Current peripheral bypass surgery: various clinical studies

Alexander te Slaa

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Chapter 1

General introduction and thesis outline

GENERAL INTRODUCTION

Peripheral arterial disease (PAD) refers to a range of syndromes that are caused by alterations in function and structure of non-coronary arteries that supply the brain, visceral organs and the limbs.

Atherosclerosis is the disease process than commonly affects peripheral arteries[1]. PAD has a prevalence of 3-10% in the general population and up to 15-20% in patients aged 70 years and older[2, 3]. Patients with symptomatic PAD typically present with intermittent claudication[1]. However, the majority of patients with PAD are asymptomatic or have atypical leg symptoms and may not be recognized as having systemic cardiovascular disease[1]. The coexistence of other cardiovascular conditions is common in patients suffering from PAD. Up to 60%-80% of PAD patients suffer from coronary artery disease of at least one coronary artery[4] and 12%-15% of PAD patients present themselves with a significant carotid artery stenosis[5].

A grading system, based on Fontaine's original clinical staging, is generally used in parallel with more advanced classification systems for classifying the severity of chronic PAD (Table 1)[6]. Standardized classification systems should be used for categorizing patients in clinical research studies or trials. Claudication refers to extremity pain, discomfort or weakness that is consistently produced by the same amount of walking. Ischemic rest pain indicates diffuse pedal ischemia[7]. Typically, it is provoked by or made worse by leg elevation and is commonly associated with ankle pressures lower than 40 mmHg. Gangrene associated with diffuse pedal ischemia requires at least pharmacotherapy, but usually a revascularization procedure, to allow a debridement or amputation wound to heal. Both ischemic rest pain and gangrene embrace the term chronic critical ischemia.

Twenty-five percent of patients who are diagnosed with chronic critical limb ischemia will die from a fatal cardiovascular event within the first year[1]. The approach of PAD is aimed at modification of atherosclerotic risk factors, relieving symptoms and improving quality of life (QoL). This thesis will focus on clinical aspects of peripheral bypass surgery in patients suffering from lower limb PAD in which atherosclerosis is the underlying disease.

Supervised walking exercise is the treatment of choice in patients suffering from intermittent claudication[8]. Improvements in walking range, after six months of supervised treadmill training, are almost equal or better than invasive treatment. However, invasive treatment options can be considered when exercise therapy fails or in advanced stages of PAD[6]. Invasive treatment options of PAD include surgical and endovascular techniques. In the modern vascular practice endovascular techniques are positioned prominently to treat PAD. Nonetheless, selected patients who suffer from severe intermittent claudication, rest pain or tissue loss (Rutherford categories 3,4,5 and 6) might be treated with a peripheral bypass reconstruction so to bypass the obstructed segments of the superficial femoral and/or popliteal artery. A peripheral bypass implies in most cases to a femoropopliteal (either supragenicular of infragenicular) or a femorocrural bypass. Peripheral bypass grafts can be made of autologous material

Table 1. Clinical categories of chronic limb ischemia[3]

Fontaine Classification			Rutherford[6] Classification			
Stage	Clinical description	Objective criteria	Grade	Category	Clinical description	Objective criteria
I	Asymptomatic	No symptoms	0	0	Asymptomatic	Normal treadmill or reactive hyperemia test
IIa	Mild claudication	Claudication at a distance of greater than 100 meters	I	1	Mild claudication	Completes standard treadmill exercise*; AP after exercise > 50 mmHg but at least 20 mmHg lower than resting value
IIb	Moderate to severe claudication	Claudication at a distance of less than 100 meters		2	Moderate claudication	Between category 1 and 3
				3	Severe claudication	Cannot complete standard treadmill exercise*; AP after exercise < 50 mmHg
III†	Ischemic rest pain	Nocturnal and/or resting pain	II†	4†	Ischemic rest pain	Resting AP < 40 mmHg, flat or barely pulsatile ankle or metatarsal PVR, TP < 30 mmHg
IV†	Ulceration or gangrene	Necrosis and/or gangrene in the limb	III†	5†	Minor tissue loss: nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP < 60 mmHg, flat or barely pulsatile ankle or metatarsal PVR, TP < 40 mmHg
				6†	Major tissue loss: extended above transmetatarsal level, functional foot no longer salvageable	Same as category 5

AP, ankle pressure; PVR, pulse volume recording; TP, toe pressure; *5 minutes at 2 mph (3.2 km/h) on a 12% incline; †Stage III and IV / grades II and II / categories 4,5 and 6 are embraced by the term chronic critical ischemia.

(preferably of the ipsilateral saphenous vein) or of an artificial fabric (polytetrafluoroethylene (PTFE) or polyethyleneterephthalate (Dacron®)). An autologous bypass graft is preferred over an artificial graft and thus an autologous bypass reconstruction should be made if possible[9-11]. Two-year primary patency rates of autologous supragenicular femoropopliteal bypasses can be as high as 80% *vs.* 69% for PTFE bypasses. After 5-year, the primary patency rates drop to 74% and 39%, in favour of the autologous bypasses. In general, supragenicular femoropopliteal bypasses perform better compared to infragenicular bypasses. This also applies to autologous bypasses compared to PTFE and Dacron® bypasses.

Post-operative leg edema is seen in the majority of patients following femoropopliteal bypass surgery[12-17]. This edema occurs in a far greater extent than could be expected given the surgical incisions alone. Post-operative edema is known to impair the macrovascular and microvascular circulation[18]. These impairments may delay rehabilitation, prolong hospital stay and cause patient discomfort. The treatment of leg edema in general is based on leg elevation and external compression. The use of intermittent pneumatic compression (IPC) is an alternative concept for the treatment of edema in patients suffering from lymphatic and venous diseases[19, 20]. Moreover, IPC on the foot has been proven effective in edema reduction on the leg that occurs after orthopedic and trauma surgery[21, 22]. The effectiveness of IPC as a method to prevent and reduce post-operative edema following peripheral bypass surgery has not yet been studied.

Patients suffering from PAD cope with limited physical activity and mobility. This will have a negative influence on their health status and QoL[23]. In general, QoL improves following peripheral bypass surgery[23]. It is unknown whether post-operative edema has any negative influences on the QoL.

Previously performed studies based on medical imaging modalities showed that post-operative edema is predominantly situated in the subcutaneous compartments of the lower legs[24-27]. However, the pathophysiological mechanisms underlying edema formation are still not completely understood. Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) have become powerful instruments to image the vascular structures. MRI techniques can be used to study lymphatic structures, as well as subcutaneous and muscle tissue architecture. Enhancements of MRI techniques might help to further elucidate the pathophysiological pathways that lead to edema formation.

THESIS OUTLINE

The aims of this study were to compare the effects of IPC with the effects of compression stockings (CS) on post-operative edema that occurs after femoropopliteal bypass surgery. Changes in leg circumferences, in inflammatory parameters and in the quality of life (QoL) were analyzed in various clinical studies with attention to the edema treatment method.

In **chapter 2**, the literature will be reviewed concerning the understanding of pathophysiologic mechanisms that lead to edema formation following peripheral bypass surgery. Known treatment and prevention strategies of post-operative edema will be discussed as well. Leg edema can be assessed with different measurement techniques. The use of a tape measure is a simple and commonly used method of doing limb circumference measurements. In **chapter 3**, a study to determine the reliability and reproducibility of lower leg circumference measurements with a tape measure will be presented. This method is used in our clinical studies to measure changes in leg circumferences.

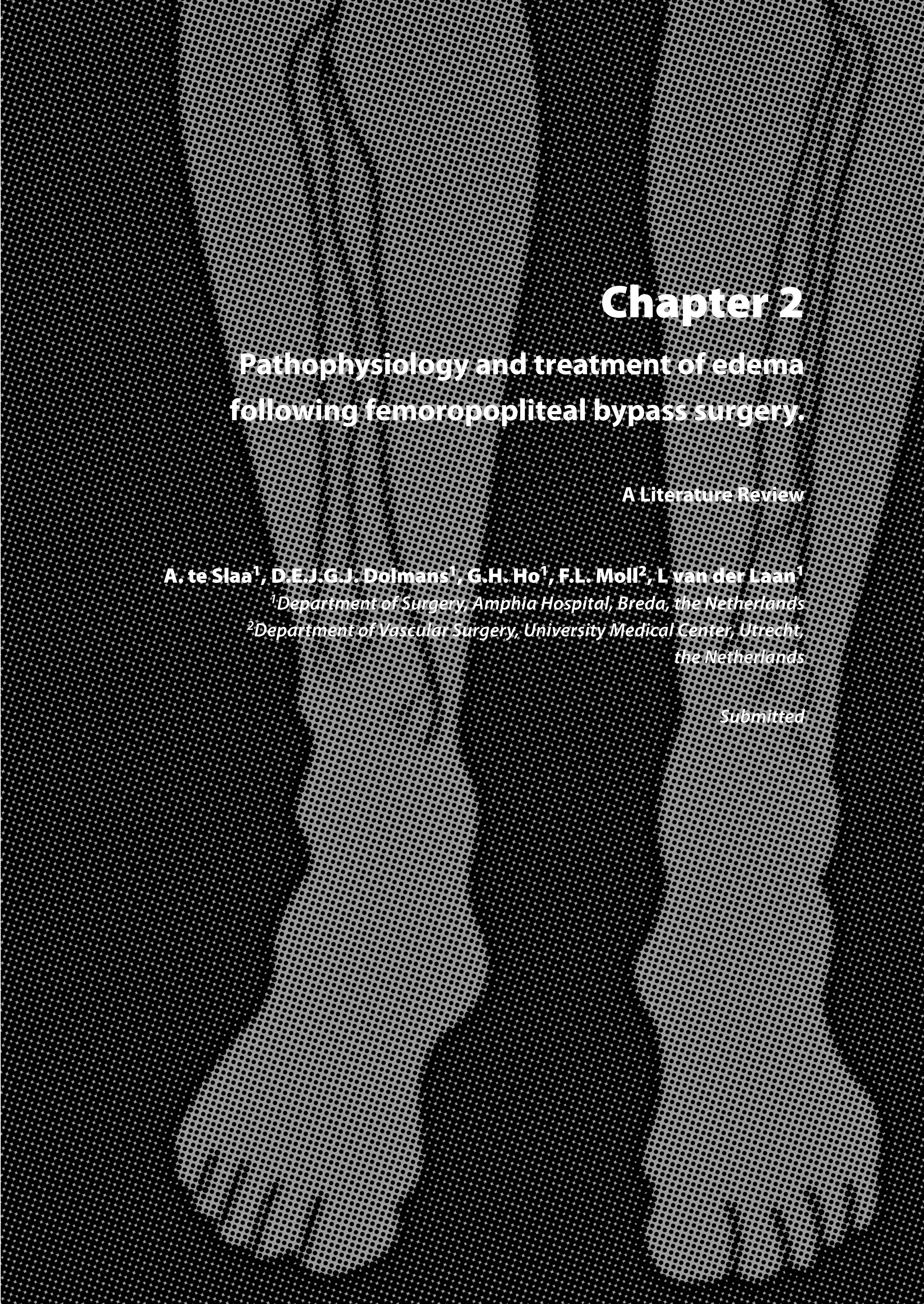
To investigate the effects of IPC on leg edema following femoropopliteal bypass surgery, a single center randomized controlled trial was held between 2006 and 2009. In this trail the use of IPC was compared to the use of CS's following femoropopliteal bypass surgery. The primary endpoint in this study was edema reduction. Two secondary endpoint were formulated: (I) differences in inflammatory parameters and (II) differences in the QoL. The effects of IPC on edema formation and changes inflammatory parameters will be presented in **chapter 4** and **chapter 5**. By type of bypass, two groups were considered. The first group consisted of patient who were revascularized using an autologous bypass. This study will be presented in **chapter 4**. In **chapter 5** the effects in patients who underwent polytetrafl uoroethylene (PTFE) femoropopliteal bypass surgery will be presented, of whom the second group consisted. In **chapter 6** the changes in QoL in patients following either autologous or PTFE femoropopliteal bypass surgery will be presented with special attention to post-operative edema.

Finally, a study to further understand the pathophysiological mechanisms that lead to edema formation will be presented in **chapter 7**. Changes in volume and tissue architecture in subcutaneous and muscle tissue were studied using magnetic resonance imaging. Preoperatively and post-operatively acquired images were compared to each other.

REFERENCES

1. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation* 2006;113:e463-654.
2. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation* 2004;110:738-43.
3. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg* 2007;33 Suppl 1:S1-75.
4. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;348:1329-39.
5. Cheng SW, Wu LL, Ting AC, Lau H, Wong J. Screening for asymptomatic carotid stenosis in patients with peripheral vascular disease: a prospective study and risk factor analysis. *Cardiovasc Surg* 1999;7:303-9.
6. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997;26:517-38.
7. Cranley JJ. Ischemic rest pain. *Arch Surg* 1969;98:187-8.
8. Leng GC, Fowler B, Ernst E. Exercise for intermittent claudication. *Cochrane Database Syst Rev* 2000;CD000990.
9. Twine CP, McLain AD. Graft type for femoro-popliteal bypass surgery. *Cochrane Database Syst Rev* CD001487.
10. Ballotta E, Renon L, Toffano M, Da Giau G. Prospective randomized study on bilateral above-knee femoropopliteal revascularization: Polytetrafluoroethylene graft versus reversed saphenous vein. *J Vasc Surg* 2003;38:1051-5.
11. Klinkert P, Post PN, Breslau PJ, van Bockel JH. Saphenous vein versus PTFE for above-knee femoropopliteal bypass. A review of the literature. *Eur J Vasc Endovasc Surg* 2004;27:357-62.
12. Hamer JD. Investigation of oedema of the lower limb following successful femoropopliteal by-pass surgery: the role of phlebography in demonstrating venous thrombosis. *Br J Surg* 1972;59:979-82.
13. Herreros J, Serena A, Casillas JA, Arcas R, Llorens R, Richter JA. Study of venous and lymphatic components in the production of edema following femoropopliteal by-pass. A comparative scintigraphy and radiologic study. *J Cardiovasc Surg (Torino)* 1988;29:540-6.
14. Hannequin P, Clement C, Liehn JC, Ehrard P, Nicaise H, Valeyre J. Superficial and deep lymphoscintigraphic findings before and after femoro popliteal bypass. *Eur J Nucl Med* 1988;14:141-6.
15. Porter JM, Lindell TD, Lakin PC. Leg edema following femoropopliteal autogenous vein bypass. *Arch Surg* 1972;105:883-8.
16. AbuRahma AF, Woodruff BA, Lucente FC. Edema after femoropopliteal bypass surgery: lymphatic and venous theories of causation. *J Vasc Surg* 1990;11:461-7.
17. Haaverstad R, Johnsen H, Saether OD, Myhre HO. Lymph drainage and the development of post-reconstructive leg oedema is not influenced by the type of inguinal incision. A prospective randomised study in patients undergoing femoropopliteal bypass surgery. *Eur J Vasc Endovasc Surg* 1995;10:316-22.
18. Jacobs MJ, Beckers RC, Jorning PJ, Slaaf DW, Reneman RS. Microcirculatory haemodynamics before and after vascular surgery in severe limb ischaemia--the relation to post-operative oedema formation. *Eur J Vasc Surg* 1990;4:525-9.

19. Klein MJ, Alexander MA, Wright JM, Redmond CK, LeGasse AA. Treatment of adult lower extremity lymphedema with the Wright linear pump: statistical analysis of a clinical trial. *Arch Phys Med Rehabil* 1988;69:202-6.
20. Pflug JJ. Intermittent compression in the management of swollen legs in general practice. *Practitioner* 1975;215:69-76.
21. Stranks GJ, MacKenzie NA, Grover ML, Fail T. The A-V Impulse System reduces deep-vein thrombosis and swelling after hemiarthroplasty for hip fracture. *J Bone Joint Surg Br* 1992;74:775-8.
22. Gardner AM, Fox RH, Lawrence C, Bunker TD, Ling RS, MacEachern AG. Reduction of post-traumatic swelling and compartment pressure by impulse compression of the foot. *J Bone Joint Surg Br* 1990;72:810-5.
23. Breek JC, de Vries J, van Heck GL, van Berge Henegouwen DP, Hamming JF. Assessment of disease impact in patients with intermittent claudication: discrepancy between health status and quality of life. *J Vasc Surg* 2005;41:443-50.
24. Vaughan BF. CT of swollen legs. *Clin Radiol* 1990;41:24-30.
25. Haaverstad R, Nilsen G, Myhre HO, Saether OD, Rinck PA. The use of MRI in the investigation of leg oedema. *Eur J Vasc Surg* 1992;6:124-9.
26. Hadjis NS, Carr DH, Banks L, Pflug JJ. The role of CT in the diagnosis of primary lymphedema of the lower limb. *AJR Am J Roentgenol* 1985;144:361-4.
27. Haselgrove J, Baekgaard N, Stodkilde-Jorgensen H, Christensen T. MRI mapping of postreconstructive edema following femoropopliteal bypass surgery. *Magn Reson Imaging* 1993;11:61-6.



Chapter 2

Pathophysiology and treatment of edema following femoropopliteal bypass surgery.

A Literature Review

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Submitted

ABSTRACT

Background

Substantial lower limb edema affects the majority of patients who undergo femoropopliteal surgery. Edema has impairing effects on the microvascular and the macrovascular circulation, causes discomfort and might delay the rehabilitation process of the patient. However, the pathophysiology of this edema is poorly understood. In this review we discuss the most likely underlying pathophysiological mechanisms and the various treatments used to prevent and reduce post-operative edema following femoropopliteal surgery.

Methods and results

A review of literature was undertaken in the Medline and Cochrane library. In the literature on this topic it is suggested that other factors than local wound healing alone must play a role given the severity and duration of this edema. Hyperemia, microvascular permeability, reperfusion associated inflammation and lymphatic disruptions are likely to facilitate the development of edema. Recent studies based on modern imaging techniques have revealed that post-operative edema is located in the subcutaneous compartment. Preventive methods could be lymphatic sparing surgery, per-operative anti-oxidative therapy and post-operative elevation. Successful treatment regimes to reduce post-operative edema are based on lymph massage and external compression.

Conclusion

The pathophysiology of edema following femoropopliteal surgery is not fully understood, although reperfusion associated inflammation and lymphatic disruptions are likely to play a crucial role. When future less invasive techniques like remote endarterectomy, percutaneous stenting and endovascular bypasses proof to be successful and (cost)effective, post-operative edema might be minimized. Until then, a careful lymphatic sparing dissection should be executed when performing a femoropopliteal bypass reconstruction. Post-operatively, the use of compression stockings and leg elevation are currently the golden standard.

INTRODUCTION

Endovascular techniques have been positioned prominently in the nowadays vascular practice. However, some patients will still be subjected to peripheral bypass surgery when they do not qualify for endovascular treatment strategies. A peripheral bypass reconstruction should be reserved to patients suffering severe intermittent claudication, rest pain or loss of tissue (Fontaine stage II, III and IV / Rutherford category 3, 4, 5 and 6)[1]. The occurrence of substantial post-operative lower-limb edema after femoropopliteal bypass reconstructions is a recognized phenomenon. Lower limb edema causes discomfort to the patient and may delay rehabilitation following an otherwise successful revascularization resulting in a prolonged in hospital stay or out of hospital care. Edema has an inhibiting effect on wound healing as it impairs the macrovascular and microvascular circulation. This review was set up to investigate the current insights in pathophysiological mechanisms that lead to edema following femoropopliteal bypass surgery and to analyze the effects of known treatment methods to prevent and reduce this edema.

METHODS

This study is based on a literature search in the Cochrane and in the Medline library. The libraries were assed via the Cochrane website and the PubMed website respectively. A formal method to conduct a systematic review was not used due to a very small number of randomized clinical trials (RCT) available on this topic. Medical Subject Headings (MeSH®) were used to find literature regarding edema occurring after femoropopliteal surgery. The terms used were "femoral artery"[MeSH] AND "edema"[MeSH] (84 hits), "popliteal artery"[MeSH] AND "edema"[MeSH] (42 hits), "limb salvage"[MeSH] AND "edema"[MeSH] (2 hits) and "femoropopliteal" AND "edema[MeSH] (17 hits). This search resulted in 145 hits. 90 articles were excluded because they did not refer to edema following femoropopliteal bypass surgery. The search was restricted to abstracts published in English. Relevant articles that were referred to in the selected articles were added to the selection. In total 13 articles were identified as RCT's. Effects of various treatment methods to prevent and/or reduce edema following femoropopliteal bypass surgery were investigated in six of these trials (Table 1).

Firstly, this review covers articles that describe the incidence and the dimensions of edema that can be witnessed prior to, and following femoropopliteal bypass surgery. Then the pathophysiology of post-operative edema is discussed. The articles describing possible pathophysiological mechanisms that lead to edema are subdivided into five categories. Finally, the known treatment methods to prevent and to reduce post-operative edema are discussed.

Table 1. Overview of RCT's of treatment options to prevent and/or reduce post-revascularization edema.

Authors	Year	Revascularization	Distal anastomis	Intervention	Control	Outcome
Husni *et al.*[29]	1967	Endarterectomy (N=23), vein bypass graft (N=80), Dacron bypass (N=19), Trauma/aneurysm (N=30).	Unspecified.	Dextran administration (N=21), heparin adiminstration (N=33).	Did not receive dextran of haparine (N=56).	No difference between intervention and control patients.
AbuRahma *et al.*[10]	1990	Femoropopliteal bypass (PTFE (N=41), reversed vein(N=31)).	Unspecified.	Lymph sparing dissection (lateral inguinal (N=15), popliteal (N=17), both (n=20)).	Conventional dissection (N=20).	Significant fewer patient developed edema following lymph sparing dissection.
Balzer *et al.*[5]	1993	Femoropopliteal bypass (in-situ vein).	Unspecified.	Lymph massage (N=12).	Without lymph massage (N=13).	Significant less gain in leg circumference with lymph massage.
Soong *et al.*[32]	1994	Gortex femoropopliteal bypass graft.	Supragenicular and infragenicular (N=unspecified)	Allopurinol administration (N=15)	Placebo (N=14)	Significant less gain in leg volume following allopurinol.
Haaverstad *et al.*[12]	1995	Femoropopliteal bypass (PTFE (N=8), reversed vein (N=16)).	Supragenicular (N=15), infragenicular (N=9)	Lateral inguinal incision (N=12).	Conventional inguinal incision (N=12).	No significant difference in gain in limb volume.
Rabl *et al.*[36]	1995	Upper and lower limb ischemia (acute (N=26), chronic (N=25)) including femoropopliteal bypass (N=14)	Unspecified	Multivitamin cocktail (Omnibionta®) (N=24)	Did not receive Omnibiota® (N=27)	Significant less gain in limb circumference following Omnibiota®

Pre-revascularization edema

Edema does often accompany peripheral arterial disease (PAD). This edema is assumed to be a combination of lymphatic and ischemic edema. Edema is caused by disturbances in the microcirculation in combination with a decreased perfusion pressure due to atherosclerosis of larger peripheral arteries[2]. Due to a decreased arterial pressure the blood flow velocity in the capillaries is reduced. This mechanism makes the pre-capillary arterioles prone to collapse. Due to spasm micro-thrombosis formation can occur in arterioles. Micro-thromboses can cause interstitial space fluid accumulation and swelling of endothelial cells. The capillary bed will eventually collapse causing ischemia. Ischemia results in loss of smooth muscle tonus in the arteriolar wall and to loss of vasoconstrictive reflexes. Thus, in depending limbs an increased capillary hydrostatic pressure can be achieved[3, 4]. This causes a typical relief in patients with ischemic rest pain, but will result in excessive capillary filtration that promotes further edema development[4]. A sequence of microvascular and macrovascular deterioration eventually causes muscle atrophy and ischemia. These events eventually trigger aggregation of blood platelets and leucocytes which activate the local immune system. Finally, the venous and lymphatic circulation are hindered as a result of an decreased arterial circulation and interstitial edema. Pre-revascularization edema is reported to be present in up to 80% of patients suffering from PAD Rutherford category 4,5 and 6. However, due to co-existing muscle atrophy this edema is easily overlooked[5].

Incidence and dimensions of post-revascularization edema

Lower limb edema occurs in 40% to 100% of cases after femoropopliteal bypass reconstructions in patients suffering from PAD[3, 6-12]. Either the presence of pitting edema[3, 13] or an increased limb circumference on the operated side are used to identify edema following femoropopliteal surgery. Based on circumference measurements, either cutoff points[6, 8-10, 14] or quantifications of limb swelling can be presented (Table 2)[12, 15]. Studies presenting cutoff points might under-report the incidence of edema as an arbitrary limit is set. Usually a gain in circumference more than 1.5 to 2.5 cm compared to the pre-operative situation or to the contralateral leg is used as a cutoff point. Haaverstad *et al.*[12, 15] quantified limb volume using a truncated cone model. An average increase of approximately 20% to 26% of initial limb volume is reported[12, 15, 16].

Table 2. Occurrence of edema after femoropopliteal bypass revascularization.

Study	Year	Edema Criteria	Incidence	Assessment Method
AbuRahma *et al.*[10]	1990	Increase of 2 cm in circumference compared to contralateral circumference	40%	Circumference measure
Campbell *et al.*[11]	1985	Presence of pitting edema	85%	Physical examination
Eickhoff *et al.*[3]	1982	Presence of pitting edema	100%	Physical examination
Haaverstad *et al.*[12, 15]	1992, 1995	Quantification of volume increase	100%	Truncated cone (circumference measure, MRI)
Hannequin *et al.*[8]	1988	Increase of 2 cm in circumference compared to pre-operative circumference	48%	Circumference measure
Hamar *et al.*[6]	1972	Increase of 1.5 cm in circumference compared to pre-operative circumference	95%	Circumference measure
Herreros *et al.*[7]	1988	Quantification of circumference increase	93%	Circumference measure
Persson *et al.*[16]	1989	Quantification of volume increase	not assessed	Circumference measure
Porter *et al.*[9]	1972	Increase of 2 cm in circumference compared to contralateral circumference	64%	Circumference measure
Rabl *et al.*[36]	1995	Quantification of volume increase	not assessed	Circumference measure
Soong *et al.*[33]	1993	10% increase in volume	75%	Truncated cone (circumference measure)
Vaughan *et al.*[14]	1970	Increase of 2.5 cm in circumference compared to contralateral circumference	70%	Circumference measure

Pathophysiology of post-revascularization edema

A local inflammatory response to surgical trauma together with the patient's immobilization may account for some edema. However, the severity and duration of the swelling following femoropopliteal bypass surgery suggests that other factors are involved. Five main pathophysiological mechanisms that might lead to post-operative edema have been formulated in literature: hyperemia, an increased of microvascular permeability, reperfusion associated inflammation, lymphatic and venous disruptions. In this review we will discuss these possible mechanisms.

Hyperemia

An hyperemic response can be seen in most patients following successful fermoropopliteal bypass surgery. This hyperemic response has been suggested as a cause of emerging edema. In this subheading the mechanisms that prevent hyperemia from occurring in healthy persons are shortly discussed, followed by possible mechanisms that cause hyperemia.

The blood flow in a leg decreases by about 50% when changing posture from supine to standing in healthy persons. Reflex vasoconstriction that leads to a decrease in blood flow is effected by a local neurogenic mechanism with a small contribution of a local myogenetic response, in addition to a centrally elicited sympathetic component[4]. This auto regulation mechanism is defined as the maintenance of a constant perfusion pressure with variations of arterial blood flow[17]. On the venous side pooling occurs due to gravitational forces in a standing position. This results in an increases autonomic activity, thereby increasing the vascular tone causing a reflex vasoconstriction at the arterial side[18].

Loss of auto regulation mechanism are thought to contribute to a hyperemic response following femoropopliteal bypass surgery. Malfunction of auto regulation mechanisms might be caused by damaged resistance vessels. Structural damage of resistance vessels could be caused by an elapsed ischemic episode. Post-revascularization edema has been associated with an hyperemic response by several authors.

In studies by Simeone *et al.*[19], Sumner *et al.*[20] and Wellington *et al.*[21] it was found that both edema and hyperemia occurred after successful peripheral revascularization. In these studies wash out of ^{133}Xenon was used as a flow indicator. Henriksen and co-workers[17] demonstrated loss of autoregulation in subcutaneous tissue during elevation an dependency in patients suffering from severe PAD (Fontaine stage III). In healthy controls and in patients from suffering less severe stages of PAD (Fontaine stage II) this did not occur[17]. A study by Jacobs and colleagues[2] revealed that patients who developed post-operative edema after femoropopliteal bypass reconstruction had a lowered (peak) red blood cell velocity pre-operatively found in the capillaries in the nail fold of the toe. In these patients the peak red blood cell (RBC) flow velocity after exercise (and before surgery) was even lower than the RBC flow velocity in rest after a femoropopliteal reconstruction. According to the authors, these low flow velocities suggest a severely affected microcirculation. In the patients who developed edema, a significant increase in flow velocity was observed after revascularization compared to the situation prior to surgery. This phenomenon was not seen in patients without edema.

The magnitude of the hyperemic response was found by several authors to correlate with the severity of the ischemia[3, 19-21]. Sumner and colleagues[20] demonstrated that post-reconstructive hyperemic legs exhibited only a limited capacity to respond to stimuli which usually produce vasodilatation or vasoconstriction compared to the normal legs. However, vasoconstrictor reflexes restore, at least partly, on the long term[3]. A partial sympathectomy occurring during the revascularization procedure might contribute to the hyperemic response, although the response after revascularization is reported to be far greater than the effects usually produced by sympathectomy alone[4, 20, 22, 23]. The hyperemic reaction to a sympathectomy alone is reported to resolve within 5 to 10 days post-operatively[24], although the blocked reflex vasoconstriction is maintained[25, 26].

In experimental studies by Sumner and Folse[20] it is also suggested that hyperemia is a contributing factor to edema. After inducing ischemia by using elastic band wrappings for four hours, they found severe edema and hyperemia persisting for 1 to 6 weeks[20]. They suggested that lack of vasoconstriction as a result of damaged resistance vessels (due to ischemia) caused edema. After a peripheral revascularization resistance vessels are nearly maximally dilated as smooth muscle fail to constrict due to ischemic disfunction[20], or as a result of chronic diminution of the normal stimulus (stretch)[19]. A contributing factor to the increased hydrostatic pressure may be failure of the venous pump function during immobilization[27].

In view of the above, hyperemia is suggested to attribute to edema formation[20], however no correlation was found between the disturbances in local blood flow regulation and edema using the ^{133}Xenon technique in a study by Eickhoff *et al.*[3, 20]. Edema developed independently of hyperemia[3]. Edema was sometimes found without hyperemia and *vice versa*[3]. Even so, Persson and co-workers[16] were not able to correlate the magnitude of ischemia to edema. Another objection to the "hyperemia theory" is that it gives no satisfactory explanation for the rare occurrence of edema after more proximal aortofemoral revascularizations. On the other hand, edema is sometimes absent or in a lesser extent pronounced after unsuccessful revascularizations, indicating that factors depending on a successful vascularization are important[16, 19]. Findings by Payne *et al.*[28], who measured limited edema development after percutaneous procedures support this.

Microvascular permeability

It could be hypothesized that patients with severe microcirculatory disorders edema formation does not occur before surgery (because of the low arterial pressure), but that restoration of the circulation after revascularization leads to a rise in arteriolar and capillary pressure. In case of a femoropopliteal bypass, clamps applied to the common femoral and popliteal artery, not only arrest the circulation in the to be bypassed artery, but also in the collateral channels[11].

Additional damage might be induced during clamping to vascular beds in the upper and lower leg. This mechanism might explain the occurrence of edema to be located not only in the foot.

When the capillary perfusion is restored, edema may develop as a result of structural adaptations in the microcirculation. An explanation of the occurrence of post-revascularization edema might be that loss of auto regulation (and thus impairment of a vasoconstrictive response) leads to an augmented increase in capillary hydrostatic pressure in low pressure vascular beds. Husni *et al.*[29] postulated that re-establishment of normal arterial pressure in a vascular tree adapted to reduced pressures, produced overstretching of the vessels[11, 19, 30]. This is supported by Junger and colleagues[31] who found increases in trans-capillary transport of sodium fluorescein with the degree of ischemia in patients with lower limb ischemia. In a study by Campbell *et al.*[11] it was found that serum concentrations of total protein and albumin are reduced postoperatively, but in general fell within the normal range. A threefold increase in albumin concentration was found in the operated leg after a femoropopliteal reconstruction, probably accumulated into the interstitial spaces[11]. The loss of albumin might occur due to increased capillary permeability in ischemic vascular beds.

Reperfusion associated inflammation

Generation of oxygen-derived free radicals during reperfusion are thought to attribute to edema formation[32, 33]. These free radicals induce the lipoxygenase pathway[33]. Lipoxygenase-derived products will injure cells by damaging the cell membranes[34]. Especially subcutaneous tissue is rich in poly-unsaturated fatty acids, making this tissue vulnerable to lipid peroxidation[33]. Oxygen-derived free radicals are also thought to activate the complement cascade[34]. Breakdown products of complements are potent chemo attractants, which stimulate leukocytes and up-regulating adhesive molecules[34]. As a consequence, attracted leukocytes are thought to release more oxygen-derived free radicals and proteolytic enzymes further damaging the endothelium, thereby increasing capillary permeability[35]. In studies by Soong *et al.*[32] and Rabl *et al.*[36] increased parameters for lipid peroxidase activity were associated with the presences of post-revascularization edema.

Lymphatic disruption

Lymphatic damage has been postulated as a cause of edema. Based on lymphatic theories there are two main lymphatic patterns in the occurrence of edema following femoropopliteal bypass reconstruction: (I) interruption of the lymphatic circulation due to surgical damage, (II) diffusion of the lymph outside the vessels without appreciable impairment of the lymphatic flow.

Research on lymph disruption and function has been performed using lymph angiography and lymph scintigraphy. Compared to lymph angiography, lymph scintigraphy is a non-invasive technique to study both the morphology and the kinetics of the lymphatics[37, 38]. More recently X-ray computed tomography (CT) and magnetic resonance imaging (MRI) techniques are used as well to study anatomical characteristics of edematous limbs.

Lymphatics are mainly responsible for the maintenance of the interstitial pressure in the subcutaneous compartment at sub-atmospheric level which is a vital factor in the prevention of edema[39]. During vascular surgery lymph nodes surrounding the femoral artery and the popliteal artery are vulnerable to damage. Vaughan *et al.*[14] and Shishido *et al.*[40] found that only a few of the superficial lymphatic channels remain after femoropopliteal surgery. Lymph vessel are especially prone to damage when a venous peripheral bypass is constructed[7]. Lymph angiograms showed a greater extent of disruption to the lymphatics when the saphenous vein was uses compared to artificial grafts[7]. Rejoining of severed lymphatics occurs occasionally, but more frequently the lymphatic function is reestablished by formation of newly formed channels and the enlargement of the remaining lymphatic channels[9, 14, 41].

In studies by Porter *et al.*[9] and by Vaughan *et al.*[14] it was demonstrated that the magnitude of inguinal lymphatic damage correlates to the extent of postoperative edema by using lymph angiograms. Haaverstad and colleagues[12] found that larger lymphatic disruptions represent a larger volume increase post-operatively as compared to smaller disruptions.

Based on lymph scintigraphy, Hannequin *et al.*[8] found that lymphatic flow is not different in patients suffering from edema *vs.* patients not suffering from edema after a femoropopliteal bypass operation. However, in this study the presence of edema is judged on cutoff point, possibly resulting in arbitrary grouping.

Others also found that the presence of morphological abnormalities correlate with edema, based on lymph scintigraphy findings[42]. Morphological abnormalities (including diffusion) might be the result of dysfunction and increased permeability of het lymphatic walls[40]. Campbell *et al.*[11] proved an increased albumin content in limbs and a correlation with the presence of edema after femoropopliteal bypass reconstructions. Fernandez found an increased washout of ^{125}Iodine labeled albumin in edematous limbs after femoropopliteal revascularizations, indicating an increased lymphatic flow of the superficial lymphatics[13].

These results agree with Stranden and Kramer[43] who found that intra lymphatic pressures and the threshold pressure necessary to induce spontaneous lymphatic contraction were normal after femoropopliteal reconstruction. Based on their finding, they could not prove that post-revascularization edema is caused by an insufficient lymph transport capacity. However, based on a remarkable findings by Persson *et al.*[16], lymph damage as cause of edema could not be ruled out. They witnessed the development of edema after only a exploration in the popliteal region, although not as pronounced as after successful revascularizations[16]. Danese *et al.*[41] showed in an animal model that edema occurred within 24 hours after transection of lymphatic trunks in the thigh. Edema became the most pronounced 24 hours after surgery and disappeared by the fifth week[41].

Modern imaging techniques like CT and MRI make it is possible to study anatomical characteristics of edematous limbs (CT)[44-47]. MRI investigations revealed that the edema was located around the entire circumference of the leg and restricted to the subcutaneous tissue. These findings correspond with previous CT studies[44]. In patients with chronic lymph edema all edema was in the subcutaneous tissue as well. The similarities between chronic lymphatic edema and post-operative edema support the idea that edema formation after bypass surgery is, at least partly, caused by impaired lymphatic drainage, as most of the lymph originates in the skin and subcutaneous tissue[48].

Persisting edema is regularly seen in trauma patients[49]. It is postulated that a persisting immune response may impair lymphatic transport. Damaged lymphatic structures could also leak lymph-containing microorganisms that are "physiologically" transported from the foot to the skin[50]. So do high levels of cytokines and chemokines that are found in lymph drainage from inflamed tissue[49]. Cytokines and chemokines released from resident an infiltrating cells are associated with dilatation of lymphatics[49]. Furthermore, heme-containing substances such as hemoglobin, oxyhemoglobin, and myoglobin absorbed from the inflamed tissue, inhibit lymph vessel contractility as seen in normal lymphatics[40, 51, 52]. It cannot be ruled out that tissue damage occurring during construction of a femoropopliteal bypass revascularization triggers a similar cascade.

Venous disruption

Few authors have mentioned venous disruptions as cause of post-revascularization edema[12]. However, it is unlikely that the removal of the greater saphenous vein alone caused edema of the leg[14, 29]. Urayama *et al.*[42] found no association between post-reconstructive edema and venous obstructions using radioisotope venography. Neither did AbuRahma *et al.*[10] found a relation between deep venous thromboses (DVT) and post-operative edema.

Nowadays a DVT is very uncommon after femoropopliteal bypass reconstructions in patients receiving anti-coagulatory therapy[3]. Due to impaired lymph drainage or hyperemia, venous flow is increased which may decrease the risk of DVT formation. However, partial or complete obstruction of the deep venous system by a thrombosis was a common cause of post-operative edema of the leg. According to a study by Hamar *et al.*[6] in the 1970's, DVT's were found in 43% of patients who underwent femoropopliteal revascularization and DVT's are correlated with an calf circumference increase in excess of 4.5 cm. Distal anastomosis of the vein graft to the artery are more often accompanied by venous thromboses than anastomosis above the knee joint[6]. The emerging trombo-phlebitis might invade peri-venous tissue, resulting in the development of lymphatic obstructions as a result of scar formation at the site where inflammation had subsided[40].

A condition in which edema is regularly observed is after a vein harvest, when the vein has to be used as a coronary artery bypass graft[53]. In these patients an impaired venous drainage, as well as lymphatic and soft tissue damage are hypothesized to contribute to the formation of edema, although this has not been studied in detail[53]. The contribution of venous impairments in emerging edema after femoropopliteal bypass reconstructions is likely to be limited in the absence of an occlusion by a DVT. Phlebograms and venous pressure in groups of patients developing edema following vascular reconstructions have shown to be normal in most studies[7, 10, 29, 54].

Summary of pathophysological mechanims.

The pathosphysiological mechanism of edema following femoropopliteal bypass surgery is likely multifactorial. MRI studies have shown that post-revascularization edema is located in the subcutaneous compartment, similar to lymphatic edema[15]. Lymphatic disruptions should therefore be considered as a major factor in edema development. A large attribution of hyperemia was only demonstrated animal models[20]. Hyperemia, reperfusion associated inflammation and an increased capillary permeability contribute probably only in a limited extend to edema development following femoropopliteal surgery. This is likely to be illustrated by the limited extend of edema development that occurs following endovascular revascularizations[28]. The attribution of venous disruptions are very limited as a cause of edema development in the absence of a DVT[6].

Treatment and prevention of edema

Treatment of edema, irrespective of the pathophysiology, should achieve a net absorption of fluid from the interstitial space into the vascular or lymphatic compartment[39]. In general treatment strategies strive to improve microcirculation and arterial perfusion, to reduce discomfort to the patient and to promote the patient's rehabilitation process following surgery. The following treatment options to prevent and to treat post-operative edema will be discussed: lymph drainage, lymph sparing surgery, compression stockings, anti-oxidative therapies and intermittent pneumatic compression (Table 1).

Lymph drainage techniques

Lymphatic disruptions are very likely to attribute in post-revascularization edema. Post-operative edema had been shown to be mostly absent following proximal arterial reconstructions[3, 11, 20] or to be present in a limited magnitude following endovascular revascularizations[28]. In both these procedures the inguinal lymphatics are spared. Lymphatics surrounding the femoral and popliteal artery are very vulnerable to damage. Facilitation of the lymphatic flow by applying lymph drainage therapy has been proven to be an effective method to reduce post-revascularization edema. A reduction in leg circumference was noticed on the sixth day after surgery, *vs.* on the twelfth day in a control group, in a RCT by Balzer and colleageus[5]. Franzeck *et al.*[55] came to similar conclusions for the treatment of lymph edema, when patients were treated with manual lymph drainage in combination with compression therapy.

lymph sparing surgery

The effects of lymph sparing dissection when constructing an femoropopliteal bypass have been investigated by two teams lead by AbuRahma[10] and Haaverstad[12]. AbuRahma and co-workers[10] used lymph angiograms to conclude that the risk of postoperative edema after a femoropopliteal bypass reconstruction was more than 8 times larger when a conventional dissection was used, *vs.* a lymphatic sparing dissection in the inguinal and popliteal region.

The lymph sparing dissection consisted of a lateral incision in the groin and in at the site of the popliteal artery without mobilizing the neurovascular bundle. However, the results are in contrast to a study by Haaverstad and colleagues[12]. In this study a conventional medial incision was compared to a lateral incision in which attention was focused on the preservation of the lymphatic network. No significant differences were found in the amount of edema that occurred in the treatment groups. Though, it was found that larger lymphatic disruptions do represent a larger volume increase post-operatively as compared to smaller disruptions. A shortcoming in the study by AbuRahma[10] it is the analysis is based on cutoff points rather than on continuous data like the study by Haaverstad[12]. This might have biased the outcome. Given the observations as displayed in Table 1, it is very unlikely that edema did not occur in the study by AbuRahma. It would be more likely to assume that edema occurred in a lesser extent following lymph sparing surgery. Based on these studies, it is very likely that post-reconstructive edema is associated with lymph damage and (adjacent) tissue trauma. However, the effects of a modified incision on the amount of edema remain questionalble.

Compression stockings and elevation

The use external compression devices, such as stockings or bandages, are commonly used to treat edema. Compression stockings are reported to exert at least a pressure of 30 mmHg[56]. The use of compression stockings is mostly based on clinical experience. So far no trials have shown a beneficial effect of the application of compression stockings following femoropopliteal surgery. The aim of compression is to increase pressure on the interstitial space[39] and to augment the peripheral circulation by reducing in peripheral arterial resistance[56]. At the arteriolar level an increase in arterial flow is witnessed. This is the result of smooth muscle relaxation precipitated by the release of endothelial-derived relaxing factor (EDRF), which has been shown to be nitric oxide[57]. Supplemented to compression therapy, leg elevation could be practiced. By elevating the leg, the hyperemic response could be subsided. Auto-regulation mechanisms normally cause reflex vasoconstriction on the arterial side, but are impaired in patients suffering from severe stages of PAD[20]. Leg elevation could slow down edema formation as it wanes the effects of impaired auto regulation mechanisms and increased microvascular permeability.

Anti-oxidative treatment

It has been hypothesized that reperfusion associated inflammation could be moderated with administration of anti-oxidants. Successful edema prevention strategies with per-operative administration of allopurinol and a vitamin cocktail during revascularization surgery have been reported by Soong *et al.*[32, 33] and by Rabl *et al.*[36]. In both RCT's a reduction of edema formation was found. According to Rabl and co-workers[36] the effect of a multivitamin cocktail resulted in a decrease in development of lipideperoxidase products and in reduced edema formation after revascularizations, either after chronic and acute arterial occlusions. Soong and colleagues[32] found a 50% decrease in swelling after allopurinol administration, although the working mechanism of allopurinol remains unclear. The use of anti-oxidants have not become widespread in the vascular practice, even though the results of these trials were encouraging.

Intermittent pneumatic compression

Intermittent pneumatic compression (IPC) has also been proven effective in edema reduction originating from orthopedic lower limb surgery[58, 59], lymphatic disorders[60, 61] and venous disorder[61, 62]. The use of IPC has been proven effective as a DVT prophylaxis[58] and for blood flow enhancements in arteries affected by PAD[63-67] as well. McGeown *et al.*[68] thought that compression empties terminal lymphatics, allowing drainage of fluids from the interstitium, and also possibly assists to move fluid from the interstitium to the lymphatics. IPC does not assists flow in the major lymphatics directly, nor does it transports fluid within the tissue directly[69]. It is assumed that with the use of IPC, proteins are cleared from the tissue as well[69, 70]. Though if it did not, edema would reoccur quickly and clinical results are generally satisfactory[60]. IPC of the leg generates an increase in arterial blood flow in both healthy subjects and in patients suffering PAD[63-67]. Up to fourfold of blood flow in rest into the calf has been reported with the use of IPC[63, 67]. This effect has been demonstrated in native arterial blood flow, as well as in infragenicular femoropopliteal bypass grafts[66]. Venous flow velocity in the common femoral vein increases during compression by a factor of 2.5 to 3, which indicates that venous emptying is facilitated[71, 72]. `in immobilized patients blood is no longer cleared from the veins due to an insufficient muscle pump function, which can result in venous hypertension. This allows fluids to move out of the capillaries and thus leads to edema formation[62]. The role of intermittent compression in chronic venous insufficiency is primarily to disperse edema in a similar way as in the treatment of lymph edema. The use of a intermittent pneumatic pump has proven effective to reduce edema and wound infections after coronary arterial bypass grafts (CABG) in a study by Ho *et al.*[53]. The device used compressed the foot, calf and thigh up to 70 mmHg pressure, in cycles during 15 minutes each, making it merely a external compression device rather than an IPC. So far, the efficacy of IPC in reduction of edema emerging after femoropopliteal revascularization has not been investigated.

CONCLUSION

The occurrence of lower limb edema is a well known problem since the introduction of the femoropopliteal bypass procedure in the late 1940's. Post-operative edema may extend the duration of in hospital stay and out of hospital care. The exact pathophysiology of edema remains unclear, but is likely to be multifactorial. These factors probably consist out of hyperemia, microvascular permeability, reperfusion associated inflammation, lymphatic disruption and venous disruption. Especially lymphatic disruption is likely to play a crucial role. However, no consensus appears to be reached on effective lymphatic sparing methods[10, 12]. Successful anti-oxidative treatment options were published. Both lymph drainage treatment techniques and the use of compression stockings are common. IPC strategies have been proven successful for edema treatment of other pathophysiology. When future treatment less invasive techniques like remote endarterectomy[73], percutaneous stenting and endovascular bypasses[74] proof to be successful and (cost)effective, postoperative edema might be minimized. Until then, careful lymphatic sparing dissection should be executed when performing a femoropopliteal bypass reconstruction. Post-operatively, the use of compression stockings and leg elevation are currently the golden standard.

REFERENCES

1. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997;26:517-38.
2. Jacobs MJ, Beckers RC, Jorning PJ, Slaaf DW, Reneman RS. Microcirculatory haemodynamics before and after vascular surgery in severe limb ischaemia--the relation to post-operative oedema formation. Eur J Vasc Surg 1990;4:525-9.
3. Eickhoff JH, Engell HC. Local regulation of blood flow and the occurrence of edema after arterial reconstruction of the lower limbs. Ann Surg 1982;195:474-8.
4. Hassan AA, Tooke JE. Mechanism of the postural vasoconstrictor response in the human foot. Clin Sci (Lond) 1988;75:379-87.
5. Balzer K, Schonebeck I. [Edema after vascular surgery interventions and its therapy]. Z Lymphol 1993;17:41-7.
6. Hamer JD. Investigation of oedema of the lower limb following successful femoropopliteal by-pass surgery: the role of phlebography in demonstrating venous thrombosis. Br J Surg 1972;59:979-82.
7. Herreros J, Serena A, Casillas JA, Arcas R, Llorens R, Richter JA. Study of venous and lymphatic components in the production of edema following femoropopliteal by-pass. A comparative scintigraphy and radiologic study. J Cardiovasc Surg (Torino) 1988;29:540-6.
8. Hannequin P, Clement C, Liehn JC, Ehrard P, Nicaise H, Valeyre J. Superficial and deep lymphoscintigraphic findings before and after femoro popliteal bypass. Eur J Nucl Med 1988;14:141-6.
9. Porter JM, Lindell TD, Lakin PC. Leg edema following femoropopliteal autogenous vein bypass. Arch Surg 1972;105:883-8.
10. AbuRahma AF, Woodruff BA, Lucente FC. Edema after femoropopliteal bypass surgery: lymphatic and venous theories of causation. J Vasc Surg 1990;11:461-7.
11. Campbell H, Harris PL. Albumin kinetics and oedema following reconstructive arterial surgery of the lower limb. J Cardiovasc Surg (Torino) 1985;26:110-5.
12. Haaverstad R, Johnsen H, Saether OD, Myhre HO. Lymph drainage and the development of post-reconstructive leg oedema is not influenced by the type of inguinal incision. A prospective randomised study in patients undergoing femoropopliteal bypass surgery. Eur J Vasc Endovasc Surg 1995;10:316-22.
13. Fernandez MJ, Davies WT, Tyler A, Owen GM. Post-arterial reconstruction edema, are lymphatic channels to blame? Angiology 1984;35:475-9.
14. Vaughan BF, Slavotinek AH, Jepson RP. Edema of the lower limb after vascular operations. Surg Gynecol Obstet 1970;131:282-90.
15. Haaverstad R, Nilsen G, Myhre HO, Saether OD, Rinck PA. The use of MRI in the investigation of leg oedema. Eur J Vasc Surg 1992;6:124-9.
16. Persson NH, Takolander R, Bergqvist D. Lower limb oedema after arterial reconstructive surgery. Influence of preoperative ischaemia, type of reconstruction and postoperative outcome. Acta Chir Scand 1989;155:259-66.
17. Henriksen O. Orthostatic changes of blood flow in subcutaneous tissue in patients with arterial insufficiency of the legs. Scand J Clin Lab Invest 1974;34:103-9.
18. Henriksen O. Local sympathetic reflex mechanism in regulation of blood flow in human subcutaneous adipose tissue. Acta Physiol Scand Suppl 1977;450:1-48.
19. Simeone FA, Husni EA. The hyperemia of reconstructive arterial surgery. Ann Surg 1959;150:575-85.
20. Sumner DS, Folse R. Persistent hyperemia following prolonged arterial occlusion. Ann Surg 1968;168:837-43.
21. Wellington JL, Olszewski V, Martin P. Hyperaemia of the calf after arterial reconstruction for atherosclerotic occlusion. A plethysmographic study. Br J Surg 1966;53:180-4.
22. Wright CB, Hobson RW. Hemodynamic effects of femoral venous occlusion in the subhuman primate. Surgery 1974;75:453-60.
23. Stallworth JM, Najib A, Kletke RR, Ramirez A. Phlegmasia cerulea dolens: an experimental study. Ann Surg 1967;165:860-8 passim.
24. Henriksen O. Effect of chronic sympathetic denervation upon local regulation of blood flow in human subcutaneous tissue. Acta Physiol Scand 1976;97:377-84.

25. Henriksen O. Local reflex in microcirculation in human subcutaneous tissue. Acta Physiol Scand 1976;97:447-56.
26. Henriksen O. Local nervous mechanism in regulation of blood flow in human subcutaneous tissue. Acta Physiol Scand 1976;97:385-91.
27. Gaskell P, Parrott JC. The effect of a mechanical venous pump on the circulation of the feet in the presence of arterial obstruction. Surg Gynecol Obstet 1978;146:583-92.
28. Payne SP, Jones K, Painter D, Galland RB, Collin J. Does the limb swell after revascularisation by percutaneous transluminal angioplasty? Eur J Vasc Endovasc Surg 1995;9:272-6.
29. Husni EA. The edema of arterial reconstruction. Circulation 1967;35:I169-73.
30. Eickhoff JH. Forefoot vasoconstrictor response to increased venous pressure in normal subjects and in arteriosclerotic patients. Acta Chir Scand Suppl 1980;502:7-14.
31. Junger M, Frey-Schnewlin G, Bollinger A. Microvascular flow distribution and transcapillary diffusion at the forefoot in patients with peripheral ischemia. Int J Microcirc Clin Exp 1989;8:3-24.
32. Soong CV, Young IS, Lightbody JH, Hood JM, Rowlands BJ, Trimble ER, et al. Reduction of free radical generation minimises lower limb swelling following femoropopliteal bypass surgery. Eur J Vasc Surg 1994;8:435-40.
33. Soong CV, Young IS, Blair PH, Hood JM, Rowlands BJ, Trimble ER, et al. Lipid peroxidation as a cause of lower limb swelling following femoro-popliteal bypass grafting. Eur J Vasc Surg 1993;7:540-5.
34. Gimbrone MA, Jr., Brock AF, Schafer AI. Leukotriene B4 stimulates polymorphonuclear leukocyte adhesion to cultured vascular endothelial cells. J Clin Invest 1984;74:1552-5.
35. Soong CV, Barros B'Sa AA. Lower limb oedema following distal arterial bypass grafting. Eur J Vasc Endovasc Surg 1998;16:465-71.
36. Rabl H, Khoschsorur G, Petek W. Antioxidative vitamin treatment: effect on lipid peroxidation and limb swelling after revascularization operations. World J Surg 1995;19:738-44.
37. Stewart G, Gaunt JI, Croft DN, Browse NL. Isotope lymphography: a new method of investigating the role of the lymphatics in chronic limb oedema. Br J Surg 1985;72:906-9.
38. Sty JR, Boedecker RA, Scanlon GT, Babbitt DP. Radionuclide "dermal backflow" in lymphatic obstruction. J Nucl Med 1979;20:905-6.
39. Pflug JJ, Calnan JS. The relationship between the blood, lymphatic and interstitial circulation in the leg. Vasa 1973;2:75-80.
40. Shishido H, Taketani H, Yoneda K, Nakajima K, Manabe H, Takeda Y. Lymphangiographic studies on swollen limbs. Med J Osaka Univ 1966;16:399-424.
41. Danese C, Howard JM, Bower R. Regeneration of lymphatic vessels: a radiographic study. Ann Surg 1962;156:61-7.
42. Urayama H, Misaki T, Watanabe Y, Bunko H. Saphenous neuralgia and limb edema after femoropopliteal artery by-pass. J Cardiovasc Surg (Torino) 1993;34:389-93.
43. Stranden E, Kramer K. Lymphatic and transcapillary forces in patients with edema following operation for lower limb atherosclerosis. Lymphology 1982;15:148-55.
44. Vaughan BF. CT of swollen legs. Clin Radiol 1990;41:24-30.
45. Stranden E, Enge I. Computed tomography in the investigation of leg edema following arterial reconstructions. Eur J Radiol 1982;2:113-6.
46. Seem E, Stranden E, Stiris MG. Computed tomography in deep venous thrombosis with limb oedema. Acta Radiol Diagn (Stockh) 1985;26:727-30.
47. Hadjis NS, Carr DH, Banks L, Pflug JJ. The role of CT in the diagnosis of primary lymphedema of the lower limb. AJR Am J Roentgenol 1985;144:361-4.
48. Olszewski WL, Engeset A, Lukasiewicz H. Immunoglobulins, complement and lysozyme in leg lymph of normal men. Scand J Clin Lab Invest 1977;37:669-74.
49. Szczesny G, Olszewski WL. The pathomechanism of posttraumatic edema of the lower limbs: II--Changes in the lymphatic system. J Trauma 2003;55:350-4.
50. Olszewski WL, Jamal S, Manokaran G, Pani S, Kumaraswami V, Kubicka U, et al. Bacteriologic studies of skin, tissue fluid, lymph, and lymph nodes in patients with filarial lymphedema. Am J Trop Med Hyg 1997;57:7-15.
51. Johnston MG, Elias R. The regulation of lymphatic pumping. Lymphology 1987;20:215-8.
52. Koller A, Mizuno R, Kaley G. Flow reduces the amplitude and increases the frequency of lymphatic vasomotion: role of endothelial prostanoids. Am J Physiol 1999;277:R1683-9.

53. Ho CK, Sun MP, Au TW, Chiu CS. Pneumatic pump reduces leg wound complications in cardiac patients. Asian Cardiovasc Thorac Ann 2006;14:452-7.
54. Storen EJ, Myhre HO, Stiris G. Lymphangiographic findings in patients with leg oedema after arterial reconstructions. Acta Chir Scand 1974;140:385-7.
55. Franzeck UK, Spiegel I, Fischer M, Bortzler C, Stahel HU, Bollinger A. Combined physical therapy for lymphedema evaluated by fluorescence microlymphography and lymph capillary pressure measurements. J Vasc Res 1997;34:306-11.
56. Schubart PJ, Porter JM. Leg Edema Following Bypass. In: Reoperative Arterial Surgery, Bergan JJ (ed). Grune & Stratton: Orlando, 1986; 328-9.
57. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;288:373-6.
58. Stranks GJ, MacKenzie NA, Grover ML, Fail T. The A-V Impulse System reduces deep-vein thrombosis and swelling after hemiarthroplasty for hip fracture. J Bone Joint Surg Br 1992;74:775-8.
59. Gardner AM, Fox RH, Lawrence C, Bunker TD, Ling RS, MacEachern AG. Reduction of post-traumatic swelling and compartment pressure by impulse compression of the foot. J Bone Joint Surg Br 1990;72:810-5.
60. Klein MJ, Alexander MA, Wright JM, Redmond CK, LeGasse AA. Treatment of adult lower extremity lymphedema with the Wright linear pump: statistical analysis of a clinical trial. Arch Phys Med Rehabil 1988;69:202-6.
61. Pflug JJ. Intermittent compression in the management of swollen legs in general practice. Practitioner 1975;215:69-76.
62. Coleridge Smith PD, Thomas P, Scurr JH, Dormandy JA. Causes of venous ulceration: a new hypothesis. Br Med J (Clin Res Ed) 1988;296:1726-7.
63. Eze AR, Comerota AJ, Cisek PL, Holland BS, Kerr RP, Veeramasuneni R, et al. Intermittent calf and foot compression increases lower extremity blood flow. Am J Surg 1996;172:130-4; discussion 5.
64. Morgan RH, Psaila JV, Stone J, Carolan G, Woodcock JP. Effect of postural change on common femoral artery volume flow, measured by duplex ultrasound, in normal subjects and patients with peripheral vascular disease. J Biomed Eng 1991;13:244-8.
65. Delis KT, Labropoulos N, Nicolaides AN, Glenville B, Stansby G. Effect of intermittent pneumatic foot compression on popliteal artery haemodynamics. Eur J Vasc Endovasc Surg 2000;19:270-7.
66. Delis KT, Husmann MJ, Szendro G, Peters NS, Wolfe JH, Mansfield AO. Haemodynamic effect of intermittent pneumatic compression of the leg after infrainguinal arterial bypass grafting. Br J Surg 2004;91:429-34.
67. Delis KT, Nicolaides AN, Labropoulos N, Stansby G. The acute effects of intermittent pneumatic foot versus calf versus simultaneous foot and calf compression on popliteal artery hemodynamics: a comparative study. J Vasc Surg 2000;32:284-92.
68. McGeown JG, McHale NG, Thornbury KD. Effects of varying patterns of external compression on lymph flow in the hindlimb of the anaesthetized sheep. J Physiol 1988;397:449-57.
69. Miranda F, Jr., Perez MC, Castiglioni ML, Juliano Y, Amorim JE, Nakano LC, et al. Effect of sequential intermittent pneumatic compression on both leg lymphedema volume and on lymph transport as semi-quantitatively evaluated by lymphoscintigraphy. Lymphology 2001;34:135-41.
70. Roztocil K, Prerovsky I, Oliva I. The effect of intermittent compression on blood and lymph flow rates in the lower limbs. Vasa 1979;8:346-8.
71. Blackshear WM, Jr., Prescott C, LePain F, Benoit S, Dickstein R, Seifert KB. Influence of sequential pneumatic compression on postoperative venous function. J Vasc Surg 1987;5:432-6.
72. Griffin M, Kakkos SK, Geroulakos G, Nicolaides AN. Comparison of three intermittent pneumatic compression systems in patients with varicose veins: a hemodynamic study. Int Angiol 2007;26:158-64.
73. Smeets L, Ho GH, Moll FL. Remote endarterectomy for occlusive iliac and superficial femoral artery disease. Future Cardiol 2007;3:43-51.
74. Landis GS, Faries PL. New techniques and developments to treat long infrainguinal arterial occlusions: use of reentry devices, subintimal angioplasty, and endografts. Perspect Vasc Surg Endovasc Ther 2007;19:285-90.

Chapter 3

Reliability and reproducibility of a clinical application of a simple technique for repeated circumferential leg measurements.

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ABSTRACT

Objectives

Aim of this study is to determine the reliability and reproducibility of repeated tape measurements to assess leg circumferences during a short and long period.

Methods

A tape measure is a simple instrument that is applicable in the presence of edema. Measurements were performed by four observers on eleven volunteers. Four measurements were done in the first week (short-term), a fifth measurement at two weeks (medium-term) and a sixth measurement was done at twelve weeks (long-term).

Results

The short, medium and long term intra-class correlation coefficients for repeated measurements were 0.90, 0.89 and 0.78 respectively. The short term and long term reproducibility indices equaled 4.4% and 6.5%. If only a single observer would be involved, the short-term intra-class correlation coefficients would improve to 0.94 (reproducibility index 3.3%).

Conclusion

Tape measurements have been proved to be a reliable and reproducible method to asses the lower limb circumference.

INTRODUCTION

Leg edema is often a major problem in patients suffering lymphatic or vascular disease. In vascular pathology, surgery due to peripheral arterial disease (PAD) or due to chronic venous disease of the leg (CVDL) contribute to the development of edema. Edema after vascular surgery in the leg occurs regularly and has negative effects on both the arterial and venous hemodynamics, as well as on the microcirculation[1, 2]. Currently there are various treatment options to reduce leg edema. To evaluate therapy effectiveness subsequent volume measurement techniques of the leg in patients are valuable.

Assessments of limb volume can be subdivided into three categories[3, 4]. They consist of indirect, direct and dynamic measurement methods. Most frequently used are the indirect methods based on leg circumference measurements. To estimate a limb volume based on an indirect methods, multiple measurements of the limb dimensions are required. Direct volume assessment methods are based on optoelectronic methods, CT- and MRI-scans and volume displacement. A third category is based on dynamic maneuvers or compression for a short period of time when using volume plethysmography. These three kinds of methods have all been validated for reproducibility, but are not interchangeable[5]. Besides high costs, direct and dynamic methods cause inconvenience to patients and are difficult to implement in a clinical situation.

Preferably, a simple and quick circumferential measurement method is required for patients who experience discomfort from edema following a vascular intervention. Such a method should be reliable and reproducible. Water displacement methods and other time-consuming and technologically complex methods are less appropriate due to wounds and relative immobilization. The procedure should be easily reproducible and hardly time-consuming. Studies based on repeated circumferential measurements in upper limbs, lower limbs and animal models have been published prior to our study[1, 6-8]. The aim of this study is to determine the reliability and the reproducibility of using a tape measure device to measure the circumference of the lower leg on anatomic landmarks with special attention to clinical application.

PATIENTS AND METHODS

In this experiment eleven healthy volunteers (7 males, 4 females) and four observers participated. The subjects were medical students in their fifth year and surgical residents. None of the observers acted as a subject or *vice versa*. The observers were surgical residents. They performed the lower leg measurements during six sessions. There were four sessions within the first week, one in the second week and finally one after twelve weeks (Table 1). All sessions were scheduled at the same time of day for each subject during the winter season.

Table 1. Measurement schedule

	Week 1	Week 2	Week 12
Measurement sessions	4	1	1
Observers	4	4	4
Subjects	11	11	11
Interval (all starting the first session)	Short-term	Medium-term	Long-term

A water-resistant circumferential marker line was applied to the subject's right lower legs at three levels at the beginning of the procedure. The first landmark was 10 cms medial below the knee joint, the second landmark was 10 cm above the medial malleolus and the third landmark in between the two lines mentioned. Leg circumference was determined by using a tape measure that was encircled around the lower leg under the marker lines without applying tension to the tape. During measurements the patient was in a supine position. There was no tension or friction between leg and bed. The circumference of each marker line was measured three times each session.

The subjects were measured in a randomized order each session. The four observers were given a clean form to fill in their measurements each time. They were not able to see their preceding measurements, nor were they able to see each other.

Statistical analysis

The 9 circumferences measured in each subject by each observer in each session were averaged after logarithmic transformation. The resulting maximum number of 264 data points (11 subjects * 4 observers * 6 sessions) was analyzed using mixed model ANOVA. A restricted maximum likelihood estimation method was used in this analysis which is able to correctly deal with missing observations. The dependent variable is the average logarithmically transformed circumference. As explanatory variables a number of random effects were specified in the ANOVA model so as to estimate the variance components of the measured circumference (log-transformed). In the analysis an adjustment was made for possible systematic changes in circumference over time by entering session as fixed factor in the model. In a first model the random factors were: subject (as inter-subject component), observer (as inter-observer component), session nested within subject (as intra-subject component) and a residual term (interpreted as intra-observer component).

The sum of these four components by definition represents the total variance of the circumference measurements after logarithmic transformation. By setting the total variance at 100%, variance components will be presented as percentages of total variance. The inter-subject component should be interpreted as the pure variance between the subjects under complete absence of all sources of measurement errors; its ratio to the total variance (including measurement error) is defined as the intra-class correlation coefficient. The intra-subject component is an error component arising merely from biological fluctuation within subjects across time. Measurements made by different observers on the same subject at the same time and repeated measurements made by the same observer on the same subject at the same time will generally not exactly coincide. Two other sources of error can be disentangled here: an inter-observer component and an intra-observer component.

The intra-subject variance component is further decomposed into a short-term component (4 observations in 1 week), an additional medium-term component (5 observations in 2 weeks) and an additional long-term component (6 observations in 12 weeks). For short-term inferences on the reliability, the medium- and long-term components remain hidden in the inter-subject component; for medium-term inferences only the long-term component remains hidden in the inter-subject component. Hence the long-term component and additionally the medium-term component shift from intra-subject to inter-subject in, respectively, medium-term and short-term inferences.

Results are presented by means of intra-class correlation coefficients (ICC) and percentage coefficients of variation (% CV). The ICC is a dimensionless number between 0 and 1 and is defined as the ratio of the inter-subject variance component to the total variance. It is a measure for the similarity of measurements within a subject. The % CV is also a dimensionless number and equals the the standard deviation as percentage of the mean level of the measurements on the untransformed scale. The natural logarithmic transformation of the measured circumferences before analysis allows the square root of a variance component estimated on the natural log scale to be directly interpretable (after multiplication by 100) as an approximate value of the % CV on the untransformed scale.

Reliability is presented as the intra-class correlation coefficient for measurements performed by four observers over repeated measurement sessions as an outcome of a mixed model ANOVA. Reproducibility will be presented as the maximum percentage of change in leg circumference within a subject that can be considered measurement error or biological fluctuation. Reproducibility is referred to as "limits of agreement"[7] when comparing two measurements. The reproducibility index can be calculated as:

$$\pm\ 100 * 1.96 * \sqrt{\{2 * (\text{total variance of the average on the log scale}) * (1 - ICC)\}}.$$

The reproducibility will be expressed as a percentage here in line with the log transformed measurement values used in the analysis. Percent changes outside these ranges can be considered real clinical changes within a single subject, as there is only a 5% chance that they are caused by measurement variability.

To estimate the systematic differences between observers, a second model was needed. In this model the inter-observer component was entered as a fixed factor along with session, rather than as a random factor. The remaining random factors were the same as in the first model. The inter-observer component vanishes in this model when there is only one observer implying the remaining components to be multiplied by:

$$100 / (100 - (\text{inter-observer component})),$$

in order to add up to 100% total variance.

RESULTS

The short-term, medium-term and long-term intra-class correlation coefficients equal 0.90, 0.89 and 0.78 respectively. The difference between short and medium-term intra-class correlation coefficients is not significant ($P = 0.32$). The difference between long and medium-term intra-class correlation coefficients is almost significant ($P = 0.053$). In Table 2 the results of the mixed model ANOVA after natural logarithmic transformation of the measurements are presented. The total variance of the average (after natural logarithmic transformation) of 9 circumference measurements equals 0.002491, which is the denominator of the variance component percentages. The reproducibility index equals ± 6.5% after 3 months (long-term) and ± 4.4% after maximally one week (short-term) within a subject.

Table 2. The intra-class correlation coefficient (ICC), components of total variance and coefficient of variation (% CV). Total variance of the average of the measurements on the log scale equals 0.002491.

Sources of variation	Components of total variance (%)	Coefficients of variation (% CV)
Inter-subject long-term (12 weeks)	78.2 (ICC = 0.78)	4.4
Inter-subject medium-term (2 weeks)	89.0 (ICC = 0.89)	4.7
Inter-subject short-term (1 week)	90.0 (ICC = 0.90)	4.7
Intra-subject long + medium + short-term	14.5	1.9
Intra-subject medium + short-term	3.8	1.0
Intra-subject short-term	2.8	0.8
Inter-observer	4.5	1.1
Intra-observer	2.7	0.8

The four different observers in this study account for 4.5% of the total variance (inter-observer component). The intra-observer component account for 2.7% of the total variance. Biological fluctuations (intra-subject component) account for 2.8% on a short term, for 3.8% on a medium term and for 14.5% on a long term. The fixed observer effect in the second model shows that observer 4 had the lowest scores, while observer 1 scored 1.6% higher, observer 2 scored 2.2% higher and observer 3 scored 2.3% higher than observer 4 ($P < 0.0001$). In this second model the inter-observer variance component no longer exists, making the total variance smaller (0.002379), while all other components remain exactly the same. The resulting inter-subject variance component accounts for 94.2% (ICC = 0.94) (short-term) and 81.9% (ICC = 0.82) (long-term). When one observer measures all subjects, the short-term reproducibility index becomes ± 3.3%.

The total number of available observations was limited to 172 due to 92 missing values. In Figure 1 a summary of the raw circumference measurements per session is presented.

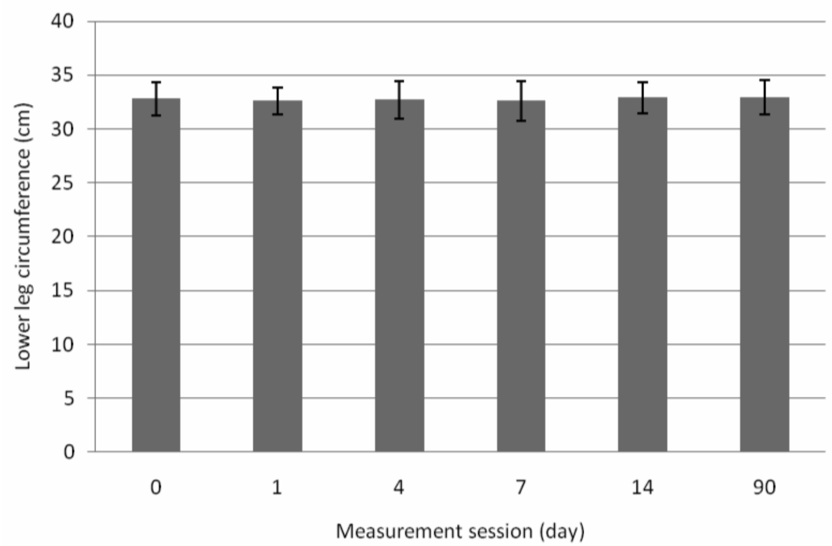

Figure 1. Summary of raw circumference data with standard deviation for the measurement sessions.

DISCUSSION

The use of repeated tape measurements for the assessment of leg edema can be considered a reliable and reproducible method. This especially applies to repeated measurements performed within a period of one week (short term). The intra-class correlation coefficient equals 0.90 and the reproducibility index equals ± 4.4%. Improvements in reliability can be obtained when repeated measurements are performed by a single observer or when an inter-observer component can be ruled out otherwise (e.g., by means of training and calibration sessions). This was illustrated in our experiment by observer 4, who possibly rounded observations more often to the next lower value or applied more tension to the limb than did the other observers. By annihilating the inter-observer component the short-term intra-class correlation coefficient becomes 0.94 (reproducibility index ± 3.3%), which is a good value for epidemiological research. Within-subject percent changes within these ranges are likely to be caused by biological fluctuation or measurement variability. By decomposing the between-session (nested within-subject) component under a constant total variance it was found that the reliability of repeated tape measurements decreased when the time interval between measurements increased. The explanation for this drop in reliability on the long term under a constant variance is the presence of long-term within-subject biological fluctuations that are indistinguishable from between-subject variability on the medium and short term. The assumption of a constant variance seems to be corroborated by the observed stable variances across sessions. Hence, there is also no conclusive evidence for the within-observer variance component to change (or increase) with time. It appeared from Table 2 that those hidden long-term fluctuations account for 11.7% of the total variance ((Intra-subject long + medium + short term) – (Intra-subject short term)). In literature reliability coefficients varying between 0.91 and 0.98 are mentioned for short-term repeated measurements[5, 9].

The choice of a natural logarithmic transformation of the circumference measurements before analysis was made for practical reasons: (I) On the log scale circumference measurements are linearly related to the section area and volume of a cylinder. (II) Changes in circumference can directly be interpreted as percent changes. (III) The square root of small variance components can approximately be interpreted as coefficients of variation on the untransformed scale of the measurements. This third reason actually expresses that by analyzing the data on the log scale, it is implicitly assumed that measurement error is proportional to measurement level on the untransformed scale. For interpretation of the precision of the circumference measurements it has to be taken into account that the measurement value, as it was used in the analysis, is an average of 9 measurements (three locations on the lower leg and triplicate measurements per location). This slightly enhanced the precision beforehand.

Several circumferential measuring methods have been documented such as the Leg-O-Meter by Bérard, edition I and II respectively[10-12]. This is a modified tape measure from which inter-observer reliability has been documented up to 98% and reliability of reproducibility is claimed to be as much as 96% for two subsequent measurement sessions with a short time interval. In contrast to our study the data have been collected over fewer measurement sessions in a short period and thus high intra-class correlations are plausible. Measurements were performed on standing subjects using a tape measure on a fixed platform at one level. These conditions may not be applicable to all patients who recently underwent surgery on a leg. Circumferential measurements performed at only one level may provide insufficient information on patients mentioned. Other tape measurements based on anatomic landmarks have been used on venectomized legs after either coronary artery bypass graft surgery or periphery artery bypass surgery, though no validation of the measurement method has been described[1, 8]. The methods used are very similar to the methods used in a study to evaluate intra-observer and inter-observer agreement using a tape measure based on three reference points[9]. Unfortunately the statistical method used was based on cut-off points rather than on continuous data, thus making it of little sense to compare the studies.

Labs and colleagues published reliability and reproducibility tests by comparing repeated spring tape measurements with volumetric techniques twice in 30 subjects with a short time interval by a single observer[5]. Results show that the spring tape and volumeter outcome are linearly in good agreement without proportional bias. Intra-class correlations for two subsequent measurements using the spring tape were up to 0.99 and 0.98 with coefficients of reproducibility equal to ± 5.1 mm and ± 4.8 mm. These are good values in contrast to our longer-term models, although we expressed the reproducibility as a percentage, being in line with our applied logarithmic transformation. An advantage of the spring tape to our standard tape could be that the spring tape applies a calibrated tension on the limb. In our research it is possible that different observers apply a different tension and therefore the intra-class correlations improve in a model having one observer. It is not possible to predict the reliability and reproducibility of the spring tape in case of more than one observer.

This investigation has been undertaken in preparation to evaluate the efficacy of different methods to treat leg edema in patients who undergo a vascular intervention. To offer a measurement method that is as "patient-friendly" as possible, a fast, reliable and reproducible method is preferable. Water displacement methods require a dependent leg. As patients who undergone a vascular intervention have wounds and often experience discomfort from leg edema, a water displacement method, which is often referred to as "the golden standard", is not suitable[13]. In order to have an uniform assessment method for all patient, method based on tape measures is preferred. In experiments by Pasley and colleagues, assessing day-to-day reliability in lower leg volume using water displacement, intra-class correlations of up to 0.97 and an intra-subject coefficient of variation of 0.7% have been found. In comparison, our study shows the tape measure to have a slightly lower intra-class correlation coefficient and a slightly higher intra-subject coefficient of variation. Our study extended over a period in which multiple measurements took place during the first week, during the second week and after three months, as compared to a five-day period in the study mentioned. As illustrated by an increased intra-subject coefficient of variation in our study on the long term, it is plausible that biological fluctuations do attribute to a decrease in reliability over long time intervals. Even though the findings are in line with studies claiming direct volume assessment methods to be more precise than indirect methods[4, 5, 13, 14], a high coefficient of reliability is claimed[9-12]. However, it is difficult to make comparisons with other studies claiming very high reliability coefficients because of an inconsistency in study design and the statistical methods used. Day-to-day reliability has been poorly documented, nor have data been published in which subjects were tested more than twice to determine reliability. In this study a method to estimate the reliability and reproducibility over a long term is described for the first time.

CONCLUSION

This is the first study to evaluate short-term and long-term reliability and reproducibility for leg circumference measurements using a tape measure. An intra-class correlation coefficient of up to 0.94 for repeated, short-term circumferential tape measurements, with a reproducibility index equal to ± 3.3% when measurements are performed by a single observer or when an inter-observer component can be ruled out otherwise, is a good value for epidemiological research. Based on these findings the use of a tape measure at specified anatomic reference points is a reliable and reproducible alternative for volume displacement methods.

REFERENCES

1. Balzer K, Schonebeck I. [Edema after vascular surgery interventions and its therapy]. Z Lymphol 1993;17:41-7.
2. Widmer L, Biland L, Barras JP. Doxium 500 in chronic venous insufficiency: a double-blind placebo controlled multicentre study. Int Angiol 1990;9:105-10.
3. Perrin M, Guex JJ. Edema and leg volume: methods of assessment. Angiology 2000;51:9-12.
4. Kaulesar Sukul DM, den Hoed PT, Johannes EJ, van Dolder R, Benda E. Direct and indirect methods for the quantification of leg volume: comparison between water displacement volumetry, the disk model method and the frustum sign model method, using the correlation coefficient and the limits of agreement. J Biomed Eng 1993;15:477-80.
5. Labs KH, Tschoepl M, Gamba G, Aschwanden M, Jaeger KA. The reliability of leg circumference assessment: a comparison of spring tape measurements and optoelectronic volumetry. Vasc Med 2000;5:69-74.
6. van der Laan L, Oyen WJ, Verhofstad AA, Tan EC, ter Laak HJ, Gabreels-Festen A, et al. Soft tissue repair capacity after oxygen-derived free radical-induced damage in one hindlimb of the rat. J Surg Res 1997;72:60-9.
7. Deltombe T, Jamart J, Recloux S, Legrand C, Vandenbroeck N, Theys S, et al. Reliability and limits of agreement of circumferential, water displacement, and optoelectronic volumetry in the measurement of upper limb lymphedema. Lymphology 2007;40:26-34.
8. Ho CK, Sun MP, Au TW, Chiu CS. Pneumatic pump reduces leg wound complications in cardiac patients. Asian Cardiovasc Thorac Ann 2006;14:452-7.
9. Tunc R, Caglayan-Tunc A, Kisakol G, Unler GK, Hidayetoglu T, Yazici H. Intraobserver and interobserver agreements of leg circumference measurements by tape measure based on 3 reference points. Angiology 2007;58:593-6.
10. Berard A, Kurz X, Zuccarelli F, Abenhaim L. Validity of the Leg-O-Meter, an instrument to measure leg circumference. Angiology 2002;53:21-8.
11. Berard A, Zuccarelli F. Test-retest reliability study of a new improved Leg-O-meter, the Leg-O-meter II, in patients suffering from venous insufficiency of the lower limbs. Angiology 2000;51:711-7.
12. Berard A, Kurz X, Zuccarelli F, Ducros JJ, Abenhaim L. Reliability study of the Leg-O-Meter, an improved tape measure device, in patients with chronic venous insufficiency of the leg. VEINES Group.(Venous Insufficiency Epidemiologic and Economic Study). Angiology 1998;49:169-73.
13. Pasley JD, O'Connor PJ. High day-to-day reliability in lower leg volume measured by water displacement. Eur J Appl Physiol 2008;103:393-8.
14. Tierney S, Aslam M, Rennie K, Grace P. Infrared optoelectronic volumetry, the ideal way to measure limb volume. Eur J Vasc Endovasc Surg 1996;12:412-7.

Chapter 4

A prospective randomized controlled trial to analyze the effects of intermittent pneumatic compression on edema following autologous femoropopliteal bypass surgery.

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ABSTRACT

Objective

Patients who undergo autologous femoropopliteal bypass surgery develop post-operative edema in the revascularized leg. In this study the effects of intermittent pneumatic compression (IPC) to treat and to prevent post-reconstructive edema were examined.

Methods

In a prospective randomized trial two patient groups were arranged. All patients suffered from peripheral arterial disease. In all these patients an autologous femoropopliteal bypass reconstruction was performed. Patients in group 1 used a compression stocking (CS) above the knee exerting 18 mmHg (Class I) on the leg post-operatively during one week day and night, patients in group 2 used IPC on the foot post-operatively at night during one week. The lower leg circumference was measured pre-operatively and at five post-operative time points. A multivariate analysis was done using a mixed model ANOVA.

Results

57 patients were analyzed (CS:28 / IPC:29). Indications for operation were severe claudication (CS:13 / IPC:13), rest pain (10 / 5) or tissue loss (7 / 11). Revascularization was performed with either a supragenicular (CS:13 / IPC:10) or an infragenicular (15 / 19) autologous bypass. Leg circumference increased on day 1 (CS:-0.4% / IPC:2.7%), day 4 (2.1% / 6.1%), day 7 (2.5% / 7.9%), day 14 (4.7% / 7.3%) and day 90 (1.0% / 3.3%) from baseline (pre-operative situation). On day 1, 4 and 7 there was a significant difference for leg circumference between treatment groups.

Conclusion

Edema following femoropopliteal bypass surgery occurs in all patients. For the prevention and treatment of edema the use of a class I CS proved superior over treatment with IPC. The use of CS remains the recommended practice following femoropopliteal bypass surgery.

INTRODUCTION

Patients experiencing disabling claudication, rest pain, or tissue loss might be treated with a femoropopliteal bypass. In general, an autologous bypass graft is preferred to an artificial graft[1]. Edema occurs post-operatively in most patients who are revascularized with a femoropopliteal bypass[2-6]. This edema causes discomfort to the patient and may delay rehabilitation and wound healing. Besides, edema is known to impair macrovascular and microvascular circulation[7]. The pathophysiology of post-reconstructive edema is thought to be a combination of hyperemia[8-11], increased capillary permeability[7, 12], lymphatic[3, 4, 13-16] and venous disruptions[4, 17]. Reperfusion of ischemic tissue leads to up regulation of inflammatory processes as well[18, 19]. Edema typically emerges in the first post-operative week and lasts up to three months, although cases of chronic edema are also reported[20]. Treatment of lower limb edema is mostly based on leg elevation, external compression with stockings[21] or lymph massage[13]. The use of external compression is mostly based on clinical experience, as prospective studies on the effect of compression stockings on post-operative edema are missing. The use of intermittent pneumatic compression (IPC) is an alternative concept in edema reduction following surgical procedures on a limb. IPC on the foot has been proven effective in edema reduction on the lower limb after orthopedic and trauma surgery[22, 23]. IPC is also known to increase arterial flow and pressure in the lower limb in patients suffering peripheral arterial disease (PAD)[24-26]. An effective treatment of post-operative edema might reduce inflammatory processes and improve wound healing. The aim of this trial is to compare the effect of IPC on leg edema and changes in inflammatory parameters with class I compression stocking (delivering 18 mmHg) above the knee following autologous femoropopliteal bypass surgery.

METHODS

Study design

Approval was granted by both a nationally recognized medical ethical review committee and the hospital's medical ethical review committee to perform a single center randomized controlled trial. Due to a lack of information about the magnitude of a differential treatment effect on lower limb circumference, a power analysis performed prior to the trial was based on a Cohen's *d* equal to 0.75, representing a medium to large treatment effect[27]. This effect should be detectable with 80% power in 30 patients eligible per group and a test size of 0.05 (2-sided). Using sealed envelopes, each patient was allocated to one of two groups according to randomly permuted blocks of size ten. Vascular assessment included an ankle-brachial pressure index (ABI), a walking test, a venous and arterial duplex ultrasound assessment and either a digital subtraction angiography (DSA) or a magnetic resonance angiography (MRA) scan. All patients gave their written informed consent.

Inclusion criteria

All patients suffered from peripheral vascular disease Rutherford category 3, 4, 5 and 6 on principal lower limb vessels or crural vessels as defined by the inter-society consensus for the management of peripheral arterial disease (TASC II)[28]. There was an unobstructed iliac inflow and there was sufficient outflow through at least one crural vessel based on arterial duplex, DSA and/or MRA findings gathered pre-operatively. In addition we tested the iliac inflow clinically prior to revascularization.

Exclusion criteria

Patients suffering from severe cardiac failure (NYHA class III and IV) were excluded due to hemodynamic effects of IPC that are not completely understood. Patients with known deep vein thrombosis or pulmonary embolism on admission were not included for the same reason. Patients who demanded hemodialysis due to severe renal impairment were excluded. So were patients who experienced pre-existing limb edema due to severe liver impairment (Child-Pugh score B and C), venous insufficiency, endocrinology diseases or who experienced manifest edema caused by medication. Patients with large ulcers (> 3cm^2) on the plantar aspect of the foot or who had undergone amputations that would compromise the fit of the IPC pad were excluded. A greater saphenous vein that was occluded, calcified or varicose, or had a minimal caliber less than 2.0 mm was considered unsuitable to be used as an autologous bypass graft[29, 30]. Further exclusion criteria were known malign diseases, enrolment in other trials and mental inability to understand the contents of the trial.

Surgical Procedure

Surgery was performed under general and/or spinal anesthesia. A deep-tunneled reversed or in-situ, supragenicular or infragenicular femoropopliteal bypass was constructed. A standardized medial incision was made in the groin at the site of the bifurcation of the femoral artery. The popliteal dissection was made above or below the knee. Smaller lymphatic structures were coagulated while larger lymphatic structures were ligated using Vicryl® (Ethicon Inc. Somerville, NJ, USA). The grafts were implanted end-to-side. A routine Doppler assessment was performed before closure of surgical wounds. Patients underwent systemic heparinazation (5000 IE) during the operation. Oral anticoagulant administration (acenocoumarol) was initiated for a two year period or resumed post-operatively[31].

Treatment groups

Group 1 patients received a compression stocking (BREVET tx, Mölnlycke, Göteborg, Sweden) post-operatively. The stocking delivers graduated pressure up to 18 mmHg (class I) on the lower and upper leg and features low-pressure areas on the heel and over the popliteal vein. During hospitalization the patients wore the stocking on the affected limb day and night. After discharge from hospital the patients continued using the stocking during the day until the eighth week after surgery. Group 2 patients received IPC (A-V impulse technology, Orthofix Vascular Novamedix, Andover, UK) on the affected limb during the night, 20:00 hrs till 08:00 hrs, seven days post-operatively in hospital. After discharge from hospital patients continued using a compression stocking (as mentioned for group 1) until the eighth week after surgery during the day.

IPC

The A-V impulse technology is an IPC device. It works by intermittently pumping compressed air into a pad that fits the foot. The pad flattens the plantar arch of the foot on inflation, thereby deflating the venous plexus. The pad is inflated in 0.4 seconds in which a pressure is built up to 130 mmHg. Deflation occurs through perforations in the pad. A cycle of 20 seconds allows for efficient priming of the venous pump[22, 23]. A sudden inflation impulse reproduces a physiological ratchet-like flow pattern of venous return.

Measurements

Lower limb circumference measurements were performed at six different time points: the day prior to surgery, one day, four days, seven days, two weeks and three months after surgery. Three circumferential marker lines that were applied pre-operatively were assessed by using a tape measure[32]. The first marker line was 10 cm medial below the knee joint, the second marker line was 10 cm above the medial malleolus and the third marker line in between the two lines mentioned. At each time point each marker line was measured three times and the wound condition was assessed. Administration of antibiotics and diuretics were registered. Leukocyte counts and C-reactive protein (CRP) concentration measurements were performed at four time points: the day prior to surgery and one day, seven days and two weeks after surgery. Patients were hospitalized during the first week after surgery. At day four and at three months an ABI was repeated. At three months a duplex ultrasound assessment was repeated as well.

Intention-to-treat

This study was carried out on an "intention-to-treat" basis. Patients were encouraged to carefully mobilize from the first day post-operative if possible. No restrictions were laid down on early rehabilitation schedules. Group 1 patients who used the compression stocking mobilized while wearing their stocking. Group 2 patients only used IPC at night as they were not able to mobilize when the device was active. Patients who did not tolerate or experienced discomfort from the IPC device were offered a compression stocking and *vice versa*. Patients experiencing post-operative complications were treated according to common medical insights. Occurring complications did not result into exclusion from analysis unless they were lost to follow up in the first two post-operative weeks. A duplex ultrasound assessment was performed if there was suspicion for in-graft stenosis or obstruction. Original grouping was maintained in the data analysis.

Statistical Analysis

Statistical analysis was performed with SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). The nine circumferences measured at each time point in each patient were averaged after logarithmic transformation. The choice of a natural logarithmic transformation of the circumference measurements before analysis was made for a practical reason: a change or difference on the log scale can be back-transformed to a percentage as a common effect measure in this field. Leukocyte counts and CRP concentrations were logarithmically transformed as well because of the positive skewness of their distribution. The data were analyzed using a mixed model ANOVA. A restricted maximum likelihood method was used for estimating the various effects. This method is known to be able to correctly deal with missing observations. The dependent variable is the average logarithmically transformed circumference as just defined. The following independent variables were entered in the model: a between-subject factor group (2 levels), a within-subject factor measurement beyond baseline (five levels: days 1, 4, 7, 14 and 90), the group-by-measurement interaction factor and the baseline value of the average logarithmically transformed circumference as a continuous between-subjects covariate. The following effects were tested and estimated with their 95% confidence intervals: the difference in circumference between the two groups at each time point beyond baseline, an overall test (across all five measurements simultaneously) of this difference and the within-subject changes from baseline per time point in either group. These effects were back-transformed by exponentiation so as to obtain percent differences and changes in circumference with their 95% confidence limits. In the analysis no structure was imposed on the (co)variances of the five repeated measurements.

Similar analyses were done per level (10 cm below the knee, 10 cm above the malleolus and in between) and for CRP and leukocyte counts, where the dependent variable was the averaged logarithmically transformed circumference.

To test the contribution of the position of the distal anastomisis (supragenicular/infragenicular) to the explanation of the outcome variable considered, we compared the original statistical model (as described above) with an extended model containing all additional effects of the position of the distal anastomisis (main effects and treatment-interactions) by means of the likelihood ratio test.

Categorical variables were compared between two groups using Fisher's exact test. A value of $P < 0.05$ denotes statistical significance.

RESULTS

Between 2006 and 2009 a total of sixty-two autologous femoropopliteal bypass reconstructions using the ipsilateral saphenous vein were performed. Thirty-one patients were randomized to each arm: group 1 patients used the compression stocking, group 2 patients used IPC. Fifty-seven patients were analyzed in this trial (Figure 1). Five patients were excluded. Three of

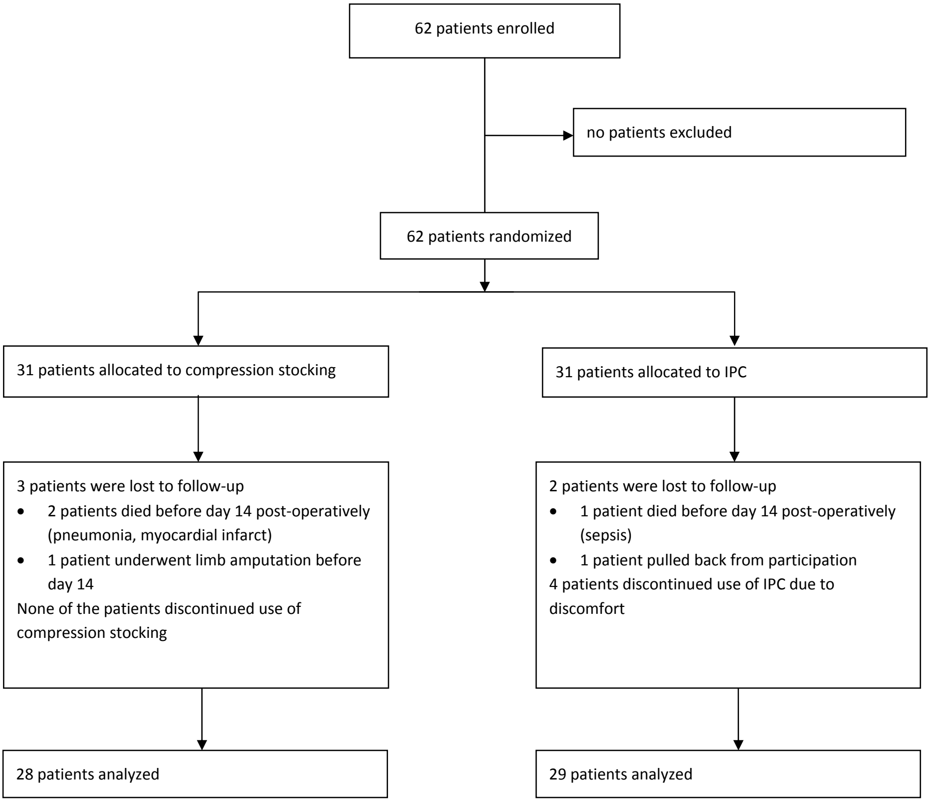

Figure 1. Trial profile

them died before the 14th day after the operation (pneumonia (compression stocking group), myocardial infarct (compression stocking group), sepsis (IPC group), one patient underwent an amputation before the 14th day after surgery (compression stocking group) and one patient pulled back from participation in the trail (IPC group). The resulting maximum number of data points is 1026. Of them 15 data points are missing (1.46%). Baseline characteristics and surgical characteristics are given in Table 1 and Table 2 respectively. The randomized groups appear to be in balance for baseline characteristics as judged by the uniform distribution of *P*-values over the interval (0-1).

Leg circumference

After surgery an increase of the leg circumference was measured in both groups. The increase in leg circumference in the IPC group was significantly larger than in the compression stocking group as illustrated in Figure 2. At day 1, day 4 and day 7 the differences between the treatment groups were significant. At day 14 and day 90 there were no significant differences between the groups. Table 3 shows the original leg circumferences and the magnitude of increase in both treatment groups. All effects indicate a larger rate of increase in circumference in the IPC group

Table 1. Baseline characteristics.

Variable	Compression stocking	IPC
N	28	29
Age, mean (range)	69 (57-84)	67 (39-88)
Sex, male/female	23/5	22/7
Rutherford stage 3/4/5-6	11/10/7	13/5/11
ABI, mean (SD)	0.49 (0.14)	0.45 (0.21)
ABP, mean (SD)	150 (21)	148 (24)
Risk factors		
Diabetes	10	15
Serum cholesterol (mmol/L)	4.9 (1.3)	5.0 (1.3)
Positive family history for cardiovascular disease	13	12
Smoking, current or recent	13	16

Table 2. Bypass graft characteristics.

Reconstruction characteristics	Compression stocking	IPC	*P*-value
Distal anastomosis			0.42
Supragenicular	13	10	
Infragenicular	15	19	
Graft			0.19
In-situ	4	1	
Reversed deep tunneled	24	28	

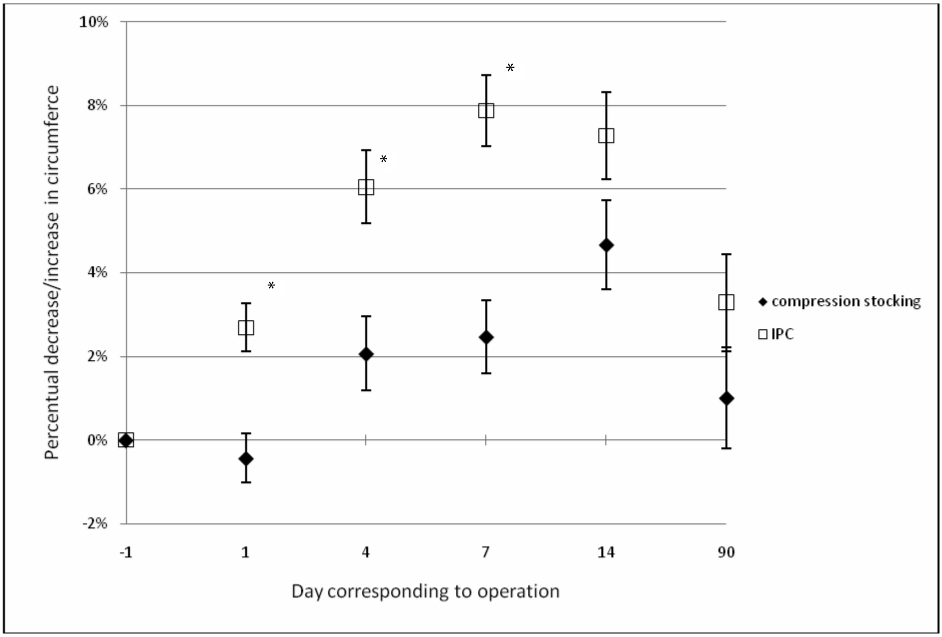

Figure 2. Percent increase of averaged lower limb circumference with standard error markers. Differences between groups are significant on day 1, day 4 and day 7 post-operatively.
* Denotes significant differences between groups

Table 3. Raw summary of absolute circumferences (cm) per session.

Day	Group	Mean	N	SD
-1	Compression stocking	29.5	28	2.9
	IPC	31.1	29	3.7
1	Compression stocking	29.4	28	2.9
	IPC	31.9	29	3.6
4	Compression stocking	30.1	28	2.8
	IPC	32.9	29	3.7
7	Compression stocking	30.5	27	3.0
	IPC	33.4	29	3.7
14	Compression stocking	30.9	28	3.3
	IPC	33.3	29	3.8
90	Compression stocking	30.3	25	3.3
	IPC	31.9	27	3.8

Table 4. Baseline adjusted mean percent differences in circumference between groups averaged over 3 levels and per height as estimated by mixed model ANOVA. A positive percentage means a larger increase in leg circumference in the IPC group compared to the compression stocking group.

Day	Mean of 3 heights (%) (95% CI)	10 cm above malleolus (%)	middle (%)	10 cm below knee (%)
1	3.1 [a] (1.4 to 4.9)	1.7	4.0 [a]	4.4 [a]
4	3.9 [a] (1.4 to 6.5)	3.5 [a]	4.3 [a]	4.6 [a]
7	5.3 [a] (2.8 to 7.9)	5.5 [a]	6.6 [a]	4.3 [a]
14	2.5 (-0.5 to 5.6)	1.7	4.0 [a]	2.3
90	2.3 (-1.1 to 5.7)	0.5	3.8	2.3
Overall *P*-value	0.0006	0.0074	0.0003	0.0175

[a] $P < .05$

compared to the compression stocking group. Percent differences in circumference between groups (at each level) are presented in Table 4. At each level there was an overall (across all measurements) significant difference between the treatment groups. At day 1 and day 4 this was particularly so at the highest level measured (10 cm below the knee joint). The position of the distal anastomisis made no significant explanatory contribution to the amount of edema ($P = 0.82$). Four patients did not tolerate the IPC device. These patients were further treated with the compression stockings. All patients tolerated the compression stockings.

Laboratory results

In both groups leukocyte counts and CRP concentrations were increased compared to the pre-operative levels at all time points, except for the leukocyte counts on day 7 in group 1. Changes in leukocyte counts and CRP concentration are plotted in Figure 3 and Figure 4. Differences in leukocyte count and CRP concentration between the treatment groups were not significant in the overall model. The increase in the CRP concentration was significant in both treatment groups post-operatively on all days. There were no significant correlations between circumferential measurements and leukocyte counts or CRP concentrations at any moment. The position of the distal anastomisis made no significant explanatory contribution ($P = 0.89$) to the increase in the CRP concentration. However, the position of the distal anastomisis showed a significant contribution ($P = 0.0008$) to the leukocyte counts. At day 1 post-operatively patients who used IPC had 29% higher ($P = 0.004$) leukocyte counts than patients who used a compression stocking following supragenicular bypass surgery. However, following infragenicular bypass surgery we found a nearly significant ($P = 0.080$) reverse difference at day 1: patients who used IPC had an 11% lower leukocyte counts than patients who used a compression stocking.

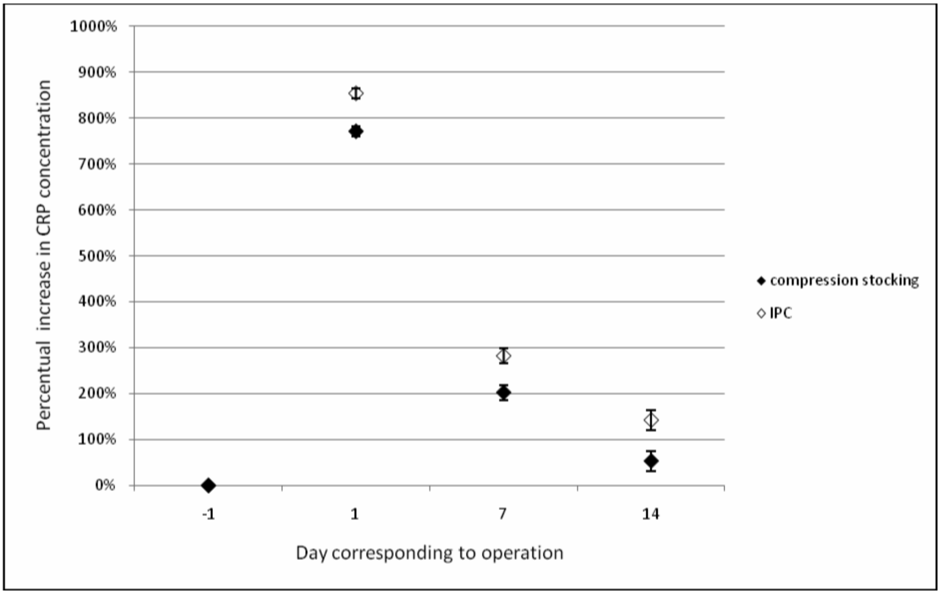

Figure 3. Percent increase in CRP concentration with standard error markers

Complications

Post-operative course and characteristics are listed in Table 5. There were no significant differences in the occurrence of complications between the groups. Wound infections occurred in eight patients (two patients in the compression stocking group, six patients in the IPC group) and were treated with antibiotic therapy.

DISCUSSION

Post-operative edema has been observed and quantified after revascularization surgery using an autologous femoropopliteal bypass in this randomized controlled trial. The patients who used IPC have developed significantly more edema than the patients that have used the compression stockings. The null hypothesis that there is no difference between treatment groups

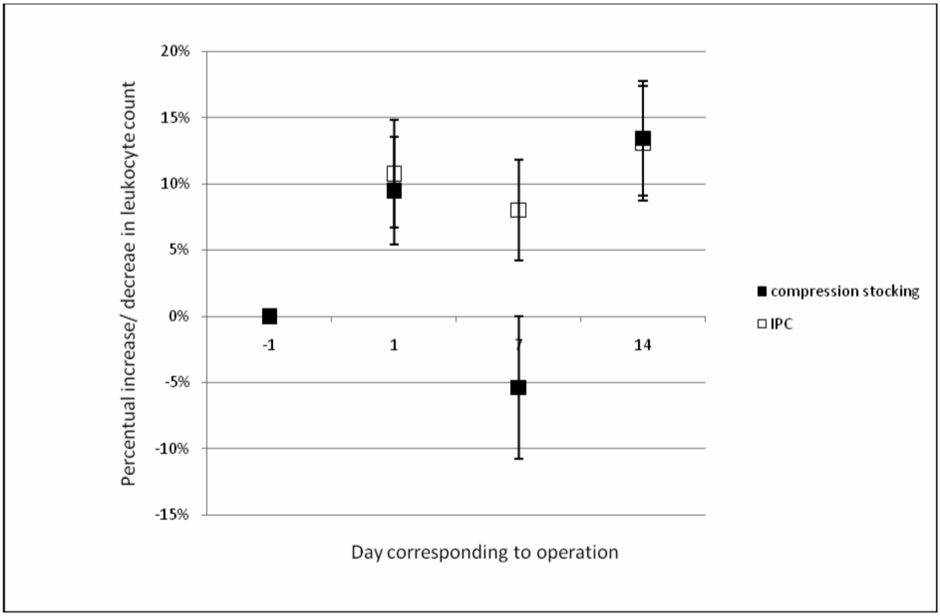

Figure 4. Percent increase in leukocyte concentration with standard error markers.

Table 5. Post-operative course and complications.

Event / post-operative course	Compression stocking	IPC	*P*-value
Wound infection	2	6	.25
Infection (other than wound)	1	1	1.00
Hematoma	3	4	1.00
Seroma	0	2	.49
Occlusion	2	2	1.00
Myocardial infarct	1	0	.49
Treatment device switch	0	4	.12
Hospital stay (range)	7.9 (6–19)	9.7 (7–34)	.16
Diuretic use	10	6	.25

across all measurements could be significantly rejected. The position of the distal anastomisis did not affect the amount of post-operative edema. In none of previously performed studies the use of an IPC device has been compared to a compression stocking. The difference in developed edema between the groups vanishes within a week after the use of IPC was discontinued. Starting day 8 post-operatively, all patients used a compression stocking during the day. The occurrence of post-operative edema in all revascularized patients with a femoropopliteal bypass is in accordance with findings in literature[2-6].

In addition, we observed increases in leukocyte counts and CRP concentrations following femoropopliteal surgery. No significant differences in the occurrence of wound infections and in CRP concentrations between treatment groups were detected. Patient who used IPC following a supragenicular femoropopliteal bypass had higher leukocyte counts immediately after the operation than patients who used a compression stocking.

Soong *et al.*[18] and Rabl *et al.*[19] hypothesized that reperfusion of ischemic tissue could lead to cell damage and results in up regulating of inflammatory processes and edema formation. The presence of edema as a contributing factor to increases in inflammatory parameters could not be proved. Significantly higher leukocyte counts in the IPC group were only found at day 1 post-operatively following a supragenicular bypass operation, whereas significantly more edema formation was seen in the IPC group as a whole and at most post-operative time points. These analyses concerning the explanatory contribution of the position of the distal anastomosis to the model were not pre-specified as hypotheses in the protocol. Formally then, these analyses are of an explorative nature. The inconclusive significant results concerning leukocyte count have to be considered as hypothesis-generating rather than as hypothesis-testing.

The difference in leukocyte counts and CRP concentrations might be associated with wound infections, although a firm correlation was not found. A significant difference in the occurrence of wound infections between groups could not be detected either. However, there seems to be a trend of more wound infections and a prolonged hospital stay in patients who had a larger amount of edema: patients who used IPC. Based on this study, it is too far going to associate the amount of edema to increases in inflammatory parameters or wound infections.

Edema following femoropopliteal surgery is likely to be multi-factorial, with a large attribution of lymphatic disruptions[3, 4], hyperemia[10, 33] and microvascular permeability[12, 18, 34]. The lymphatics can be damaged as a result of surgery, or can be impaired in function due to inflammatory processes or adjacent tissue trauma[6]. Edema following arterial reconstructions due to popliteal aneurysms is surprisingly of the same magnitude as edema following revascularizations for PAD, suggesting a large contribution of lymphatic disruptions in the pathophysiology[6]. Studies on the effect of lymph sparing approaches during femoropopliteal surgery are not conclusive[4, 6]. Dysfunctional autoregulation mechanisms are also likely to contribute to hyperemia[8, 10]. Autoregulation mechanisms do maintain a constant perfusion pressure in the limbs, although this mechanism fails in severe PAD. An increase in arterio-venous pressure gradient may cause an increase in microvascular permeability for fluids and proteins[5, 9], and inflammatory responses following revascularization, resulting in edema[10, 34]. However, the attribution of hyperemia is probably limited, as illustrated by the occurrence of only a small increase in limb volume following percutaneous revascularizations, since no lymphatics get damaged then[35].

We used a graduated (class I) compression stocking, exerting 18 mmHg pressure to the limb. There have been no large, quality studies on the effects of compression stocking for the treatment and prevention of post-reconstructive edema are lacking. We selected a class I stocking, since class II stockings and above might exert too much pressure on the leg, possibly resulting in even more patient discomfort or graft failure. The working mechanism of the compression stocking is to increase pressure on the interstitial space[21] and to augment the peripheral circulation by lowering the flow resistance at the arteriolar level[36].

IPC devices do facilitate lymphatic and hemodynamic circulation in the lower limb. Of them, the A-V impulse technique has been tested successfully for edema reduction following orthopedic surgery on the lower limb[22, 23]. It is thought that when the IPC is active, compression of the foot is followed by emptying of terminal lymphatics, allowing drainage of fluids from the interstitium. It possibly also assists in moving fluids from the interstitium to the lymphatics[37].

As mentioned, the A-V impulse system is an IPC on the foot only. This might be a shortcoming of the study because there are also IPC system that fit the calf. However, we chose an IPC on the foot because of the satisfying results following orthopedic and trauma surgery[22, 23]. Another reason that we have chosen IPC on the foot is avoidance of surgical wounds on the calf from being compressed intermittently. Surgical wounds on the calf were made in some patients when the superficial saphenous vein was (partly) harvested in the lower leg. IPC is also thought to attribute to arterial[25, 38] and venous blood flow[39, 40]. For patients suffering PAD and in healthy subjects IPC combined on the foot and calf can double the arterial flow into the limb immediately after compression. This effect has been demonstrated in native arterial blood flow, as well as in infragenicular femoropopliteal bypass grafts[38]. Venous flow velocity in the common femoral vein increases during compression by a factor of 2.5 to 3, which indicates that venous emptying is facilitated[39, 40]. In immobilized patients the venous muscle pump function is not maintained and blood is no longer cleared from the veins, which results in venous hypertension. The use of IPC might prevent fluids to move out of the capillaries[41].

In this trial we chose to apply the IPC on the foot in a controlled situation, when the patient was hospitalized. We decided not to introduce the system in an uncontrolled out of hospital situation since edema emerges mostly in the first post-operative week[20] and knowledge of the effect of IPC on freshly revascularized patients was lacking. The results however, do not encourage to investigate the effect of IPC on the foot only over a longer period.

The use of IPC on the foot resulted in significantly more edema compared to the use of compression stockings following femoropopliteal bypass surgery. This was contrary to what could be expected based on the orthopedic and trauma findings[22, 23]. However, in these studies IPC was applied day and night. We choose to only apply IPC at night, so not to interfere with early rehabilitation schedules. Using IPC immediately post-operatively has probably resulted in an amplification of the hyperemic effect. This hyperemic effect probably outweighed the enhancements in venous and lymphatic flow. This hyperemic effect was probably limited in the patients who used the compression stockings, as less edema developed in them. Patients who used IPC at night, did not use compression stockings during the day. The absence of these stockings or IPC on the calf might also have contributed to increased edema. It cannot be ruled out that the application of IPC on the foot and the calf might result in another outcome.

CONCLUSION

In this study the development of post-operative edema following autologous femoropopliteal bypass surgery has been quantified on subsequent time points up to three months of follow up. The use of compression stockings has been the standard practice post-operatively. A study on the effect of IPC, which was expected to have a beneficial effect on edema, has resulted in the conclusion that it leads to a short-term increase in edema. However, the amount of edema decreases to the same extent when using a compression stocking after the use of IPC is halted. The use of compression stockings following femoropopliteal surgery remains the recommended practice.

REFERENCES

1. Veith FJ, Gupta SK, Ascer E, White-Flores S, Samson RH, Scher LA, et al. Six-year prospective multicenter randomized comparison of autologous saphenous vein and expanded polytetrafluoroethylene grafts in infrainguinal arterial reconstructions. *J Vasc Surg* 1986;3:104-14.
2. Eickhoff JH, Engell HC. Local regulation of blood flow and the occurrence of edema after arterial reconstruction of the lower limbs. *Ann Surg* 1982;195:474-8.
3. Hannequin P, Clement C, Liehn JC, Ehrard P, Nicaise H, Valeyre J. Superficial and deep lymphoscintigraphic findings before and after femoro popliteal bypass. *Eur J Nucl Med* 1988;14:141-6.
4. AbuRahma AF, Woodruff BA, Lucente FC. Edema after femoropopliteal bypass surgery: lymphatic and venous theories of causation. *J Vasc Surg* 1990;11:461-7.
5. Campbell H, Harris PL. Albumin kinetics and oedema following reconstructive arterial surgery of the lower limb. *J Cardiovasc Surg (Torino)* 1985;26:110-5.
6. Haaverstad R, Johnsen H, Saether OD, Myhre HO. Lymph drainage and the development of post-reconstructive leg oedema is not influenced by the type of inguinal incision. A prospective randomised study in patients undergoing femoropopliteal bypass surgery. *Eur J Vasc Endovasc Surg* 1995;10:316-22.
7. Jacobs MJ, Beckers RC, Jorning PJ, Slaaf DW, Reneman RS. Microcirculatory haemodynamics before and after vascular surgery in severe limb ischaemia--the relation to post-operative oedema formation. *Eur J Vasc Surg* 1990;4:525-9.
8. Henriksen O. Orthostatic changes of blood flow in subcutaneous tissue in patients with arterial insufficiency of the legs. *Scand J Clin Lab Invest* 1974;34:103-9.
9. Eickhoff JH. Forefoot vasoconstrictor response to increased venous pressure in normal subjects and in arteriosclerotic patients. *Acta Chir Scand Suppl* 1980;502:7-14.
10. Sumner DS, Folse R. Persistent hyperemia following prolonged arterial occlusion. *Ann Surg* 1968;168:837-43.
11. Henriksen O, Paaske WP. Local regulation of blood flow in peripheral tissue. *Acta Chir Scand Suppl* 1980;502:63-74.
12. Junger M, Frey-Schnewlin G, Bollinger A. Microvascular flow distribution and transcapillary diffusion at the forefoot in patients with peripheral ischemia. *Int J Microcirc Clin Exp* 1989;8:3-24.
13. Balzer K, Schonebeck I.Edema after vascular surgery interventions and its therapy. *Z Lymphol* 1993;17:41-7.
14. Storen EJ, Myhre HO, Stiris G. Lymphangiographic findings in patients with leg oedema after arterial reconstructions. *Acta Chir Scand* 1974;140:385-7.
15. Vaughan BF. CT of swollen legs. *Clin Radiol* 1990;41:24-30.
16. Fernandez MJ, Davies WT, Tyler A, Owen GM. Post-arterial reconstruction edema, are lymphatic channels to blame? *Angiology* 1984;35:475-9.
17. Sullivan WG, Thornton FH, Baker LH, LaPlante ES, Cohen A. Early influence of popliteal vein repair in the treatment of popliteal vessel injuries. *Am J Surg* 1971;122:528-31.
18. Soong CV, Young IS, Lightbody JH, Hood JM, Rowlands BJ, Trimble ER, et al. Reduction of free radical generation minimises lower limb swelling following femoropopliteal bypass surgery. *Eur J Vasc Surg* 1994;8:435-40.
19. Rabl H, Khoschsorur G, Petek W. Antioxidative vitamin treatment: effect on lipid peroxidation and limb swelling after revascularization operations. *World J Surg* 1995;19:738-44.
20. Vaughan BF, Slavotinek AH, Jepson RP. Edema of the lower limb after vascular operations. *Surg Gynecol Obstet* 1970;131:282-90.
21. Pflug JJ, Calnan JS. The relationship between the blood, lymphatic and interstitial circulation in the leg. *Vasa* 1973;2:75-80.
22. Stranks GJ, MacKenzie NA, Grover ML, Fail T. The A-V Impulse System reduces deep-vein thrombosis and swelling after hemiarthroplasty for hip fracture. *J Bone Joint Surg Br* 1992;74:775-8.
23. Gardner AM, Fox RH, Lawrence C, Bunker TD, Ling RS, MacEachern AG. Reduction of post-traumatic swelling and compartment pressure by impulse compression of the foot. *J Bone Joint Surg Br* 1990;72:810-5.

24. Delis KT, Nicolaides AN, Wolfe JH, Stansby G. Improving walking ability and ankle brachial pressure indices in symptomatic peripheral vascular disease with intermittent pneumatic foot compression: a prospective controlled study with one-year follow-up. *J Vasc Surg* 2000;31:650-61.
25. Eze AR, Comerota AJ, Cisek PL, Holland BS, Kerr RP, Veeramasuneni R, et al. Intermittent calf and foot compression increases lower extremity blood flow. *Am J Surg* 1996;172:130-4; discussion 5.
26. van Bemmelen PS, Mattos MA, Faught WE, Mansour MA, Barkmeier LD, Hodgson KJ, et al. Augmentation of blood flow in limbs with occlusive arterial disease by intermittent calf compression. *J Vasc Surg* 1994;19:1052-8.
27. Cohen J. *Statistical Power Analysis for the Bahavioral Sciences* (2nd edn). Lawrence Erlbaum Associates: Hillsdale, 1988.
28. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg* 2007;33 Suppl 1:S1-75.
29. Schanzer A, Hevelone N, Owens CD, Belkin M, Bandyk DF, Clowes AW, et al. Technical factors affecting autogenous vein graft failure: observations from a large multicenter trial. *J Vasc Surg* 2007;46:1180-90; discussion 90.
30. Panetta TF, Marin ML, Veith FJ, Goldsmith J, Gordon RE, Jones AM, et al. Unsuspected preexisting saphenous vein disease: an unrecognized cause of vein bypass failure. *J Vasc Surg* 1992;15:102-10; discussion 10-2.
31. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. *Lancet* 2000;355:346-51.
32. te Slaa A, Mulder P, Dolmans D, Castenmiller P, Ho G, van der Laan L. Reliability and reproducibility of a clinical application of a simple technique for repeated circumferential leg measurements. *Phlebolgy* 2010;Electronic publication ahead of press.
33. Simeone FA, Husni EA. The hyperemia of reconstructive arterial surgery. *Ann Surg* 1959;150:575-85.
34. Husni EA. The edema of arterial reconstruction. *Circulation* 1967;35:I169-73.
35. Payne SP, Jones K, Painter D, Galland RB, Collin J. Does the limb swell after revascularisation by percutaneous transluminal angioplasty? *Eur J Vasc Endovasc Surg* 1995;9:272-6.
36. Schubart PJ, Porter JM. Leg Edema Following Bypass. In: *Reoperative Arterial Surgery*, Bergan JJ (ed). Grune & Stratton: Orlando, 1986; 328-9.
37. McGeown JG, McHale NG, Thornbury KD. Effects of varying patterns of external compression on lymph flow in the hindlimb of the anaesthetized sheep. *J Physiol* 1988;397:449-57.
38. Delis KT, Husmann MJ, Szendro G, Peters NS, Wolfe JH, Mansfield AO. Haemodynamic effect of intermittent pneumatic compression of the leg after infrainguinal arterial bypass grafting. *Br J Surg* 2004;91:429-34.
39. Blackshear WM, Jr., Prescott C, LePain F, Benoit S, Dickstein R, Seifert KB. Influence of sequential pneumatic compression on postoperative venous function. *J Vasc Surg* 1987;5:432-6.
40. Griffin M, Kakkos SK, Geroulakos G, Nicolaides AN. Comparison of three intermittent pneumatic compression systems in patients with varicose veins: a hemodynamic study. *Int Angiol* 2007;26:158-64.
41. Coleridge Smith PD, Thomas P, Scurr JH, Dormandy JA. Causes of venous ulceration: a new hypothesis. *Br Med J (Clin Res Ed)* 1988;296:1726-7.

Chapter 5

Evaluation of A-V impulse technology as a treatment for edema following polytetrafluoroethylene femoropopliteal surgery in a randomized controlled trial.

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ABSTRACT

Objective

To investigate the efficacy of A-V impulse technology (A-V) for edema prevention and treatment following PTFE femoropopliteal surgery.

Design

Prospective randomized clinical trial.

Materials

36 patients undergoing PTFE femoropopliteal bypass reconstructions, either being treated postoperatively with a compression stocking (CS) (Group 1, N = 19) or with A-V (Group 2, N = 17).

Methods

Patients in treatment group 1 used a CS post-operatively during one week day and night, patients in group 2 were treated with A-V post-operatively at night during one week. The lower leg circumference was measured pre-operatively and at five post-operative time points.

Results

Limb circumference has increased post-operatively on day 1 (CS:1.5% / A-V:1.4%), on day 4 (5.7% / 6.3%), on day 7 (6.6% / 6.1%), on day 14 (7.9% / 7.7%) and on day 90 (5.8% / 5.2%). Differences between treatment groups were not significant. A re-operation gives a significant 3.9% increase in circumference as compared to a first operation (95% CI: 1.5% – 6.4%; $P = 0.002$).

Conclusion

No significant differences were found in the extent of developed edema between the groups following PTFE femoropopliteal bypass surgery. A redo peripheral bypass operation results in significantly more post-operative edema than a first time performed bypass operation.

INTRODUCTION

In selected patients suffering from severe peripheral arterial disease (PAD) an artificial femoropopliteal bypass might be constructed. An artificial graft is indicated when a patient does not have a suitable vein to be used as graft[1]. The material used for an artificial graft can be polyethyleneterephthalate (Dacron®) or polytetrafluoroethylene (PTFE). There is no evidence of superiority of one material over the other[2]. Post-operative edema occurs in a majority of patients who are treated with a femoropopliteal bypass[3-9]. Following successful revascularizations, patients do regularly report discomfort from post-operative edema. Post-operative edema might delay rehabilitation and prolong hospital stay. Post-operative edema is also known to impair macrovascular and microvascular circulation and wound healing[10]. The pathophysiology of post-reconstructive edema is thought to be a combination of hyperemia[11], increased capillary permeability[10, 12], lymphatic[5, 7, 9, 13] and venous disruptions[7, 14, 15]. Post-operative edema typically lasts for three months[16]. In general, the treatment of lower limb edema is based on leg elevation, the use of external compression stockings[17] or lymph drainage[18]. Following peripheral bypass surgery, external compression is mostly based on clinical experience, since prospective trials to the efficacy of the use of stockings following bypass surgery are lacking. Post-operative limb edema occurs as well after orthopedic and trauma surgery. The use of A-V impulse technology, an intermittent pneumatic compression device (IPC) on the foot, has been proven effective to reduce this edema[19]. IPC is also known to increase arterial inflow and pressure in the lower limb in patients suffering PAD[20].

The primary aim of this study is to investigate the effect of A-V impulse technology as a treatment method to reduce post-revascularization edema. Improvements in edema reduction strategies might accelerate post-operative rehabilitation and improve wound healing. A second aim of this study is to detect differences in post-operative C-reactive protein (CRP) and leukocyte concentrations between treatment strategies, which are of interest as increases in inflammatory parameters are associated with events and mortality in vascular patients[21, 22]. A third aim of this study is to investigate the effect of a redo bypass operations compared to first time bypass operations on edema development.

METHODS

Study design

A prospective randomized controlled trial was performed in a non-academic teaching hospital in the Netherlands between 2006 and 2009. The work-up included an ankle-brachial pressure index (ABI), a walking test, a venous and arterial duplex ultrasound assessment and either a digital subtraction angiography (DSA) or a magnetic resonance angiography (MRA) scan. The medical ethical board of the hospital approved the protocol. All patients gave their written informed consent pre-operatively. Randomization was done post-operatively in a two-by-two order. The randomization strategy was unknown to the surgical team.

Inclusion criteria

All patients included were suffering from PAD Rutherford category 3 to 6 on principal lower limb vessels or crural vessels as defined by the international (TASC II) consensus criteria[23]. None of the patients were eligible for endovascular treatment options. PTFE grafting was indicated due to inability to construct an autologous bypass. This inability was due to absence of a suitable vein to be used as a bypass on either the affected or contralateral leg, or due to loss of patency of a prior performed autologous bypass reconstruction more than one year before. There was an unobstructed iliac inflow and there was sufficient outflow through at least one crural vessel based on duplex, DSA or MRA findings gathered pre-operatively.

Exclusion criteria

Patients suffering from severe cardiac failure (NYHA class-III and IV) were excluded due to hemodynamic effects of IPC that are not completely understood. Patients with known deep vein thrombosis or pulmonary embolism on admission were not included for the same reason. Patients who demanded hemodialysis due to severe renal impairment were excluded. So were patients who experienced pre-existing limb edema due to severe liver impairment (Child-Pugh score B and C), venous insufficiency, endocrinology diseases or who experienced manifest edema caused by medication. Patients with large ulcers (> 3cm^2) on the plantar aspect of the foot or who had undergone amputations that would compromise the fit of the IPC pad were excluded. Further exclusion criteria were known malign diseases, enrolment in other trials and mental inability to understand the contents of the trial.

Surgical Procedure

Surgery was performed under general and/or spinal anesthesia. A deep-tunneled Distaflo® (Bard Peripheral Vascular Inc.,Tempe, AZ, USA) PTFE supragenicular or infragenicular femoropopliteal bypass was constructed. The Distaflo® graft is used as our standard graft for all peripheral revascularizations. A standardized medial incision was made in the groin at the site of the bifurcation of the femoral artery. The popliteal dissection was made above or below the knee. Smaller lymphatic structures were coagulated while larger lymphatic structures were ligated using Vicryl® (Ethicon Inc. Somerville, NJ, USA). Patients underwent systemic heparinazation (5000 IE) during the operation. The iliac inflow was checked prior to revascularization. The grafts were implanted end-to-side. A routine Doppler assessment was performed before closure of surgical wounds. The use of acetylsalicylic acid (ASA) was initiated or continued post-operatively.

Treatment groups

The control group patients (Group 1) used the current post-operative protocol. These patients received graduated compression stocking (CS) above the knee (BREVET-tx, Mölnlycke, Göteborg, Sweden) post-operatively. The stocking delivers 18 mmHg of pressure (class I compression stocking) on the foot and features low-pressure areas on the heel and over the popliteal vein. Patients were hospitalized during one week. In this week the patients wore the stocking on the affected limb day and night. After their discharge from hospital group-1 patients used the compression stocking only at day. Group 2 patients received the A-V impulse technology (Orthofix Vascular Novamedix, Andover, UK) on the affected limb during the night, from 20:00 hrs till 08:00 hrs, during one week in hospital. Starting the second week, group 2 patients wore compression stocking (as mentioned for group 1) until the eighth week after surgery during the day as well.

A-V impulse technology

The A-V impulse technology is an IPC device. It works by pumping intermittently compressed air into a pad that fits the foot. The pad flattens the plantar arch of the foot on inflation, thereby deflating the venous plexus. The pad is inflated in 0.4 seconds in which a pressure is build up to 130 mmHg. Deflation occurs through perforations in the pad. The cycle of 20 seconds allows for efficient priming of the venous pump[19]. The sudden inflation impulses reproduce the physiological ratchet-like flow pattern of venous return.

Measurements

Lower limb circumference measurements were performed at six different time points: the day prior to surgery and one day, four days, seven days, two weeks and three months after surgery. The repeated limb measurements were done by using a tape measure[24]. At each time point the wound condition was also assessed. Leukocyte counts and C-reactive protein concentration measurements were performed at four points of time: the day prior to surgery and one day, seven days and two weeks after surgery. Patients were hospitalized during the first week after surgery. At day four and at three months ABI was repeated. After three months a duplex ultrasound assessment was performed to check the bypass for in-graft stenosis or obstruction.

Intention-to-treat

This study was carried out on an "intention-to-treat" basis. Patients were encouraged to carefully mobilize from the first day post-operative if possible. No restrictions were laid down on early rehabilitation schedules. Group 1 patients who used CS's mobilized while wearing their stocking. Group 2 patients weren't able to mobilize when the A-V impulse technology device was active. Group 2 patients who did not tolerate or experienced discomfort from the A-V impulse technology were offered a CS and *vice versa*. Patients experiencing post-operative complications were treated according to common medical insights. Occurring complications did not result into exclusion from analysis unless they were lost in follow up in the first post-operative week. A duplex ultrasound assessment was performed prior to three months if there was suspicion for in-graft stenosis of obstruction. Original grouping was maintained in the data analysis.

Statistical Analysis

Due to a lack of information on the magnitude of a differential treatment effect on lower limb circumference, the power analysis performed prior to the trial was based on a Cohen's *d* equal 0.90, representing a large effect size[25]. This effect is detectable with 80% power with 20 patients eligible per group and a test size of 0.05 (2-sided). Statistical analysis was performed with SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). The nine circumference measurements at each time point in each patient were averaged after logarithmic transformation. The choice of a natural logarithmic transformation of the circumference measurements prior to analysis was made for practical reasons: (I) on the log scale circumference measurements are linearly related to the section area and volume of a cylinder; (II) a change or difference on the log scale can be back-transformed to a percentage as a common effect measure in this field. Leukocyte counts and CRP concentrations were logarithmically transformed as well because of the positive skewness of their distribution. The data were analyzed using mixed model ANOVA. A restricted maximum likelihood method was used for testing and estimating the various effects. This method is known to be able to correctly deal with missing observations. The dependent variable is the average logarithmically transformed circumference as just defined. The following independent variables were taken into account for explaining circumference: a between-subject factor "group" (two levels: CS and A-V), a within-subject factor time since baseline (five levels: 1, 4, 7, 14 and 90 days) and the baseline covariates circumference and re-operation (yes/no). By entering the appropriate interaction terms in the model we simultaneously tested the modification by time of the effect of the baseline covariates and the modification of the (evolution of the) treatment effect by the baseline covariates. Eventually, the "group-by-time" interaction factor was also tested. The estimated differences between treatment groups and within-subject changes from baseline and their 95% confidence intervals were back-transformed by exponentiation so as to obtain percent differences and changes in circumference with their 95% confidence limits. In the analysis no structure was imposed on the (co)variances of the five repeated measurements. Similar analyses were done for CRP and leukocyte counts.

Categorical variables were compared between two groups using Fisher's exact test. A value of $P < 0.05$ denotes statistical significance.

RESULTS

Between 2006 and 2009, thirty-nine patients received a PTFE femoropopliteal bypass reconstruction due to severe PAD. Data from thirty-six patients were analyzed. Three patients were excluded from analysis. Two of these three patients underwent an amputation in the first week following surgery and the other patient died in the first week following surgery. Nineteen patients were randomized in group 1 (CS) and seventeen patients were randomized in group-2 (A-V impulse technology). Baseline characteristics are outlined in Table 1. Surgical characteristics are outlined in Table 2. There were no substantial imbalances between the treatment groups.

Table 1. Baseline characteristics.

Variable	Compression group	A-V group
N	19	17
Age, mean (range)	72 (46-84)	71 (40-86)
Sex, Male/Female	13/6	11/6
Indication for operation, Rutherford 3/4/5-6	6/5/8	2/8/7
ABI, mean (SD)	0.43 (0.14)	0.51 (0.21)
ABP, mean (SD)	149 (29)	147 (23)
Risk factors		
Diabetes	5	7
Serum Cholesterol (mmol/L) (SD)	5.3 (1.6)	4.5 (1.2)
eGFR (mL/min/1.73m^2) (SD)	77 (29)	72 (24)
Liver impairment	0	0
Positive family history of cardiovascular disease	11	6
Smoking, current or recent	11	6
Medication		
Calcium channel blockers	10	4
Vasodilatators	6	2
NSAID	1	2
Estrogens	0	1

ABI; ankle-brachial pressure index, ABP; arterial blood pressure, eGFR; estimated glomerular filtration rate.

Table 2. Bypass graft characteristics.

Reconstruction characteristics	Compression group	A-V group
Distal anastomosis		
Supragenicular	6	6
Infragenicular	13	11
Re-operation	6	3
Saphenous vein		
Absent	6	5
Small-caliber	13	12
Operation time (min) (SD)	161 (33)	143 (40)
Necessity for blood transfusion	0	1

After surgery an increase in the leg circumference was measured in both groups; see the summary statistics of the raw data in Table 3. From the mixed model ANOVA it appeared that there is a significant ($P < 0.0005$) effect of baseline circumference on circumference later in time in both groups. Also a re-operation gives a significant 3.9% increase in circumference as compared to a first operation (95% CI : 1.5% to 6.4% ; $P = 0.002$), given measurement day and treatment group. Testing the appropriate interaction terms in the mixed model ANOVA gave no indication that these effects are modified by time, or that the (evolution of the) treatment effect is modified by these baseline covariates (chi-square = 23.124 ; 18 *df* ; $P = 0.19$). The results of a model fitted without these interaction terms are presented in Table 4. At none of the five measurement days a significant difference in circumference between the two treatments is seen using *t*-tests (*P*-values ranging from 0.20 to 0.99), which is corroborated by an overall *F*-test

Table 3. Summary statistics of circumference (cm) and its percent change from baseline across the two patient groups at the various measurement days.

Day	Group	Level (cm)						Change (%) from baseline		
		N	Mean	SD	Median	Min.	Max.	Median	Min.	Max.
-1	CS	18	29.0	3.7	29.5	22.0	37.0	0	0	0
	A-V	17	29.6	3.5	31.2	23.7	33.8	0	0	0
1	CS	18	29.6	3.8	30.6	21.5	36.8	1.5	-8.3	8.7
	A-V	17	30.0	3.4	31.2	24.5	35.2	2.0	-10.5	6.5
4	CS	18	30.7	3.7	31.1	23.7	37.7	6.6	-1.3	28.5
	A-V	17	31.4	3.2	32.4	24.5	35.1	5.1	-4.9	20.3
7	CS	19	30.9	3.3	30.7	23.9	36.9	8.0	-3.0	14.1
	A-V	17	31.3	2.8	31.5	25.9	35.4	6.4	-8.2	18.6
14	CS	19	31.3	3.6	31.6	24.5	38.4	6.7	-3.6	16.2
	A-V	15	31.4	3.0	32.2	25.8	36.7	7.3	-0.2	23.7
90	CS	16	30.4	3.1	30.7	24.0	36.1	5.9	-1.2	13.6
	A-V	13	31.1	3.4	31.5	26.6	36.8	5.7	-0.9	17.1

Table 4. Point and interval estimates of percent changes from baseline and percent differences in circumference between the treatment groups, adjusted for the baseline circumference level and re-operation effect, resulting from mixed model ANOVA.

Day	Group	% Change from baseline			A-V vs. CS (%)			
		estimate	95% CI		estimate	*P*-value	95% CI	
			lower	upper			lower	upper
1	CS	1.30	-1.03	3.68	0.33	0.84	-2.92	3.70
	A-V	1.64	-0.70	4.03				
4	CS	7.13	4.63	9.69	-1.01	0.54	-4.32	2.41
	A-V	6.04	3.50	8.65				
7	CS	6.38	4.25	8.56	-0.02	0.99	-2.90	2.93
	A-V	6.36	4.16	8.60				
14	CS	6.69	4.12	9.33	2.27	0.20	-1.25	5.93
	A-V	9.12	6.41	11.89				
90	CS	5.51	3.61	7.43	0.15	0.91	-2.49	2.87
	A-V	5.67	3.62	7.76				
		overall *P*-value				0.75		

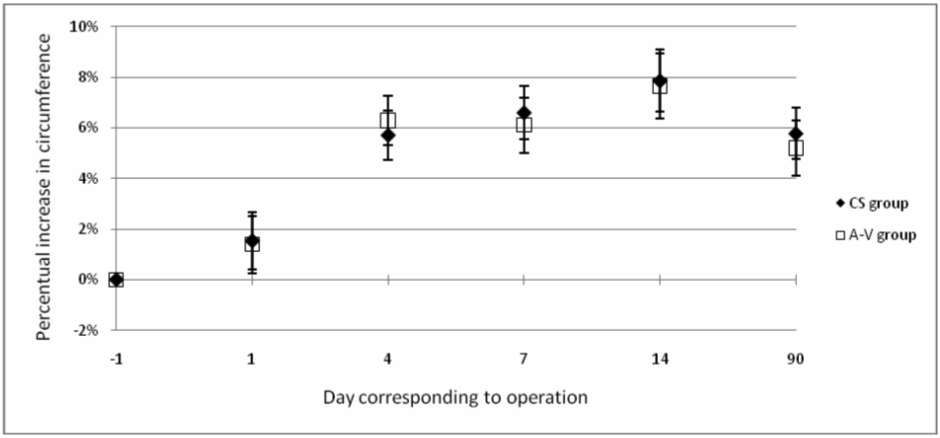


Figure 1. Percent increase of averaged lower limb circumference with standard deviation markers.

(F (5,30) = 0.532 ; P = 0.75), adjusted for baseline circumference and the re-operation effect. As the estimated treatment effects (A-V *vs.* CS) also do not significantly vary across the measurement days (F (4,32) = 0.659 ; P = 0.63) a common effect of A-V *vs.* CS on circumference can be estimated at + 0.16% (95% CI : -1.81% to + 2.16% ; P = 0.87), adjusted for baseline circumference level and the re-operation effect. Three patients using the A-V impulse system did not tolerate the device. These patients were further treated with CS. All patients who used the CS tolerated them.

Changes in leukocyte counts and CRP concentration are plotted in Figure 2 and 3. Differences in leukocyte counts and CRP concentration between the groups were not significant at any time point and for the whole model. There was a significant increase in leukocyte counts after surgery from the baseline (pre-operative), except in the stocking group on day 7. The increase

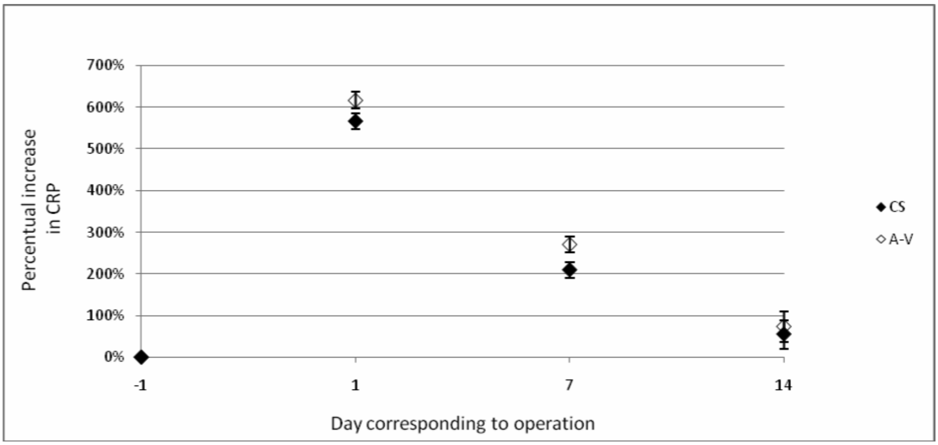


Figure 2. Percent increase in CRP concentration with standard deviation markers.

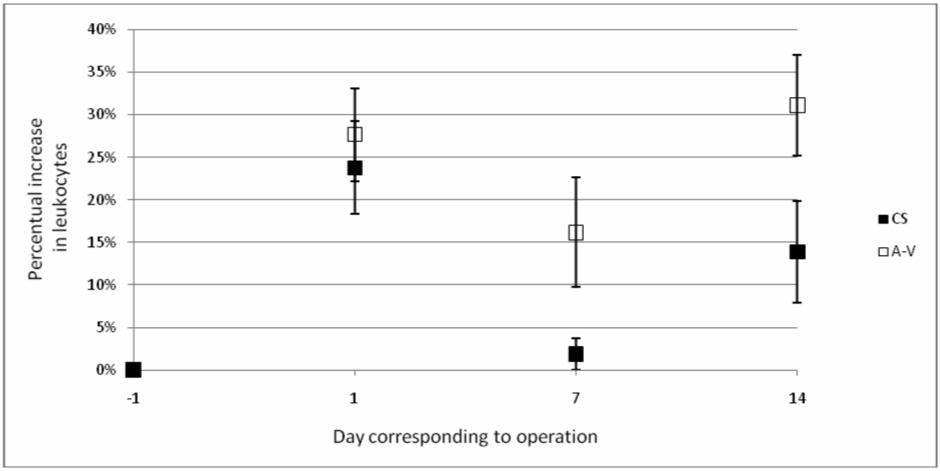


Figure 3. Per cent increase in leukocyte concentration with standard deviation markers.

(from the baseline) in the CRP concentration was significant in both groups post-operatively on day 1 and day 7, but not on day 14. There were no significant correlations between circumferential measurements and leukocyte counts or CRP concentrations at any time.

Relevant complications are shown in Table 5. Two patients died before the 14th day (one in both groups) and two patients underwent an amputation before the 14th day (one in both groups). There were six wound infections (three in both groups). No significant were found in the occurrence of complications between the groups.

Table 5. Complications. Patients in group 1 used the compression stocking. Patients in group 2 used the AV-impulse technology.

Complication	Compression group	A-V group
Wound infection	3	3
Infection (other origin than wound)	1	1
Hematoma	1	0
Persisting seroma (> 3 months)	1	0
Lymphocutanous fistula	0	0
Occlusion	5	3
Hyper-perfusion syndrome	0	0
Amputation	1	1
Death	1	1

DISCUSSION

Edema developed irrespective to the use of CS or the A-V impulse technology following femoropopliteal PTFE bypass grafting. The null-hypothesis that there is no difference in circumference between the groups across all time points could not be rejected. In this randomized trial edema was observed and quantified. Edema developed in all patients following PTFE bypass

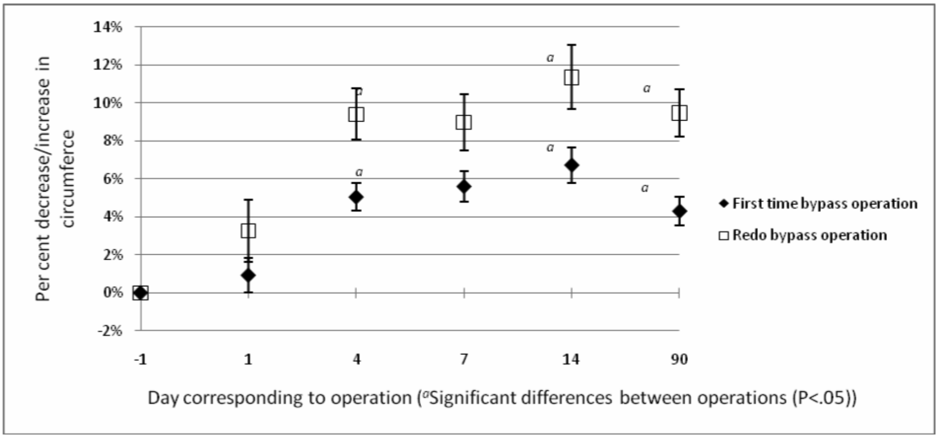


Figure 4. Per cent increase of averaged lower limb circumference with standard deviation markers.

surgery, which is in accordance with findings in literature[5, 7-9]. Patients who underwent a redo bypass operation developed significantly more and longer lasting edema than patients who underwent first time PTFE bypass surgery. These findings have not been reported before in literature.

Indications for peripheral bypass revascularizations have narrowed as newer minimally invasive techniques have been widely introduced. The "intention-to-treat" basis underlying this trial implied that patients were treated according to up to date medical insights. What's more, patients were revascularized using an autologous bypass graft whenever possible[1]. These factors did attribute to "small numbers". Patients who underwent a re-operation experienced loss of patency of an autologous femoropopliteal bypass in their case history. Most of the patients who underwent first time PTFE grafting had a small-caliber saphenous vein, unsuitable to be used as an autologous bypass graft.

It is known from literature that increased leukocyte counts en CRP concentrations correlate with higher morbidity, mortality and cardiovascular events[21, 22]. A difference in our primary endpoints, post-revascularization edema, could have led to a difference in leukocyte counts and CRP concentrations. However, in our study both the extent post-revascularization edema, and leukocyte counts and CRP concentrations did not differ significantly between the groups. No differences in the occurrence of wound infections between the groups could be found either.

The power calculation underlying the design of this trial was based on large treatment effects on circumference in terms of Cohen's *d*. However, at none of the measurement days a significant treatment difference was seen, nor an assumed common treatment difference across the five measurement days. The 95% confidence interval of the treatment difference should also be taken into account in the interpretation of such a result. The lower and upper limit of the confidence intervals give an indication of the minimum and maximum true treatment effect that may have been overlooked (due to a type-2 error), given the sample size of this study. This roughly implies that a true common effect of A-V impulse *vs.* CS smaller than – 2% or larger than +2 % would have been detectable with the sample size of this trial.

Edema following femoropopliteal surgery is likely to be of multifactorial origin with a large contribution of lymphatic disruptions[5, 7, 9, 13]. Surgical damage or functional impairment due to inflammatory processes or adjacent tissue trauma could affect the lymphatics[9]. Studies that have focused on lymph sparing methods to reduce post-operative edema are not conclusive. All patients were operated on using a standardized medial approach. Therefore it is unlikely that the approach could have been of influence on the endpoints[7, 9]. Lymphatic function does restore as damaged lymphatic channels rejoin and new lymphatic channels are formed[6, 16]. When we presume that the lymphatics have rejoined or that new lymphatics have been formed in the group of re-operated patients, then it cannot be ruled out that venous disruptions do attribute to edema formation. Such findings correspond to findings of an increased magnitude in edema formation following both arterial and venous injury[14, 15]. On the other hand, it may also be possible that re-operations might lead to further lymphatic damage in scarred tissue. This study does not reveal new insights into theories concerning hyperemia and an increased capillary filtration as a cause of post-operative edema.

In our trial we used a graduated (class-I) compression stocking above the knee, exerting up to 18 mmHg pressure to the limb. The use of compression stockings post-operatively is mostly based on clinical experience. We used a class-I stocking, since class-II stockings and above might exert too much pressure on the leg, possibly resulting in even more patient discomfort or graft failure. The working mechanism of the compression stocking is to increase pressure on the interstitial space[17] and to augment the peripheral circulation by lowering the flow resistance at the arteriolar level[26].

When an IPC device is active, it attributes to the arterial[27] and venous blood flow[28]. The A-V impulse technique has also been tested successfully for edema reduction following orthopedic and trauma surgery on the lower limb[19]. The use of A-V impulse technology could not prevent post-operative edema from occurring in a lesser extent compared to the use of compression stockings following PTFE femoropopliteal bypass surgery. This was disappointing to what could be expected based on the results after orthopedic and trauma surgery[19]. The A-V group patients in our study only used the system during the night. Application of A-V impulse technology during the day would compromise early mobilization and therefore conflict with "intention-to-treat" basis of this trial. However, absence of compression stockings during the day might have contributed to edema in these patients.

This trial has been set up to investigate the efficacy of A-V impulse technology following PTFE femoropopliteal surgery in a controlled situation. A lack of knowledge on hemodynamic effects in recently operated patients restrained us from continuing the use of A-V impulse technology after discharge from hospital. In future trials A-V impulse technology might be used over a prolonged period. A solution to promote arterial blood flow, and thereby decreasing the risk of early in graft stenosis or occlusion, as well as to reducing edema, might be to combine

A-V impulse technology with external compression. The successful use of IPC in unsupervised conditions has been proved by Delis *et al.* on patients suffering from intermittent claudication[27].

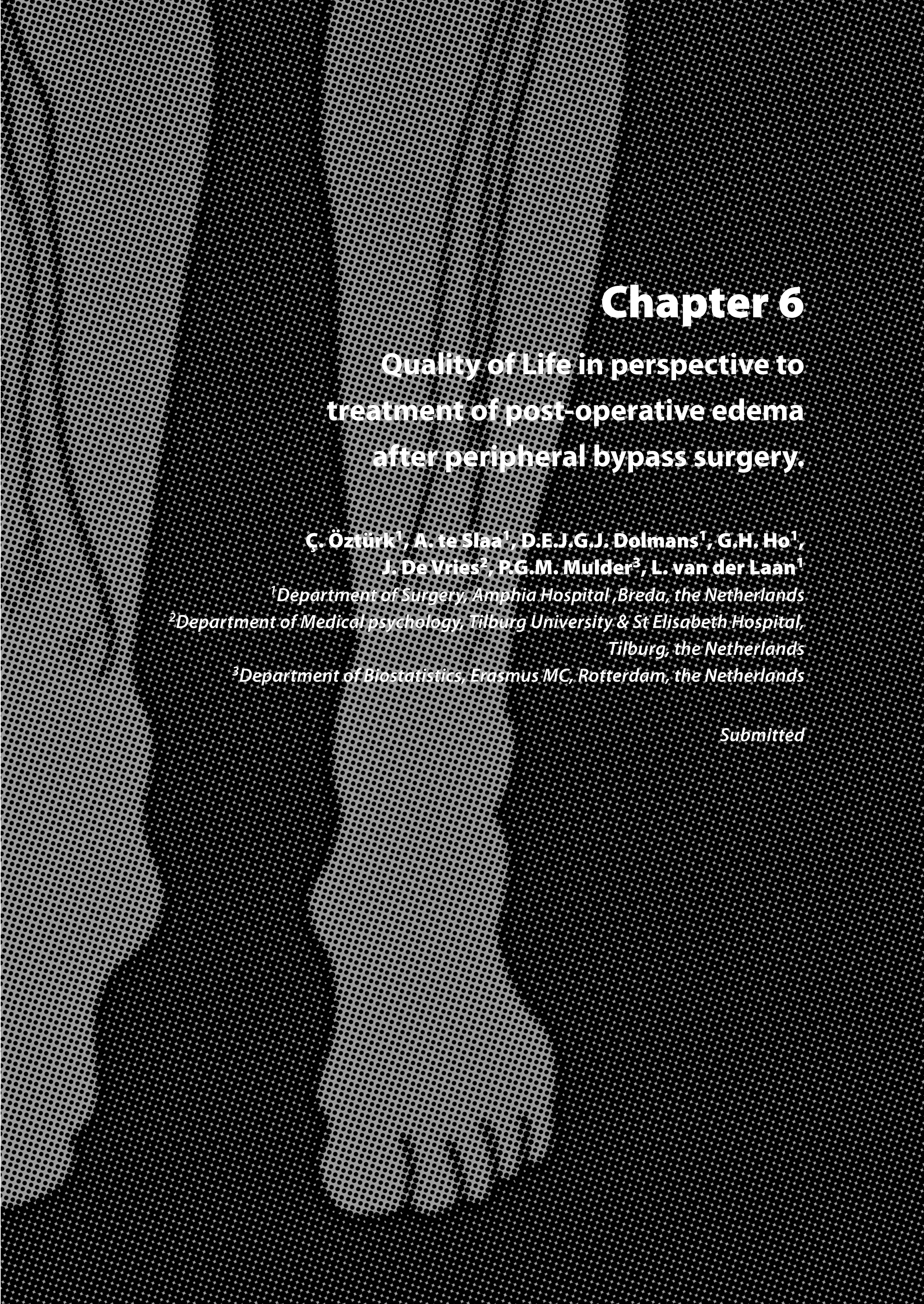
CONCLUSION

Post-operative edema developed in all patients who underwent PTFE femoropopliteal bypass surgery. No significant differences in the extent of edema could be detected between patients who used compression stocking and those who used A-V impulse technology post-operatively, nor were differences in increased inflammatory parameters detected between treatment groups. Patients who underwent a redo operation with a PTFE graft (due to a failed autologous graft) developed significantly more edema than patients who underwent first time PTFE grafting. The use of compression stockings has been the standard practice post-operatively. This trial on the effect of A-V impulse technology, which was expected to treat and prevent post-operative edema effectively, resulted in the conclusion that it gave similar results as compression stockings. The use of A-V impulse technology following PTFE femoropopliteal surgery should be further investigated.

REFERENCES

1. Ballotta E, Renon L, Toffano M, Da Giau G. Prospective randomized study on bilateral above-knee femoropopliteal revascularization: Polytetrafluoroethylene graft versus reversed saphenous vein. *J Vasc Surg* 2003;38:1051-5.
2. Jensen LP, Lepantalo M, Fossdal JE, Roder OC, Jensen BS, Madsen MS, et al. Dacron or PTFE for above-knee femoropopliteal bypass. a multicenter randomised study. *Eur J Vasc Endovasc Surg* 2007;34:44-9.
3. Hamer JD. Investigation of oedema of the lower limb following successful femoropopliteal by-pass surgery: the role of phlebography in demonstrating venous thrombosis. *Br J Surg* 1972;59:979-82.
4. Herreros J, Serena A, Casillas JA, Arcas R, Llorens R, Richter JA. Study of venous and lymphatic components in the production of edema following femoropopliteal by-pass. A comparative scintigraphy and radiologic study. *J Cardiovasc Surg (Torino)* 1988;29:540-6.
5. Hannequin P, Clement C, Liehn JC, Ehrard P, Nicaise H, Valeyre J. Superficial and deep lymphoscintigraphic findings before and after femoro popliteal bypass. *Eur J Nucl Med* 1988;14:141-6.
6. Porter JM, Lindell TD, Lakin PC. Leg edema following femoropopliteal autogenous vein bypass. *Arch Surg* 1972;105:883-8.
7. AbuRahma AF, Woodruff BA, Lucente FC. Edema after femoropopliteal bypass surgery: lymphatic and venous theories of causation. *J Vasc Surg* 1990;11:461-7.
8. Campbell H, Harris PL. Albumin kinetics and oedema following reconstructive arterial surgery of the lower limb. *J Cardiovasc Surg (Torino)* 1985;26:110-5.
9. Haaverstad R, Johnsen H, Saether OD, Myhre HO. Lymph drainage and the development of post-reconstructive leg oedema is not influenced by the type of inguinal incision. A prospective randomised study in patients undergoing femoropopliteal bypass surgery. *Eur J Vasc Endovasc Surg* 1995;10:316-22.
10. Jacobs MJ, Beckers RC, Jorning PJ, Slaaf DW, Reneman RS. Microcirculatory haemodynamics before and after vascular surgery in severe limb ischaemia--the relation to post-operative oedema formation. *Eur J Vasc Surg* 1990;4:525-9.
11. Henriksen O. Orthostatic changes of blood flow in subcutaneous tissue in patients with arterial insufficiency of the legs. *Scand J Clin Lab Invest* 1974;34:103-9.
12. Junger M, Frey-Schnewlin G, Bollinger A. Microvascular flow distribution and transcapillary diffusion at the forefoot in patients with peripheral ischemia. *Int J Microcirc Clin Exp* 1989;8:3-24.
13. Fernandez MJ, Davies WT, Tyler A, Owen GM. Post-arterial reconstruction edema, are lymphatic channels to blame? *Angiology* 1984;35:475-9.
14. Sullivan WG, Thornton FH, Baker LH, LaPlante ES, Cohen A. Early influence of popliteal vein repair in the treatment of popliteal vessel injuries. *Am J Surg* 1971;122:528-31.
15. Hobson RW, 2nd, Howard EW, Wright CB, Collins GJ, Rich NM. Hemodynamics of canine femoral venous ligation: significance in combined arterial and venous injuries. *Surgery* 1973;74:824-9.
16. Vaughan BF, Slavotinek AH, Jepson RP. Edema of the lower limb after vascular operations. *Surg Gynecol Obstet* 1970;131:282-90.
17. Pflug JJ, Calnan JS. The relationship between the blood, lymphatic and interstitial circulation in the leg. *Vasa* 1973;2:75-80.
18. Balzer K, Schonebeck I. [Edema after vascular surgery interventions and its therapy]. *Z Lymphol* 1993;17:41-7.
19. Gardner AM, Fox RH, Lawrence C, Bunker TD, Ling RS, MacEachern AG. Reduction of post-traumatic swelling and compartment pressure by impulse compression of the foot. *J Bone Joint Surg Br* 1990;72:810-5.
20. Delis KT, Nicolaides AN, Wolfe JH, Stansby G. Improving walking ability and ankle brachial pressure indices in symptomatic peripheral vascular disease with intermittent pneumatic foot compression: a prospective controlled study with one-year follow-up. *J Vasc Surg* 2000;31:650-61.
21. Arain FA, Khaleghi M, Bailey KR, Lahr BD, Rooke TW, Kullo IJ. White blood cell count predicts all-cause mortality in patients with suspected peripheral arterial disease. *Am J Med* 2009;122:874 e1-7.
22. Biancari F. Regarding "Elevated C-reactive protein levels are associated with postoperative events in patients undergoing lower extremity vein bypass surgery". *J Vasc Surg* 2007;46:402; author reply -3.

23. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg* 2007;33 Suppl 1:S1-75.
24. te Slaa A, Mulder P, Dolmans D, Castenmiller P, Ho G, van der Laan L. Reliability and reproducibility of a clinical application of a simple technique for repeated circumferential leg measurements. *Phlebolgy* 2010;Electronic publication ahead of press.
25. Cohen J. *Statistical Power Analysis for the Bahavioral Sciences* (2nd edn). Lawrence Erlbaum Associates: Hillsdale, 1988.
26. Schubart PJ, Porter JM. Leg Edema Following Bypass. In: *Reoperative Arterial Surgery*, Bergan JJ (ed). Grune & Stratton: Orlando, 1986; 328-9.
27. Delis KT, Nicolaides AN. Effect of intermittent pneumatic compression of foot and calf on walking distance, hemodynamics, and quality of life in patients with arterial claudication: a prospective randomized controlled study with 1-year follow-up. *Ann Surg* 2005;241:431-41.
28. Griffin M, Kakkos SK, Geroulakos G, Nicolaides AN. Comparison of three intermittent pneumatic compression systems in patients with varicose veins: a hemodynamic study. *Int Angiol* 2007;26:158-64.



Chapter 6

Quality of Life in perspective to treatment of post-operative edema after peripheral bypass surgery.

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Submitted

ABSTRACT

Objectives

To examine the effects of peripheral bypass surgery on patients' Quality of life (QOL), as well as to compare two treatment modalities to reduce postoperative edema with regard to patients' QoL.

Design

Randomized controlled trial.

Methods

Patients were operated on preferably using an autologous bypass. Alternatively a PTFE bypass was used. Patients were assigned to intermittent pneumatic compression (IPC) or to compression stockings (CS). QoL was measured with the World Health Organization Quality of Life assessment instrument, short form (WHQOL-BREF).

Results

QoL improved on the domain of Physical health by 7.18 points ($P < 0.001$ (range 0-100)) after two weeks and by 10.03 points ($P < 0.001$) after three months. Patients who received a PTFE bypass scored 0.45 points ($P = 0.0008$ (range 1-5)) lower at baseline on Global QoL than patients who received an autologous bypass. The type of bypass or the edema treatment method did not affect the improvements. Neither did edema correlate with QoL.

Conclusion

Improvements in QoL on the domain of Physical health following femoropopliteal bypass surgery can be found as soon as two weeks after surgery. Improvement in QoL domains was not influenced by the type of bypass reconstructions. Specific effects of edema on the QoL could not be detected.

BACKGROUND

Traditionally, key outcome measures of vascular interventions include limb salvage, graft patency and operative mortality[1]. In addition, quality of life (QoL) is increasingly considered a key outcome measure of vascular interventions. Measures of health that include the impact of disease and impairment on daily activities and behavior, perceived health and disability and functional status have been described as "the missing measurements in health"[2]. With the introduction of QoL measurements, in which these elements are imbedded, health care has gained a humanistic and patient-oriented perspective[3].

QoL is a broad concept with multiple dimensions. It is an individual assessment of physical, psychological and social well-being that is in line with the definition of health by the World Health Organization (WHO)[4]. QoL incorporates a patient's individual perception of its disease and functioning[5]. A generic QoL assessment instrument which has been satisfactorily used in patients suffering from cardiovascular diseases is the World Health Organization Quality of Life assessment instrument (WHOQOL)[3, 4]. The original WHOQOL-100, as well as an abbreviated version (WHOQOL-BREF) have good reliability and validity and are sensitive to treatment-related change and correlate highly with each other[6-8].

Patients suffering from peripheral arterial disease (PAD) cope with a deprived health status and QoL due to the effects of PAD and comorbid conditions[5]. Improvements in both health status and QoL following peripheral bypass surgery have been observed between three months and two years[9-11].

Substantial post-operative edema occurs following peripheral bypass surgery[12]. This edema can cause discomfort, hinders early mobilization, and has an inhibiting effect on wound healing because of the underlying hemodynamic disturbances[13]. It is unknown if post-operative edema effects the QoL.

The present study was part of a randomized controlled trial (RCT) to evaluate the efficacy of intermittent pneumatic compression (IPC), compared to compression stockings (CS), as a treatment method of edema following femoropopliteal bypass surgery. IPC was used successfully to treat edema following orthopedic and trauma surgery on a limb[14]. However, failure of IPC to decrease edema formation following autologous and PTFE femoropopliteal bypass surgery was reported recently[15, 16]. As part of this study, the effects of femoropopliteal bypass surgery on patients' QoL, was prospectively assessed with the WHOQOL-BREF instrument, one day before, and two weeks and three months after surgery.

This study aims to answer four research questions. First, what is the effect of femoropopliteal bypass surgery on patients' QoL? Second, is there a difference in QoL in patients who underwent either autologous or PTFE bypass surgery? Third, is there a difference in QoL between patients who were treated with IPC or CS? Fourth, are edema treatment effects modified by time or by bypass type (heterogeneity)?

MATERIALS AND METHODS

Trial design

A single-center RCT was performed to study the effects of IPC and CS's on post-operative edema formation following femoropopliteal bypass surgery. The patients were enrolled between August 2006 and September 2009.

The key endpoints were edema reduction, changes in inflammatory parameters and improvements in QoL. Patients who suffered from pre-existing leg edema were not allowed to participate in the trial. The effects on the formation of post-operative edema and changes in inflammatory parameters, including the trial design and detailed information on the inclusion and exclusion criteria, are reported elsewhere[15, 16].

Approval was granted by both a nationally recognized medical ethical review committee and the hospital's medical ethical review committee. All patients who participated in this study gave written informed consent.

Surgical Procedure

All patients underwent supragenicular or infragenicular femoropopliteal bypass surgery. Whenever possible, autologous grafting was performed[17, 18]. Alternatively, a PTFE graft (Dystaflo®, Bard Peripheral Vascular Inc., Tempe, AZ, USA) was used. Thus, by bypass graft type, two surgery groups (strata) were considered: autologous and PTFE.

Edema treatment groups

Patients in both surgery groups were allocated to either the CS group or the IPC group according to the randomization strategies[15, 16]. The patients in the CS group used an above the knee class I stocking (BREVET tx, Mölnlycke, Göteborg, Sweden), exerting up to 18 mmHg pressure to the leg continuously during one week following surgery. IPC group patients received the A-V impulse technology (Orthofix Vascular Novamedix, Andover, UK) during one week at night, starting the night following the operation. The A-V impulse technology is an IPC device on the foot which was developed to compress the venous plexus artificially and activate the physiological foot pump[14]. Starting in the second week, all patients were discharged from hospital when possible and used the CS's at day on the operated legs only until the eight week after surgery.

QoL assessment

Patients were asked to complete the WHOQOL-BREF assessment questionnaire the day before surgery, and two weeks and three months after surgery. The WHOQOL-BREF is an abbreviated version of the original WHOQOL-100[3, 4]. The WHOQOL-BREF has 26 questions of which 24 questions assess the domains: Physical health (7 questions), Psychological health (6 questions), Social relationships (3 questions) and Environment (8 questions). Each question has a five-point Likert scale. The remaining two questions asses overall QoL and the perceived health and make up the facet Global QoL. Scoring of the various QoL domains was based on instructions of the World Health Organization (WHO)[19]. The Likert scale data were converted into raw domain scores of the four distinct domains and transformed on a range from 0 to 100, with higher scores corresponding with a better QoL. The Global QoL facet was left untransformed.

The time of reference is the previous two weeks. Studies concerning the psychometric properties of the WHOQOL-BREF have shown good internal consistency, validity[6] and good sensitivity to change[7].

Statistical analysis

The SPSS 16.0 (SPSS Inc., Chicago, IL, USA) package was used for the statistical analysis.
To detect the effect of surgery on QoL, first MANOVA repeated measures analysis was used. Further analysis was carried out, while taking two surgical groups (strata) into account. The pooled stratified analysis of the difference between two edema treatment groups (IPC / CS) across two surgery groups (autologous / PFTE) was carried out using mixed model ANOVA. The dependent variables were the various QoL-domains having a Gaussian-shaped distribution. The independent variables were: surgery group (autologous / PTFE), edema treatment group (IPC / CS) and measurement moment (two weeks and three months). The baseline level at the pre-operative day of the QoL-domain at hand was entered as covariate. We tested if the effect of this baseline level was modified by day and bypass type (stratum), and if this baseline level modified the treatment effect. We also tested if the treatment effect was modified by measurement day or by surgery group (heterogeneity).

Mixed model ANOVA was also used to test the correlation between leg circumference and domain scores, adjusted for bypass graft type, edema treatment (group) and time.

The outcome variable Global QoL was analyzed using nonparametric methods as its distribution deviated strongly from a Gaussian-shaped distribution. The change-from-baseline of Global QoL was trichotomized into three ordered categories: change for worse, no change, and change for better. This ordered categorical change was compared between the two edema treatment groups (IPC and CS) using a stratified chi-square trend test, where the stratification was by bypass graft type (autologous / PTFE). This analysis was done for the two measurement moments (two weeks and three months) separately. To detect changes from baseline in Global QoL sign tests were used by bypass graft type, edema treatment and measurement moment.

Binary categorical variables (complications) were compared between the two edema treatment groups using Mantel-Haenszel chi-squared tests stratified by bypass graft type.

A P-value < 0.05 was considered to denote statistical significance.

RESULTS

Between August 2006 and September 2009, 101 patients underwent femoropopliteal bypass surgery due to severe PAD (Figure 1). Baseline characteristics are summarized in Table 1, subdivided by bypass graft type (autologous / PTFE) and edema treatment method (IPC/CS). From the 93 patients, 76 (82%) completed the QoL questionnaire pre-operatively, 78 (84%) at two weeks post-operatively, and 69 (74%) patients three months post-operatively.

Post-operative course and the effect of surgery on QoL

Post-operative events are presented in Table 2. No significant differences in the occurrence of post-operative events were found between the treatment groups.

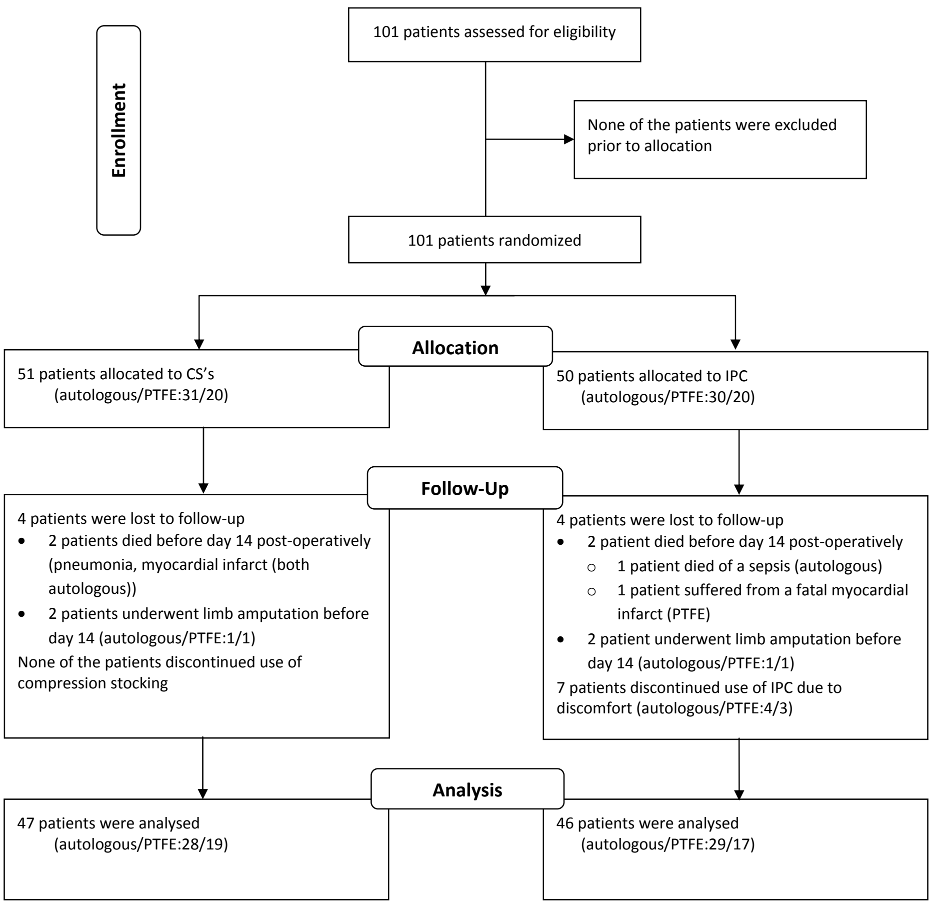

Figure 1: Trial profile

Table 1.

	Autologous		PTFE	
	CS	IPC	CS	IPC
N	28	29	19	17
Age, mean (range)	69 (57-84)	67 (39-88)	72 (46-84)	71 (40-86)
Sex (M/F)	23/5	22/7	13/6	11/6
DM (%)	10 (36)	15 (52)	5 (26)	7 (41)
Smoke (%)	13 (46)	16 (55)	11 (58)	6 (35)
Rutherford 3/4/5-6	11/10/7	13/5/11	6/5/8	2/8/7
Absent vein (Re-operation)	n.a.	n.a.	6 (6)	5 (3)
Small Caliber vein	n.a.	n.a.	13	12

Regarding QoL, a general improvement was found for all patients on the domain Physical health ($P < 0.001$) as shown in Figure 2, whereas no significant improvements were found on the domains of Psychological health ($P = 0.93$), Social relationships ($P = 0.43$), Environment ($P = 0.35$) and Global QoL ($P = 0.35$). Item analysis on the domain Physical health was performed. Significant improvement was found on 3 of the 7 items: pain ($P < 0.001$), need for medical treatment in daily functioning ($P < 0.001$) and energy for daily functioning ($P < 0.05$).

Difference in bypass graft type and edema treatment group and the effect on QoL

Summary statistics of the raw domain scores are listed in Table 3. Means of the QoL domains at baseline adjusted for bypass type (stratum) and treatment group and adjusted mean differences between strata and treatment groups are presented in Table 4.

On the domain of Global QoL a significant difference was detected at baseline between patients who were revascularized with an autologous graft *vs.* patients who where revascularized using a PTFE graft in the disadvantage of the latter. A nearly significant difference ($P = 0.051$) was detected on the domain of Psychological health.

Concerning efficacy, a simultaneous test of all interactions with the baseline measurement at hand was not significant for any of the four specified domains considered. Hence, there was no suspicion that the baseline level of a domain modifies the effects of the bypass graft type (autologous / PTFE), the edema treatment method (IPC / CS) and time on each domain. Also

Table 2. Incidence of complications compared between the two treatment groups (P-values from Mantel-Haenszel chi-squared tests stratified by type of graft)

Complication	CS (N=47)	IPC (N=46)	*P*-value
Wound infection (autologous/PTFE)	5 (2/3)	9 (6/3)	0.14
Infection (other origin than wound) (autologous/PTFE)	2 (1/1)	2 (1/1)	0.98
Hematoma (autologous/PTFE)	4 (3/1)	4 (4/0)	0.97
Persisting seroma (> 3 months) (autologous/PTFE)	1 (0/1)	2 (2/0)	0.55
Occlusion (autologous/PTFE)	7 (2/5)	5 (2/3)	0.57
Myocardial infarct (autologous/PTFE)	1 (1/0)	0 (0/0)	0.33

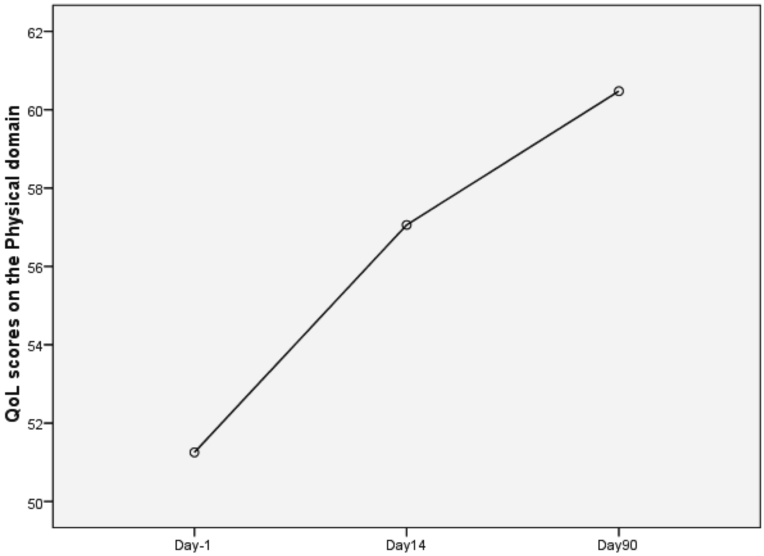

Figure 2. Results of a multivariate analysis (MANOVA) of the domain of Physical health ($P < 0.001$).

none of the treatment-by-time interactions appeared to be significant. The test for heterogeneity of the treatment effect across the two strata appeared to be significant only for the domain of Social relationships ($P = 0.020$), so that for this domain the estimated treatment results are listed separately for the two surgery groups (autologous / PTFE) (see Table 4). For the other specific domains a simple model with only the main effects of the baseline level, time, surgery group and edema treatment group appeared to suffice. The only significant treatment effect ($P = 0.015$) was seen for Social relationships in the patient who received a PTFE bypass. None of the other edema treatment and bypass graft type effects reached significance. For significance of the changes-from-baseline using similar analyses as those yielding the results of Table 5, see Table 6. Significant increases were seen consistently in the domain of Physical health for either surgery group, for either edema treatment group and for either measurement moment.

In an efficacy test of the Global QoL domain there was no significant difference in the changes between the two edema treatment groups, adjusted for bypass type (stratum). *P*-values are 0.17 and 0.81 for the respective measurements at two weeks and at three months. A significant change from baseline of the Global QoL could not be detected either.

Limb edema and QoL.

Patients who used IPC following autologous femoropopliteal bypass surgery developed significantly more edema than patients who used CS's. This effect was only significant in the first week and disappeared after patients in the IPC group switched to using CS's after one week at discharge from hospital[16]. This effect was not seen in patients who underwent PTFE femoropopliteal bypass surgery[15].

The association between leg circumference and QoL was analyzed. Partial correlation analysis (adjusted for surgery group, edema treatment group and time) on day 14 and 90 between

Table 3. Summary of raw QoL domain scores by stratum, treatment and measurement moment.

		Domain	Physical health*			Psychological health*			Social relationships*			Environment*			Global QoL†		
Day	Stratum	Treatment	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
-1	autologous	CS	23	49.69	15.61	23	68.48	14.26	23	64.49	16.33	23	64.81	11.70	23	3.37	0.66
		IPC	25	54.31	11.34	25	75.67	17.33	25	69.33	22.66	25	70.45	16.81	25	3.88	0.58
	PTFE	CS	15	49.44	8.90	15	66.33	12.55	15	66.67	17.82	14	65.47	14.28	15	3.37	0.83
		IPC	13	44.09	14.53	13	63.14	14.62	12	66.32	15.94	13	65.87	11.59	13	2.96	0.52
14	autologous	CS	23	54.81	15.31	23	67.39	14.84	23	63.95	18.95	23	69.37	14.46	23	3.54	0.66
		IPC	24	59.67	16.20	24	71.70	17.80	24	69.44	21.23	24	71.52	17.26	24	3.79	0.67
	PTFE	CS	17	57.88	14.16	17	66.52	13.07	16	69.79	19.45	17	68.93	15.84	17	3.50	0.61
		IPC	14	52.55	17.91	14	63.39	17.69	14	66.37	16.38	14	62.85	17.42	14	3.32	0.91
90	autologous	CS	21	60.71	17.53	21	67.30	15.75	21	63.10	19.47	21	68.90	12.90	21	3.57	0.95
		IPC	26	65.68	15.65	26	73.40	14.53	25	71.67	23.69	26	71.19	16.44	26	3.83	0.65
	PTFE	CS	12	58.28	13.61	13	65.64	11.68	13	62.82	18.82	13	66.35	16.04	13	3.46	0.75
		IPC	9	50.40	13.88	9	55.56	15.02	9	49.54	13.89	9	61.11	11.60	9	3.11	0.60

* range 0-100, † range 1-5.

Table 4. Adjusted means of the QoL domains at baseline and adjusted mean differences between strata (autologous/PTFE) and treatment groups (CS/IPC); results from multiple linear regression analyses.

	Residual SD	Group	n	Adj. mean	Difference	SE	*P*-value
Physical health*	13.10	autologous	48	52.08	-5.08	3.12	0.11
		PTFE	28	46.99			
		CS	38	49.73	0.95	3.01	0.75
		IPC	38	50.68			
Psychological health*	15.23	autologous	48	72.15	-7.18	3.63	0.051
		PTFE	28	64.97			
		CS	38	67.82	3.37	3.50	0.34
		IPC	38	71.19			
Social relationships*	18.83	autologous	48	66.93	-0.27	4.54	0.95
		PTFE	27	66.66			
		CS	38	65.36	2.99	4.36	0.50
		IPC	37	68.35			
Environment*	14.03	autologous	48	67.69	-1.94	3.38	0.57
		PTFE	27	65.75			
		CS	37	65.09	3.75	3.24	0.25
		IPC	38	68.84			
Global QoL†	0.69	autologous	48	3.63	-0.45	0.16	0.008
		PTFE	28	3.18			
		CS	38	3.38	0.17	0.16	0.27
		IPC	38	3.55			

* range 0-100, † range 1-5.

Table 5. Estimated stratum and treatment effects on each of the four QoL-domains, adjusted for one another, for the baseline level of the domain considered and for the time effect (results from mixed model ANOVA).

Domain	Contrast	Estimate	*P*-value	95% Confidence Interval	
				Lower	Upper
Physical health*	autologous - PTFE	0.44	0.87	-4.79	5.66
	IPC - CS	-0.38	0.88	-5.34	4.58
Psychological health*	autologous - PTFE	-1.15	0.60	-5.55	3.25
	IPC - CS	0.16	0.94	-3.95	4.26
Social relationships*	autologous - PTFE	2.27	0.40	-3.09	7.63
	IPC - CS (autologous)	2.03	0.53	-4.44	8.51
	IPC - CS (PTFE)	-10.74	0.015	-19.33	-2.16
Environment*	autologous - PTFE	1.28	0.63	-4.04	6.60
	IPC - CS	-2.18	0.40	-7.27	2.91

* range 0-100

leg circumference and QoL domains showed no significant correlations between leg circumference and the subsequent domains of QoL (*P*-values ranging from 0.16 to 0.82).

Table 6. Adjusted mean changes from baseline of the four QoL-domains as estimated from mixed model ANOVA using a similar model to that underlying Table 5.

Domain	Condition	Estimate	SE	*P*-value	95% Confidence Interval	
					Lower	Upper
Physical health*	autologous	8.78	1.55	0.000	5.68	11.87
	PTFE	8.34	2.08	0.000	4.18	12.50
	day 14	7.18	1.46	0.000	4.27	10.10
	day 90	10.03	1.52	0.000	7.00	13.06
	CS	8.80	1.74	0.000	5.32	12.28
	IPC	8.42	1.76	0.000	4.89	11.94
Psychological health*	autologous	-1.42	1.29	0.27	-4.00	1.15
	PTFE	-0.28	1.74	0.88	-3.75	3.20
	day 14	-1.28	1.22	0.30	-3.71	1.15
	day 90	-0.68	1.14	0.55	-2.96	1.60
	CS	-1.06	1.44	0.47	-3.93	1.82
	IPC	-0.90	1.46	0.54	-3.81	2.01
Social relationships*	autologous	-0.22	1.63	0.89	-3.48	3.04
	PTFE	-2.49	2.18	0.26	-6.84	1.86
	day 14	0.04	1.47	0.98	-2.90	2.97
	day 90	-2.23	1.86	0.24	-5.96	1.50
	CS autologous	-1.23	2.36	0.60	-5.95	3.49
	CS PTFE	2.88	2.83	0.31	-2.76	8.53
	IPC autologous	0.80	2.23	0.72	-3.67	5.26
	IPC PTFE	-7.86	3.28	0.019	-14.41	-1.31
Environment*	autologous	3.04	1.57	0.057	-0.10	6.17
	PTFE	1.76	2.14	0.41	-2.52	6.03
	day 14	2.72	1.49	0.072	-0.25	5.70
	day 90	2.36	1.50	0.12	-0.65	5.37
	CS	3.63	1.80	0.047	0.05	7.21
	IPC	1.45	1.80	0.42	-2.13	5.04

* range 0-100

DISCUSSION

The aims of this study were to assess the effect of peripheral bypass surgery on patients' QoL and to investigate if this effect was influenced by type of bypass graft and/or the edema treatment method. Patients suffering from severe PAD who underwent peripheral bypass surgery had a low QoL at baseline on all domains, especially on the domain Physical health. On the this domain an average score of approximately 50 (range 0-100) was detected. Scores on the other domains were slightly higher but still lower compared with healthy elderly. Healthy older people generally score approximately 75 on all domains[5, 20]. Two weeks and three months following peripheral bypass surgery, QoL increased significantly on the domain of Physical health. This effect was seen regardless of the type of bypass graft or the edema treatment method. The facet of pain is incorporated in the domain of Physical health. Improvements on this domain are understandable as a large portion of the participants (66%) presented with chronic critical ischemia (Rutherford class 4-6). Item analysis showed that patients suffered significantly less pain after surgery. Also, they experienced significantly more energy for daily functioning.

We explored the effects of bypass graft type on QoL. A difference at baseline in Global QoL was detected between patients who were revascularized with an autologous graft *vs.* patients who were revascularized with a PTFE graft, in the disadvantage of the latter. In our hospital we prefer autologous grafting over PTFE grafting whenever possible[17, 18]. As a consequence, over the years this policy resulted in a 25% revision operation rate in patients with a PTFE graft due to failures of previous constructed autologous bypasses. It is not unlikely that progression of PAD and accompanying comorbid conditions attribute to lower QoL scores. On the other domains there were tendencies to lower scores in the PTFE stratum at baseline, although they did not reach significance.

Analysis on patients in the PREVENT III study revealed a significant improvement in QoL after infragenicular femoropopliteal bypass reconstruction using the Vascular Quality of Life Questionaire (VascuQol)[11]. The VascuQol is a disease specific questionnaire in which 25 questions reflecting health status are grouped into five domains, comprising of physical, social and emotional facets[21]. Patients scored significantly higher in all domains at three months and at twelve months following revascularization compared to the situation prior to surgery. We were not able to pick up such changes with the WHOQOL-BREF in our study. A possible explanatory factor might be the use of a generic instrument. Also, this study might deal with "too small numbers" in comparison to the PREVENT III trial (101 patients *vs.* 1404 patients) to detect significant differences. The sample size calculation underlying our trial was based on the detection of medium to large treatment effect in the amount of edema as primary endpoints[15, 16]. However, the tendency of lower scores in the domain of Psychological health must not be overlooked as recent studies revealed that depressive symptoms occur regularly in patients suffering from PAD[22, 23].

In most QoL studies on patients suffering from PAD, a questionnaire is completed prior to surgery and after 3 and 12 months. Typically, post-revascularization edema vanishes in three months. We expected to observe a relationship between reduction in leg circumference and QoL at two weeks. However, at that time the significant differences in the amount of edema between the treatment groups had already vanished. It has been established that QoL improves more after successful revascularization than after failed revascularization[11]. It could therefore be hypothesized that the use of adequate edema reduction therapies could improve QoL after revascularization sooner than a passive regime.

Health status and QoL are different concepts[5, 24] and subsequently this affects its use in clinical practice. Breek and colleagues[5] showed that both health status and QoL are affected in patients with intermittent claudication. Health status was affected in all domains, such as physical, social, emotional, and mental functioning. QoL was mainly affected in the domain of Physical health and, thus, not in all domains. They conclude that functioning (health status) and subjective appraisal of functioning (QoL) are different concepts and, therefore, instruments measuring health status are potentially misleading. A functional limitation does not necessarily influence the patients' QoL. With the results in our study, we also have to unite with this conclusion. QoL after surgery significantly improved, whereas significant results on other domains were lacking. This indicates that patients are relatively comfortable with their functioning in the different domains, even though the health status may be affected.

QoL is an important outcome measure in clinical studies, but interpretation is hindered by several factors, such as incompleteness of data. A bias mentioned regularly in QoL research in vascular surgery, is that a large proportion of patients, are lost to follow up[11, 25]. In our study we had to exclude several questionnaires that were incompletely filled in: the WHOQOL-BREF instruction orders to include only those questionnaires in which the total number of items completed, is greater or equal to 80%[19]. It is plausible that the patients with the lowest quality of life are overrepresented in the group of patients lost to follow up. QoL reports may therefore very well hold out too beneficial an impression of improvement in QoL after revascularization, because the use of the available data will tend to overestimate QoL[25]. It is also known that patients with very poor pre-operative status do not benefit from revascularizations[26, 27].

Another factor we want to mention is called response shift[28, 29]. Response shift in QoL refers to a change in the meaning of a person's evaluation of his/her QoL as a result of factors such as adaptation to illness, changed internal standards and values. This means that individuals can give different answers to a questionnaire when time has passed, not only because of differences in their health, but also because they have changed. This factor makes this field of research extremely difficult, because it affects the interpretation of QoL data. Ring and colleagues[28] mention individualized measures of QoL (IQoL) where the patient selects the domains most important to their QoL. It is possible that more significant improvements could have been found, if we had used a more individualized measure of QoL.

Furthermore, other factors influencing QoL in the elderly population, should not be overlooked. Breek and colleagues underline that comorbidity e.g., joint symptoms of back, knee and hip, have significant influence on patients' QoL and, therefore, should be taken into account[5].

Since maximizing QoL is increasingly important in vascular surgery with the majority of patients being elderly and chronically ill, this is an important research area.

Conclusion

In this study we have evaluated QoL before and after peripheral bypass surgery and we have explored the relationship between QoL and revascularization-induced edema using two treatment options.

This is, as far as we know, the first attempt to explore the effects of post-revascularization edema on patients' QoL. Differences in the amount of edema between treatment groups were not significant at the time that QoL was measured. A correlation between the extent of post-operative edema and QoL was not detected. However, QoL improved as soon as two weeks after a peripheral bypass revascularization, regardless of type of bypass.

REFERENCES

1. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997;26:517-38.
2. Fallowfield L. *Quality of life; Health status indicators; Evaluation*, 1990; 234.
3. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. *Psychol Med* 1998;28:551-8.
4. Saxena S, Orley J. Quality of life assessment: The world health organization perspective. *Eur Psychiatry* 1997;12S3:263s-6s.
5. Breek JC, de Vries J, van Heck GL, van Berge Henegouwen DP, Hamming JF. Assessment of disease impact in patients with intermittent claudication: discrepancy between health status and quality of life. *J Vasc Surg* 2005;41:443-50.
6. Nelson CB, Lotfy M. The World Health Organization's WHOQOL-Bref quality of life assessment of psychometric qualities. Results of field trial. In: WHO, editor.; 1999.
7. O›Carroll RE, Smith K, Couston M, Cossar JA, Hayes PC. A comparison of the WHOQOL-100 and the WHOQOL-BREF in detecting change in quality of life following liver transplantation. *Qual Life Res* 2000;9:121-4.
8. De Vries J, Van Heck GL. The World Health Organization Qualilty of LIfe assessment instrument (WHOQOL-100): validation of the Dutch version. *Eur J Physiol Assess* 1997;13:164-78.
9. Aquarius AE, Denollet J, Hamming JF, Breek JC, De Vries J. Impaired health status and invasive treatment in peripheral arterial disease: a prospective 1-year follow-up study. *J Vasc Surg* 2005;41:436-42.
10. Engelhardt M, Bruijnen H, Scharmer C, Wohlgemuth WA, Willy C, Wolfle KD. Prospective 2-years follow-up quality of life study after infrageniculate bypass surgery for limb salvage: lasting improvements only in non-diabetic patients. *Eur J Vasc Endovasc Surg* 2008;36:63-70.
11. Nguyen LL, Moneta GL, Conte MS, Bandyk DF, Clowes AW, Seely BL. Prospective multicenter study of quality of life before and after lower extremity vein bypass in 1404 patients with critical limb ischemia. *J Vasc Surg* 2006;44:977-83; discussion 83-4.
12. Porter JM, Lindell TD, Lakin PC. Leg edema following femoropopliteal autogenous vein bypass. *Arch Surg* 1972;105:883-8.
13. Cho S, Atwood JE. Peripheral edema. *Am J Med* 2002;113:580-6.
14. Gardner AM, Fox RH, Lawrence C, Bunker TD, Ling RS, MacEachern AG. Reduction of post-traumatic swelling and compartment pressure by impulse compression of the foot. *J Bone Joint Surg Br* 1990;72:810-5.
15. te Slaa A, Dolmans DEJGJ, Ho GH, Mulder PGH, van der Waal JCH, de Groot HGW, et al. Evaluation of A-V Impulse Technology as a Treatment for Oedema Following Polytetrafluoroethylene Femo-ropopliteal Surgery in a Randomised Controlled Trial. *Eur J Vasc Endovasc Surg* 2010;40(5);635-42.
16. te Slaa A, Dolmans DEJGJ, Ho GH, Mulder PGH, van der Waal JCH, de Groot HGW, et al. A prospective randomized trial to the analyze the effect of A-V impulse technology on edema following autologous femoropopliteal bypass surgery. *World J Surg* 2011;35(2):446-54.
17. Mamode N, Scott RN. Graft type for femoro-popliteal bypass surgery. *Cochrane Database Syst Rev* 2000;CD001487.
18. Klinkert P, Post PN, Breslau PJ, van Bockel JH. Saphenous vein versus PTFE for above-knee femoro-popliteal bypass. A review of the literature. *Eur J Vasc Endovasc Surg* 2004;27:357-62.
19. World Health Organization. WHOQOL-Bref: Introduction, administration, scoring and assessment of the generic version—field trial version.; 1996.
20. Hinterseher I, Saeger HD, Koch R, Bloomenthal A, Ockert D, Bergert H. Quality of life and long-term results after ruptured abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 2004;28:262-9.
21. Morgan MB, Crayford T, Murrin B, Fraser SC. Developing the Vascular Quality of Life Questionnaire: a new disease-specific quality of life measure for use in lower limb ischemia. *J Vasc Surg* 2001;33:679-87.
22. Aquarius AE, Denollet J, de Vries J, Hamming JF. Poor health-related quality of life in patients with peripheral arterial disease: type D personality and severity of peripheral arterial disease as independent predictors. *J Vasc Surg* 2007;46:507-12.

23. Aquarius AE, Denollet J, Hamming JF, Van Berge Henegouwen DP, De Vries J. Type-D personality and ankle brachial index as predictors of impaired quality of life and depressive symptoms in peripheral arterial disease. *Arch Surg* 2007;142:662-7.
24. Hamming JF, De Vries J. Measuring quality of life. *Br J Surg* 2007;94:923-4.
25. Chetter IC, Spark JI, Scott DJ, Kent PJ, Berridge DC, Kester RC. Prospective analysis of quality of life in patients following infrainguinal reconstruction for chronic critical ischaemia. *Br J Surg* 1998;85:951-5.
26. Taylor SM, Kalbaugh CA, Blackhurst DW, Hamontree SE, Cull DL, Messich HS, et al. Preoperative clinical factors predict postoperative functional outcomes after major lower limb amputation: an analysis of 553 consecutive patients. *J Vasc Surg* 2005;42:227-35.
27. Taylor SM, Kalbaugh CA, Blackhurst DW, Langan EM, 3rd, Cull DL, Snyder BA, et al. Postoperative outcomes according to preoperative medical and functional status after infrainguinal revascularization for critical limb ischemia in patients 80 years and older. *Am Surg* 2005;71:640-5; discussion 5-6.
28. Ring L, Hofer S, Heuston F, Harris D, O›Boyle CA. Response shift masks the treatment impact on patient reported outcomes (PROs): the example of individual quality of life in edentulous patients. *Health Qual Life Outcomes* 2005;3:55.
29. Postulart D, Adang EM. Response shift and adaptation in chronically ill patients. *Med Decis Making* 2000;20:186-93.

Chapter 7

MRI reveals edema-like changes not only subcutaneously, but also in muscle tissue following femoropopliteal bypass surgery.

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Submitted

ABSTRACT

Introduction

The pathofysiological mechanisms that induce post-revascularization edema following femoropopliteal bypass surgery are not completely understood. Reperfusion associated injury of revascularized tissue and damage of lymphatic structures are both likely to play a role. Aim of this study is to elucidate the pathofysiological mechanisms of post-revascularization edema formation with magnetic resonance imaging (MRI).

Materials and Methods

Nine patients suffering from severe PAD were subjected to MRI scans prior to and one week following autologous femoropopliteal or femorocrural bypass surgery.

Results

A 12% increase in volume of the upper and an 11% increase in volume of the lower legs were measured in patients post-operatively. These volume increase were largely due to expansion of the subcutaneous compartments: a 35% increase on the upper legs and a 41% increase on the lower legs. Edema in the upper legs was predominantly located medially at the site of the surgical wound. In contrast, edema on the lower legs was homogenously distributed around the entire leg circumference. The muscle compartment showed no significant change of volume. However, in all patients fluid accumulations were seen in the interfascial spaces in the upper legs and in seven of these patients in the muscles as well.

Conclusion

Substantial leg edema occurs following peripheral bypass surgery. Swelling of the subcutaneous compartments is primarily responsible for the increase in leg volume. However, the majority of patients had fluid accumulations in muscles compartments as well, suggestive for reperfusion associated injury.

INTRODUCTION

Postoperative leg edema occurs frequently following peripheral bypass surgery in patients suffering from peripheral arterial occlusive disease (PAD). This edema is likely to be caused due to damage of lymphatic structures during surgery[1, 2], as well as reperfusion associated injury[3, 4]. However, the exact pathophysiological mechanisms of edema formation following peripheral bypass surgery remain unclear. Studies based on X-ray computed tomography (CT) and magnetic resonance imaging (MRI) revealed that most of the edema was located in the subcutaneous compartment[5-8]. These findings suggest that damage to lymphatic structures are likely to play a key role in edema formation. T1 relaxation times were used as an indicator of the presence of edema-like changes in the revascularized legs in one of these studies[8]. Apart from the presence of fluid in the subcutaneous tissue, a slight increase in the presence of fluid in muscle tissue was seen as well. Lymphscintigraphy was for many years considered the primary imaging modality to study lymphatic structures in patients with limb edema[9]. Abnormalities of the lymphatic system were found to correlate with edema formation following peripheral bypass surgery[10]. Recently, magnetic resonance lymphography (MRL) became available as a safe modality to image the lymphatic structures, without the disadvantages of ionizing radiation[11, 12]. Lymph flow characteristics can be recorded when repeated scans are performed following the intracutaneous administration of a contrast agent. However, this is a costly and time consuming method. Alternatively, heavily T2 weighted MRI can be used to image the lymphatic structures[13]. To study edema-like changes in muscles in patients suffering from neuromuscular diseases, T1 weighted and fat suppressed inversion recovery scan techniques can be used[14]. Aim of this study is to obtain insights in changes in subcutaneous and muscle tissue following peripheral bypass surgery that induce edema formation with fat suppressed inversion recovery scan techniques.

MATERIAL AND METHODS.

In this study, nine patients were included who underwent autologous peripheral bypass surgery. All patients suffered from severe PAD. The surgical work-up consisted of a MRI scan, including a magnetic resonance angiography (MRA) sequence, using a 1,5 Tesla MRI scanner (Magnetom Avanto, Siemens AG, Medical Technology, Erlangen, Germany). A second MRI was performed one week post-operatively after patients gave their informed consent (excluding a MRA sequence). Exclusion criteria were the usual contraindications for MRI, severe renal impairment, or a known allergy for gadolinium contrast agents. All patients used class I compression stockings (CS) above the knee postoperatively[15, 16]. The CS's were used day and night but they were removed an hour prior to the MRI scan.

Axial turbo inversion recovery magnitude (TIRM), in general referred to as fat suppressed inversion recovery scan technique, (TR 3720 ms; TE 31 ms) sequences were used to produce cross sectional images of both legs at the following six locations: I: 10 cm below the major trochanter, III: 10 cm above the knee joint space and, II: in between location I and III (Figure 1a), IV: 10 cm below the knee joint space, VI: 10 cm above the lateral malleolous and V: in between location IV an VI (Figure 1b).

Regions of interest were placed in the defined anatomic regions with a workstation (IMPAX Radiology Suite v5.2, AGFA, Mortsel, Belgium) in cooperation with an experienced radiologist. Leg circumference and the joined muscle compartments were marked up (by following the path of the fascia lata/cruris) in all cross sectional images. The marked up areas were measured with automated pixel counting and expressed in cm^2. The resulting three cross sectional areas at each location were: the whole leg, the joined muscle compartments and the subcutaneous compartment (calculated by subtracting the muscle compartment area from the whole leg area).

Regions of Interest (ROI's) counting 1 cm^2 were located in the muscles on three spots in the upper leg: vastus intermedius (flexor lodge), adductor longus (adductor lodge) and semitendinosus or semimembranosus (flexor lodge). In the lower leg ROI's were placed in the gastrocnemicus or soleus muscles (superficial flexor lodge) and in tibialis anterior or extensor digitorum longus muscles (extensor lodge). ROI's were placed in a symmetrical order in each patient. On each cross sectional image, the mean signal intensities of the ROI's were measured in the symptomatic and contralateral legs and ratio's were calculated between corresponding ROI's.

Statistical analysis was performed with Statistical Package for Social Sciences program (SPSS) 15.0 software (SPSS Inc., Chicago, IL, USA). In each subject it was determined how much the change in area of a certain location on the operated leg differed from the corresponding change in the contralateral (unaffected) leg. This resulting difference in cm^2 was considered the outcome variable of interest and taken as the dependent variable in a mixed model ANOVA. The location (with six levels) was entered in the model as explanatory within-subject factor.

A similar analysis was done after logarithmic transformation of the area-measurements. The resulting location effects were then back-transformed (by taking the antilog) so as to become interpretable as the additional percent change in the operated leg, relatively to the percent change in the unaffected control leg. For example, a change of 50% in the operated on leg *vs.* a change of 10% in the control leg would result in an additional change in the operated leg of $100 * (1.5 / 1.1 - 1) = 36\%$.

In order to limit the number of unknown parameters to be estimated, a compound symmetry structure was imposed on the residual (co)variance matrix of the repeated measurements at the six locations.

A restricted maximum likelihood method was used to estimate the location effects; this method is known to appropriately taking account of missing observations.

Figure 1a. Cross sectional images were obtained on three locations on the upper leg. From top to bottom: location I, II and III.

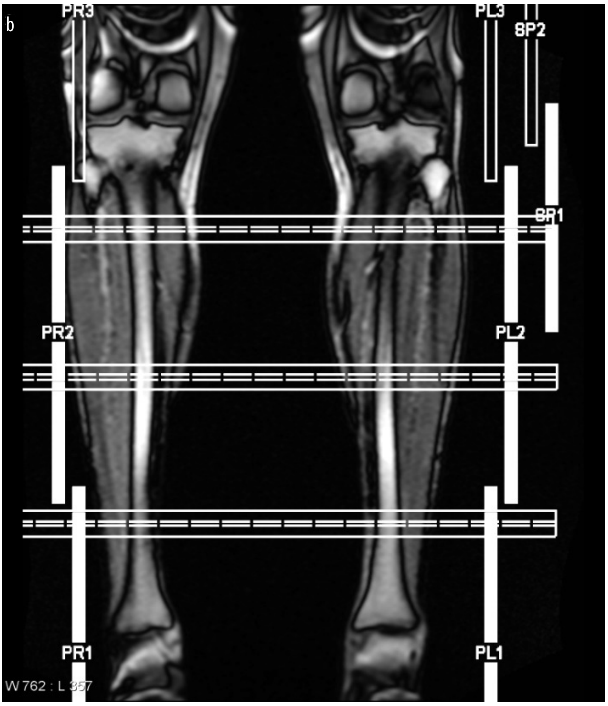

Figure 1b. Cross sectional images were obtained on three locations on the lower leg. From top to bottom: location IV, V, VI.

Two overall statistical tests were performed: (I) an overall significance test of the location effect (null-hypothesis: all location effects are zero), and (II) an overall test against heterogeneity of the location effect (null-hypothesis: all location effects are the same).

A P-value < 0.05 denotes statistical significance.

In five patients, whole leg cross sectional areas at the highest location on the upper leg (location I) could not be measured due to continuity of subcutaneous tissue of the legs with the pelvic floor. Percent gains of the upper leg were calculated by averaging outcomes of location II and location III. The images on the lowest location of the lower leg (location VI) could not be analyzed in one patient due to insufficient image quality of the fascia cruris. These images were therefore not used to calculate the percentage gain of the lower leg. Outcomes of location IV and location V were averaged to calculate percent gains of the lower legs.

Edema-like changes were recorded when fluid accumulations were seen in the subcutaneous compartment (signal increase in the subcutaneous tissue), in the interfascial spaces (signal increase in the interfascial space alone) or in the muscular compartment (signal increase in the space between single myofibres).

RESULTS

Axial scans from nine patients who underwent peripheral bypass surgery due to severe PAD (Rutherford category 3/4/5 : 3/4/2) were examined. An autologous femoropopliteal bypass was constructed in six patients (supragenicular/infragenicular: three/three), while a femorocrural bypass was constructed in three patients. Prior to surgery, there was a tendency of slightly smaller cross sectional areas of whole affected leg caused by both the subcutaneous and muscle compartments. A summary of surface measurements is presented in Table 1. Following surgery, significant differences were detected in the subcutaneous compartments and the whole leg cross sectional areas between both legs with the overall statistical test (Table 2). Significant differences between muscle compartments could not be detected with the overall model.

Significant percent increases in the cross sectional areas of the subcutaneous compartment and the whole leg were detected with the overall tests (Table 3). The whole leg cross sectional areas increased by 12% on the upper legs and by 11% on the lower legs. The subcutaneous compartment areas increased by 35% and by 41%, respectively on the upper and lower legs. An increase of the muscle compartments (including the interfascial spaces), less than 5% on the upper legs and less than 3% on the lower legs, did not reach significance at any location.

A systematic analysis of the ROI's drawn in the upper and lower leg muscles revealed no significant changes in signal intensity at any location. However, accumulations of fluid were seen in the subcutaneous compartments in revascularized legs in all patients. These accumulations were located predominantly at the medial side of the upper legs surrounding the surgical wounds. Besides, the accumulations on the upper legs were distributed inhomogenously. In

Table 1. Summary of raw surface measurements (cm^2).

			Pre-operative				Post-operative			
			affected leg		unaffected leg		affected leg		unaffected leg	
Area	Location		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Whole leg	Upper leg	Highest	237.4	43.4	232.0	40.9	255.6	43.3	232.3	39.7
		Middle	181.2	38.7	183.3	42.0	192.8	42.2	181.3	45.2
		Lowest	123.3	19.4	129.1	21.7	143.6	28.7	130.3	28.7
	Lower leg	Highest	93.1	15.0	95.7	16.7	100.6	17.8	92.0	21.5
		Middle	66.4	14.7	67.4	16.6.	74.5	17.1	69.0	16.6
		Lowest	36.8	4.8	36.1	5.1	40.2	7.4	36.4	8.1
Muscle	Upper leg	Highest	140.0	21.4	145.1	21.7	141.7	18.0	138.9	20.6
		Middle	119.6	22.3	123.7	22.9	119.7	26.6	121.4	26.3
		Lowest	83.1	10.6	86.6	12.6	89.5	10.9	87.7	16.3
	Lower leg	Highest	71.0	14.6	73.4	13.9	69.8	11.8	69.9	14.7
		Middle	49.9	10.3	50.8	11.1	50.9	12.8	51.5	13.3
		Lowest	26.6	3.1	25.9	3.6	27.4	4.8	26.2	4.5
Subcutaneous	Upper leg	Highest	100.8	18.5	92.7	20.8	116.0	22.7	98.6	19.3
		Middle	61.6	36.5	59.6	34.9	73.1	33.5	59.8	36.1
		Lowest	40.2	19.1	42.6	20.8	54.1	26.0	42.6	25.7
	Lower leg	Highest	22.1	10.2	22.2	10.3	30.8	11.4	22.1	11.0
		Middle	16.5	6.7	16.6	7.6	23.6	7.6	17.4	6.1
		Lowest	10.8	3.4	10.4	4.0	14.4	4.5	10.8	6.4

contrast, fluid accumulations on the lower leg were homogenously distributed around the entire circumference. Fluid accumulations in the upper legs were seen in the interfascial spaces in all patients, and in the muscle compartments in seven patients (Figure 2 and Figure 3). Fluid accumulations in the lower legs were seen in four patients in the interfascial spaces and in two patients in the muscle compartments.

DISCUSSION

Post-revascularization leg edema occurred following autologous peripheral bypass surgery. This edema is mainly located in the subcutaneous compartment. Cross sectional areas of the subcutaneous compartment increased by 35% on the upper legs and by 41% on the lower legs. Edema was mainly located medially surrounding the surgical wound in the upper legs. In contrast, edema was located along the entire circumference in the lower legs. Resulting increases of the whole leg cross sectional areas (by 12% and by 11% in the upper and lower legs) were mainly due to swelling of the subcutaneous areas. A small increase in size of the muscle compartment areas (including the interfascial spaces) did not reach significance.

A systematic analysis of signal intensities in the ROI's did not result in detectable significant changes in leg muscles following peripheral bypass surgery. However, accumulations of fluid

Table 2. Effect (cm^2) = change in operated leg minus change in unaffected leg

Compartment	Location		Effect (cm^2)	*P*-value	95% Confidence Interval	
					Upper Bound	Lower Bound
Whole leg	Upper leg	Highest	17.11	0.005	5.54	28.67
		Middle	13.63	0.001	6.24	21.01
		Lowest	19.10	0.000	11.72	26.48
	Lower leg	Highest	11.18	0.004	3.80	18.56
		Middle	6.51	0.082	-0.87	13.89
		Lowest	3.07	0.40	-4.31	10.45
	Overall test locations			0.000		
	Between-locations test			0.019		
Muscle	Upper leg	Highest	7.92	0.034	0.64	15.20
		Middle	2.35	0.37	-2.89	7.60
		Lowest	5.27	0.049	0.02	10.51
	Lower leg	Highest	2.38	0.36	-2.87	7.62
		Middle	0.26	0.92	-4.98	5.51
		Lowest	0.60	0.83	-4.98	6.18
	Overall test locations			0.22		
	Between-locations test			0.41		
Subcutaneous	Upper leg	Highest	9.13	0.045	0.23	18.03
		Middle	11.27	0.000	5.77	16.77
		Lowest	13.84	0.000	8.34	19.34
	Lower leg	Highest	8.80	0.003	3.31	14.30
		Middle	6.25	0.027	0.75	11.74
		Lowest	2.74	0.35	-3.13	8.61
	Overall test locations			0.000		
	Between-locations test			0.099		

appeared in selected muscles in seven out of nine patients post-operatively, as well as in the interfascial spaces in all patients.

The presence of fluid accumulations in the interfascial spaces might suggest hematoma following deep tunneled autologous bypass surgery. Although, it cannot be ruled out that this fluid originates from the subcutaneous tissue or muscle tissue: slightly elevated hydrostatic interstitial pressures have been measured in subcutaneous tissue compared to muscle tissue following femoropopliteal bypass surgery[6]. The presence of fluid accumulation in muscles however, might be more suggestive for reperfusion associated injury[3, 4, 17] . Accumulations of fluids correspond to areas with a high signal intensity on fat suppressed inversion recovery scan technique (or TIRM) MRI. Research based on this technique revealed insights in edema-like changes in muscles in patients suffering from neuromuscular diseases[14]. We used the same MRI technique to study muscular changes in PAD patients following peripheral bypass surgery. Although volume increases in the muscle compartments were not significant, edema-like

Table 3. Effect (%) = percent change in operated leg corrected for percent change in unaffected leg.

Compartment	Location		Effect (%)	*P*-value	95% Confidence Interval	
					Upper Bound	Lower Bound
Whole leg	Upper leg	Highest	6.7	0.26	-4.9	19.7
		Middle	7.8	0.064	-0.5	16.9
		Lowest	15.6	0.001	6.6	25.2
	Lower leg	Highest	13.4	0.004	4.6	22.9
		Middle	9.5	0.029	1.0	18.6
		Lowest	8.7	0.043	0.3	17.8
	Overall test locations			0.030		
	Between-locations test			0.50		
Muscle	Upper leg	Highest	6.9	0.17	-2.9	17.8
		Middle	1.7	0.63	-5.4	9.4
		Lowest	7.0	0.07	-0.5	15.1
	Lower leg	Highest	4.7	0.21	-2.7	12.5
		Middle	0.7	0.84	-6.3	8.3
		Lowest	2.0	0.61	-5.5	10.1
	Overall test locations			0.49		
	Between-locations test			0.66		
Subcutaneous	Upper leg	Highest	3.6	0.83	-25.9	45.0
		Middle	27.1	0.029	2.6	57.4
		Lowest	42.9	0.002	15.4	77.0
	Lower leg	Highest	46.9	0.001	18.6	82.0
		Middle	35.6	0.007	9.5	67.9
		Lowest	33.6	0.014	6.5	67.6
	Overall test locations			0.003		
	Between-locations test			0.51		

changes in muscle tissue might be of interest in the clinical setting as patients regularly suffer from post-operative pain following peripheral bypass surgery[18].

MRI mapping of lower leg edema following femoropopliteal bypass surgery was performed earlier by Haselgrove *et al.*[8] and by Haaverstad *et al.*[6] following either Dacron and autologous femoropopliteal bypass surgery. Whole lower leg cross sectional areas increased by 20% and limb volumes increased by 26%. When we assume that the cross sectional area of a (lower) leg is shaped circularly, then these findings are comparable to each other as long as the height of cylinder remains a constant factor. In other words, the scan images (and thus the anatomical location) from prior to surgery and following surgery should correspond to each other. In both studies fluid accumulations were detected predominantly in the subcutaneous tissue. The patterns of subcutaneous edema following femoropopliteal bypass surgery were found to show large similarities to edema in patients suffering lymphatic diseases[6]. Unfortunately, the upper legs were not imaged in these studies. It remains unknown how edema would be distributed in the upper legs when an in-situ graft, an artificial graft or an endoscopic saphenous vein harvest

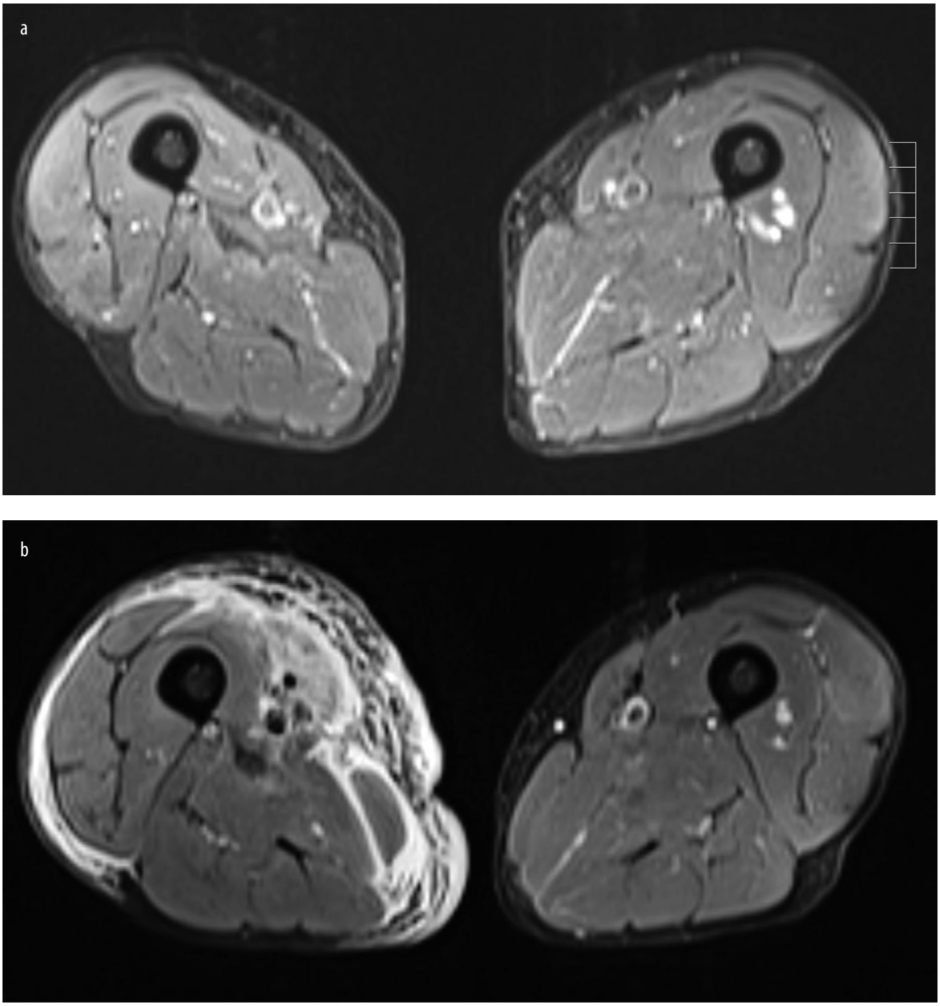

Figure 2. Cross sectional images of an upper leg before (a) and after autologous femoropopliteal bypass surgery (b). Post-operatively an increase in size of the subcutaneous compartment can be seen, as well as fluid accumulations in the subcutaneous compartment, surrounding the gracilis muscle and in the sartorius muscle.

method was used instead of a deep tunneled reversed technique[19]. An open saphenous harvest can be avoided in all these situations, leaving only two small incisions necessary to construct a peripheral bypass. A smaller wound with potentially less damage to lymphatic structures might result in a smaller amount of edema on the upper leg.

To determine the effects of CS's, this study was compared to other studies in which the use of CS's are not mentioned. Hasselgrove *et al.*[8] and Haaverstad *et al.*[6] measured whole lower leg areas, respectively volume increases of 20% and 26%. In contrast, in this study we measured an 11% increases. These findings are suggestive that CS's might reduce the amount of edema by 42% to 55%.

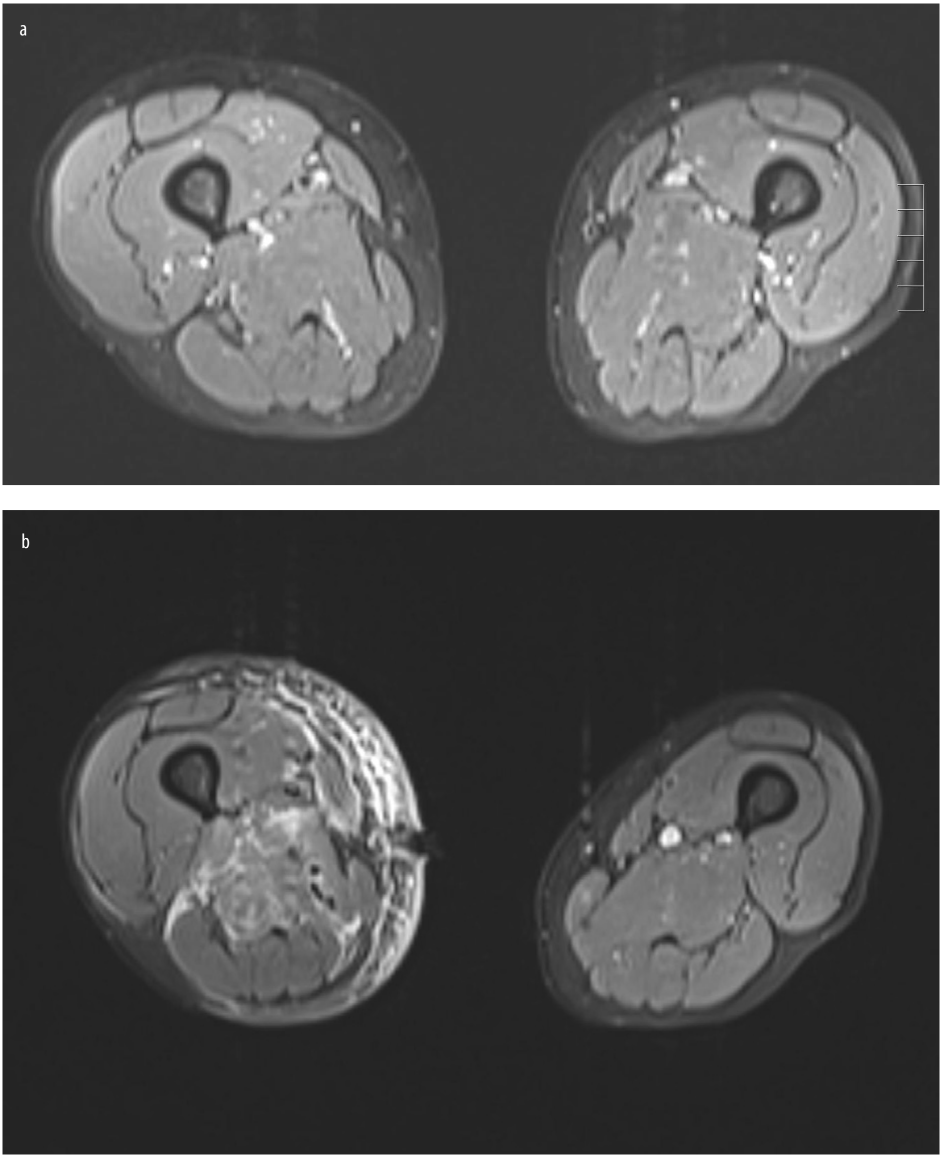

Figure 3. Upper legs of a patient who underwent autologous femoropopliteal bypass surgery pre-operatively (a) and post-operatively (b). An increase of size in the subcutaneous compartment can be seen. Fluid accumulations are seen in the subcutaneous compartment, interfascially and in the adductor longus muscle.

Nevertheless, no conclusions on these numbers can be made as this study may represent too small a sample size of patients compared to other reports. As only nine subjects were enrolled in this study, moreover suffering from missing observations on some locations, the estimated effects turned out to be rather imprecise. The wide confidence intervals of the location effects represent that imprecision. Therefore, the overall test results, especially the non-significant

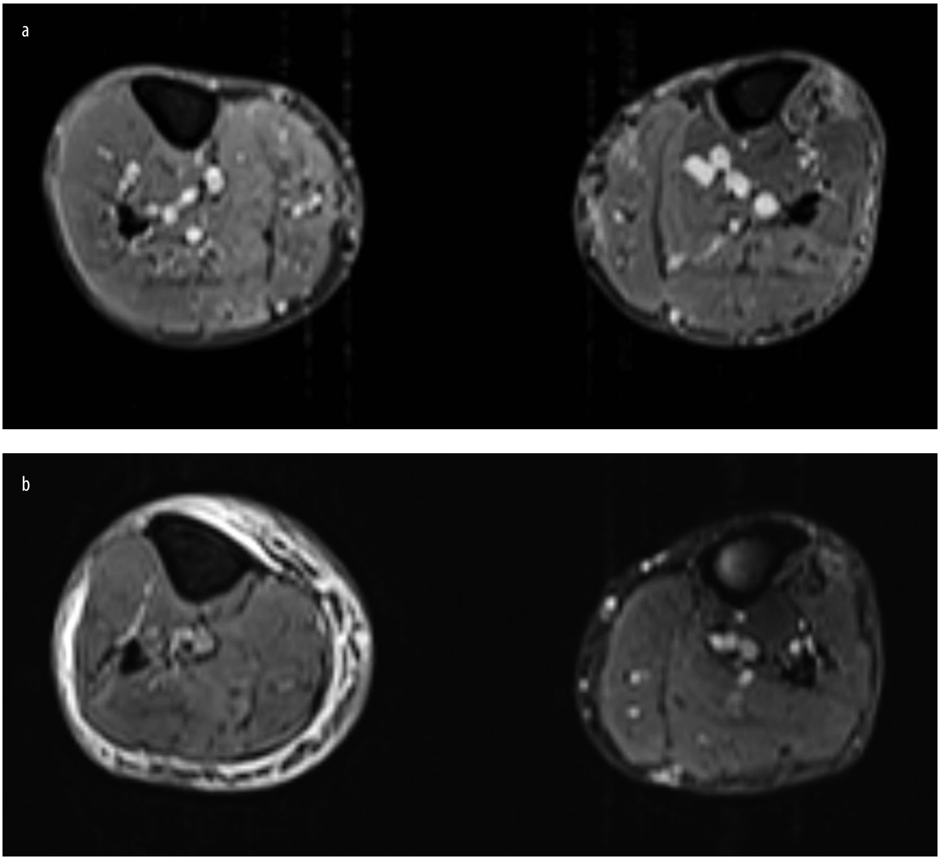

Figure 4. Lower legs of a patient who underwent autologous femoropopliteal bypass surgery pre-operatively (a) and post-operatively (b). An increase of size in the subcutaneous compartment can be seen as well as fluid accumulations. No changes to the muscular compartment can be seen.

ones, have to be interpreted with care, as it might well be the case that due to the small sample size substantial effects have been overlooked.

In a recent study by Lui *et al.* the lymphatic system was studied using MRL[11] after administrating contrast agent intracutaneously into the interdigital webs of the dorsal foot. T1 weighted images were obtained at several time points after contrast administration. In a study by Lohrmann[12], the lymphatics were imaged using a T2 weighted MRI, followed by MRL. These are new and promising methods which revealed highly detailed spatial images of the lymphatic structures, as well as dynamic information of lymph flow. Unfortunately, MRL investigation are time consuming.

The images obtained in our study, especially the images from the upper legs, suggest that damage to the lymphatics play a key role in the development of edema following femoropopliteal bypass surgery. In the upper legs the edema appeared mainly medially at the site of the surgical wounds. However, the presence of edema in the muscle compartment in seven out of nine patients cannot be overlooked. Our results do not discriminate between mechanisms such as reduced lymph drainage and increased lymph production as a result of reperfusion induced injury. To our knowledge, MRL has not yet been performed following peripheral bypass surgery. A future investigation based on dynamic MRL might elucidate the pathophysiological mechanisms of post-revascularization edema following peripheral bypass surgery.

CONCLUSION

Leg edema occurs following peripheral bypass surgery. Swelling of the subcutaneous compartments are predominantly responsible for the volume increases in upper and lower legs. Fluid accumulations appeared mainly surrounding the surgical wounds on the upper legs and appeared around the entire leg circumference on the lower legs. In addition, in a majority of patients, edema like changes in muscles were seen especially on the upper legs. These changes are suggestive for reperfusion associated injury.

REFERENCES

1. Hannequin P, Clement C, Liehn JC, Ehrard P, Nicaise H, Valeyre J. Superficial and deep lymphoscintigraphic findings before and after femoro popliteal bypass. *Eur J Nucl Med* 1988;14:141-6.
2. Storen EJ, Myhre HO, Stiris G. Lymphangiographic findings in patients with leg oedema after arterial reconstructions. *Acta Chir Scand* 1974;140:385-7.
3. Jacobs MJ, Beckers RC, Jorning PJ, Slaaf DW, Reneman RS. Microcirculatory haemodynamics before and after vascular surgery in severe limb ischaemia--the relation to post-operative oedema formation. *Eur J Vasc Surg* 1990;4:525-9.
4. Soong CV, Young IS, Lightbody JH, Hood JM, Rowlands BJ, Trimble ER, et al. Reduction of free radical generation minimises lower limb swelling following femoropopliteal bypass surgery. *Eur J Vasc Surg* 1994;8:435-40.
5. Vaughan BF. CT of swollen legs. *Clin Radiol* 1990;41:24-30.
6. Haaverstad R, Nilsen G, Myhre HO, Saether OD, Rinck PA. The use of MRI in the investigation of leg oedema. *Eur J Vasc Surg* 1992;6:124-9.
7. Hadjis NS, Carr DH, Banks L, Pflug JJ. The role of CT in the diagnosis of primary lymphedema of the lower limb. *AJR Am J Roentgenol* 1985;144:361-4.
8. Haselgrove J, Baekgaard N, Stodkilde-Jorgensen H, Christensen T. MRI mapping of postreconstructive edema following femoropopliteal bypass surgery. *Magn Reson Imaging* 1993;11:61-6.
9. Williams WH, Witte CL, Witte MH, McNeill GC. Radionuclide lymphangioscintigraphy in the evaluation of peripheral lymphedema. *Clin Nucl Med* 2000;25:451-64.
10. Urayama H, Misaki T, Watanabe Y, Bunko H. Saphenous neuralgia and limb edema after femoropopliteal artery by-pass. *J Cardiovasc Surg (Torino)* 1993;34:389-93.
11. Liu NF, Lu Q, Jiang ZH, Wang CG, Zhou JG. Anatomic and functional evaluation of the lymphatics and lymph nodes in diagnosis of lymphatic circulation disorders with contrast magnetic resonance lymphangiography. *J Vasc Surg* 2009;49:980-7.
12. Lohrmann C, Foeldi E, Speck O, Langer M. High-resolution MR lymphangiography in patients with primary and secondary lymphedema. *AJR Am J Roentgenol* 2006;187:556-61.
13. Lu Q, Xu J, Liu N. Chronic lower extremity lymphedema: a comparative study of high-resolution interstitial MR lymphangiography and heavily T2-weighted MRI. *Eur J Radiol* 73:365-73.
14. Stramare R, Beltrame V, Dal Borgo R, Gallimberti L, Frigo AC, Pegoraro E, et al. MRI in the assessment of muscular pathology: a comparison between limb-girdle muscular dystrophies, hyaline body myopathies and myotonic dystrophies. *Radiol Med* 2010;115:585-99.
15. te Slaa A, Dolmans DEJGJ, Ho GH, Mulder PGH, van der Waal JCH, de Groot HGW, et al. A prospective randomized trial to the analyze the effect of A-V impulse technology on edema following autologous femoropopliteal bypass surgery. *World J Surg* 2011;35(2):446-54.
16. te Slaa A, Dolmans DE, Ho GH, Mulder PG, van der Waal JC, de Groot HG, et al. Evaluation of A-V Impulse Technology as a Treatment for Oedema Following Polytetrafluoroethylene Femoropopliteal Surgery in a Randomised Controlled Trial. *Eur J Vasc Endovasc Surg* 2010;40(5):635-42
17. Campbell H, Harris PL. Albumin kinetics and oedema following reconstructive arterial surgery of the lower limb. *J Cardiovasc Surg (Torino)* 1985;26:110-5.
18. Allen PD, Walman T, Concepcion M, Sheskey M, Patterson MK, Cullen D, et al. Epidural morphine provides postoperative pain relief in peripheral vascular and orthopedic surgical patients: a dose-response study. *Anesth Analg* 1986;65:165-70.
19. Illig KA, Rhodes JM, Sternbach Y, Shortell CK, Davies MG, Green RM. Reduction in wound morbidity rates following endoscopic saphenous vein harvest. *Ann Vasc Surg* 2001;15:104-9.

Chapter 8

General discussion

Summary

GENERAL DISCUSSION

The basis of today's vascular surgery was set through the work of Alexis Carrel at the beginning of the twentieth century. "Between 1901 and 1910, Alexis Carrel, using experimental animals, performed every feat and developed every technique known to vascular surgery today" (except for some recent technology driven innovations) writes Julius H. Comroe[1]. However, it was not until 1949 that Jean Kunlin performed the first autologous femoropopliteal bypass reconstruction. But the true advent of reconstructive vascular surgery was the Korean war, especially for arterial injury[2]. Massive edema following arterial repairs could be avoided if accompanying venous injuries were repaired simultanously[3]. However, it remains questionable whether venous obstructions contribute to edema development following peripheral bypass surgery in patients suffering from peripheral arterial disease (PAD). Edema typically emerges in the first post-operative week and lasts up to three months, although cases of chronic edema have been reported[4]. On average, limb volume increases of 20 to 26% of the initial volume have been reported[5, 6]. The pathophysiological mechanisms that cause formation of post-revascularization edema following peripheral bypass surgery have been studied since the 1960's.

Chapter 3 of this thesis consists of a review of possible pathophysiological mechanisms that lead to edema formation following peripheral bypass surgery, and strategies to reduce the amount of edema. Besides venous impairment, four other mechanisms that might cause post-revascularization edema have been formulated in literature: hyperemia[7-9], an increased microvascular permeability[10-12], reperfusion associated injury[13, 14] and lymphatic disruptions[15, 16].

Remarkably, edema is almost absent following endovascular revascularizations[17] and aorto-iliac or iliacfemoral arterial reconstructions[18]. As peripheral lymphatic structures are spared in these procedures, it is very likely that lymphatic disruptions do play a key role in edema formation following femoropopliteal bypass reconstructions, since lymphatic structures are prone to damage during surgery[15, 16]. It must be noted that conflicting results have been reported of strategies that comprise modified inguinal incisions to spare the lymphatic structures[19, 20].

A study presented in **chapter 7** of this thesis showed that post-operative edema following autologous femoropopliteal bypass surgery was mainly due to swelling of the subcutaneous compartments, alike lymphedema[5]. Edema was located predominantly at the medial side of the upper legs surrounding the surgical wounds, while on the lower legs it surrounded the entire circumference. Distribution of edema in the upper legs had not been reported before[5, 6]. These finding favor the idea that damage to lymphatic structures play a major role in the formation of post-operative edema that occurs after femoropopliteal bypass surgery. Edema-like changes were detected in selected muscles as well following bypass surgery. These edema-like changes are likely due to reperfusion associated injury[12, 21, 22]. However, the muscle compartments did not swell significantly and therefore reperfusion associated injury is unlikely to be a major contributing factor in postoperative edema formation.

Preventive and treatment strategies of post-revascularization edema include the administration of anti-oxidative medicine[22, 23], lymph massage techniques[24], the use of compression stockings (CS)[25] and leg elevation (Table 1). The use of anti-oxidative medicine has not become widespread in the vascular practice, even though the results of these trials were encouraging. CS's are widely used, but the effectiveness is mostly judged on clinical experience and was not studied thoroughly yet.

Table 1. Overview of RCT's of treatment options to prevent and/or reduce post-revascularization edema.

Authors	Intervention	Control	Outcome
Husni *et al.*[10]	Dextran administration or heparin adiminstration	Did not receive dextran of haparine	No difference between intervention and control patients.
AbuRahma *et al.*[19]	Lymph sparing dissection	Conventional dissection	Significant fewer patient developed edema following lymph sparing dissection.
Balzer *et al.*[24]	Lymph massage	Without lymph massage	Significant less gain in leg circumference with lymph massage.
Soong *et al.*[22]	Allopurinol administration	Placebo	Significant less gain in leg volume following allopurinol.
Haaverstad *et al.*[20]	Lateral inguinal incision	Conventional inguinal incision	No significant difference in gain in limb volume.
Rabl *et al.*[23]	Multivitamin cocktail (Omnibionta®)	Did not receive Omnibiota®	Significant less gain in limb circumference following Omnibiota®

The use of intermittent pneumatic compression (IPC) has been proven effective in reducing edema originating from orthopedic lower limb surgery[26, 27], lymphatic disorders[28, 29] and venous disorder[29, 30]. In **chapter 4** and **5** of this thesis, two studies are presented based on a randomized controlled trial to investigate the efficacy of IPC on post-operative edema following femoropopliteal bypass surgery. In these studies, patients were either operated on using an autologous or a polytetrafluoroethylene (PTFE) bypass graft. Leg circumference measurements (by using a tape measure), as well as inflammatory parameters were obtained prior to surgery and at post-operative moments. The intervention group consisted of patients who were treated with IPC on the foot (A-V impulse technology, Orthofix Vascular Novamedix, Andover, UK) on the affected limb during seven nights after the operation. Control group patients received a class-I compression stocking (CS) post-operatively day and night during a week.

The use of IPC resulted in significantly more edema than the use of CS's in patients who were operated on using an autologous bypass,: 7.9% *vs.* 2.5% increase in lower leg circumference. Significant differences between groups were not found in patients who underwent PTFE femoropopliteal bypass surgery: 6.6% *vs.* 6.1% increase in lower leg circumference. However, patients who underwent revision peripheral bypass surgery, gained an 3.9% additional increase in lower leg circumference compared to patients who were operated on for the first-time. It is likely that a revision operation leads to further lymphatic damage, and thus more edema in already scarred tissue.

The results of the application of IPC to reduce post-operative edema were disappointing in comparison to what could have been expected from the orthopedic findings. It could be that following orthopedic surgery, hematoma resulting from a fracture of intra-articular swelling compresses venous vessels and lymphatic structures[31]. The satisfactory application of IPC in these situations might be through the assistance in emptying of the terminal lymphatics and in increasing the venous blood pressure[32, 33]. However, IPC also attributes to the arterial flow[34, 35]. Autoregulation mechanisms in the legs that normally maintain a constant perfusion pressure through vasoconstriction and vasodilatation at the arterial side, fail in patients suffering from PAD[36, 37]. Using IPC immediately post-operatively has could have amplified a hyperemic effect. Under normal circumstances, hyperemia attributes marginally at most to the development of edema. This hyperemic effect probably outweighed the enhancements in venous and lymphatic flow. Symptoms of hyperemia were not seen in the patients who used the CS's. Surprisingly, no significant differences could be detected between patients who used IPC or CS's following PTFE femoropopliteal bypass surgery. However, it seemed that IPC group patients who received an autologous bypass, developed slightly more edema than patients who received a PTFE bypass. Possibly, the removal of an autologous vein contributes to an inadequate venous backflow when IPC is applied postoperatively. Patients in the CS groups who underwent autologous bypass surgery developped a smaller amount of edema than patients who underwent PTFE bypass surgery. It remains unclear why CS's were more effective following autologous grafting in comparison to PTFE grafting. In the absence of CS's, the type of graft has not previously been mentioned to influence the amount of post-operative edema[19, 20].

Following peripheral bypass surgery, limb volume increases 20% to 26%, that can be measured using magnetic resonance imaging (MRI)[5, 6]. The use of CS's were not mentioned in these studies. An MRI study of postoperative changes following autologous peripheral bypass surgery is presented in **chapter 7**. In patients who used CS's postoperatively, leg volume increase of only 11% to 12% was be measured. In **chapter 4** and **5**, tape measures were used to quantify the amount of edema. Volume changes can be estimated using circumferential measurements, assuming that leg cross sectional surfaces are circularly shaped. By doing so, all patients developed less edema (5% to 16% volume increase) compared to the MRI measurements found in literature[5, 6]. However, such numbers should be interpreted very carefully as outcomes of different measurement methods are not interchangeable[38]. Moreover, all these studies deal with relatively small numbers. Nonetheless, by comparing our findings with literature, we proved that CS's reduce the amount of post-operative edema that occurs following peripheral bypass surgery. It is observed however, that the application of IPC does not seem to have worsened the situation, but it cannot be considered an effective method to treat post-revascularization edema.

Changes in inflammatory parameters following peripheral bypass surgery were recorded as well in **chapter 4** and **5**. Increases of C-reactive protein (CRP) levels and leukocyte counts are associated with the cardiovascular disease severity and are of a predictive value of cardiovascular events[39, 40]. Elevated levels of CRP are associated with graft related events as well[41]. Inflammatory parameters were increased following peripheral bypass surgery. No significant differences could be detected between patients who used IPC postoperatively and patients who used CS's. A firm correlation could not be detected between edema, inflammatory parameters and postoperative events. However, a tendency of more wound infections and a prolonged hospital stay seemed to be present in patients who developed more edema. An standard approach towards edema with the use of CS's will probably be beneficial to all patients following peripheral bypass surgery.

Measures of health that include the impact of disease and impairment on daily activities and behavior, perceived health and disability and functional status have been described as "the missing measurements in health"[42]. QoL measurements that include the mentioned elements, have introduced a humanistic element in health care[43]. We studied the effects of peripheral bypass surgery on the QoL in **chapter 6** of this thesis. Using an abbreviated version of the World Health Organisation Quality of Life assessment instrument, we measured an increase in QoL on physical health as soon as after two weeks following peripheral bypass surgery. Improvements in QoL and health status were measured following peripheral bypass surgery at two weeks and at three months after surgery[44, 45]. Although PAD patients often suffer from comorbid conditions, an aggressive approach towards revascularisation seems to be justified from the patient's perspective.

This thesis is based on a basic clinical research project. Surprisingly, we detected beneficial effects of CS's on post-reconstructive edema that has not been documented before. The sole use of IPC following peripheral bypass surgery cannot reduce the amount of post-operative edema. Potential beneficial effects on edema of applying IPC day and night, might negatively influence other clinical parameters. In possible future studies, the application of IPC might be combined with the use of CS's.

The pathophysiological mechanisms that lead to post-revascularization edema are not fully elucidated yet, although it is very likely that this edema is mainly due to damage of lymphatic structures. Fat suppressed inversion recovery scan techniques and T1 MRI revealed that post-revascularization edema is alike lymph edema, but they did not reveal any information about the lymph flow[5]. Recently, magnetic resonance lymphography (MRL) has become available as a safe modality to image the lymphatic structures and funtion[46, 47]. To our knowledge, MRL has not yet been performed following peripheral bypass surgery. A future investigation based on dynamic MRL might elucidate the pathophysiological mechanisms of post-revascularization edema following peripheral bypass surgery.

REFERENCES

1. Comroe JH. *Exploring the Heart: Discoveries in Heart Disease and High Blood Pressure*. WW Norton & Co Inc: New York, 1983; 348.
2. Hughes CW. Arterial repair during the Korean war. *Ann Surg* 1958;147:555-61.
3. Sullivan WG, Thornton FH, Baker LH, LaPlante ES, Cohen A. Early influence of popliteal vein repair in the treatment of popliteal vessel injuries. *Am J Surg* 1971;122:528-31.
4. Vaughan BF, Slavotinek AH, Jepson RP. Edema of the lower limb after vascular operations. *Surg Gynecol Obstet* 1970;131:282-90.
5. Haaverstad R, Nilsen G, Myhre HO, Saether OD, Rinck PA. The use of MRI in the investigation of leg oedema. *Eur J Vasc Surg* 1992;6:124-9.
6. Haselgrove J, Baekgaard N, Stodkilde-Jorgensen H, Christensen T. MRI mapping of postreconstructive edema following femoropopliteal bypass surgery. *Magn Reson Imaging* 1993;11:61-6.
7. Simeone FA, Husni EA. The hyperemia of reconstructive arterial surgery. *Ann Surg* 1959;150:575-85.
8. Sumner DS, Folse R. Persistent hyperemia following prolonged arterial occlusion. *Ann Surg* 1968;168:837-43.
9. Wellington JL, Olszewski V, Martin P. Hyperaemia of the calf after arterial reconstruction for atherosclerotic occlusion. A plethysmographic study. *Br J Surg* 1966;53:180-4.
10. Husni EA. The edema of arterial reconstruction. *Circulation* 1967;35:I169-73.
11. Junger M, Frey-Schnewlin G, Bollinger A. Microvascular flow distribution and transcapillary diffusion at the forefoot in patients with peripheral ischemia. *Int J Microcirc Clin Exp* 1989;8:3-24.
12. Campbell H, Harris PL. Albumin kinetics and oedema following reconstructive arterial surgery of the lower limb. *J Cardiovasc Surg (Torino)* 1985;26:110-5.
13. Soong CV, Young IS, Blair PH, Hood JM, Rowlands BJ, Trimble ER, et al. Lipid peroxidation as a cause of lower limb swelling following femoro-popliteal bypass grafting. *Eur J Vasc Surg* 1993;7:540-5.
14. Gimbrone MA, Jr., Brock AF, Schafer AI. Leukotriene B4 stimulates polymorphonuclear leukocyte adhesion to cultured vascular endothelial cells. *J Clin Invest* 1984;74:1552-5.
15. Hannequin P, Clement C, Liehn JC, Ehrard P, Nicaise H, Valeyre J. Superficial and deep lymphoscintigraphic findings before and after femoro popliteal bypass. *Eur J Nucl Med* 1988;14:141-6.
16. Storen EJ, Myhre HO, Stiris G. Lymphangiographic findings in patients with leg oedema after arterial reconstructions. *Acta Chir Scand* 1974;140:385-7.
17. Payne SP, Jones K, Painter D, Galland RB, Collin J. Does the limb swell after revascularisation by percutaneous transluminal angioplasty? *Eur J Vasc Endovasc Surg* 1995;9:272-6.
18. Eickhoff JH, Engell HC. Local regulation of blood flow and the occurrence of edema after arterial reconstruction of the lower limbs. *Ann Surg* 1982;195:474-8.
19. AbuRahma AF, Woodruff BA, Lucente FC. Edema after femoropopliteal bypass surgery: lymphatic and venous theories of causation. *J Vasc Surg* 1990;11:461-7.
20. Haaverstad R, Johnsen H, Saether OD, Myhre HO. Lymph drainage and the development of post-reconstructive leg oedema is not influenced by the type of inguinal incision. A prospective randomised study in patients undergoing femoropopliteal bypass surgery. *Eur J Vasc Endovasc Surg* 1995;10:316-22.
21. Jacobs MJ, Beckers RC, Jorning PJ, Slaaf DW, Reneman RS. Microcirculatory haemodynamics before and after vascular surgery in severe limb ischaemia--the relation to post-operative oedema formation. *Eur J Vasc Surg* 1990;4:525-9.
22. Soong CV, Young IS, Lightbody JH, Hood JM, Rowlands BJ, Trimble ER, et al. Reduction of free radical generation minimises lower limb swelling following femoropopliteal bypass surgery. *Eur J Vasc Surg* 1994;8:435-40.
23. Rabl H, Khoschsorur G, Petek W. Antioxidative vitamin treatment: effect on lipid peroxidation and limb swelling after revascularization operations. *World J Surg* 1995;19:738-44.
24. Balzer K, Schonebeck I. [Edema after vascular surgery interventions and its therapy]. *Z Lymphol* 1993;17:41-7.
25. Schubart PJ, Porter JM. Leg Edema Following Bypass. In: *Reoperative Arterial Surgery*, Bergan JJ (ed). Grune & Stratton: Orlando, 1986; 328-9.
26. Stranks GJ, MacKenzie NA, Grover ML, Fail T. The A-V Impulse System reduces deep-vein thrombosis and swelling after hemiarthroplasty for hip fracture. *J Bone Joint Surg Br* 1992;74:775-8.

27. Gardner AM, Fox RH, Lawrence C, Bunker TD, Ling RS, MacEachern AG. Reduction of post-traumatic swelling and compartment pressure by impulse compression of the foot. *J Bone Joint Surg Br* 1990;72:810-5.
28. Klein MJ, Alexander MA, Wright JM, Redmond CK, LeGasse AA. Treatment of adult lower extremity lymphedema with the Wright linear pump: statistical analysis of a clinical trial. *Arch Phys Med Rehabil* 1988;69:202-6.
29. Pflug JJ. Intermittent compression in the management of swollen legs in general practice. *Practitioner* 1975;215:69-76.
30. Coleridge Smith PD, Thomas P, Scurr JH, Dormandy JA. Causes of venous ulceration: a new hypothesis. *Br Med J (Clin Res Ed)* 1988;296:1726-7.
31. Schroder D, Passler HH. Combination of cold and compression after knee surgery. A prospective randomized study. *Knee Surg Sports Traumatol Arthrosc* 1994;2:158-65.
32. Blackshear WM, Jr., Prescott C, LePain F, Benoit S, Dickstein R, Seifert KB. Influence of sequential pneumatic compression on postoperative venous function. *J Vasc Surg* 1987;5:432-6.
33. Griffin M, Kakkos SK, Geroulakos G, Nicolaides AN. Comparison of three intermittent pneumatic compression systems in patients with varicose veins: a hemodynamic study. *Int Angiol* 2007;26:158-64.
34. Eze AR, Comerota AJ, Cisek PL, Holland BS, Kerr RP, Veeramasuneni R, et al. Intermittent calf and foot compression increases lower extremity blood flow. *Am J Surg* 1996;172:130-4; discussion 5.
35. Delis KT, Husmann MJ, Szendro G, Peters NS, Wolfe JH, Mansfield AO. Haemodynamic effect of intermittent pneumatic compression of the leg after infrainguinal arterial bypass grafting. *Br J Surg* 2004;91:429-34.
36. Henriksen O. Local sympathetic reflex mechanism in regulation of blood flow in human subcutaneous adipose tissue. *Acta Physiol Scand Suppl* 1977;450:1-48.
37. Henriksen O. Orthostatic changes of blood flow in subcutaneous tissue in patients with arterial insufficiency of the legs. *Scand J Clin Lab Invest* 1974;34:103-9.
38. Labs KH, Tschoepl M, Gamba G, Aschwanden M, Jaeger KA. The reliability of leg circumference assessment: a comparison of spring tape measurements and optoelectronic volumetry. *Vasc Med* 2000;5:69-74.
39. Arain FA, Khaleghi M, Bailey KR, Lahr BD, Rooke TW, Kullo IJ. White blood cell count predicts all-cause mortality in patients with suspected peripheral arterial disease. *Am J Med* 2009;122:874 e1-7.
40. Wilson AM, Ryan MC, Boyle AJ. The novel role of C-reactive protein in cardiovascular disease: risk marker or pathogen. *Int J Cardiol* 2006;106:291-7.
41. Owens CD, Ridker PM, Belkin M, Hamdan AD, Pomposelli F, Logerfo F, et al. Elevated C-reactive protein levels are associated with postoperative events in patients undergoing lower extremity vein bypass surgery. *J Vasc Surg* 2007;45:2-9; discussion
42. Fallowfield L. *Quality of life; Health status indicators; Evaluation*, 1990; 234.
43. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. *Psychol Med* 1998;28:551-8.
44. Engelhardt M, Bruijnen H, Scharmer C, Wohlgemuth WA, Willy C, Wolfle KD. Prospective 2-years follow-up quality of life study after infrageniculate bypass surgery for limb salvage: lasting improvements only in non-diabetic patients. *Eur J Vasc Endovasc Surg* 2008;36:63-70.
45. Aquarius AE, Denollet J, Hamming JF, Breek JC, De Vries J. Impaired health status and invasive treatment in peripheral arterial disease: a prospective 1-year follow-up study. *J Vasc Surg* 2005;41:436-42.
46. Liu NF, Lu Q, Jiang ZH, Wang CG, Zhou JG. Anatomic and functional evaluation of the lymphatics and lymph nodes in diagnosis of lymphatic circulation disorders with contrast magnetic resonance lymphangiography. *J Vasc Surg* 2009;49:980-7.
47. Lohrmann C, Foeldi E, Speck O, Langer M. High-resolution MR lymphangiography in patients with primary and secondary lymphedema. *AJR Am J Roentgenol* 2006;187:556-61.

SUMMARY

This thesis is based on a clinical research project which was carried out in the Amphia hospital (Breda, the Netherlands). It consists of six studies desribed in **Chapters 2** to **7**.

Chapter 2 reviews historic up to present insight into the pathophysiological mechanisms that underlay edema formation following peripheral bypass surgery. Various factors, including hyperemia, increases in capillary permeability, reperfusion associated injury, lymphatic and venous disorders, are described to contribute to edema formation following femoropopliteal bypass surgery. In addition, preventive and treatment strategies of post-operative edema are reviewed. These strategies consist of the administration of anti-oxidative drugs, lymph sparing surgical techniques, lymphatic massages, the use of compression stockings (CS) and the application of intermittent pneumatic compression (IPC).

In **chapter 3** a method to assess leg circumferences based on tape measures, was tested for repeatability and reproducibility. Four observers performed leg measurements on eleven subjects at six moments. The short-term (one week) and long-term (three months) intra-class correlation coefficients equal 0.90 and 0.78 respectively. The reproducibility index (limits of agreement) equaled 6.5% on the long-term and 4.4% on the short-term within a subject. The intra-class correlation increased to 0.94 on the short-term and 0.82 on long-term when only one observer was involved. The short-term reproducibility index then became 3.3%. These findings were in accordance to findings in the literature. The use of a tape measure to do repeated leg circumference measurement on clinical patients can be considered a proper method.

In **chapter 4**, **chapter 5** and **chapter 6** we presented the effects of IPC on leg edema, inflammatory parameters and quality of life in patients following femoropopliteal bypass surgery. A single center randomized controlled trial (RCT) was held between 2006 and 2009 in the Amphia Hospital. In this trial the use of IPC was compared to the use of compression stocking (CS) therapy following either autologous and polytetrafluoroethylene (PTFE) femoropopliteal bypass surgery. We choose to use IPC on the foot (A-V impulse technology, Orthofix Vascular Novamedix, Andover, UK). The trial was held on an "intention-to-treat basis". Patients who were assigned to the IPC group, used IPC at night only, so not to infer with early rehabilitation and mobilization schedules. IPC was used only during the stay in hospital. Patients in the IPC group, did not use a CS's during the day. Patients in the CS group used class I stockings above the knee day and night. At discharge from hospital, all patients used CS's at day during seven more weeks. Key endpoints in this study were: (I) edema reduction, (II) changes in inflammatory parameters and (III) gains in quality of life (QoL).

In **chapter 4** the effects of IPC on post-revascularization edema and inflammatory parameters following autologous femoropopliteal bypass surgery are presented. A total of 62 patients were included in this study. Of them, data from 57 patients were analyzed (CS:28 / IPC:29). Indications for operation were severe claudication (CS:13 / IPC :13), rest pain (10 / 5) or tissue loss (7 / 11). Revascularization was performed with either a supragenicular (CS:13 / IPC:10) or an infragenicular (15 / 19) bypass. Leg circumference increased on day 1 (CS:-0.4% / IPC:2.7%), day 4 (2.1% / 6.1%), day 7 (2.5% / 7.9%), day 14 (4.7% / 7.3%) and day 90 (1.0% / 3.3%) from baseline (pre-operative situation). On day 1, 4 and 7 there was a significant difference for leg circumference between treatment groups: the application of IPC resulted in more edema then the use of CS's. Inflammatory parameters increased following surgery, but did not correlate with the leg circumference. No significant differences in concentrations of inflammatory parameters between the groups were detected. However, there was a tendency of more wound infections and a prolonged hospital stay in patients who had a larger amount of edema: patients who used IPC. So this study has resulted in the conclusion that the use of IPC leads to a short-term increase in edema. However, the amount of edema decreased to the same extent when patients switched to using CS's at discharge from hospital. It was concluded that the use of CS's should remain the recommended practice following femoropopliteal surgery.

In **chapter 5** the effects of IPC are presented in patients who underwent PTFE femoropopliteal bypass surgery. A total of 39 patients were revascularized using PTFE bypass. All patients who underwent PTFE femoropopliteal bypass surgery were not available for autologous grafting due to a missing of small caliber saphenous vein. Thirty-six patients were included in the analysis (CS:19 / IPC:17). Indications for operation were severe claudication (CS:6 / IPC:2), rest pain (5 / 8) or tissue loss (8 / 7). Of the 36 patients, 9 patients were re-operated. Revascularization was performed with either a supragenicular (CS:6 / IPC:6) or an infragenicular (13 / 11) bypass. Limb circumference has increased post-operatively on day 1 (CS:1.5% / IPC:1.4%), on day 4 (5.7% / 6.3%), on day 7 (6.6% / 6.1%), on day 14 (7.9% / 7.7%) and on day 90 (5.8% / 5.2%). Inflammatory parameters increased following surgery, but did not correlate with the leg circumference. Differences in leg circumferences and inflammatory parameters between the treatment groups were not significant. A re-operation gave a significant 3.9% increase in circumference as compared to a first time performed operation. Unlike patients who underwent autologous femoropopliteal bypass surgery, the use of CS's could not reduce the amount of edema in patients who underwent PTFE femoropopliteal bypass surgery.

In **chapter 6** the results were presented from QoL assessments that were taken from the patients who underwent peripheral bypass surgery. These patients were enrolled in a RCT presented in **chapter 4** and **chapter 5**. By type of bypass two groups were considered: patients who underwent autologous femoropopliteal bypass surgery and patients who underwent PTFE femoropopliteal bypass surgery. We used a QoL assessment instrument provided by the World Health Organization: the WHOQOL-BREF, an abbreviated version of the WHOQOL-100. In the WHOQOL-BREF 24 facets of quality of life are incorporated into four domains: Physical health, Psychological health, Social relationships and Environment. In addition, two facets representing the General Health are included.

At baseline significant differences in General health and nearly signficant differences in Psychological health were detected to the disadvantage of patient in the PTFE group. No significant differences were detected on the other domains. The most pronounced depressions in

Qol detected on de domain of Physical health: on average, 47% to 52% of the highest possible score was responded. Following peripheral bypass surgery, significant increases were detected on the domain of Physical health at two weeks and at three months following femoropopliteal bypass surgery. On all domains, no effects of the bypass type could be detected on the changes in QoL.

The domain of physical health incorporates among others facets like pain and discomfort, sleep and rest, mobility and activities of daily living. It is understandable that QoL improved as soon as after two weeks, when most of the ischemic pain was reduced (54% of the patients experienced PAD Rutherford category 4-6). However, we could not detect effects of edema on the QoL. This is probably reflected by the fact that no significant differences in leg circumference could be detected at two weeks and three months, when the QoL assessments were taken.

In **chapter 7** we presented a study in which magnetic resonance imaging (MRI) was used in patients prior to and following autologous peripheral bypass surgery. We used a fat suppressed inversion recovery scan technique to study edema-like changes in both muscle and subcutaneous tissue. Axial scans were made of the legs at six levels. All patients used CS's day and night the first week following surgery as described in **Chapter 3**. The CS's were removed an hour before the MRI scan. A fat-suppressed inversion recovery MRI scan technique was used.

Following peripheral bypass surgery, leg edema is mainly located in the subcutaneous compartment surrounding the surgical incision on the upper legs. Edema appeared following the entire circumference of the lower legs. Cross sectional areas of the whole legs increased by 12% and by 11% in the upper and lower legs, respectively. Cross sectional areas of the subcutaneous compartment increased by 35% on the upper legs and by 41% on the lower legs. A significant increase in the muscle compartments could not be detected. However, accumulations of fluid appeared in selected muscles in seven out of nine patients post-operatively. Although the swelling of the subcutaneous compartments associated with post-revascularization edema is alike lymphatic edema, the presence of fluid accumulation in muscles might be suggestive for some reperfusion associated injury.

Chapter 9

Summary in Dutch / Nederlandse samenvatting

SAMENVATTING

Dit proefschrift is gebaseerd op klinisch wetenschappelijk onderzoek dat werd verricht in het Amphia Ziekenhuis te Breda. Het omvat zes samenhangende studies die zijn beschreven in de **hoofdstukken 2** tot en met **7**.

In **Hoofdstuk 1** wordt een algemene introductie gegeven op dit proefschrift. Deze bestaat uit een korte uiteenzetting van de symptomen waarmee perifeer arterieel obstructief vaatlijden gepaard gaat. Hierna wordt een overzicht gegeven van de aan dit proefschrift onderliggende onderzoeken.

Hoofdstuk 2 bestaat uit een overzicht van de bestaande literatuur over pathofysiologische mechanismen die kunnen leiden tot oedeem na perifere bypasschirurgie. Het ontstaan van dit oedeem wordt toegeschreven aan verschillende factoren, zoals hyperemie, toename van de capillaire permeabiliteit, door reperfusie geïnduceerde schade en beschadiging van lymfatische en veneuze structuren. In dit hoofdstuk worden tevens de bekende preventie- en behandelstrategieën van dit postoperatief optredende oedeem besproken. Deze strategieën zijn gebaseerd op een reeks van maatregelen, zoals anti-oxidatieve medicatie, chirurgische technieken om de lymfatische structuren te sparen, lymfemassagetechnieken, compressiekousen (CK) en intermitterende pneumatische compressie (IPC).

In **hoofdstuk 3** wordt een onderzoek beschreven waarin de betrouwbaarheid en de reproduceerbaarheid is onderzocht van een in de kliniek gangbare methode om beenomtrekken te meten. Hierbij wordt gewoonlijk gebruik gemaakt van meetlinten en anatomische referentiepunten. In dit prospectief uitgevoerde onderzoek werden door vier waarnemers, op zes momenten in de tijd, omtrekmetingen verricht aan de onderbenen van elf gezonde proefpersonen. Van deze herhaalde metingen bleken de korte termijn (één week) en de lange termijn (drie maanden) intraklasse correlatiecoëfficiënten 0,90 en 0,78 te bedragen. De reproduceerbaarheidsindex (limieten van overeenkomst) binnen één proefpersoon kwam overeen met 6,5% op de lange termijn en 4,4% op de korte termijn. De intraklasse correlatiecoëfficiënt kon worden verhoogd tot 0,94 op de korte termijn en tot 0,82 op lange termijn, wanneer de metingen zich beperkten tot één waarnemer. De korte termijn reproduceerbaarheidsindex verbeterde in dat geval naar 3,3%. De uit dit onderzoek gebleken intraklasse correlatiecoëfficiënten en reproduceerbaarheidsindices komen overeen met soortgelijke meetmethoden, zoals reeds eerder zijn beschreven in de literatuur. Het gebruik van een meetlint om herhaalde beenomtrekken te meten, kan beschouwd worden als een eenvoudige, maar geschikte methode.

In de **hoofdstukken 4, 5** en **6** worden de effecten van de postoperatieve toepassing van IPC bij patiënten die perifere bypasschirurgie ondergingen, geanalyseerd. De mate van postoperatieve oedeemvorming, alsook de veranderingen in ontstekingsparameters die zich in deze periode voordoen, waren onderwerp van studie. Bovendien werden de effecten op van perifere bypasschirurgie en de toepassing van IPC in het bijzonder op de kwaliteit van leven onderzocht.

Deze hoofdstukken hebben hun basis in een prospectief gerandomiseerd onderzoek dat werd verricht in het Amphia ziekenhuis in Breda in de periode 2006 tot 2009. Patiënten bij wie in de postoperatieve fase IPC werd toegepast, vormden de interventiegroep. De controlegroep bestond uit patiënten die postoperatief een compressiekous kregen voorgeschreven. De effecten van IPC werden zowel bestudeerd bij patiënten die een autologe femoropopliteale bypassoperatie ondergingen, als bij patiënten die polytetrafluorethyleen (PTFE) femoropopliteale bypass kregen. Geen van de patiënten die deelnamen aan dit onderzoek kwamen in aanmerking voor een zogenaamde "minimaal invasieve" behandelingen. Er werd gebruik gemaakt van IPC op de voet (A-V impuls technologie, Orthofix Vascular Novamedix, Andover, Verenigd Koninkrijk). Dit onderzoek was gebaseerd op 'intention-to-treat' uitgangspunten, inhoudende dat alle patiënten werden behandeld naar op dat moment geldende inzichten en dat van het gebruik van IPC, respectievelijk compressiekousen, afgeweken kon worden naar inzicht van de behandelaar. Patiënten in de IPC-groep, gebruikten IPC alleen 's nachts zodat zij overdag niet werden gehinderd tijdens het mobiliseren en revalideren. IPC werd alleen toegepast in de eerste week na de operatie, tijdens het verblijf in het ziekenhuis. Patiënten in de IPC-groep, kregen geen compressiekousen op de tijdstippen dat de IPC niet actief was. Patiënten in de compressiekousengroep kregen direct na de operatie een klasse I kous aangemeten aan het geopereerde been. De patiënten in de compressiekousengroep droegen de kousen gedurende de eerste week 24 uur per dag. Na ontslag uit het ziekenhuis, werden patiënten uit beide groepen gedurende zeven weken nabehandeld met het overdag dragen van een compressiekous. De belangrijkste eindpunten in deze studie waren: (I) oedeemreductie, (II) veranderingen in de ontstekingsparameters en (III) verbeteringen in de kwaliteit van het leven.

In **hoofdstuk 4** worden de resultaten van een studie gepresenteerd over de effecten van de IPC op post-revascularisatie-oedeem en ontstekingsparameters na autologe femoropopliteale bypasschirurgie. In dit onderzoek werden tweeënzestig patiënten geïncludeerd. De gegevens van zevenenvijftig patiënten konden worden geanalyseerd (CK:28 / IPC:29). De operatie-indicaties bestonden uit perifeer arteriële vaatlijden: ernstige claudicatio intermittens (CK:13 / IPC:13), ischemische rustpijn (10 / 5) en weefselverlies (7 / 11). Er werd bij drieëntwintig patiënten (CK:13 / IPC:10) een supragenuale bypass aangelegd en in vierentwintig een infragenuale (15 / 19) bypass. Toegenomen beenomtrekken werden gemeten op dag 1 (CK:-0,4% / IPC:2,7%), op dag 4 (2,1% / 6,1%), op dag 7 (2,5% / 7,9%), op dag 14 (4,7% / 7,3%) en op dag 90 (1,0% / 3,3%) en werden vergeleken met de uitgangswaarden (preoperatieve situatie). Op de dagen 1, 4 en 7 waren er significante verschillen in beenomtrekken tussen de behandelgroepen. De patiënten in de IPC-groep ontwikkelden meer oedeem dan de patiënten in de compressiekousengroep. Toenames van ontstekingparameters werden gemeten na de operatie, maar correleerden niet met toenames van de beenomtrekken en verschilden evenmin significant van elkaar. Het leek er echter wel op dat toename van oedeem was gerelateerd aan stijging van de incidentie van wondinfecties en aan langere verblijfsduur in het ziekenhuis.

Uit dit onderzoek blijkt dat gebruik van IPC de mate van oedeemvorming niet kan verminderen ten opzichte van het gebruik van compressiekousen. Het tegenovergestelde blijkt: het gebruik van compressiekousen na autologe perifere bypasschirurgie reduceert de hoeveelheid oedeem in vergelijking met het gebruik van IPC. Het postoperatieve gebruik van compressiekousen blijft de aanbevolen behandelmethode na autologe perifere bypasschirurgie.

In **hoofdstuk 5** worden de effecten van de IPC gepresenteerd bij patiënten die een PTFE femoropopliteale bypassoperatie ondergingen. In totaal werden negenendertig patiënten in deze studie geïncludeerd. De patiënten in deze studie kwamen niet in aanmerking voor een autologe bypassoperatie vanwege het ontbreken van een geschikte vene die gebruikt kon worden als autologe bypass. In de analyse werden de gegevens van zesendertig patiënten (CK:19 / IPC:17) meegenomen. De operatie-indicaties waren ernstige claudicatio intermittens (CK:6 / IPC:2), ischemische rustpijn (5 / 8) en weefselverlies (8 / 7). In negen van de zesendertig patiënten werd een heroperatie uitgevoerd. De distale anastomose werd zowel supragenuaal (CK:6 / IPC:6) als infragenuaal (13 / 11) gepositioneerd. De toename van de beenomtrekken werden gemeten op dag 1 (CK:1,5% / IPC:1,4%), op dag 4 (5,7% / 6,3%), op dag 7 (6,6% / 6,1%), op dag 14 (7,9% / 7,7%) en op dag 90 (5,8% / 5,2%). Tussen de groepen konden geen significante verschillen worden gedetecteerd. De gemeten toenames van ontstekingsparameters correleerden niet met de beenomtrekken. Evenmin konden significante verschillen in ontstekingsparameters tussen de onderzochte groepen worden gedetecteerd. Een heroperatie zorgde voor een 3,9% grotere beenomtrek ten opzichte van een voor de eerste maal uitgevoerde bypass operatie.

Na een PTFE femoropopliteale bypass operatie kon geen verschil worden gedetecteerd in de hoeveelheid oedeem die ontstaat na het bebruik van een CK, danwel het gebruik van IPC. Dit is anders dan na een autologe perefere bypass operatie, wanneer de postoperatieve toepassing van een CK wel resulteert in een kleinere hoeveelheid oedeem in vergelijking tot de toepassing van IPC.

In **hoofdstuk 6** worden de resultaten gepresenteerd van een onderzoek naar veranderingen in de kwaliteit van leven bij patiënten die een perifere bypassoperatie ondergingen. De kwaliteit van leven werd gemeten bij dezelfde patiënten als die waren geïncludeerd in de onderzoeken die werden gepresenteerd in de hoofdstukken 4 en 5. Twee onderzoeksgroepen van patiënten werden beschouwd: patiënten na een autologe femoropopliteale bypassoperatie en patiënten na een PTFE femoropopliteale bypassoperatie. In dit onderzoek werd gebruik gemaakt van het (verkorte) Nederlandstalige "World Health Organization Quality of Life" meetinstrument (WHOQOL-BREF). Deze vragenlijst is afgeleid van de originele WHOQOL-100. In de WHOQOL-BREF worden 24 facetten van de kwaliteit van leven gemeten, verdeeld over vier domeinen: lichamelijke gezondheid, psychische gezondheid, sociale relaties en omgeving. Daarnaast zijn twee facetten opgenomen die algemene gezondheid meten.

Preoperatief kon bij patiënten in het PTFE-onderzoeksgroep een significant lagere algemene gezondheid en een bijna significant lagere psychische gezondheid worden gemeten ten opzichte van patiënten in de autologe groep. Over de overige domeinen werden geen significante verschillen gedetecteerd. Patiënten die lijden aan ernstig vorm van perifere arteriele vaatziekten hebben een lage kwaliteit van leven. De meest uitgesproken verminderingen van de kwaliteit van leven ten opzichte van gezonde leeftijdsgenoten werden aangetroffen op het gebied van de lichamelijke gezondheid. Gemiddeld scoorden de geïncludeerde patiënten tussen de 47 en 52 procent van de maximaal te behalen score. Twee weken na een perifere bypassoperatie werden al significante verbeteringen gemeten. Na drie maanden werd een verdere verbetering gemeten. Het type bypass (autologe vene *vs.* PTFE) had geen effect op de toename van kwaliteit van leven.

Het domein van de lichamelijke gezondheid omvat onder andere facetten zoals pijn en ongemak, slaap en rust, mobiliteit en activiteiten in het dagelijkse leven. Het is invoelbaar dat de kwaliteit van leven wat betreft deze parameters reeds na twee weken was verbeterd, toen de meeste ischemische pijn was verdwenen (54% van de patiënten ervoer een zeer ernstige vorm perifeer arterieel vaatlijden). Het was echter niet mogelijk om de effecten van oedeem en de postoperatieve behandeling daarvan op de kwaliteit van leven te meten. Dit kwam mede doordat er geen significante verschillen in beenomtrekken tussen de groepen bestonden op het moment dat de kwaliteit van leven werd gemeten: preoperatief, twee weken en drie maanden na de operatie.

Tot slot wordt in **hoofdstuk 7** een studie gepresenteerd waarin bij negen patiënten, die een autologe perifere bypassoperatie ondergingen, met magnetische resonantie scans (MRI) onderzoek werd verricht naar het postoperatief optredende oedeem. In dit onderzoek werd een preoperatieve scan vergeleken met een scan die een week na de operatie werd gemaakt. Er werd gebruik gemaakt van vetsuppressiescantechniek om oedeem in zowel spieren als in subcutaan weefsel op te sporen. Van de patiënten werden op zes niveaus axiale scans gemaakt van beide benen. Alle patiënten gebruikten postoperatief compressiekousen zoals beschreven in hoofdstuk 3. Deze compressiekousen werden verwijderd voorafgaand aan het scanonderzoek. De bevindingen zijn dat het oedeem dat ontstaat na een perifere bypassoperatie, voornamelijk gelokaliseerd blijkt te zijn in de subcutane ruimtes. In het bovenbeen bevindt het oedeem zich voornamelijk nabij de chirurgische incisie, terwijl het zich in het onderbeen rond de gehele omtrek bevindt . Op de axiale doorsnedes werd een oppervlaktoename van 11% (onderbenen) en 12% (bovenbenen) gemeten. Deze toenames waren grotendeels toe te schrijven aan zwelling van de subcutane compartimenten (41% in de onderbenen, 35% in de bovenbenen). Deze veranderingen in de subcutane compartimenten vertonen een grote gelijkenis met lymfoedeem. De spiercompartimenten toonden postoperatief geen significante groei van hun omvang. De veranderingen in de spiercompartimenten dragen dan ook niet tot nauwelijks bij aan de toename van de beenomtrekken. Er was echter wel een toename van de hoeveelheid vocht zichtbaar in enkele spieren in zeven van de negen patiënten na de operatie. Het valt niet uit te sluiten dat deze veranderingen in de spieren het gevolg zijn van door reperfusie geïnduceerde schade.

Appendix

Review Committee

Acknowlegdements / Dankwoord

List of publications

Curriculum Vitae

REVIEW COMMITTEE

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LIST OF PUBLICATIONS

1. te Slaa A, Tetteroo EJ, Mulder PGH, Ho GH, Vos LD, Moll FL, et al. MRI reveals edema-like changes not only subcutaneously, but also in muscle tissue following femoropopliteal bypass surgery. Submitted.
2. te Slaa A, Dolmans DEJGJ, Ho GH, Moll FL, van der Laan L. Pathophysiology and treatment of edema following femoropopliteal bypass surgery. A Literature Review. Submitted.
3. Donker JMW, Ho GH, te Slaa A, de Groot HGW, van der Waal JC, Veen EJ, van der Laan, L. Midterm results of autologous saphenous vein and ePTFE pre-cuffed bypass surgery in peripheral arterial occlusive disease. Submitted.
4. Öztürk Ç, te Slaa A, Dolmans DEJGJ, Ho GH, de Vries J, Mulder PGM, van der Laan, L. Quality of Life in perspective to treatment of post-operative edema after peripheral bypass surgery. Submitted.
5. te Slaa A, Dolmans DEJGJ, Ho GH, Mulder PGH, van der Waal JCH, de Groot HGW, van der Laan. Prospective Randomized Controlled Trial to Analyze the Effects of Intermittent Pneumatic Compression on Edema Following Autologous Femoropopliteal Bypass Surgery *World J Surg* 2011;35(2):446-54.
6. te Slaa A, Mulder PGH, Dolmans DEJGJ, Castenmiller P, Ho GH, van der Laan L. Reliability and reproducibility of a clinical application of a simple technique for repeated circumferential leg measurements. *Phlebology* Electronic publication ahead of press.
7. te Slaa A, Dolmans DEJGJ, Ho GH, Mulder PGH, van der Waal JCH, de Groot HGW, van der Laan, L. Evaluation of A-V impulse technology as a treatment for oedema following polytetrafluoroethylene femoropopliteal surgery in a randomised controlled trial. *Eur J Vasc Endovasc Surg* 2010;40:635-42.
8. te Slaa A, Vos DI, Geenen GP, Dolmans DEJGJ, van der Laan L. Endovascular Treatment of an Axillary Pseudoaneurysm Following a Traumatic Shoulder Dislocation. *Eur J Trauma Emergency Surg* 2009;35:417-20.
9. Dolmans DEJGJ, Ho GH, te Slaa A, Vos LD, Geenen GP, van der Laan L. Surgical removal of an infected aortic endoprosthesis using a wire cutter. *J Cardiovasc Surg (Torino)* 2009;50:411-4.

CURRICULUM VITAE

Alexander te Slaa werd geboren op 26 december 1979 te Warnsveld. In zijn vroege jeugd woonde hij in Maleisië, Bangladesh en Colombia, alwaar hij lager onderwijs volgde op een Amerikaanse school. De lagere school voltooide hij in Nijmegen, waarna zijn middelbare schoolperiode zich ook daar voltrok. In 1999 begon hij zijn studie geneeskunde aan de Erasmus Universiteit in Rotterdam. Zijn eerste wetenschappelijke stappen zette hij als student onder leiding van Prof. dr. ir. C.J. Schnijders, in een onderzoek dat deels plaats vond aan de University of Queensland in Brisbane, Australië. Na het behalen van zijn artsexamen begon hij met werken als arts-assistent in het Amphia ziekenhuis in Breda onder leiding van Dr. L van der Laan. Tegelijkertijd startte hij daar met het verrichten van klinisch wetenschappelijk onderzoek wat resulteerde in dit proefschrift (promotor Prof. dr. F.L. Moll, Universitair Medisch Centrum, Utrecht). Op 1 januari 2011 is Alexander begonnen met zijn opleiding tot algemeen chirurg onder de supervisie van Dr. L. van der Laan en Prof. dr. J.N.M. IJzermans (Erasmus MC, Rotterdam).

CURRICULUM VITAE

Alexander te Slaa was born on December 26, 1979 in Warnsveld. During his early childhood he lived in Malaysia, Bangladesh and Colombia, where he attended an American primary school. Upon return to the Netherlands he completed primary school in Nijmegen, where he also attended high school. In 1999 he began his study Medicine at Erasmus University in Rotterdam. He commenced his first scientific work on his Master's thesis under the supervision of Prof. dr.ir. C.J. Schnijders, in a study that took place partly at the University of Queensland (Brisbane, Australia). He began working as a physician at the Amphia hospital (Breda) under supervision of Dr. L van der Laan after obtaining the degree of Medical Doctor in 2007. At the same time he started working on a clinical research project which resulted in this PhD thesis (promotor Prof. dr. F.L. Moll, University Medical Center, Utrecht). On January 1, 2011, Alexander started working as a resident in training for general surgeon at the Amphia Hospital under supervision of Dr. L. van der Laan and Prof.dr. J.N.M. IJzermans (Erasmus MC, Rotterdam).