvantage of DA is that it is of limited use in narrow (< 3 mm) grafts.

In summary, the role of PTA is controversial as a therapy for vein graft stenoses. PTA is a temping treatment modality, as it is less invasive, associated with low morbidity and gives access to anatomical locations that are difficult to reach with open surgical techniques. A "PTA first"-policy may be proposed, but that seems to lead to some extra risk for the graft and the patient, as well as to the increased cost of repeated procedures. Many authors prefer surgical repair of peripheral bypass stenoses, because it is likely to result in better long-term patency. (Perler, BA et al. 1990; Bandyk, DF et al. 1991; Whittemore, AD et al. 1991; Sanchez, LA et al. 1994) However, the ability to draw firm conclusions is hampered by a significant difference in the analysis of results. Perhaps only a prospective randomised clinical trial to evaluate PTA in comparison with surgical interventions will provide some answers. However, PTA can be regarded as a reasonable option for cases with high operative risk, lesions with difficult anatomy or extensive scarring from previous procedures. The potential benefits and disadvantages of interventional radiological techniques in comparison to surgical techniques are listed in **Table 6**.

Table 6. The potential advantages and drawbacks of the currently used radiological and surgical techniques in the treatment of infrainguinal vein graft stenoses

Method	Advantages	Disadvantages
Open surgical procedure	Excellent long-term results Low-technology proven procedures The diseased segment can be excluded	Consumes autogenous vein material Higher morbidity At times technically very demanding
PTA	Well tolerated by the patients Access to difficult anatomic locations Repeatable Relatively inexpensive	Higher recurrence rate Unproven durability Risks of radiation and contrast agents
Directional atherectomy	Diseased segment is excised	Not for small-calibre vein grafts Expensive Very limited experience

5. Vein graft surveillance

5.1. Rationale for vein graft surveillance

The outcome for a thrombosed graft is bleak, as the reported salvage patency rates following graft occlusions requiring thrombectomy or thrombolysis combined with correction of the underlying defect range from 20% to 37%. (Hye, RJ et al. 1994) In addition, the increasing knowledge of the high incidence of vein graft stenoses, the 3-6 fold increase in the risk of graft occlusion which they probably cause and the successful outcome of prophylactic revision procedures all provide circumstantial evidence in favour of active identification of failing grafts in order to improve the overall outcome of infrainguinal bypass surgery. Therefore, periodic surveillance, typically consisting of colour duplex scanning and ABI measurements, has become a widely accepted common policy (TASC 2000).

The ultimate goal of an active surveillance programme is to prevent unnecessary amputation. According to a U.K. calculation, a surveillance programme can, in principle, be justified as cost-effective if it can be demonstrated that 2% patients undergoing reconstruction will avoid a major lower limb amputation thanks to surveillance. (Harris, PL 1992)

5.2. The length and intensity of a surveillance programme

Surveillance programmes, however, put a considerable strain on the workload of a vascular surgery unit. The necessity of repetitive testing over longer periods of time is expensive, time consuming, and requires adequate technical support. In the modern climate of increasing cost-awareness, strong arguments for the economy in surveillance programmes have been put forward. (Idu, MM et al. 1998) The theoretical ways of improving the cost effectiveness of surveillance programmes are to simplify the surveillance methods, to identify the risk groups at risk of graft failure and to reduce the length and intensity of the surveillance programme.

There is a fairly uniform consensus that during the first year after surgery the first post-discharge test should be performed within 4-6 weeks and thereafter at 3-month intervals. (Cohen, JR et al. 1986; Disselhoff, B et al. 1989; Sladen, JG et al. 1989; Taylor, PR et al. 1990; Davies, AH et al. 1994) As reviewed earlier, the value of pre-discharge duplex scanning is still unsettled. (Passman, MA et al. 1995; Wilson, YG et al. 1995; Olojugba, DH et al. 1998) It is potentially of benefit in detecting abnormalities missed by intraoperative assessment. A good-quality duplex scan is, however, laborious and difficult to accomplish at that point in time due to the tenderness of the wound and the poor visualisation caused by oedema and haematoma in the area operated. Furthermore, that point in time is not optimal for reintervention because the patient is still recovering from the primary procedure.

The vast majority of lesions develop within the first 12 months, and for that reason many authors agree, that surveillance can be discontinued at that time (Taylor, PR et al. 1990; Mohan, CR et al. 1995; Giannoukas, AD et al. 1996; Idu, MM et al. 1998). Taylor et al. (1990) were among the first to propose a limit on the duration of surveillance programme. In their study of 412 femoro-distal grafts, all stenoses were detected within one year after the operation, and none occurred after this. In a series of 171 pure in situ bypasses, only two grafts that had normal duplex findings for up to 6

months had to be revised later. (Mohan, CR et al. 1995) Similarly, Idu et al. (1998), in a study of 300 grafts, discovered an incidence of 2% at 9 months and 1% at 12 months for the development of an event causing de novo stenosis. They recommended a surveillance protocol that, following discharge, includes examinations at 6 weeks, 3 months and 6 months and discontinuation thereafter if duplex abnormalities or previous revisions are absent.

Many centres, however, have maintained the opposite view and propose further biannual assessment after the first postoperative year. Some authors favour surveillance for at least 2 years, (Bandyk, DF 1990; Sanchez, LA et al. 1991) but others advocate that vigorous surveillance should be continued indefinitely and have provided long-term follow-up data as an evidence of a low but steady graft revision requirement. (Dunlop, P et al. 1995; Erickson, CA et al. 1996; Ihnat, DM et al. 1999) Dunlop et al. (1995) surveyed 112 grafts for a median of 34 months. Thirty-eight grafts (34%) developed at least one stenosis; of these, 8 primary stenoses occurred more than 1 year after the initial surgery. Erickson et al. (1996) observed that, in 169 of 556 bypasses where at least one reintervention was performed for the maintenance of graft patency, thirty occurred more than 24 months after the initial bypass. However, seven of these were revisions remote from the conduit with no effect on primary patency. In addition, in this series stenoses in the vein itself developed after a median of 8.5 months, whereas inflow and outflow obstructions occurred at a median of 15 and 29 months, respectively. This was explained by the different nature of the lesions, with slower progressing arteriosclerosis in the native arteries being the dominant factor after 24 months. These findings were further supported by the most recent study, in which 341 grafts were followed up for a mean of 35 months. (Ihnat, DM et al. 1999) Of these, 116 required revision, most (82%) within the first two postoperative years. However, an annual 2% to 4% incidence of late-appearing initial graft stenosis which persisted during long-term follow-up was also observed.

It has been established, that early-appearing lesions are more "malignant" in nature and that the majority of stenoses will develop within the first year. It is clear that after this time frame it is more questionable whether a surveillance programme is still practical and effective as the number of stenoses found is relatively low.

5.3. The impact in outcome

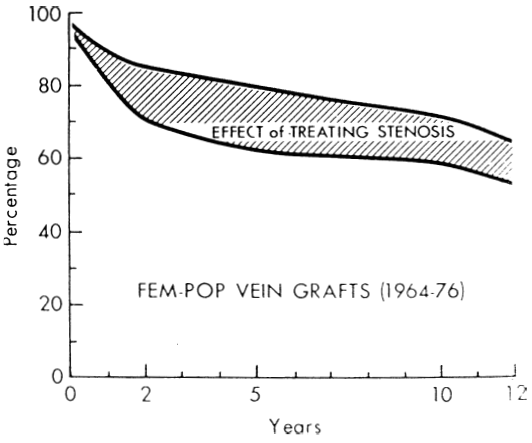
Before factors like cost-effectiveness and quality of life can be considered, the potential clinical merits of surveillance must be demonstrated, firstly as a maintenance of patency of a number of grafts which would otherwise fail and secondly, and more importantly, as improved limb salvage.

5.3.1 Retrospective series

The first positive reports on the merits of surveillance were based on the assumption that all stenotic grafts revised would inevitably have led to occlusion if left uncorrected. Thus, the total differential between primary and secondary patency would represent the improved graft salvage achieved by careful surveillance (**Figure 5**). Berkowitz et al. (1987) demonstrated a secondary patency rate of 70%, compared with a primary patency rate of 47%, at 5 years. They stated that this improvement in patency was attributed to surveillance programme thus salvaging 23% of grafts from occlusion.

Figure 5. The first reports on the benefits of surveillance were based on an assumption that all grafts with detected stenoses would have occluded without intervention. Thus the total difference between primary and secondary patency represents the improved outcome thanks to graft surveillance (reproduced with permission from Am J Surg).

Sladen et al. Am J Surg 1981;141:p. 552 Fig 6.



Likewise, Bandyk et al. (1987) found differences between 3-year secondary and primary patency in femoral-popliteal and femoral-tibial in situ bypasses of 41% and 22% respectively, and similarly credited postoperative surveillance of graft hemodynamics and the success of graft revision for the superior long-term outcome. (Bandyk, DF et al. 1987) This view has been strongly echoed by several authors. (Disselhoff, B et al. 1989; Mills, JL et al. 1990; Bergamini, TM et al. 1991; Laborde, AL et al. 1992; Stierli, P et al. 1992; Erickson, CA et al. 1996) This difference is, however strongly influenced by the unit's activity in performing revision procedures on patent bypasses; the less strict the intervention criteria the greater the arbitrary shift from primary to secondary patency. Thus, it is difficult to justify surveillance simply on the basis of a significantly better secondary or primary-assisted patency compared to primary patency.

As previously stated, even though stenotic grafts can be identified relatively accurately by means of duplex, which grafts will go on to occlude, and should therefore be revised, is less clear. Despite the fact that only some of the stenotic grafts eventually fail, it is estimated that with meticulous surveillance and selective secondary intervention, a durable long-term improvement of 10-19% in primary-assisted and secondary patency rates can be achieved. (Sladen, JG and Gilmour, JL 1981; Moody, P et al. 1990) Indeed, the long-term outcome in reported surveillance series during the last 10-15 years has been quite acceptable, with five-year secondary patency rates ranging from 67% to 89% (**Table 7)**. The data accumulated show that the higher the number of revised grafts, the greater the difference between primary and secondary patency. The secondary patency rates and limb salvage rates does not, however, follow a linear ascending pattern which one might expect as a response to increasing number of revisions. There are several potential explanations for the failure to demonstrate the merits of surveillance, in addition to the possible inefficiency of the revision procedures, on the basis of these outcome studies. Problems when comparing these series include differences with respect to the presence of CLI and the different types of bypasses performed. Although it has been shown that the outcome of in situ and reversed vein bypass are similar, the amount of ectopic vein graft varies and, furthermore, the distribution between femoropopliteal and infrageniculate bypasses is variable. An additional difficulty when reviewing this data is that only a minority of studies report limb salvage rates.

A comparison with non-surveillance series is difficult to perform, as all modern series comprise a protocol of some form of surveillance and elective revision. Thus, only comparison with historical control series is available. A summation analysis compared the outcomes of published vein bypass series undergoing duplex-based surveillance and prophylactic treatment of stenoses to those of vein grafts followed clinically. (Golledge, J et al. 1996) A total of 2680 surveillance and 3969 non-surveillance vein grafts were analysed; the non-surveillance grafts were from studies published from 1971 to 1990. While the total number of occluded grafts was significantly greater for the non-surveillance group (15% versus 27%), no difference in the number of amputations was observed. However, the principles of meta-analysis could not be strictly followed due to poor reporting, especially regarding limb salvage rates, and the absence of randomised patients. Some of the other problems encountered which hindered direct comparison were that it was not always stated, especially in the non-surveillance series, how an occlusion was defined and, in cases where several series were published by the same author, it was not certain that there was no repetition of patients.

5.3.2. Comparative studies

There have been few studies directly comparing duplex and clinical follow-up following infrainguinal bypass. Moody et al. compared 63 femoro-popliteal vein grafts that were prospectively followed-up using duplex scanning with a historical series of 216 femoro-popliteal vein grafts. (Moody, P et al. 1990) They found an improvement of 15% in cumulative 1-year secondary patency. Accordingly, Idu et al. demonstrated a

Table 7. Results of infrainguinal bypass with vein graft in surveillance series with a special reference to the incidence of revised grafts

Author	Year	Grafts	Revised		Primary patency			Secondary patency			Limb salvage		
				(%)	1y	3y	5y	1y	3y	5y	1y	3y	5y
Donaldson	1991	440[6]	18	(4)	81	76	72	87	84	83	-	-	88
Grigg	1988	80[6]	5	(6)	79	-	-	85	-	-	-	-	-
Golledge	1996	50	3	(6)	-	-	-	88	-	-	94	-	-
Disselhoff	1989	69[6]	6	(9)	-	63[1]	-	-	79[1]	-	-	-	-
Rhodes	1999	228[5]	20	(9)	68	-	57	78	-	68	85	-	78
Green	1990	177[3,4]	20	(11)	86	70	66	92	80	80	-	-	-
Shah	1995	2058[6]	253	(12)	84	77	72	91	86	81	97	-	95
Sladen	1981	173[9]	33	(19)	-	-	65	90	85	81	-	-	-
Wilson	1996	275[11]	59	(21)	67	49	-	84	69	-	91	86	-
Berkowitz	1987	102	22	(22)	-	-	47	-	-	70	-	-	86
Laborde	1992	124[6]	30	(24)	-	62	-	-	87	-	-	-	-
Bergamini	1991	361[6]	95	(26)	78	67	63	92	86	81	-	-	-
Mohan	1995	171[6]	45	(26)	-	-	60	-	-	89	-	-	92
Stierli	1992	43	12	(28)	54	54	-	88	88	-	-	-	-
Idu	1998	300[3,8]	84	(28)	65	58[1]	-	91	84[1]	-	-	-	-
Erickson	1996	556[6]	169	(30)	73	64	62	94	89	86	-	-	-
Dunlop	1995	112[7,10]	38	(34)	42	32	27[2]	79	72	67[2]	-	-	79[2]

[1]Patency rates at 2 years
[2]Patency and limb salvage rates at 4 years
[3]Occlusions within 30 days of primary procedure excluded
[4]The series include 31 prosthetic bypass grafts
[5]Only pedal bypasses; CLI indication in all procedures
[6]In situ vein grafts only
[7]79 in situ and 33 reversed vein grafts
[8]172 (57%) other than in situ grafts
[9]Reversed vein grafts only
[10]PTA as a primary treatment for all stenoses
[11]The series include 24 prosthetic bypass grafts

significantly higher assisted primary patency rate in 160 vein grafts which underwent duplex surveillance, compared to 41 vein grafts whose postoperative follow-up comprised only conventional clinical follow-up (91% and 72% respectively at 3 years; first month graft failures excluded). (Idu, MM et al. 1993) In addition, limb salvage rate at 5 years improved by 7% in favour of duplex surveillance group. These findings were later echoed by a large retrospective study, in which 317 vein bypasses which had intensive surveillance were compared with 222 vein bypasses which had clinically indicated follow-up. (Bergamini, TM et al. 1995) Both secondary patency and limb salvage were improved for bypasses followed by intensive surveillance, but the difference attained statistical significance only after 3 years from the primary procedure. In this study, the groups were not directly comparable, as more patients who had CLI at presentation and had undergone long crural or pedal bypasses were more frequent in the non-surveillance group. In both of these last-quoted studies, however, the primary patency rates were no different in the two groups, indicating that the duplex surveillance group, for some reason, would have fared better than the non-surveillance group even without prophylactic revisions. In contradistinction to previous studies, Golledge et al. failed to show any significant difference in the outcome of duplex surveillance compared with clinical follow-up, albeit that the comparison was retrospective to a historical control series from the same institute. (Golledge, J et al. 1996) However, as both secondary patency and limb salvage were improved in the surveillance group and the sample size in this study was small (50 vein grafts in each group), a type II statistical error may be present.

5.3.3 Randomised studies

There has been only one randomised controlled trial comparing duplex with clinical assessment in lower limb bypasses (Lundell, A et al. 1995). A total of 106 vein grafts were randomised, with 56 allocated to intensive duplex surveillance and 50 to routine follow-up including annual out-patient visits and measurement of ABI. In this study, Lundell et al. showed that intensive duplex surveillance had a 25% advantage in assisted primary patency rates at 3 years. However, whilst only 6 more grafts were revised in the intensive surveillance group, the total number of occlusions in both the intensive surveillance group and the routine follow-up group was high (11 and 20 respectively). This indicates that the observed advantage in patency rates may not be attributable solely to the intensive surveillance. No significant difference was observed in the limb salvage rates.

There appears to be little firm evidence in the current literature that infrainguinal vein graft surveillance programmes unequivocally improve patency and limb salvage. This has led some to call for a large randomised prospective study to definitively evaluate the merits of surveillance. (Golledge, J et al. 1996; Beattie, DK et al. 1997; Kirby, PL et al. 1999)

Aims of the present study

The purposes of this study were:

1. To analyse the predictive value of intraoperative flow measurements for the development of vein graft stenoses.
2. To examine the accuracy of duplex scanning as a method of detecting vein graft stenoses.
3. To test a new, easily performed non-invasive method for vein graft surveillance.
4. To evaluate the potential merits of intensive duplex surveillance on the outcome of infrainguinal arterial reconstruction in a randomised prospective study.

Materials and methods

1. Patients

The study material consisted of patients who underwent infrainguinal arterial bypass reconstruction during the period 1991 to 1999 at the Department of Vascular Surgery, Helsinki University Central Hospital. This unit serves as an academic teaching hospital and vascular surgery referral center serving the population of 1.59 million people living in the Helsinki metropolitan area. This unit had adopted an active policy for the treatment of CLI in the 1980s. As part of this policy, all potentially mobile patients without absolute contraindications for surgery and even at times with limited technical prerequisites, were offered an open surgical bypass operation. During these years, a total of 1357 infrainguinal bypass reconstructions for arterial disease were performed of which 830 utilised vein graft as a bypass material. The indication for procedure was, in 78% of cases, CLI.

The characteristics of the patients in the different studies are presented in **Table 8**. The pertinent risk factors were reported in

Table 8. Patient characteristics and indications for the surgical procedure.

	Study I	Study II	Study III	Study IV	Study V
Study period	7/1994-6/1999[1]	3-12/1998	1-8/1999	1/1991-12/1993[1]	1/1991-12/1995[1,2]
No. of patients	195	67	51	179	344/142[4]
No. of grafts	207	69	63	185	362/147[4]
Mean age	71	68	71	69[3]	72
Gender (M/F)	113/94	49/20	36/27	103/49[3]	86/61
Diabetes (%)	97 (47)			55 (36)[3]	58 (39)
Hypertension	87 (42)				47 (33)
CAD	91 (44)			72 (47)[3]	67 (46)
CVD	35 (17)			21 (14)[3]	23 (16)
COPD	23 (11)				
Renal insufficiency	23 (11)				
Previous vascular procedure	87 (42)			60 (39)[3]	
Indication:					
Claudication	23 (11)	9 (13)		20 (13)[3]	52 (14)
CLI	175 (86)	58 (84)	63 (100)	128 (84)[3]	302 (83)
Rest pain	47 (24)				
Ulcer	83 (40)				
Gangrene	45 (22)				
Other	9 (5)	2 (3)		4 (3)[3]	8 (2)

[1]Time of the bypass operation; [2]All the patients in Study IV are also included in the Study V; [3]30-day occlusions, amputations and deaths are not in the numbers; [4]Grafts that had totally accomplished follow-up

accordance with the Finnvasc Registry criteria. (Salenius, JP et al. 1993) CLI was defined in accordance with criteria laid down by the European Working Group on Critical Leg Ischaemia whenever applicable (Beard, JD 1992)

All patients with prosthetic and composite bypass grafts were excluded, as were immediate reoperations, i.e. takeback procedures performed within 30 days of previous vascular or endovascular reconstruction. In the randomised studies, only primary reconstructions were included (**IV,V**). Bypass grafts which were subjected to adjuvant procedures, such as AVF at the distal anastomosis (**I, III**) and microvascular free flap transfer anastomosed to the bypass graft (**I**), were excluded.

2. Methods

2.1. Data acquisition

The patients were identified in the registry of the Department of Vascular Surgery as having had an infrainguinal bypass with vein as the graft material (**I**). The vascular laboratory, hospital, and outpatient clinical records were reviewed and the data were tabulated in a computer database. For comparative studies on surveillance methods (**II,III**), the patients were identified and recruited during routine outpatient clinical visits and prospectively followed up with continuous recording thereafter. For the randomised studies (**IV,V**), the patients were recruited during the immediate post-operative period following the bypass operation prior to discharge and their follow-up data was collected from outpatient clinical records into a computer database.

2.2. Preoperative examinations

The routine preoperative evaluation included detailed patient history, physical examination, chest x-ray, resting ECG and serume concentration of creatinine. Ankle blood pressure measurements were performed in the vascular laboratory by dedicated technicians using a hand-held Doppler probe and the ABI calculated. Toe blood pressure was measured using photo pletysmography. Selective angiography of the affected limb was, as a rule, performed by experienced interventional radiologists, who routinely examined the ipsilateral suprainguinal arteries with a duplex scan to rule out significant flow disturbances in the aorto-iliac segment.

2.3. Operative technique

The patients were routinely operated on under combined spinal and epidural anaesthesia. General anasthesia was chosen for patients with a concomitant suprainguinal procedure or when free muscle flap transfer for coverage of major tissue loss was combined with the bypass procedure. Continuous direct arterial pressure and ECG monitoring was maintained during the operation and extended to the postoperative period as necessary. Vancomycin and/or cefuroxime was given as an antibiotic prophylaxis. Prior to arteriotomy, the patients received heparin at a dose of 1 mg/kg which was neutralised using protamine sulphate if necessary before the wounds were closed. No dextran was given.

The vein grafting technique varied with the surgeon's preference, vein availability, and the sites selected for the inflow and outflow graft anastomoses (**Table 9**). With the in situ technique, a policy of only

partially exposing the graft at the sites of side branches, located by means of an on-table angiogram, was preferred until 1994. Since then, the graft has been fully exposed and intraoperative angiography has been largely abandoned. This partly explains the decreasing number of in situ bypasses performed during the last few years. The policy of this unit has been to route the grafts subcutaneously for easier surveillance and access. This is another reason for fewer in situ bypasses, since the grafts to anterior tibial and fibular arteries are translocated anterolaterally in the limb. For non-reversed veins, the valves were destroyed using various types of valvulotomes according to surgeon's preference and the size of the vein. The two most generally used types were a standard-size plastic valvulotome (In situ cut®, B. Braun Melsungen AG, Melsungen, Germany) and a metal valvulotome with changeable cutting head (Eze-Sit®, W.L. Gore & Associates, Flagstaff, Arizona, USA).

The majority of procedures were performed by attending vascular surgeons and the remaining by vascular surgeons-in-training under the guidance of a senior vascular surgeon

2.4. Intraoperative assessment

Before 1994, the reconstruction was intraoperatively assessed by means of an on-table angiogram and rarely by means of continuous-wave Doppler. The angiographic technique included injection of contrast medium directly into the proximal graft while the inflow artery was kept cross-clamped. Since the advent of transit-time flow measurement in July 1994, it has replaced other modalities, which have been used only if flow was regarded as insufficient or if they were otherwise regarded as necessary. During recent years angioscopy has increasingly emerged as an intraoperative method both for the graft preparation and completion assessment.

The measurement of graft flow was performed with a transit-time flowmeter (CardioMed® CM4006, Medistim A/S, Oslo, Norway). The ultrasonic transit-time flow-meter uses an ultrasonic pulsed beam technique, and measures volume flow within the conduit. A precalibrated probe, sized to fit the graft, is placed around the vein graft. The flow measurements have been found to be highly valid and reproducible, and are not dependent on vessel diameter, wall thickness

Table 9. Characteristics of the performed procedures

	Study I	Study II	Study III	Study IV	Study V
Study period	7/1994-6/1999[1]	3-12/1998	1-8/1999	1/1991-12/1993[1]	1/1991-12/1995[1,2]
Nr of patients	195	67	51	179	344/142[4]
Nr of grafts	207	69	63	185	362/147[4]
Outflow artery					
Popliteal	67 (32)	14 (20)	5 (8)	53 (35)[3]	50 (34)
Crural	83 (40)	24 (35)	33 (52)	65 (43)[3]	52 (35)
Pedal	57 (28)	31 (45)	25 (40)	34 (22)[3]	45 (31)
Bypass type					
In situ	100 (48)	44 (64)		118 (78)[3]	110 (75)
Ex situ[5]	107 (52)	25 (36)		34 (22)[3]	37 (25)

[1]Time of the bypass operation; [2]All the patients in the Study IV are also included in the Study V; [3]30-day occlusions, amputations and deaths are not in the numbers; [4]Grafts that had totally accomplished follow-up; [5]Ex situ refers to bypasses done with non-anatomical position of the graft

or hematocrit changes. (Drost, CJ 1978; Lundell, A et al. 1993; Albäck, A et al. 1996) The graft flow was measured at the proximal part of the graft after the distal anastomosis was completed and the flow opened and become stable. The measurement was repeated after injecting 40 mg of papaverine hydrochloride into the graft. This acts as a smooth muscle relaxant which causes a transient vasodilation of the distal vascular bed and maximal flow capacity (MFC). This was performed at the discretion of the operating surgeon and only in patients who were considered hemodynamically stable, i.e. in whom the systolic blood pressure was over 100 mmHg and not fluctuating. If the intraoperative assessment prompted corrective measures for technical errors within the bypass, the flow measurement was repeated thereafter.

2.5. Follow-up and criteria for graft stenosis or occlusion

2.5.1 Immediate postoperative period

ABI measurements were done routinely on the first and seventh postoperative day or before discharge. No predischarge duplex studies were performed.

2.5.2. Surveillance programme

All patients with infrainguinal vein bypass grafts were enrolled into a prospective graft surveillance protocol at outpatient visits, which included physical examination, ankle/brachial indices and colour-flow duplex scanning at 4-6 weeks and 3, 6, 9, 12, 18 and 24 months postoperatively.

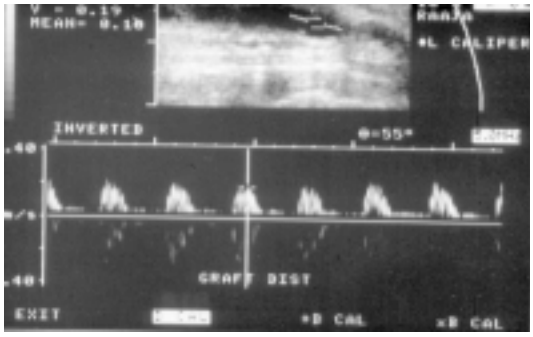
2.5.3 Duplex scanning

Colour-flow duplex scanning was used to scan the entire bypass for anatomic and flow abnormalities, using a standardised technique. An ATL Ultramark 9 (Advanced Technology Laboratories, Stevenage, UK) or HP Image Point (Hewlett Packard, Andover, Massachusetts, U.S.A.) (**I, II, III**) colour duplex scanner with 7,5 MHz transducer was used. For deeply located grafts a 5 MHz probe was used as necessary. Patients were routinely examined in the supine position. The whole graft including anastomotic areas, inflow artery and a few centimeters of outflow vessel were serially scanned to search for specific structural abnormalities or exceptional flow patterns in color-flow images (lumen narrowing, increased velocity, aliasing, colour-flow jet). Changes in velocity are indicated by alterations in the colour-coded images which can be interrogated more carefully with doppler. Even when the colour-flow images are normal, routine samples of graft flow velocity and blood flow patterns were collected at multiple sites on the course of the bypass. The representative velocity spectra were recorded at a Doppler scan-corrected angle of 60 degrees from the middle of the vessel's lumen.

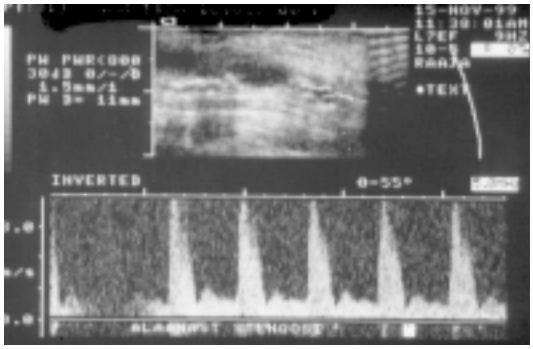
If evidence of a flow disturbance was detected in the colour flow image or spectral waveform, recordings of peak flow velocities at sites proximal, distal and within the area of abnormal flow were made in addition to routine measurements. The severity of the lesion was assessed by calculating the velocity ratio, where the V2/V1 ratio = $PSV_{\text{at lesion}}$/ $PSV_{\text{within 2 cm of stenosis}}$ (**Figure 6**).

2.5.4. Detection of graft stenosis and intervention criteria

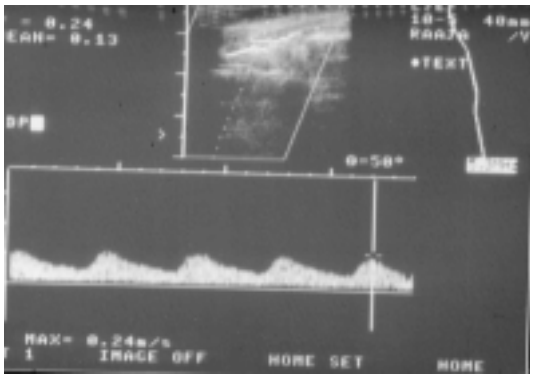
Intervention criterias included clinical signs of a failing graft such as onset of disabling claudication, ischaemic pain or ischaemic ulcers. A decrease in ABI of 0,15 or more compared to the immediate postoperative ABI was considered to indicate for



a)



b)



c)

Figure 6. A stenosis is detected in duplex scan. Doppler velocity spectra a) proximal to, b) at the site of, and c) distal to the stenosis are depicted. The PSV inreases to over 10-fold at the site of the stenosis with a significant end-diastolic flow.

significant hemodynamic deterioration of the bypass.

The duplex scans were compared with the previous studies. A graft was defined to be stenosed in the case of a focal stenosis when exhibiting a velocity disturbance designated by a V2/V1 ratio greater than 2.0. If the V2/V1 ratio was greater than 3.0, the velocity shift was defined separately as a high-degree stenosis. In addition, cases where no discrete stenosis was found, but where either the PSV remained under 45 cm/s throughout the course of the graft or the end-diastolic velocity (EDV) exceeded 25 cm/s, were classified as 'at-risk' grafts.

2.5.5. Graft revision

Borderline stenoses were dealt by means of intensified surveillance which usually included a repeat examination within one month. Lesions which were high-degree or where progressive increase in stenosis severity was identified, were selected for repair, as were grafts that had a low-flow state. A prompt angiographic confirmation was usually scheduled. Angiography-verified stenoses of more than 50% diameter reduction underwent revision. However, during the last two years of the study period, revision was performed on the basis of duplex findings alone on condition that the stenosis was clearly identified and was limited to the graft.

Open surgical correction was preferred with a vein segment interposition, vein patch angioplasty or distal extension grafts as necessary. From 1997 onwards, PTA has been performed for graft stenoses in selected cases, which include short segment (<2cm) stenoses in the body of a large-caliber graft. After secondary correction on open graft, the bypass had the same surveillance protocol as if it were a primary procedure.

2.5.6. Graft occlusion

A graft occlusion was suspected in cases showing a sudden return of the symptoms and signs of CLI and/or loss of previously palpable pulses on the graft or runoff arteries with concomitant significant drop in the ABI measurement. The graft occlusion was verified either with continuous-wave doppler, duplex scanning or angiography.

The need for secondary procedures was considered on an individual basis. In general, if less than a week had elapsed from the appearance of graft occlusion symptoms to patient presentation, graft salvage with catheter-directed intra-arterial thrombolysis and subsequent revision of the underlying causative lesion was attempted. Otherwise a redo bypass operation was considered.

2.6. Study-specific methods

2.6.1 Retrospective study for risk group identification (I)

The study consisted of 207 infrainguinal vascular reconstructions performed on 195 patients from July 1994 to June 1999. Only patients who had had intraoperative flow measurement carried out, who had undergone their first scheduled surveillance visit and duplex scan or who had had an adverse outcome (graft occlusion or amputation) before that visit were included. If a graft stenosis was detected, only the first stenosis was recorded, i.e. if a recurrent stenosis developed at the same bypass later on during the follow-up it was not added to the total number of stenoses.

2.6.2 Comparative studies on the methods for detection of vein graft stenoses (II, III)

Study II

This study was designed to assess the accuracy of duplex scanning on vein graft stenosis detection. The subjects were 69 infrainguinal vein grafts in 69 patients. During the same outpatient visit, two duplex examinations were performed on the same graft, where the one was performed by one of two experienced angioradiologists and the other by one of two vascular surgeons-in-training with rather limited duplex-experience prior to the conduction of the study. Each operator was blinded to the other's findings. A pro forma diagram of the bypass anatomy was included, in which the observer was asked to fill in graft-flow velocity and blood-flow patterns at multiple sites in the course of the bypass. The same diagram also contained questions regarding the patency of the graft, presence, localisation and degree of stenoses and whether any other pathology in the bypass was present.

If one or both of the scans defined the graft as abnormal, the patient was referred promptly for an angiogram. The angiograms were reviewed at a daily meeting of surgeons and radiologists. If neither of the scans indicated abnormality in the vein grafts, the patients were followed as a part of a normal surveillance program with repeated duplex scans, as scheduled, for a minimum of three months thereafter, and occurrences of graft occlusion or other graft-related problems were recorded. A built-up diagnostic standard was created to control the possibility that the variation was caused by a unidirectional systematic error in one of the examinations. This standard consisted of angiography when available and three-month follow-up data on

the grafts that were judged as normal in the duplex scan by both examiners.

Study III

A total of 70 testing procedures on 58 different grafts and patients were performed. The aim was to develop and validate a new non-invasive test for the detection of vein graft stenosis. The study was designed as blinded comparative trial in which duplex scanning was used as the diagnostic standard.

The test is based on a comparison of the complex waveform analysis of pulse volume recordings (PVR) obtained simultaneously at two sites. The principle of the test is to take an inflow PVR waveform from the aorto-iliac segment, where, due to obvious anatomical obstacles in a living patient, the upper arm serves as a surrogate measure. The outflow PVR is taken at the lower limb segment distally to the distal anastomosis of the bypass. This test is automated on a portable vascular laboratory multi-cuff unit that is commercially available (Vasoguard®, Scimed, Bristol, U.K.). This microprocessor-based device has custom-made software that collects a set amount of pulse volume waveforms. These are averaged, normalized in amplitude and digitized. The representative waveform is then put through an integrated 128-point fast Fourier transform analyser which produces a discrete spectrum for each waveform, known as a frequency response curve. Once produced, the inflow (FTp) and outflow (FTd) frequency response curves are displayed as a graph and compared by simple division. This determines the transfer function (TF), where TF(f) = FTd(f)/FTp(f). Identical curves produce a straight line, and the area beneath this line is equal to 1. If the line descends, the area is less than 1 and, conversely, if it ascends the area is greater than one. This yields a quantitative index of the transfer function (TFI) which, in theory, correlates with the relative patency of the intervening arterial segment (**Figure 7**)(**Appendix 1**)

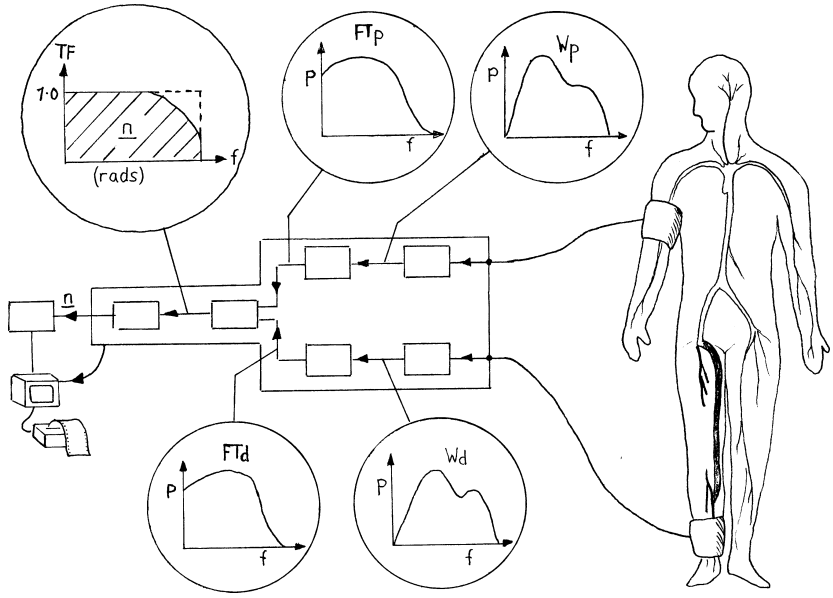


Figure 7. Schematic illustration of the test performance. The inflow cuff is placed on the upper arm and the outflow cuff distally to the distal anastomosis. An averaged waveform (Wp,Wd) is collected and a fast Fourier analysis is performed (FTp, FTd). The transfer function (TF) = FTd(f)/ FTp(f). If the curves are identical, a straight line is produced. The transfer function index (TFI) is the area under the line (n).

The patient is examined in the supine position in a quiet room with a constant air temperature of 21 °C. The TFI-program is selected from the on-screen menu. The standard pneumatic cuffs are placed on the right arm and on the revascularized limb at the segment below the distal anastomosis of the bypass graft. The cuffs are then autoinflated to a venous occlusion pressure of 60 mmHg and the pulse volume tracing obtained. When they have settled into a regular pattern, waveforms are collected for 40 seconds and averaged to produce a mean. Calculations are then performed and the TFI derived and displayed.This can be printed out using the built-in thermal printer.

To produce further data on the repeatability of TFI, two additional cuffs were placed on the proximal and distal thigh of both the operated and the contralateral limb, as allowed by the multi-cuff unit. After the first measurement was recorded, the test was repeated using the same method.

2.6.3 Randomised prospective studies (IV,V)

Patients were randomized at the time of operation into two different surveillance groups according to the date of birth. Patients born on odd-numbered days were enrolled in a surveillance program using clinical examination and ankle brachial index measurement (ABI-group) whereas for patients born on even-numbered days duplex scans were added to the above at control visits (DD-group). The study end points were graft occlusion or major amputation.

In study IV, 185 grafts in 179 patients were randomised; 90 grafts to the ABI group and 95 grafts to the DD group. The groups were well matched with regard to demographics, risk factors, indications for and the type of surgical procedure. The study period was from 1991 to 1993.

StudyV is an extension of Study IV where, originally, 362 grafts in 344 patients where randomised during the period 1991 to 1995. A total of 183 grafts were enrolled in the ABI group and 179 in the DD group. Furthermore, in order to eliminate a potential bias caused by patient non-compliance with the results, the subset of patients who had surveillance which completely adhered to the surveillance protocol were more extensively analysed. The inclusion criteria for this analysis were: patients alive, not amputated and with an open graft at the first outpatient visit and complete surveillance thereafter during the first postoperative year.

2.7. Statistical analysis

Statistical analysis was performed with the aid of the SPSS statistical software package (SPSS for Windows versions 7.0 and 8.0, SPSS, Chicago, Ill). Continuous variables were presented as a mean and as 95% confidence intervals (CI) for the mean (**III**) or median and interquartile range (**IV,V**). For skewed flow distributions, continuous variables are presented as a geometricallly corrected mean and 95% (CI) for mean (**I**). The significance of any difference was calculated using the Student's T-test or using the Mann Whitney test. For categorical parameters, comparisons were performed using Pearson's Chi-squared analysis and when appropriate, Fishers exact test.

The graft patency rates, free-of-stenosis rates and limb salvage rates were calculated by means of the life table method (**IV**) or by means of Kaplan-Meier survival estimates (**I,V**) and comparison was performed using the logrank test (according to the guidelines of the SVS/ISCVS (Rutherford, RB et al. 1997)).

For the methodological studies (II,III), sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated. An assessment of repeatability for continuous data was made using the Bland and Altman test statistics expressed as limits of agreement of the mean and ±2 S.D. (Bland, JM and Altman, DG 1986) The agreement of categorical data was studied by the use of the Kappa (k) statistics (**II**). (Sumner, DS 1985) A multivariate analysis with the Cox proportional hazard model using stepwise backward selection was used to identify independent associations for significant group differences as well as to adjusted risk estimates (**I**).

P values of less than 0.05 were considered as statistically significant

Results

1. The incidence of graft stenosis

The overall incidence of duplex-detected graft stenoses in the follow-up series at one year was, for the unselected patient population (**IV**), 19% and at two years 22% (**I**) The 1-year incidence of graft stenosis rose to 32%, when patients who died, whose grafts occluded, whose legs were amputated with an open graft during the immediate postoperative period or who did not completely attend the surveillance programme were excluded (**V**).

In the ABI-based surveillance programme, the detected incidence of graft stenosis was from 8 to 9% (**IV,V**).

The median time for the detection of graft stenosis from the bypass operation varied from 180 to 238 days (**I,V**). The location of these stenoses were categorized as follows: 1 (2%) at the inflow artery; 2 (4%) at the proximal anastomosis; 7 (15%) in the proximal graft; 26 (57%) in the distal graft; 8 (17%) at the distal anastomosis and 2 (4%) at the outflow artery (**I**). At the time of detection, the mean V2/V1 ratio was 5.3 (range 2 to 15) (**I**).

2. Overall outcome of infrainguinal arterial bypasses

In the aggregated data from 1991 to 1995 (**IV,V**), the 1-year primary assisted patency, secondary patency and limb salvage rates were 67%, 74% and 83% respectively. In the material collected from July 1994 to June 1999 (**I**), the respective primary patency and assisted primary patency rates were 53% and 71% at one year and 48% and 68% at 2 years. The one-month occlusion rate has remained constant during the study period at 11% both in the earlier and in the more recent series (**I,V**).

3. Retrospective study for risk group identification (I)

Pertinent systemic risk factors and intra-operative parameters were tested for free-of-stenosis survival. The variables tested included gender, presence of diabetes mellitus, smoking, hypertension, CAD, CVD, COPD, renal insufficiency or a previous vascular operation, preoperative ABI, indication for procedure, operative technique and bypass anatomy, resting graft flow and maximal flow capacity (MFC). Of these, only flow variables and female gender significantly increased the risk for stenosis development ($P = .029$). In the multivariate analysis, gender and graft flow remained as independent risk factors.

The sample for graft flow was divided into quartiles (Groups 1 through 4). The 25%, 50% and 75% percentiles where at 60 mL/min, 90 mL/min and 136 ml/min, respectively. At 24 months the primary patency rates for Groups 1 through 4 were 32%, 41%, 43% and 75% respectively ($P < .001$), and the assisted primary patency rates were 51%, 66%, 65% and 87% respectively

(P = .0014). The RR for graft thrombosis or development of stenosis was 3.9 times higher in the lowest flow quartile than in the highest quartile. The 24-month free-of-stenosis rates for Groups 1 through 4 were 66%, 59%, 66% and 86% respectively (P = .038). Four *de novo* stenoses, defined as those which occurred later than two months after graft implantation and a normal first scheduled duplex scan, developed in the highest flow quartile. Three of these were female patients. The only male had a late-appearing stenosis 14 months after implantation.

The sample of MFC values was also divided into quartiles. The results of survival analysis were similar to those for graft flow. The 2-year free-of-stenosis survival for the highest maximal flow capacity quartile (> 225 mL/min) was 87% compared to 63% for the other quartiles (P = .030).

4. Comparative studies on the methods for detection of vein graft stenoses (II, III)

Study II

69 vein bypass grafts were provided for comparing two different duplex examinations on the same graft. For the interobserver agreement in differentiating normal grafts from stenosed grafts, a Kappa value of 0.69 was obtained, indicating "good" agreement. A plot of observed PSV values in the graft by the two examinations is indicated in **Figure 8**. The limits of agreement for the measured PSV values, as calculated with the Bland and Altmann test statistics, were lowest in the graft (3.0 ± 42.0) and highest in the anastomotic areas (proximal anastomosis 3.7 ± 116.6 and distal anastomosis 14.6 ± 117.8). The mean difference in the measured V2/V1 ratios of the detected stenoses was 2.2 (range 0.0–11.0). The sensitivity, specificity, accuracy, PPV and NPV for Duplex 1 were 80%, 91%, 88%, 80% and 91% respectively. For Duplex 2 the respective figures were 85%, 93%, 91%, 85% and 93%.

Study III

Four patients were excluded because a reliable TFI waveform was not obtained due to atrial fibrillation, and a further three were excluded because of incomplete visualisation in the duplex scanning. This resulted in 63 grafts eligible for further analysis. The limbs with normal duplex scanning findings had a mean TFI of 1.09 (1.01 to 1.16). At-risk grafts had a mean TFI of 0.89 (0.77 to 1.03) (P = .005). The difference in the TFI of grafts with mild and high-degree stenoses was not significant. When a value of 1.02 was used as a discriminator, the TFI correctly detected 22 out of 23 at-risk grafts. Of the 40 normal grafts the TFI correctly detected 26 as being free of disease. The sensitivity, specificity, PPV, NPV and accuracy were 96%, 65%, 61%, 96% and 76% respectively. The only false negative

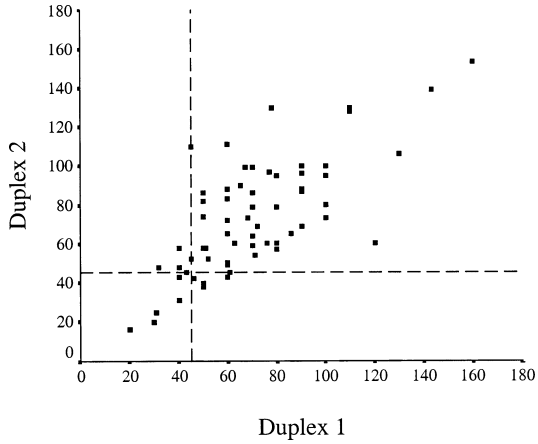


Figure 8. A scatterplot of the highest PSV values in the graft by the two examinations. The broken lines are at 45 cm/sec.

was a clear outlier value of 2.1, which could be explained by a false inflow value due to a right-sided subclavian artery stenosis.

If a drop in ABI of 0.15 or more from the previous value was obtained, the sensitivity, specificity, PPV, NPV and accuracy were 32%, 78%, 50%, 64% and 63% respectively.

In 12 cases where testing of TFI was repeated on the same graft with a minimum interval of one month, 5 grafts where classified as normal on both visits, whereas in 7 grafts a graft stenosis had been successfully corrected between the testing occasions. This was invariably reflected in the TFI values; in the former group the mean difference in the measured TFI was 0.06 (range 0.02 to 0.14) and in the latter group it was higher, with a mean of 0.33 (range 0.13 to 0.84)(P =.026). When the repeatability was tested, the limits of agreement in the proximal thigh, distal thigh and proximal thigh were ±0.21, ±0.07 and ±0.15 respectively.

5. The impact of an intensive surveillance programme on the outcome (IV,V)

Study IV

Four grafts were revised in the ABI group and 11 in the DD group. The number of occluded grafts in the ABI group and in the DD group during the study period were 7 and 12 respectively. The overall 1-year primary patency, primary assisted patency, secondary patency and limb salvage rates in the ABI group were 68%, 74%, 84% and 88% and in the DD group 56%, 65%, 71% and 81% respectively. The differences were not statistically significant.

In the DD group, 60% of duplex scan were carried out as planned. In addition, in the ABI group 8% of all examinations had also been done with duplex outside the study protocol. The duplex scans were performed by 22 different radiologists or radiologist-in-training. The mean numbers of control visits were 3.3 and 3.7 respectively.

Study V

A total of 362 primary infrainguinal bypass reconstructions on 344 patients were performed. Of these, 19 grafts (10.4%) in the ABI group and 21 (11.7%) in the DD group occluded, 13 (7.1%) and 11 (6.1%) patients died, whereas the legs of 4 (2.2%) and 8 (4.5%) were respectively amputated within the first postoperative month. Thus, 147 grafts in the ABI group and 139 grafts in the DD group entered the surveillance period. For the whole study population, the primary assisted patency, secondary patency and limb salvage rates for the ABI group and the DD group were 67%, 74%, and 85% and 67%, 73%, and 81%, respectively.

The numbers of grafts which completely adhered to the surveillance programme in the ABI group and DD group were 90 and 57 respectively. There were no differences between the groups regarding preoperative risk factors or the indication for, or the type of, surgical procedure. In addition, the preoperative and immediate postoperative ABI values did not differ between the groups.

Six grafts in the ABI group and 8 grafts in the DD group underwent 6 and 11 independent revision procedures. Of the revised grafts, none in the ABI group and two in the DD group occluded later during the follow-up. The number of occluded grafts was 13 in the ABI group and 11 in the DD group. The respective primary assisted patency, secondary patency and limb salvage rates in the ABI group and DD group were 77%, 87%, and 94% and 77%, 85% and 93%.

Discussion

1. The incidence of graft stenosis

Our findings on the incidence of vein graft stenosis are well in line with those of previous studies using duplex surveillance. Furthermore, in a recent prospective multicenter study of 277 patients the overall stenosis rate at 12 months was 27%. (Watson, HR et al. 2000) There was however, a large variation between the centres, as the incidence of stenosis at individual centres which entered more than 20 patients varied from 9% to 56%, even though the definition of a hemodynamically significant stenosis was uniform at all centres. Thus, the variation is likely to be a result of differences in patient material, completeness of surveillance follow-up, or differences in qualifications and experience of duplex scan operators and vascular laboratories.

This study confirms that the ABI measurement as a surveillance method is of limited use, as its sensitivity in finding stenoses was only one-third that of duplex scanning. This is in line with the data from other groups, where the sensitivity of ABI measurements has been reported to be 38-55% in the detection of failing lower extremity revascularisations. (Lepäntalo, M et al. 1996) In a considerable number of limbs a drop in ankle pressure is not evident before occlusion occurs. (Berkowitz, HD et al. 1981; Cohen, JR et al. 1986) Furthermore, when suprasystolic pressure is applied to the graft, as is the case in long crural and inframalleolar bypasses, a stump pressure is obtained and hemodynamic changes in the graft cannot be detected. Toe:brachial indices do not provide better discrimination. (Ray, SA et al. 1997) However, as the measurement is simple to perform, it will probably remain as an adjunct to other methods which, in selected cases, may have an effect on clinical decision-making.

2. Overall outcome of infrainguinal arterial bypasses

Overall patency and limb salvage rates are comparable to those in previous studies of modern surveillance series (**Table 7**). However, clearly superior results with secondary patency rates exceeding 90% at one year have been reported mainly in North American studies. Exact comparison with these studies is not possible. Nevertheless a possible reason for lower results may lie in the policy of aggressive treatment of CLI. During the period 1988 to 1992 66% of all patients referred for evaluation of CLI to the outpatient clinic of our institution underwent a revascularisation procedure. (Lepäntalo, M and Mätzke S, 1996) The principles of treatment have remained unchanged since then.

3. Retrospective study for risk group identification (I)

It has not been settled whether the origin of graft stenoses lies in local graft-related or systemic factors. Pre-existing abnormalities could explain the focal nature of graft MIH. This is supported by recent studies, in which graft borderline abnormalities detected intraoperatively using duplex were highly predictive of subsequent graft revision or occlusion during a 3-month follow-up (Johnson, BL et al. 2000) In those studies, a longer follow-up would have provided further evidence of whether intraoperative duplex can identify the grafts at risk for MIH. The higher incidence of vein graft stenosis in females has been confirmed recently by others too. (Watson, HR et al. 2000) The prevalence of venous disease has been recognized as more common in women. (Laurikka, J et al. 1993) Thus, a plausible explanation for the higher incidence of graft stenosis in females would be poor vein quality, which is in accordance with the hypothesis on preimplantation morphological changes as a cause of vein graft stenosis. The other explanation could be a smaller vein calibre in females. However, it can be anticipated, that vein graft diameter cannot be used as such for risk group definement, as the measurement of the diameter shows evident variation depending on the measuring device used, whether the measurement is performed pre- or post-implantation, which part of the graft the measurement is made at and, additionally, the variable thickness of the vein wall.

It has been suggested that hyperhomocysteinaemia and hypercholesterolemia may have an association with MIH. (Rapp JH et al. 1987; Beattie, DK et al. 1999) The risk analysis in this study had limitations as coagulation disorders and hyperlipidemia were not included in the analysis as they were not routinely screened. However, it is probable that these factors can be regarded to be of minor clinical significance.

Since the advent of transit time flowmeter measurements it has been easy to measure graft flow accurately and reliably during surgery. As a method for intraoperative assessment of the technical adequacy of the bypass, its role is dubious. When using in situ grafting technique, unligated side branch A-V-fistulas are easily detected. Otherwise, possible technical errors in the bypass cannot be assessed sufficiently with flow measurement only. (Blankensteijn, JD et al. 1995) As a predictor of outcome, it has been demonstrated that low graft flow increases the risk of graft thrombosis not only during the immediate postoperative period, but also later during the follow-up. (Lundell, A and Bergqvist, D 1993) Our data confirms these findings as the difference in assisted primary patency at 2 years between lowest and highest flow quartile was 36% with a tendency to increase during the first postoperative year.

From a theoretical point of view, the association of wall shear stress with MIH is very interesting. Wall shear stress is related to flow, and inversely related to the third power of vessel wall diameter, as dictated by Poiseuille's law. Wall shear stress has been shown to be an important determinant of the release of vasoactive compounds from the endothelial cells. (Ando, J et al. 1994; Gimbrone, MA, Jr. et al. 1999) As referred to in the review of the literature, experimental studies suggest that low flow and low shear stress induce MIH, and high flow and high shear stress inhibit MIH. However, when a short segment of inferior vena cava was implanted into the abdominal aorta in rats,

the intima-media area of the vein graft increased significantly, and this process was reversed when the vein segments were re-implanted into the venous circulation. (Sterpetti, AV et al. 1996) This fact does not necessarily rule out the low flow hypothesis, as it merely suggests that endothelial cell damage caused by the arterial environment is required to induce the formation of MIH, but once the vein is implanted into the arterial circulation flow conditions regulate the further development of MIH. Our study is the first reported clinical verification that the intraoperatively measured graft flow is associated with the development of hemodynamically significant stenoses, but does not, however, provide any explanation for the localised nature of the lesions.

Creation of an adjuvant AVF distal from the bypass increases the flow through the graft. Already in the 1970's it had been demonstrated that application of AVF decreases the amount of subendothelial proliferation in vein grafts in dogs and it has been comfirmed in later studies also that these high flow bypasses developed less MIH than normal flow bypasses. (Faulkner, SL et al. 1975; Calligaro, KD et al. 1990; Kohler, TR et al. 1991; Mattsson, EJ et al. 1997) In clinical outcome studies, the interest has been concentrated on combining adjuvant AVF with a prosthetic infrainguinal bypass, but the potential clinical advantage of this method is still undetermined. (Jacobs, MJHM et al. 1992; Eagleton, MJ et al. 1999; Hamsho, A et al. 1999) The clinical value of AVF as an adjunct to vein bypass grafting has not been studied.

It would be beneficial to find flow criteria for risk group stratification for a future surveillance programme. On the basis of the data reported herein, it seems that high graft flow is protective against the development of *de novo* graft stenosis, as only four grafts in the highest quartile developed a stenosis after a normal aerly duplex scan. It is a matter of discussion whether this risk is low enough to justify a recommendation that surveillance for grafts with high flow and a normal early duplex scan can be discontinued, and whether also the gender of the patient matters. At this point, however, the merits of the data presented in this series should be viewed as a preliminary clinical verification that the intimal growth and regression in infrainguinal vein grafts is regulated by blood flow. In our opinion a larger sample size is needed for more reliable risk calculation and optimal cut-off point definition before clinical guidelines can be drawn.

4. Comparative studies on the methods for detection of vein graft stenoses (II, III)

The optimal surveillance method should be sensitive, specific, reproducible, operator-independent and economical; none of the methods available fulfills all of these criteria. Duplex scanning is the most widely used method for assessing infrainguinal bypasses. It is generally considered accurate, provided it is performed by a skillful and experienced operator, but this issue has not been more precisely addressed, nor the length of the learning curve been stated. In addition, a duplex examination takes a considerable amount of time, up to 30 minutes, with the time doubling if both lower extremities need to be examined. This causes a marked increase in the workload of the unit. Thus, there is a clear need for simpler methods in vein graft surveillance.

Previous studies on the accuracy of duplex

scanning identifying graft stenosis have compared it with angiography, which is historically regarded as the 'gold standard'. (Sladen, JG et al. 1989; Buth, J et al. 1991; Taylor, PR et al. 1992) To summarize the results of these studies, it seems that the specificity of duplex scanning is excellent, as grafts which were found to be stenosed in the duplex scan were invariably verified as pathological in the angiogram. The sensitivity of duplex scanning is more difficult to establish, as normal-appearing grafts in the duplex scan were tested with IV-DSA, a method apparently inferior to standard multiplanar intra-arterial angiography.

In study II, the accuracy of duplex scanning was tested in a different way. When the operators are suitably blinded, the accuracy can be studied utilising reproducibility analysis. In order to allow maximum variance to take place, different duplex ultrasound machines and operators of varying experience were always paired.

The agreement for categorical data was found to be 'good'. Remarkable is the fact that cases of high-degree stenosis were found very reliably. There was disagreement between the observers in only two of these grafts; for one of these grafts the subsequent angiogram did not verify the presence of stenosis. The other case was verified as a 70% stenosis next to the distal anastomosis in a patient whose distal graft was located in dense fibrous tissue under a free-flap muscle transfer anastomosed more proximally to the graft. However, consideration of results obtained from continuous variables reveals a greater variation. The limits of agreement for doppler velocity measurements at different sites in the course of the graft are very wide. This could be explained in the inflow- and outflow-arteries, as well as in the graft itself, where the velocity can vary markedly from one point to another; in practice it is difficult to standardize a study in such a way that both observers make their measurements at exactly the same point. But the same phenomenon also occurred in the measurement of velocities at the anastomotic sites. This, too, is explainable when one considers the flow pattern in the anastomotic areas, where flow velocity and flow pattern change abruptly with relation to the anatomy. Moreover the correct doppler angle is more difficult to determine. It is undetermined whether the use of different duplex ultrasound machines contributes to the variation, even though calibrated modern scanners were used. A large variation could also be seen in the determination of the V2/V1 ratio of detected stenoses. This relates to the fact that the higher the PSV, the more imprecise its measurement. In addition, the place where V1 is measured ('within 2 cm of the stenosed segment') is quite unsettled. It is not clear whether this variation in the assessment of the degree of stenosis also has clinical relevance. It has been suggested that the V2/V1 criteria for intervention can be raised to 3.0. (Olojugba, DH et al. 1998) The critical issue is whether such a high-degree stenosis can be reliably differentiated from a milder one.

The duplex scans were also tested against built-up control, comprising angiography or prospective follow-up data. This data could not reveal whether the observed variation was caused by a unidirectional error in one of the examinations. This form of analysis can only be used as an adjunct to interobserver analysis, and does not reveal the "true" accuracy of duplex scanning.

It is worthy of note that the operators who had had quite limited experience with duplex scanning of vein grafts prior to the commencement of the study achieved results

comparable to those of very experienced angioradiologists. This fact suggests that the required length of hands-on training is perhaps not as long as anticipated, provided that the trainee is well-motivated and has a thorough theoretical knowledge. Furthermore, it seems quite evident that no special aptitude is needed to perform reproducible studies.

The TFI proved to be a very sensitive method for the detection of hemodynamically compromised bypass grafts and, in practice, all graft stenoses were detected. It seems that the method is also sensitive for hemodynamic alterations in the aorto-iliac segment and in the run-off arteries, as many false-positive tests were obtained. This is further supported by findings in those cases where repeated measurements were available. When a hemodynamically successful graft revision was performed, an increase in the TFI-value was invariably observed. When a graft appeared normal in repeated scans, the TFI-value remained stable.

Transfer function index measurement combines pulse volume recordings with complex waveform analysis. Complex waveform analysis, such as Fourier and Laplace transformation, has been shown to enhance the accuracy of waveform studies, but, because of the complexity of the calculations needed, it has not been adopted in clinical practice. (Junger, M et al. 1984; Macpherson, DS et al. 1984) However, with modern microprocessors and programming the analysis can be performed with ease and applied in portable vascular laboratory machinery. The system concentrates on maintaining the venous occlusion pressure at 60 mmHg, and the pulse volume waveform itself is analysed. The requirement for exact air volume and calibration of the cuffs is obviated. When both inflow and outflow curves are obtained and normalised in amplitude, only the difference in shape remains important. Furthermore, when both curves are obtained, information on hemodynamics from abdominal aorta to outflow vascular bed is gathered. This leads to a well-standardized test which measures the hemodynamic system physiologically with open arterial circulation.

In practice, the measurement of TFI is quick and simple to carry out, as the test takes approximately 10 minutes to perform and bilateral testing can be performed simultaneously. Good quality waveforms are easily obtained, providing valid and well-repeatable results even with very limited experience. The system is not operator-dependent, because the equipment is fully automatic and the calculations made by the computer. The testing is well tolerated by the patients, due especially to the fact that the cuffs do not need to be inflated to supra-systolic pressures. With the commercially available device the measurement of the ABI, when needed, can be done subsequently with the same setting.

Some limitations exist. The system is not suitable for some patients with cardiac arrhytmias such as atrial fibrillation. The limits of agreement are quite wide in the upper thigh. This indicates that the accuracy of TFI measurement is perhaps not acceptable when the volume of the measured segment increases. Nevertheless, this should not pose as big a problem in vein graft surveillance as in the diagnosis of aortoiliac disease.

In order to improve the specificity of the test, further validation is needed. This can be accomplished with a prospective study, in which follow-up values are compared with the baseline value obtained after the immediate postoperative period. Thus, only developing *de novo* lesions are detected and

the confounding impact of hemodynamic alterations in the native arterial tree already present at the time of the primary procedure is likely to be eliminated.

To summarize, it seems that good methods exist for the detection of vein graft stenosis. Duplex scanning can be regarded as the best method for this purpose, and the historical value of angiography as the "gold standard" in screening can be questioned; furthermore, its compulsory use prior to the treatment decisions is perhaps not necessary. However, the initial outlay and maintenance costs of duplex scanning are high. In the absence of the economic resources and technical skills required for duplex, TFI can become an excellent alternative for more simplified screening programmes. After further validation, the specificity of the TFI can be expected to improve to a level where no other non-invasive testing is needed. When pathological values are encountered, a prompt angiogram could be performed solely on the basis of TFI findings.

5. The impact of an intensive surveillance programme on the outcome (IV,V)

These studies demonstrated that, with the use of duplex scanning in the postoperative surveillance of infrainguinal vein grafts, a 2.5-fold increase in the detection and revision rate of significant graft stenoses could be achieved compared to ABI surveillance. Disappointingly, the higher revision rate in the DD group over the ABI group was not reflected as an improvement in outcome; neither in patency nor limb salvage rates. A significant proportion of grafts occluded without warning signs, and for the majority of these the cause of occlusion could not be retrospectively defined. Thus, the question remains: does the surveillance programme actually detect those grafts that are predestined to fail without intervention, or was our result falsely negative due to inherent problems in the study design?

According to power estimations, the sample size of over 362 vein grafts should be sufficient to demonstrate, when present, a difference in survival of about 14% with a power of 80%. So, despite a relatively large study, a type II statistical error cannot be ruled out. However, as the survival curves of the both groups followed an equal pattern throughout the follow-up period, it is very unlikely that increasing the sample size would have given a different result. Our method of randomisation according to day of birth can be criticised, as it was not blinded. It was already known prior to surgery which group the patient belonged to, and, theoretically, this could have had an effect on the treatment decisions. However, as the surveillance programme was actually commenced one month after randomisation, and the failures due to technical reasons had virtually taken place before that point time, this should not cause any bias. As a result, it could be verified that the groups were found to be well matched with regard to pre-operative and operation data.

The results of a surveillance programme can be disappointing if a considerable proportion of the scheduled visits are actually missed. The critically ischaemic patient group is elderly and frequently multi-diseased, requiring treatment by other specialities and institutions. This leads to difficulties in keeping to the surveillance protocols, if they are kept to at all. The proportion lost-to-follow-up can be reasonably low, as in our study (9%), but the screening might still have been unacceptably incomplete, leading to a

lower than expected stenosis detection rate. The accomplishment of the surveillance programme in our study cannot be compared with that of other groups, as this kind of data has not been reported previously, although it should be included in future studies on vein graft surveillance. However, no difference in outcome could be demonstrated between the groups, even when only grafts whose surveillance was carried out strictly as planned were included in the analysis (**V**). Thus, the poor accomplishment of surveillance does not suffice as the only explanation of why no difference was found between the groups.

It can be suspected that the quality of duplex studies was variable, as 22 different radiologists performed the duplex scans, 39% of which were performed by radiologists-in-training under supervision. However, as discussed earlier, the incidence of detected stenoses compares well with other single-center studies. The results of Study II also indicate that duplex scanning can be performed with acceptable accuracy even after a short period of training. This study was prompted after analysing the results of Studies IV and V, partly to obtain some answers to the question of why these studies failed to show any benefit from the duplex-based surveillance. The majority of grafts that occluded did so without any obvious reason, and the question of whether significant pathology was missed in the duplex examination prior to occlusion remains partly unanswered. It seems quite evident that a considerable number of vein grafts can also occlude after the immediate postoperative period without the presence of a distinct focal lesion.

As referred to in the review of the literature, the duplex criteria defining a stenosed graft are well established, and they were applied in the present study. The threshold for intervention was probably sensitive enough, as others have suggested that stenoses with a V2/V1 ratio below 3.0 to 3.5 can be dealt by means of intensified follow-up for stenosis progression without endangering the graft patency. The revision procedures were by large successful; only two of the revised grafts subsequently occluded.

Previous studies have been able to provide only circumstantial evidence that patients actually do benefit from vein graft surveillance. In addition, prior to our studies, only one small randomised trial has been published. (Lundell, A et al. 1995) That study can be criticised for small sample size and frequent occlusions in the intensive surveillance group too. Thus, the scientific basis for vein graft surveillance is not solid, and our studies were not able to prove the case either.

The clinical benefits must be demonstrated first before even trying to analyse the cost-effectiveness of surveillance. Nevertheless, it seems obvious that frequent surveillance beyond 1 year cannot be regarded as cost-effective because of the reduced incidence of graft stenosis after this period. (Ho, GH et al. 1995; Idu, MM et al. 1998)

To demonstrate the potential benefits of vein graft surveillance on the outcome of infrainguinal bypass surgery, a large randomised multicenter trial (which has already begun) is definitely needed. (Kirby, PL et al. 1999) The patient recruitment for this study is taking place at present, and it is estimated that a sample of 1200 vein grafts will be needed to prove the case. Hopefully, in the near future, this trial will be able to provide some definite answers to several critical issues in vein graft surveillance.

Whatever the result might be, it can already be seen, on the basis of our studies

that the results of vein graft surveillance will be disappointing without a very serious approach to surveillance. Furthermore, it is evident that the surveillance programmes need to be economised. This is achievable when surveillance is concentrated on patients at high risk of vein graft stenosis. Intraoperative flow measurements seem very promising in this respect. The workload of surveillance programmes can be further decreased by simplifiying the methods of surveillance. The preliminary results of TFI measurement have shown that this new method of assessing circulation in the lower extremities can become a very valuable tool for this purpose.

Summary

Infainguinal arterial bypass reconstruction with a good-quality autogenous vein graft is the treatment of choice for symptomatic PAOD, especially when the vitality of the leg is threatened. Despite increasing experience and technical refinements, the high failure rate of these procedures is still a matter of concern. In the intermediate postoperative period, bypass failures are mainly caused by the development of hemodynamically significant focal vein graft stenoses, which account for approximately 60% of all graft occlusions. As the outcome of an occluded bypass is dismal and no effective measures against the development of hyperplastic lesions exist, the strategy has been one of prophylactic surgical or endovascular correction of established stenoses. The present study consists of clinical investigations into vein graft stenosis in infrainguinal arterial bypasses with a special emphasis on risk group definement, diagnostic methods and the impact of an intensive postoperative surveillance programme on the outcome.

Intraoperative graft volume flow measurement with a transit-time flowmeter was performed in 207 infrainguinal vein grafts. After the operation the patients were enrolled in an intensive duplex-based surveillance programme. The clinical end points were stenosis development or graft occlusion. The median follow-up time was 13.3 months; the graft flow for event-free grafts was 102 ml/min compared to 82 ml/min for grafts where development of a stenosis was detected and 68 ml/min for grafts which occluded. The respective 2-year primary and assisted primary patency rates in the lowest through the highest flow quartiles were 32%, 41%, 43% and 75% ($p < 0.001$) and 51%, 66%, 65% and 87% ($p = 0.0014$). The free-of-stenosis rates were significantly higher for the highest flow quartile. In univariate and multivariate analysis of pertinent potential risk factors, female gender and low graft flow remained as independent predictors of stenosis development.

The interobserver agreement in duplex scanning for vein grafts was studied in a blinded comparative trial of 69 infrainguinal vein grafts. The examinations showed a perfect agreement on the type of pathology in 58 grafts. In k statistics the value was 0.69, representing good agreement. The mean differences and limits of agreement were, however, wide for PSV measurements made at different sites of the graft.

The transfer function index (TFI) of pulse volume recordings was studied as a potential new method of detecting hemodynamically significant graft stenoses. Seventy testing procedures were performed, of which 12 were repeated measurements on the same grafts with at least a one-month time interval between the measurements. Duplex scanning was used as a diagnostic standard. With a cut of value of 1.02, the TFI correctly identified 22 out of 23 grafts, in which pathology was present in the duplex scan. The sensitivity, specificity and accuracy were 96%, 65%, and 76%, respectively. The

repeatability of the method was satisfactory.

A total of 362 infrainguinal vein grafts were prospectively randomised into a follow-up regime with or without duplex scanning (DD group and ABI group) at 1, 3, 6, 9, and 12 months postoperatively. Although the grafts were revised more frequently in the DD group, the effect of revision procedures was not reflected in the clinical outcome measures. The primary assisted patency, secondary patency and limb salvage rates were 67%, 74%, and 85% for the ABI group and 67%, 73%, and 81% for the DD group. However, surveillance which completely adhered to the protocol was difficult to accomplish, which may bias the results. When only the grafts for which surveillance was completely accomplished were included in the analysis, the outcome was still similar for both groups.

In conclusion, this study verifies that the development of MIH is associated with chronic alterations in blood flow in the graft and that intraoperative volume flow measurements may have a role in risk group stratification with consequences in clinical practice. Duplex scanning is, at present, the best method for detecting hemodynamically significant vein graft lesions, but it needs manpower and technical skills, and thereby considerably increases the workload of a vascular unit. In this respect, the TFI is a very promising new method for detecting an at-risk vein graft accurately and reliably. After further validation, the TFI could become the first-line screening method in vein graft surveillance. This study failed to show the potential benefits of intensive duplex-based surveillance in improving the patency or limb salvage of infrainguinal vein graft reconstructions in the intermediate post-operative period. A large, randomised multicenter trial on vein graft surveillance is needed.

Conclusions

1. Intraoperative graft flow predicts the outcome of infrainguinal arterial bypasses with a vein graft also after the immediate postoperative period. Furthermore, low graft flow is strongly associated with the development of clinically significant vein graft stenoses.
2. Duplex scanning is an accurate tool for detecting vein graft stenoses. With a theoretical knowledge of the principles of examination of the vein graft with duplex, the required practical skills can be acquired after a relatively short learning curve
3. The TFI of pulse volume recordings is a new method for assessing circulation in the lower extremities. The results showed that, with the use of TFI, a stenosed vein graft is detected very reliably.
4. This study failed to demonstrate the potential merits of an intensive vein graft surveillance programme. A large randomised multicenter trial is warranted.

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Leo Ihlberg

APPENDIX

PVR Transfer Function Index

The PVR Transfer Function Index is based on estimating , $A_N(\omega)$, the normalised oscillatory pressure wave frequency response for the arterial segment , A , under consideration. The shape of the oscillatory PVR trace being similar to that of the oscillatory part of the arterial pressure wave. Considering the proximal PVR trace , $P_1(t)$, during a single cardiac cycle as the input to the arterial segment , A , and the distal PVR trace , $P_2(t)$, the corresponding output. The frequency response can be expressed as :-

$$A(\omega) = |A(j\omega)| = \frac{|P_2(j\omega)|}{|P_1(j\omega)|}$$

where , in sampled data form

$$P_2(j\omega) = T\sum_{N=0}^{D} P_2(NT)\cos(\omega NT) - jT\sum_{N=0}^{D} P_2(NT)\sin(\omega NT)$$

$$P_1(j\omega) = T\sum_{N=0}^{D} P_1(NT)\cos(\omega NT) - jT\sum_{N=0}^{D} P_1(NT)\sin(\omega NT)$$

D = number of sample for one cardiac cycle
T = sampling period

The normalised frequency response is given by

$$A_N(\omega) = \frac{|A(\omega)|}{|A(0)|}$$

The Transfer Function Index is defined as

$$TFI = \frac{\sum_{\omega=0}^{25} A_N(\omega)}{25}$$

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Original publications