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Studies on Venous Function after Deep Venous Thrombosis

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Stockholm 2011

Published by Karolinska Institutet. Printed by Reproprint AB

ISBN 978-91-7457-4

To Anton and Elin

Abstract

Background
The incidence of deep venous thrombosis (DVT) is estimated to be about 1-2/1000 per year of which approximately 4 % are located in the arm veins. Some of the most important late effects of a DVT are chronic venous dysfunction and the development of post-thrombotic syndrome (PTS). Objective diagnosis with detailed information on disease extent and location and global venous function is often important for clinical management of the patient. Color duplex ultrasonography (CDU) and computerized strain-gauge plethysmography (CSGP) are currently available non-invasive methods to study venous function after earlier DVT.

Aims
The aim of this thesis was to study venous function after earlier deep venous thrombosis assessed by CDU and CSGP; to study how findings with those methods are related to long-term sequelae, and development of postthrombotic diseases after different types of DVT.

Study I and II
These studies were performed to assess the efficiency of CSGP for evaluation of venous outflow capacity of the upper extremities, to receive reference values and to describe venous function using CSGP and CDU in patients with earlier primary upper extremity deep venous thrombosis (UEDVT). Thirty-four healthy controls and 32 patients with earlier UEDVT were included. The results showed that CSGP is easy to handle and can be used in a reproducible way to study venous function in the upper extremities. CSGP reference values were established for upper extremities. Patients with earlier UEDVT had reduced venous outflow, residual thrombus was a common finding, and one third had a moderate grade of PTS. CSGP and CDU are useful methods that can provide objective information regarding venous function after UEDVT.

Study III
This study was performed to determine whether asymptomatic deep venous thrombosis (ADVT) following minor surgery affects venous function and contributes to development of PTS. Eighty-three patients operated for Achilles tendon rupture were included; 38 patients with postoperative ADVT and 45 patients without (control group). The follow-up examinations five years after the operation consisted of CSGP, CDU and clinical scoring. More than 50 % of patients with ADVT developed post-thrombotic changes according to CDU, but these changes did not affect global venous function. Eight percent of ADVT patients and 4 % of control group patients developed PTS. Therefore, PTS is not a common sequel to ADVT after minor orthopaedic surgery.

Study IV
This follow-up study included 83 patients with postoperative DVT examined after a mean of 7 years. There was two series of patients, 45 with symptomatic deep venous thrombosis (SDVT) and 38 with ADVT. The objective was to describe long-term effect of SDVT and ADVT on venous function and subsequent incidence of PTS in patients operated for Achilles tendon rupture. Examinations comprised CSGP, CDU and clinical scoring. The results showed that post-operative DVT after minor surgery consists mainly of distal DVTs and is associated with a low risk for PTS, found in approximately 10 % of the patients. Deep venous reflux was more common in SDVT than in ADVT patients (84 % vs. 55 %). Abnormal plethysmographic results were seen in only a few patients without difference between the two groups. This indicates that DVT provoked by minor orthopaedic surgery represents a transient risk factor with minor long-term sequelae.

In summary
This thesis concerns studies of venous function and evaluation of clinical sequelae and frequency of PTS in patients with previous primary upper extremity DVT and in patients with postoperative DVT following minor orthopaedic surgery. In general, these studies show that the clinical signs as well as symptoms stated by the patients in these types of DVT are rather non-specific and often consist of pain, paresthesias, cramps, swelling and functional impairment. Therefore, in addition to the clinical examination, objective assessment of venous function and evaluation of the extent of disease are of value. Ultrasonograhy and plethysmograpy are non-invasive tests that can be used for this purpose.

Keywords: venous plethysmography, color duplex ultrasonography, scoring for venous disease, post-thrombotic syndrome, venous function, upper extremity deep venous thrombosis, lower extremity deep venous thrombosis, asymptomatic, symptomatic, postoperative deep venous thrombosis, plethysmographic reference values

ISBN 978-91-7457-439-5

List of publications

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (Study I-IV).

I. Persson LM, Arnhjort T, Haneby C, Lärfars G, Rosfors S. A methodological study of computerized venous strain-gauge plethysmography of the upper extremitites.
Clin Physiol Funct Imaging 2005; 25: 281-285.

II. Persson LM, Arnhjort T, Lärfars G, Rosfors S. Hemodynamic and morphologic evaluation of sequelae of primary upper extremity deep venous thromboses treated with anticoagulation.
J Vasc Surg 2006; 43: 1230-1235.

III. Persson LM, Lapidus LJ, Lärfars G, Rosfors S. Asymptomatic deep venous thrombosis is associated with a low risk of postthrombotic syndrome.
Eur J Vasc Endovasc Surg 2009; 38: 229-233.

IV. Persson LM, Lapidus LJ, Lärfars G, Rosfors S. Deep venous thrombosis after surgery for Achilles tendon rupture: a provoked transient event with minor long-term sequelae.
J Thromb Haemost 2011; 9: 1493-1499.

Contents

List of abbreviations

ADVT	Asymptomatic deep venous thrombosis
CDU	Color duplex ultrasound
CEAP	Clinical Etiology Anatomy Pathology (classification system)
CSGP	Computerized strain-gauge plethysmography
DVT	Deep venous thrombosis
EV_4/V	Volume expelled during the initial 4 seconds divided by V
LEDVT	Lower extremity deep venous thrombosis
PE	Pulmonary embolism
PTS	Post-thrombotic syndrome
QOL	Quality of life
RV	Refilling volume
SDVT	Symptomatic deep venous thrombosis
T½	Half-refilling time
UEDVT	Upper extremity deep venous thrombosis
VE	Venous emptying
VTE	Venous thromboembolism
V or VV	Venous volume

Introduction

Venous anatomy and physiology

Veins of the extremities are divided into two systems: the superficial and the deep. The pressure in the venous system under physiological conditions is largely determined by gravity. In upright position there is a considerable increase in venous pressure distally and there is an accumulation of blood in the lower extremities. This is mainly due to reflux through the valveless vena cava and iliac veins. The venous valves play an important role in the transport of blood from the lower extremities in proximal direction. Venous flow usually consists of phasic flow pattern, and venous valves undergo regular opening and closing cycles. Flow through the valve consists of a proximally directed jet and swirling flow into the sinus pocket following the valve cusp. Valve closure occurs when the swirling flow pressure exceeds the proximally directed jet flow (Bergan et al. 2006).

The lower extremity muscle pump is of great importance for the return of blood to the heart. With normally functioning venous valves, the muscle pumps reduces the pressure peripherally in the limb. The venous muscle pump contains series of smaller interconnecting venous pumps from the foot to the upper thigh. The main venous pumps of the lower leg are located in the foot and the calf. Less is known about the venous function in the upper extremities but, as in the legs, muscle pumps exist and are necessary for the return of blood against the force of gravity. Flow studies in cubital veins suggest that the venous muscle pump sequence is similar to that of the legs (Gardner & Fox 1989). The hand pump, activated by fist clenching is important,

as well as axillary vein pump which is emptied by adduction of the shoulder by swinging the arm.

Deep venous thrombosis

Deep venous thrombosis (DVT) is a serious disease not only because of the risk of developing pulmonary embolism (PE), but also of its risk for long-term sequelae. Venous thromboembolism (VTE) comprises DVT and/or PE and either of them can be asymptomatic. The incidence of VTE is estimated to be about 1-2/1000 per year (Nordström et al. 1992) and according to the Swedish Council on Technology Assessment in Health Care (2002) about 10 000 to 15 000 patients/year are estimated to be affected of the disease in Sweden. At least 50 % of patients who present with symptomatic DVT have asymptomatic PE and conversely, a majority presenting with symptomatic PE have asymptomatic DVT (Kearon et al. 2003).

The pathophysiology of DVT was recognised by Virchow in the nineteenth century and his triad of hypercoagulability, stasis and vessel wall damage as a cause remains appropriate even today (Virchow 1856). Today several risk factors for DVT, either acquired or congenital, are recognized. The aquired may further be divided into primary/idiopathic (unprovoked) or secondary (due to e.g. surgery, trauma or cancer) and the congenital comprise a wide variety of inherited haematological conditions including mutation of Factor V Leiden causing APC-resistance, and Factor II prothrombin mutation. The predictive value of different risk factors differs between patient groups and should be assessed individually as well as the cumulative weight of all risk factors, especially with regard to justify the use of prophylaxis. Risk factors include increasing age, prior DVT, immobility, recent surgery or trauma, malignancy, and congenital vascular anomalies (Anderson et al. 2003).

Lower extremity deep venous thrombosis

Lower extremity deep venous thrombosis (LEDVT) may occur in a wide spectrum of severity ranging from small limited one-segmental clots in calf veins to large thromboses extending into pelvic veins. The clot can cause partial or complete blocking of circulation in the vein. Typical symptoms are pain, swelling, tenderness, discoloration of the affected area, signs of inflammation and prominent superficial veins. In an analysis of 885 DVTs diagnosed phlebographycally, Ouriel et al (1999) showed that the engaged veins in 83 % were calf veins, 53 % femoro-popliteal veins and 9 % iliac veins. They also found that the most common single stem affected was the fibular vein.

DVT is sometimes diagnosed in asymptomatic patients by performing screening tests in a high-risk situation, e.g. postoperatively. A significant proportion of all DVTs are asymptomatic (ADVT), but the true incidence is unknown. It is often believed that many of these clots resolve spontaneously (Kearon et al. 2003). Due to the lack of symptoms, the condition goes mostly unnoticed and consequently leave the patient untreated (Schindler & Dalziel 2005).

Postoperative deep venous thrombosis

Surgery is one of the most important risk factors for DVT. In patients who are not given prophylaxis before hip or knee arthroplasty, 40-70 % will develop DVT; 20-30 % proximal DVT (i.e. in the poplitean vein and above) and the remainder isolated to the calf veins (Clagett et al. 1995). Besides the surgical trauma itself there are also other important factors for development of postoperative DVT such as immobilization, operating time, type of anaesthesia and major blood loss. In a series of patients undergoing surgery for Achilles tendon rupture almost 40 % of the patients had DVT

at postoperative screening, although half of them were given prophylaxis (Lapidus et al. 2007).

Upper extremity deep venous thrombosis

Because of relatively high flow rate and less stasis from gravitational effect the venous pathways of the arms are less likely than those of the leg to form thromboses (Saijd et al. 2007). In addition, arm veins have fewer valves that can serve as a starting point for thrombus formations and veins in the arms are shorter and therefore have lesser surface on which to form clots. Moreover, we have a tendency to move our arms more than the legs which may contribute to a more continuous and active venous return (Marshall & Cain 2010). The subclavian and axillary veins are the most common sites for thrombosis. The appearance and diagnostic procedures of DVT in the upper extremities are similar to DVT in the lower extremities.

It has been estimated that 1-4 % of DVT cases involve the upper extremities (Kröger et al. 1998, Mustafa et al. 2003). Upper extremity deep vein thrombosis (UEDVT) is an increasing clinical problem due to more use of intravenous devices such as central venous catheters, pacemakers and intracardiac defibrillators. UEDVT is classified into two groups; primary (includes idiopathic, effort-related and those with thoracic outlet syndrome) and secondary (provoked by central venous catheters/devices or cancer) (Joffe et al. 2002). Primary UEDVT is rare with an occurrence of approximately 2 per 100 000 individuals per year (Lindblad et al. 1988)

Post-thrombotic syndrome

The post-thrombotic syndrome (PTS) is a long-term and chronic complication of earlier DVT and consists of a number of symptoms and clinical signs such as: ache, heaviness, swelling, cramps and itching in the affected limb. It is believed that post-

thrombotic disease occurs primarily as a consequence of impaired venous return and venous hypertension. In the lower leg, this in turn leads to reduced calf muscle perfusion, abnormal function of the microcirculation with increased tissue permeability followed by clinical symptoms and manifestations of the syndrome (Pesavento et al. 2006, Vedantham et al. 2009, Kahn 2011). Symptoms can be intermittent or persistent and often tend to be worsening with standing or walking and tend to improve when resting and with the leg in a raised position. Clinical signs include edema, brown pigmentation and venous eczema. Varicose veins are common and lipodermatosclerosis may develop in some cases followed by leg ulcers (Kurz et al. 1999, Prandoni & Kahn 2009).

One identified risk factor for PTS is recurrent DVT in the ipsilateral leg which constitutes a sixfold increased risk when compared with patients without recurrent DVT (Saarinen et al. 1995, Prandoni et al. 1997a, Labropoulos et al. 2010a). Despite thromboprophylactic regimens and anticoagulant therapy it is reported that at least one of every two to three patients with symptomatic DVT in lower extremities will develop post-thrombotic disease. In one of five patients the post-thrombotic disease is severe. The number of patients affected by PTS seems to have declined in recent years. Some reasons for this might be improved diagnostic and therapeutic approaches, a more uniform definition of PTS and the use of elastic compression stockings (Kahn & Ginsberg 2004, Kahn et al. 2008, Prandoni & Kahn 2009). However, the reported frequency of both overall and severe PTS still shows considerable variability. Less is known regarding to what extent asymptomatic DVT leads to PTS. Wille-Jorgensen et al (2005) found an incidence of PTS after postoperative ADVT of 21 %, but for example Lonner et al (2006) described a considerable lower frequency.

PTS of the upper extremities is less well studied compared to lower extremities and few studies have reported the incidence of PTS following UEDVT. Moreover, the results are difficult to compare due to variations in follow-up time and definitions of PTS (Elman & Kahn 2005). One commonly used definition include pain, swelling and functional limitation of the affected arm. The overall frequency of PTS following UEDVT is in the range of 7-46 %, with a weighted mean frequency across studies of 15 %.

Villalta post-thrombotic scale

In the beginning of the 1990s a clinical scale known as the Villalta post-thrombotic scale was proposed as a scoring for the severity of PTS (Villalta et al. 1994). The scale consisted of five patients-rated venous symptoms and six clinician-rated physical signs which were each rated on a four-point scale. During the last decade this scale has been further developed and used in a number of studies concerning PTS in both lower and upper extremities. For lower extremities the scale has been validated and is a widely used instrument that takes into account the range and severity of both subjective symptoms and physical signs of PTS. Patients are diagnosed as having PTS if the score is ≥5 and the PTS is classified as mild if the Villalta score is 5-9, moderate if the score is 10-14 and severe if the score is ≥15 or if a venous ulcer is present regardless of the score (Kahn et al. 2009a, Kahn 2009b).

Regarding upper extremities several studies have used a modification of the lower extremity Villalta PTS scale to diagnose upper extremity PTS (Prandoni et al. 2004, Elman & Kahn 2005, Kahn et al. 2005). This scale has not been formally validated and there exists no other well elaborated scale that is specifically developed for use after UEDVT.

CEAP classification

CEAP is a descriptive classification that categorizes patients into one of eight clinical classes of increasing severity of chronic venous disease. The CEAP is based on clinical signs with modifiers that reflect the underlying etiology (congenital, primary or secondary to DVT), anatomic distribution (superficial, deep or perforating veins) and pathophysiologic condition (reflux, obstruction or both). Although the scale classifies patients as symptomatic or asymptomatic it does not specify individual symptoms or grade their severity. The CEAP classification was originally introduced in 1994 (Porter & Moneta 1995) and was revised in 2004 (Eklöf et al. 2004).

Quality of life

Health-related quality of life may be considerably reduced in individuals with venous disease. Assessment of quality of life should ideally include both generic and disease specific measures. Generic measures allow comparison across populations of patients with different conditions, whereas disease-specific measures are more responsive in detecting treatment effects and changes over time in patients who have the same disease (Patrick & Deyo 1989, Wiebe et al. 2003).

The VEINES-QOL/Sym is a validated patient-based questionnaire designed for self-completion and its content and format were modelled after the commonly used generic SF-36 (Ware & Kosinski 2001). The VEINES-QOL/Sym is a venous disease specific instrument that is regarded as more sensitive than generic questionnaires in capturing clinically relevant changes related to venous disease (Lamping et al. 2003, Kahn et al. 2006, Enden et al. 2008).

Methods to assess venous function

Deep venous thrombosis and varicose veins are conditions that often require objective testing to assist the clinician with information for further processing of the patient. Over the last 20 years investigation of venous disease has changed to become increasingly non-invasive and more detailed. Diagnostic methods may be divided into those which provide anatomical/morphological information and those which provide functional information. In many cases both approaches are needed to achieve a more complete assessment of the venous circulation.

Color duplex ultrasound (CDU)

Ultrasound is in the first line of choice and often the only method used in venous disease. Some of the methods advantages are its non-invasive technique and repeatability (Baxter et al. 1992, Miller et al. 1996, Cogo et al. 1998, Baarslag et al. 2002). The technical progresses of equipment as well as the increased experience of technologists and physicians continuously improve the accuracy of the method. Today, the technique can provide high-resolution imaging of the veins in order to define the anatomy and morphologic changes. In conjunction with the use of spectral and color Doppler the technique offer opportunities to quickly and easily identify for example small vessels in distal segments or segments with reflux. These modalities provide useful information for assessment of the flow condition in both the region of interest and surrounding segments of the venous circulation (Killewich et al. 1989, Lensing et al. 1989, Zwiebel 1992, Thrush & Hartshorne 2005).

CDU was earlier considered to be an accurate diagnostic alternative to phlebography only for proximal DVT (i.e. at popliteal vein and above), but later adequate sensitivity and specificity have been shown also for diagnosis of distal DVT (Atri et al. 1996, Miller et al. 1996, Theodorou et al. 2003). Furthermore, CDU has recently shown to

be an accurate method for detecting asymptomatic proximal and distal DVT (Kassai et al. 2004, Lapidus et al. 2006). It is not only a suitable non-invasive instrument for accurate diagnosis of DVT, but also for repeated studies of thrombus progression/resolution (van Ramshorst et al. 1992, Rosfors et al. 1997).

CDU is commonly used to detect chronic venous disease, including post-thrombotic signs with persistent obstruction of vein segments, vessel wall abnormalities (e.g. irregularities, wall thickening, reduced lumen and reduced compressibility) (Johnson et al. 1995). Furthermore, pulsed Doppler and color flow imaging provide blood flow information and detection of venous reflux (van Ramshorst et al. 1994).

Ultrasound is a diagnostic tool also for UEDVT (Chin et al. 2005). The modality has the same benefits as for DVT in lower extremity (i.e. 2D imaging including compressibility of the vessel, spectral and color flow Doppler). Acoustic shadowing from the clavicle will, however, frequently limit visualization of a short segment of the subclavian vein. Moreover, brachiocephalic vein and/or superior caval vein are often difficult to visualize and in some cases it is not possible to make any morphological assessments of the most central veins. The presence of a more central clot may be inferred from secondary signs such as absence of respiratory variations and absence of cardiac pulsatility (Katz et al. 2004).

Plethysmography

Venous plethysmography records volume changes in a tissue segment in order to assess global venous function (Hallböök & Göthlin 1971, Struckmann & Mathiesen 1985). The static part of the method includes measures of venous outflow from the limb to assess venous obstruction. The dynamic part of the method is used to assess venous pump function and venous reflux during and after a standardized exercise.

Since the late 90:ies plethysmography has been less used, possible due to increased availability of CDU. However, in the last few years the technique has been more frequently used, not only for scientific purposes but also for clinical issues in order to achieve objective functional information. The design of today available devices (computerized, easier to handle) has increased the usefulness of the technique (Ahlström et al. 1991, Rooke et al. 1992, Shi et al. 1992b, Rosfors et al. 1996).

Different plethysmographic methods exist including strain-gauge plethysmography, air plethysmography and photoplethysmography (Browse et al. 1999). The usefulness of the different techniques has not been compared. Plethysmographic studies almost exclusively concern the lower extremity, and the technique has only occasionally been performed in upper extremities (Lindblad et al. 1990, Zufferey et al. 1992).

Other imaging techniques

Phlebography is the gold standard for the diagnosis of DVT. The technique described by Rabinov and Paulin (1972) is widely adopted in both clinical and scientific practice (Rossi & Agnelli 1998). Ascending phlebography provides anatomical information and diagnoses DVT as filling defects and contrast surrounded thrombi. It might even provide some functional information such as calf perforator incompetence. However, exposure to ionizing radiation, the invasiveness and the risk to induce allergic or toxic reactions somewhat reduces the usefulness.

Other imaging techniques such as magnetic resonance imaging (MRI) and computerized tomography (CT) has been introduced to study the venous system, but their role in common clinical practice are not yet defined.

Aims of the thesis

The overall aim of this thesis was to study venous function after earlier deep venous thrombosis assessed by color duplex ultrasonography and strain-gauge plethysmography; to study how findings obtained with those methods are related to post-thrombotic disease after different types of deep venous thrombosis.

The specific aims were

- To establish reference values for venous plethysmography in upper limbs, to study reproducibility and the effect of age and gender on commonly used plethysmographic variables (Study I)

- To evaluate venous function and PTS in patients with previous primary upper extremity deep venous thromboses (Study I and II)

- To evaluate venous function following asymptomatic and symptomatic postoperative deep venous thromboses in the lower limb (Study III and IV)

- To evaluate the frequency of PTS after surgery for Achilles tendon rupture and the correlation between PTS and venous function abnormalities detected with CDU and CSGP (Study III and IV)

Material and Methods

Upper extremity, healthy subject and patients

Healthy subjects (Study I)

We intended to assess the usefulness of computerized strain-gauge plethysmography for evaluation of venous volume and outflow capacity of the upper extremities and to receive reference values. For this purpose, we investigated 34 healthy subjects without any history or signs of venous disease in upper or lower extremities. We included 16 males and 18 females with a mean age of 45 years (range 31–58 years) (Fig. 1).

Patients with primary upper extremity DVT (Study I and II)

A retrospective search of our medical records identified 37 patients with a previous, conservatively treated, primary UEDVT diagnosed during the years 1995 to 2002. Thirty-two patients were included in Study I and 31 patients in Study II (one patient treated with thrombolysis was excluded) (Fig. 1). Mean patient age was 45 years (range 21 to 84 years), and 22 (71 %) were women. None of the patients had UEDVT secondary to a malignancy or treatment with a central venous catheter, device or pacemaker. The diagnosis of UEDVT had been established objectively by phlebography, color duplex ultrasonography or CT. There was equal distribution between the affected arms (i.e. right and left side). The mean time interval between the acute UEDVT and the follow-up in Study I and II was 5 years (range 2-9 years).

Design (Study I and II)

Both patients and healthy subjects were examined at a single visit at Södersjukhuset, Stockholm. All subjects underwent a plethysmographic examination including repeated measurement for calculation of reproducibility. Both groups were

interviewed for demographic data and asked for subjective symptoms. In the patient group, we used color duplex ultrasound to evaluate venous abnormalities and the Villalta score for assessment of PTS.

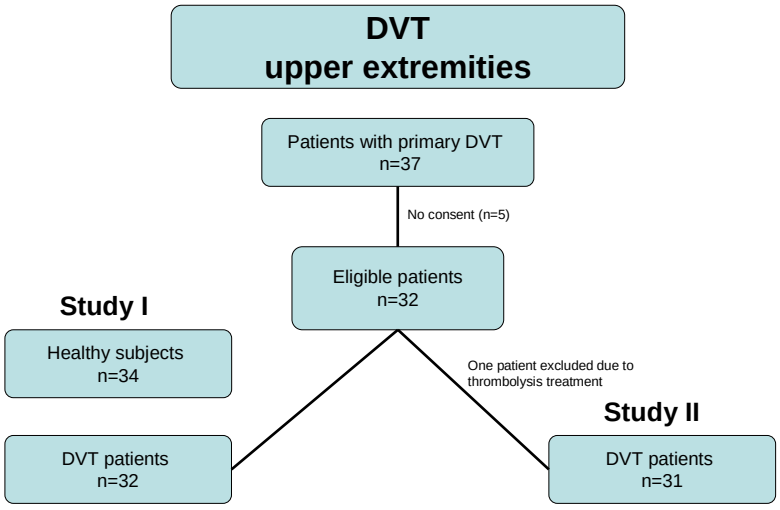

Figure 1. Flow chart for subjects included in Study I and II.

Lower extremity, patients and healthy subjects

Patients (Study III and IV)

In study III 101 consecutive patients were enrolled in a prospective study of postoperative asymptomatic deep venous thrombosis (ADVT) after minor orthopaedic surgery (Achilles tendon rupture) (Lapidus et al. 2007). Eighty-three of these were included in the follow-up five years postoperatively (range 43-74 month). Patients were classed into two groups based on the results of post-operative diagnostic test; those with definite DVT (n=38) and those with no DVT (n=45) where the latter served as controls (Fig. 2).

Study IV included 83 patients with postoperative DVT in a follow-up study at a mean time of 7 years postoperatively (range 43-163 months). There were two series of

patients; 45 with symptomatic DVT (SDVT) and 38 with ADVT (the latter included also in Study III). Patients with SDVT were included from a prospectively collected clinical audit at the Department of Orthopaedics, Södersjukhuset, Stockholm. We identified all patients (n=54) with SDVT diagnosed between the years 1996-2005 and following surgery for Achilles tendon rupture (nine patients were excluded) (Fig. 2).

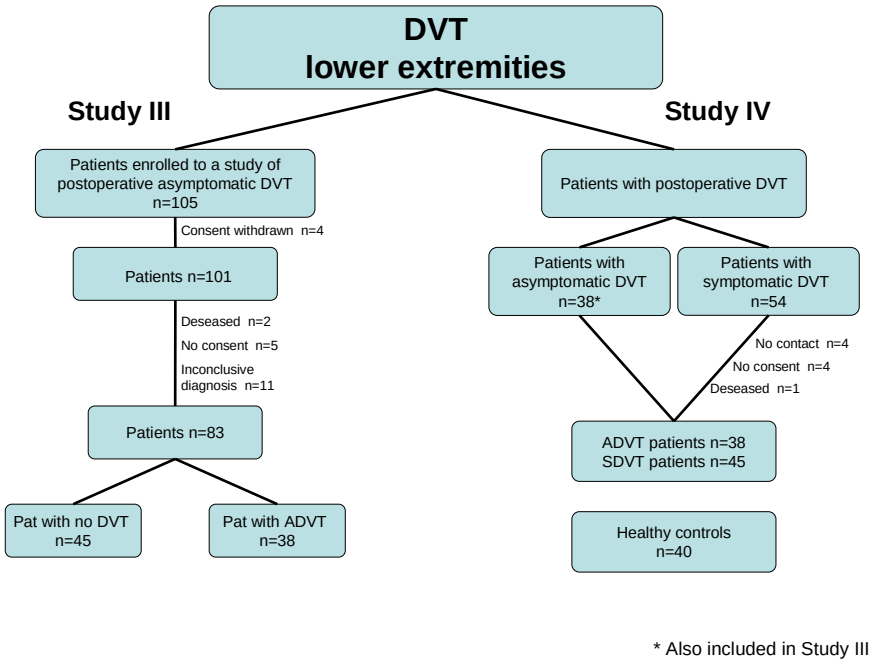

Figure 2. Flow chart for subjects included in Study III and IV.

Healthy subjects (Study IV)

Venous plethysmography was performed also in 40 healthy subjects with corresponding age and gender (33 males/7 females; 20 right/20 left limbs, mean age 50 years, range 34-69 years). The healthy subjects did not have leg problems in form of pain or swelling, they had not undergone surgical procedures the past six months, had no varicose veins or earlier DVT, no known coagulation disorder or any malignancy/cancer.

Design (Study III and IV)

The studies consisted of a single follow-up visit at the hospital. The patients underwent clinical examination, CSGP and CDU. Scoring was performed using the Villalta score for PTS, CEAP for clinical classification (only C-classes used) and quality of life was assessed by using the disease-specific VEINES-QOL/Sym questionnaire.

Methods

Strain-gauge pletysmography, lower extremity (Study III and IV)

The procedure comprised static measurement of venous volume and outflow capacity and dynamic measurement of volume changes after muscular exercise, using a computerized mercury strain-gauge plethysmograph (S.I. Veintest 2, Sels Instruments N.V., Vorselaar, Belgium).

During the static measurement the patients were kept in a supine position with the heels resting on a support elevating the lower limbs 40 cm above bed level and the knee angle in approximately 90 degrees. Inflatable cuffs were wrapped around the upper part of the thighs and the strain-gauge wires were placed around the largest part of each calf (Fig. 3).

Venous volume (V, ml per 100 ml) was measured as the maximal volume change during venous occlusion imposed by thigh cuffs inflated to a pressure of 60 mmHg and venous emptying (VE, ml per 100 ml $\times$ min) was expressed as the outflow rate during the first second after release of venous occlusion (Shi et al. 1992a, Shi et al. 1992b) (Fig. 4). Outflow relative to venous volume was expressed as EV_4/V (volume of blood expelled during the initial 4 seconds after cuff release divided by V) (Rosfors et al. 1996).

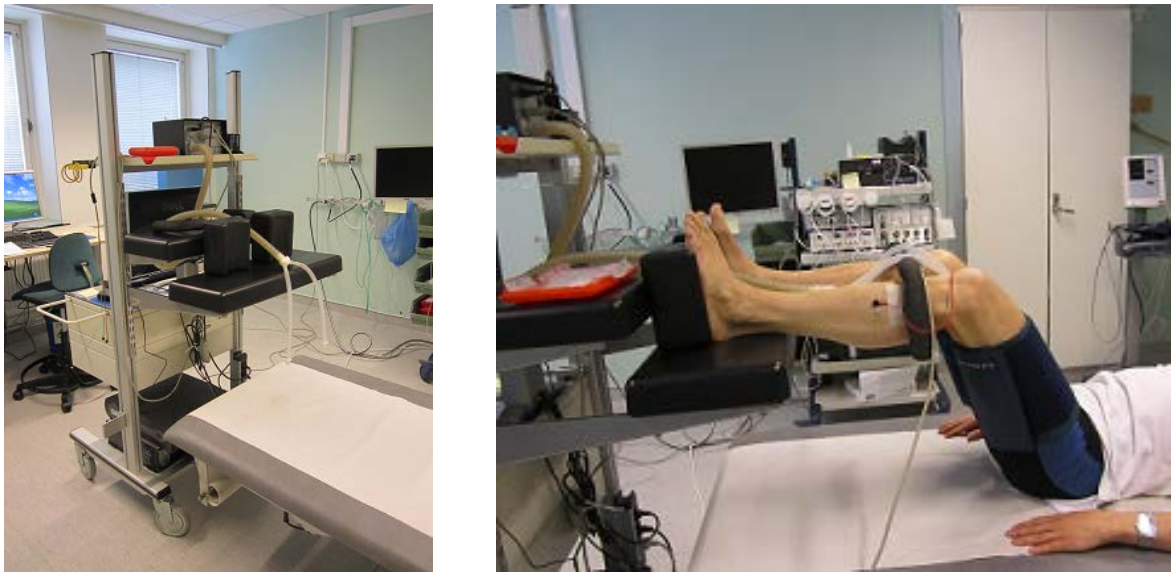

Figure 3. Equipment set-up for venous plethysmography (left). Arrangement of patient, tourniquets and strain-gauge wires for lower extremity venous plethysmography, static measurement (right).

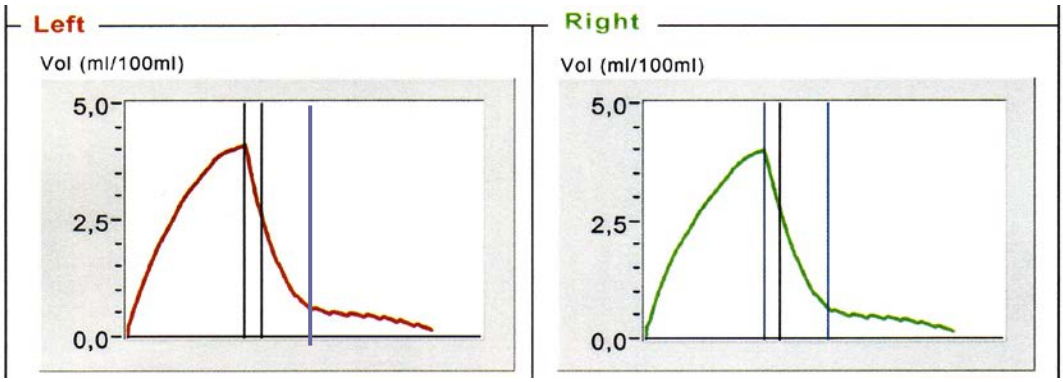

Figure 4. Example of a printout of normal plethysmographic curves, showing venous volume and venous emptying.

For dynamic measurements, the patients were in standing position and strain-gauge wires were applied just proximal to the malleolus and volume changes were measured during and after 15 knee bends (Fig. 5). Refilling volume (RV, ml per 100 ml) and half-refilling time (T½, seconds) were measured. A short T½ indicates venous reflux and a low RV indicates deterioration in muscle pump function (Rooke et al. 1992) (Fig. 6)

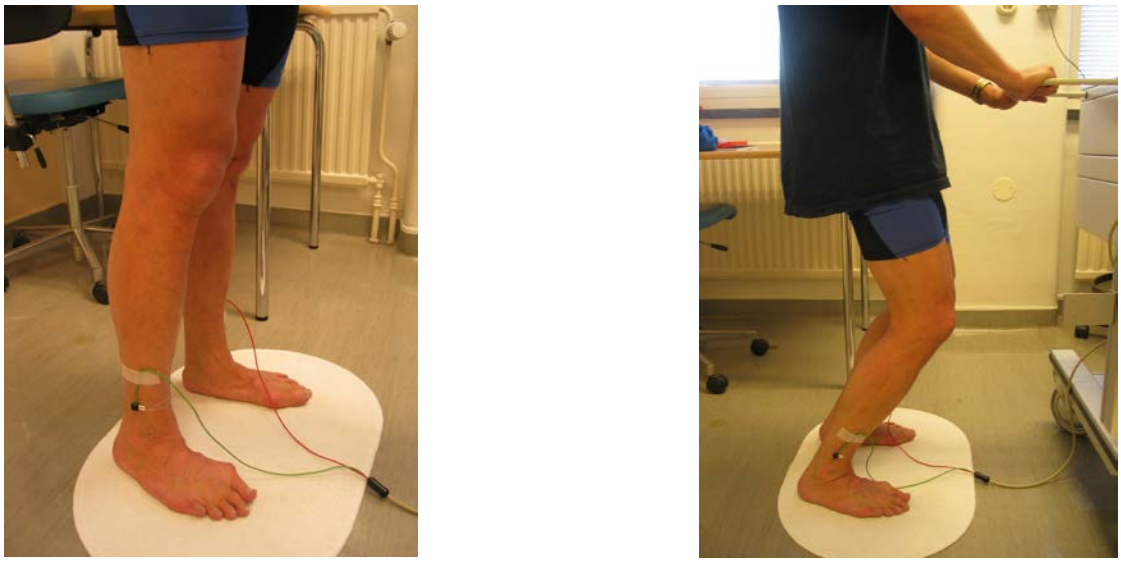

Figure 5. Arrangement of patient and strain-gauge wires for lower extremity venous plethysmography, dynamic measurement.

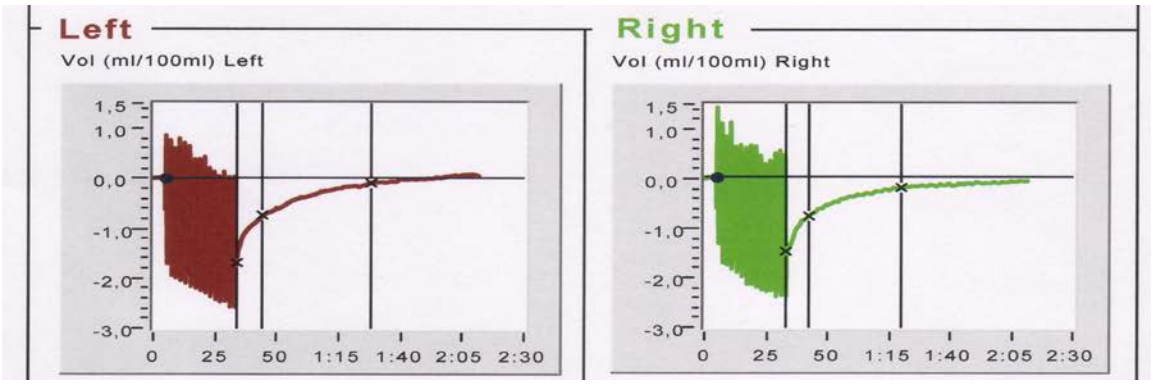

Figure 6. Example of a printout of normal plethysmographic curves, showing refilling volume (RV) and half-refilling time (T½).

The mean of two determinations was used for all pletysmographic variables. At our laboratory the coefficient of variation for repeated measurements are somewhat lower for static measurements of venous volume and outflow capacity (VE 6 %; V 6 %, EV_4/V 6 %) than for dynamic measurements of volume changes at exercise (T½ 12 %; RV 10 %). The lower limit of the normal range (mean – 2 SD), according to our reference values obtained in 63 healthy subjects aged 24-69 years, is: ≥62 ml per 100 ml × min for VE, ≥3.4 ml per 100 ml for V, ≥0.62 for EV_4/V, ≥0.61 ml per 100 ml for RV and ≥5 seconds for T½ (own unpublished observations).

Strain-gauge pletysmography, upper extremity (Study I and II)

The examinations were performed in principle as described above for static measurements of venous outflow in lower extremities, but now with specially designed arm tourniquets. Technical modifications of the unit were also performed in order to adjust the inflow pressure to the smaller arm tourniquets. The subject was sitting with the arms resting on an arm support elevating the limbs to the shoulder level. Inflatable cuffs were wrapped around the upper arms and strain-gauge wires were placed on each forearm (Fig. 7). Following variables describing the volume curve were calculated for each limb: Venous volume (V, ml per 100 ml: the maximum volume change during the occlusion phase); Venous emptying (VE, ml per 100 ml × min: the outflow rate during the first second after deflation); EV_4/V (the volume of blood expelled during the initial 4 seconds divided by the maximum venous volume). The mean of 2 determinations was used for each variable. Reproducibility of the plethysmographic procedures was tested by repeated studies in all subjects after removal and reconnection of the equipment. Also for this part the mean of 2 determinations was used.

Figure 7. Arrangement of patient, tourniquets and strain-gauge wires for upper extremity venous plethysmography.

Color duplex ultrasound, upper and lower extremitites (Study II, III, IV)

Duplex scanning was performed in order to locate post-thrombotic changes and to identify venous reflux. Retrograde flow duration longer than 0.5 seconds following distal manual compression was considered as significant reflux in deep or superficial veins (Haenen et al. 1999, Labropoulos et al. 2003) (Fig. 8).

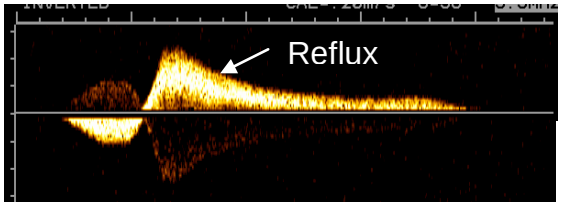

Figure 8. Venous reflux with a duration >2 seconds.

The following segments in the arms (Study II) were evaluated: radial, ulnar, brachial, cephalic, basilic, axillary, subclavian and internal jugular. According to the duplex findings the results were classified into four categories: (1) normal; (2) mild changes, patent veins with slight wall thickening, almost compressible, normal spontaneous blood flow and some dilated collateral veins; (3) moderate-to-severe changes, patent veins with a reduced lumen because of a residual thrombus, decreased compressibility and dilated collateral veins; (4) occluded, a residual thrombus with occlusion of the lumen, uncompressible lumen, absence of color flow and blood flow in several prominent dilated collateral veins. Intraoperator variability for the duplex classification was assessed by analysis of 26 examinations that were classified in a blinded manner by the same operator on two occasions separated by 30 days. Evaluation by the use of kappa statistics showed a moderate agreement between these two analyses with a kappa value of 0.52. The disagreement regarded mostly only one category step and the weighted kappa value was 0.86. There was a good strength of agreement (kappa value 0.75) when the comparison was restricted to only two groups (i.e. no residual thrombus categories 1 and 2 versus residual thrombus categories 3 and 4).

In Study III and IV the following venous segments in the legs were evalutated: common femoral, superficial femoral, popliteal, posterior tibial, fibular, muscle veins (gastrocnemius, soleus) and long saphenous (thigh and calf) (Fig. 9). Vessel wall abnormality (irregularities, wall thickening, reduced or occluded lumens) and compressibility were used to assess post-thrombotic changes.

Intraoperator variability for duplex findings regarding presence or absence of post-thrombotic changes was assessed by a blinded re-evaluation of 93 randomly selected examinations. Evaluation by the use of kappa statistics showed a good agreement between these two analyses with a kappa value of 0.71.

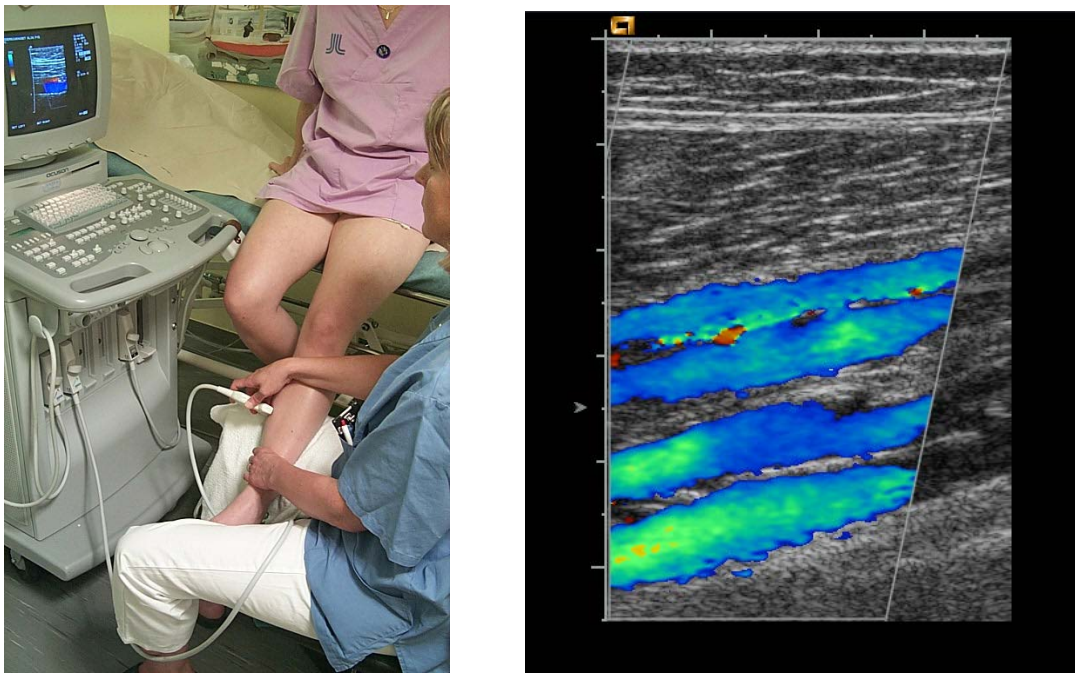

Figure 9. Ultrasound examination of calf veins (left) and longitudinal color duplex image of normal duplicated posterior tibial and fibular veins at mid-calf level (right).

Villalta scoring (Study II, III, IV)

Symptoms and clinical findings were rated according to the Villalta scale (Kahn 2009b). For the lower extremity the scale consists of five patient-rated venous symptoms: pain, cramps, heaviness, paresthesia and pruritus, and six clinician rated

physical signs: pretibial edema, skin induration, hyperpigmentation, pain during calf compression, venous ectasia and redness. The scale was slightly modified for the upper extremity consisting of four symptoms (pain, cramps, paresthesia and pruritus) and five clinically objective signs (edema, skin induration, hyperpigmentation, venous ectasia and redness). Each is rated on a four point scale: 0=none, 1=mild, 2=moderate, 3=severe and points are summed to produce a total score. A score of ≥5 was used to indicate presence of PTS. The severity category was in Study IV subcategorized as mild (score 5-9) or moderate (score 10-14).

CEAP (Study III and IV)

Clinical classification was accomplished using the C-classes of the CEAP score for clinical appearance of venous disease: C0 = no visible or palpable signs of venous disease, C1 = telangiectases or reticular veins, C2 = varicose veins, C3 = edema, C4 = skin changes, C5 = healed ulcer and C6 = active ulcer (Eklöf et al. 2004).

QOL (Study III and IV)

Quality of life was measured using VEINES QOL/Sym questionnaire (Lamping et al. 2003, Kahn et al. 2006). The 26 item questionnaire measures the impact of chronic venous disease on symptoms and quality of life from the patient perspective. The items cover symptoms (10 items), limitations in daily activities (9 items), time of day of greatest intensity (1 item), change over the past year (1 item) and psychological impact (5 items). The questionnaire was sent to the patient to be completed and brought back when visiting our department.

Statistics and ethics

Data are presented as mean ± SD or 95 % confidence intervals, or median and range. Differences between means were tested for significance using paired and unpaired two-sided Student's t-tests. Difference in Villalta PTS score between groups was tested using the Mann-Whitney U-test. Differences between proportions were analyzed using chi-square tests. Regression and correlation analyses (Pearson or Spearman rank order correlations) were used to characterize relationships between variables. When differences between means for three groups were tested (Study IV) one-way analysis of variance was used, followed by Scheffe's posthoc test if the F-ratio revealed a significant difference. Statistical significance was assumed at $P < 0.05$.

The standard error (s) of a single plethysmographic determination was estimated from duplicate measurements and calculated as: $SD_{diff} / \sqrt{2}$. The coefficient of variation (CV) describes the variation as a percentage of the pooled mean values (x) and was calculated according to the formula: $CV (\%) = s/x \times 100$.

Kappa statistics were used to assess intraoperator variability for duplex findings regarding evaluation of post-thrombotic changes in upper and lower extremities. A kappa value exceeding 0.81 represents excellent agreement, values between 0.61 and 0.80 good agreement, values between 0.41 to 0.60 moderate agreement, and values less than 0.4 poor agreement (Altman 1991).

Study I-IV was approved by the local ethics committee. Written and informed consent was obtained from all patients and healthy subject in Study I-IV.

Results

Plethysmography of upper limbs in healthy subjects (Study I)

Venous emptying (VE), V and EV_4/V were calculated for each arm and as a mean of both arms for our 34 healthy subjects (right arm + left arm/2): VE_{mean}, V_{mean} and EV_4/V_{mean}. No significant differences were found between right and left arms regarding any of these variables. Neither were there any effects of age or gender on these measurements. There was a significant positive relationship between VE_{mean} and V_{mean} ($r = 0.75$, $P<0.01$). Coefficient of variation was approximately 10 % for all variables (Table 1).

Table 1. Plethysmographic results in 34 healthy controls.

	Mean ± SD	CV	s
VE, right arm	109 ± 23	12%	13
VE, left arm	110 ± 26	9%	10
V, right arm	4.6 ± 0.8	11%	0.5
V, left arm	4.6 ± 1.0	9%	0.4
EV_4/V, right arm	0.59 ± 0.08	8%	0.05
EV_4/V, left arm	0.57 ± 0.06	9%	0.05

VE, venous emptying (ml per 100 ml × min); V, venous volume (ml per 100 ml);
EV_4/V, the volume of blood expelled during the initial 4 seconds divided by V.
CV= coefficient of variation; s= standard error of a single determination

Based on results in healthy subjects our reference values (right arm + left arm/2, mean ± SD) are 110 ± 21 ml per 100 mL × min for VE, 4.6 ± 0.81 ml per 100 ml for V

and 0.58 ± 0.06 for EV_4/V. A significant outflow obstruction can assume to be present when VE is below 68 ml per 100 ml × min (mean – 2 SD).

When plethysmographic results in healthy subjects were compared with those obtained in 32 arms with previous DVT, all plethysmographic variables were significantly lower in DVT arms (VE and V, $P < 0.01$; for EV_4/V, $P < 0.05$). There was no difference between values obtained in contralateral arms in DVT patients and in arms of the healthy subjects. CV for repeated measurements in patients with previous DVT was in the same order as those obtained for healthy subjects. This demonstrates that plethysmography is a useful method to study venous outflow function in upper extremities.

Evaluation of patients five years after primary upper limb DVT (Study II)

All patients had been diagnosed with primary UEDVT and were without earlier thromboembolic disease. Deep veins involved in the acute episode were the subclavian only in 64 %, subclavian and axillary in 22 %, subclavian, axillary and brachial in 6 %, and brachial vein only in 6 %. The patients were all treated with low-molecular–weight heparin and oral anticoagulant for 3 to 6 months. No patient had any recurrent episode of DVT or pulmonary embolization. The most commonly reported symptoms of the affected arm were swelling and tension (71 %) followed by pain and reduced strength.

Total Villalta PTS score ranged from 1 to 9 (median 3) and 71 % were classified as no or minimal PTS (score 0–4) and the remaining 29 % were classified as having mild-to moderate PTS (score 5–9).

In eight patients (26 %) the duplex findings were normal, five (16 %) hade mild changes, fourteen (45 %) were classified as having moderate-to-severe changes with residual thrombus and the remaining four patients (13 %) still had an occluded deep venous segment. Segments with post-thrombotic vessel wall changes were seen in the subclavian, axillary and brachial veins. No significant association was noted between the PTS score and the categorized duplex findings (Spearman´s r=0.22). None of the patients had deep or superficial venous reflux.

The venous emptying, venous volume and EV_4/V were significantly lower in the arms with a previous DVT than in the contralateral arms (P <0.001 for all) (Fig. 10). Thirty-five percent of the DVT arms and 6 % of the contralateral arms had a VE below the lower normal limit of 68 mL/100 mL per min (P <0.01). Corresponding figures for EV_4/V (arms with value below the lower normal limit < 0.46) were 34 % and 19 % (N.S.). No statistically significant relationship was noted between plethysmographic and duplex findings. Patients with PTS had lower mean values of VE and V than those without PTS, but these differences were not statistically significant (Table 2).

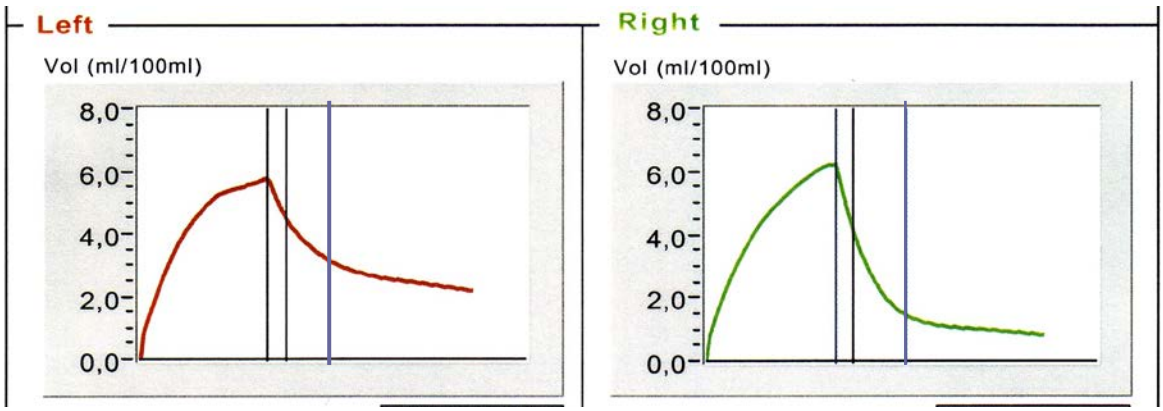

Figure 10. Example of plethysmographic curves from a patient with a reduced venous outflow after a left-sided upper extremity DVT. Left arm; VE=71 and EV_4/V=0.47. Right arm; VE=122 and EV_4/V=0.76.

Table 2. Plethysmographic results in 31 patients with earlier upper extremity deep venous thrombosis (DVT). Results are shown as mean and 95% confidence interval.

	V (ml per 100 ml)	VE (ml per 100 ml × min)	EV_4/V
DVT arm	3.7 (3.3–4.0)	80 (71–88)	0.48 (0.45–0.51)
Contralateral arm	4.4 (3.9–4.8)	99 (88–110)	0.55 (0.52–0.58)
DVT arm			
Residual DVT (n=18)	3.5 (3.1–3.9)	74 (64–83)	0.46 (0.41–0.51)
No residual DVT (n=13)	4.0 (3.3–4.6)	88 (71–104)	0.51 (0.46–0.55)
PTS (n=9)	3.3 (3.0–3.5)	69 (59–79)	0.48 (0.41–0.54)
No PTS (n=22)	3.9 (3.4–4.3)	84 (72–96)	0.48 (0.44–0.52)

VE, venous emptying; V, venous volume; EV_4/V, the volume of blood expelled during the initial 4 seconds divided by V; PTS, post-thrombotic syndrome

Ultrasonography and plethysmography in patients operated for Achilles tendon rupture with and without postoperative DVT (Study III and IV)

Post-thrombotic changes were more commonly found in the SDVT patients than in the ADVT patients, ($P<0.05$). A majority of patients in both groups had their post-thrombotic changes limited to the calf veins (30/36 and 20/21, respectively) (Fig. 11). In the SDVT group 38 patients (84 %) showed deep venous reflux compared with 22 patients (58 %) in the ADVT group ($P<0.01$). Reflux in proximal deep veins was found in four patients in the former group and in two patients in the latter. Regarding patients operated for Achilles tendon rupture without postoperative DVT (n=45), three patients had isolated deep venous reflux in the calf, but there were no post-thrombotic changes (Table 3).

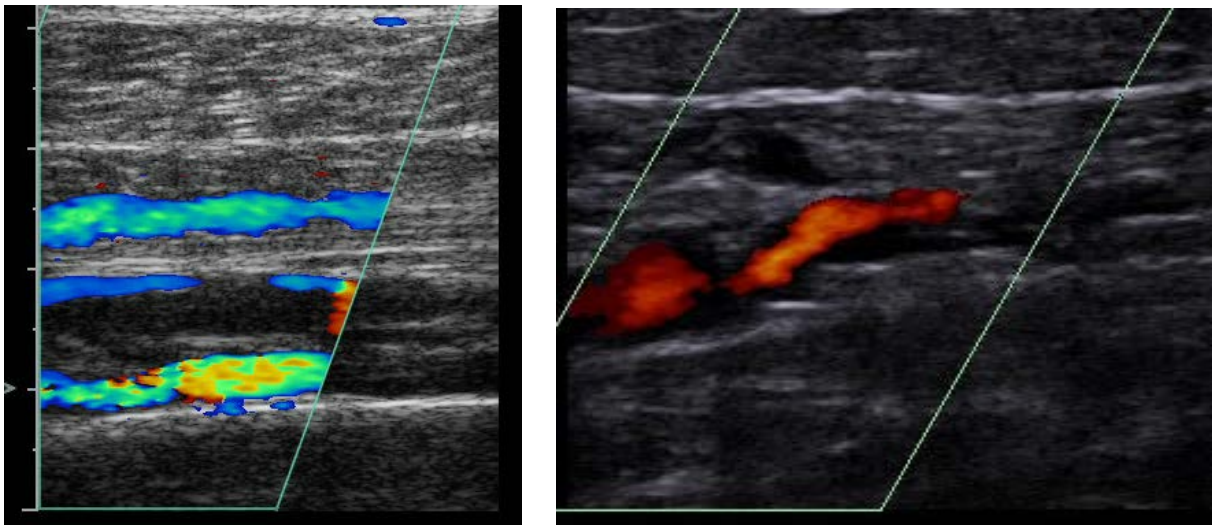

Figure 11. Post-thrombotic changes and flow disturbance. Longitudinal color Duplex image of a fibular vein with residual thrombus and flow in a recanalized lumen (left). Posterior tibial vein with reflux through a segment with post-thrombotic changes (right).

There was no difference between SDVT and ADVT patients for any of the pletysmographic variables. When patients (SDVT+ADVT, n=85) were compared with healthy controls there was a significant difference only for EV_4/V which was reduced in the patient group (0.72 ± 0.07 vs. 0.76 ± 0.06; P<0.01).

Regarding patients with postoperative DVT, only a few subjects had plethysmographic signs of venous dysfunction. Seven patients had evidence of venous outflow obstruction (VE <62 or EV_4/V <0.62); two patients with SDVT and five patients with ADVT. Evidence of significant venous reflux (T½ <5) was found in four patients with SDVT and in two ADVT patients. We found no relationship between the presence of post-thrombotic changes and static plethysmographic variables. The dynamic variable T½ was, however, significantly related to venous reflux registered by CDU.

Table 3. Results from plethysmography (mean and 95% confidence interval), color duplex ultrasound and clinical scoring in patients and healthy subjects.

	Operated for Achilles tendon rupture			
	No DVT (n=45)	Asymptomatic DVT (n=38)	Symptomatic DVT (n=45)	Healthy subj (n=40)
VE, ml per 100ml x min	105 (96-113)	103 (94-112)	114 (105-123)	113 (103-123)
V, ml per 100ml	6.3 (5.9-6.7)	6.1 (5.6-6.6)	6.4 (6.0-6.8)	6.3 (5.8-6.8)
EV_4/V	0.70 (0.68-0.72)	0.71 (0.69-0.73)	0.74 (0.72-0.76)	0.76 (0.74-0.78)
RV, ml/100ml	1.7 (1.5-1.9)	1.7 (1.4-1.9)	1.8 (1.6-1.9)	1.7 (1.4-1.9)
T½, sec	18 (15-20)	18 (14-21)	15 (12-17)	16 (14-17)
Post-thrombotic changes, n (%)	0	21 (55%)	36 (80%)	-
Deep venous reflux, n (%)	3 (7%)	22 (58%)	38 (84%)	-
Villalta score ≥5 n (%)	2 (4%)	3 (8%)	6 (13%)	-
CEAP, C-class ≥3 n (%)	0	1 (3%)	2 (4%)	-
VEINES-QOL/Sym mean (SD)	51/51 (6/7)	49/49 (7/6)	50/50 (10/10)	-

VE, venous emptying; V, venous volume; EV_4/V, the volume of blood expelled during the initial 4 seconds divided by V; RV, refilling volume; T½, half-refilling time.

Clinical results and development of PTS in patients with postoperative DVT after minor surgery (Study III and IV)

In the ADVT group (n=38) there were three proximal DVTs involving the popliteal vein and 35 distal DVTs. The distribution of DVT in the acute phase was similar in

SDVT patients (n=45) with four proximal DVTs involving the popliteal vein and 41 distal DVTs. Two patients in each group had had a new episode of DVT, in the SDVT group in the ipsilateral and in the ADVT group in the contralateral limb.

Most patients had low C-classes according to CEAP (Table 3). Only three patients had C-class 3 or higher, two in the SDVT group and one in the ADVT group. One patient had extensive varicose veins, skin pigmentation and edema (C4a); belonged to the SDVT group with a total Villalta score of 7, and had had a recurrent ipsilateral DVT. The VEINES-QOL/sym questionnaire scores were based on a mean of 50 and SD of 10 (lower scores indicate impaired QOL). Scores did not differ between the groups and the majority of patients in both groups scored between 45 and 55.

PTS (=total Villalta score ≥5) was found in nine patients; six patients in the SDVT group (range 5-9) and three patients in the ADVT group (range 6-9) (Table 3). No patient scored as moderate (Villalta score 10-14) or severe PTS (Villalta score ≥15). The most commonly reported Villalta symptom items in both groups were paresthesias and cramps. The seven patients with proximal DVT had Villalta scores between 0 and 3.

We found no significant correlation between the Villalta total score and CDU findings or any of the plethysmographic measures of venous function. However, the Villalta score of clinical objective signs correlated significantly with the plethysmographic dynamic variable T½ which demonstrate that clinical signs of venous disease relates to venous reflux according to plethysmography.

Discussion

This thesis concerns some specific types of DVT, including primary upper extremity DVT and postoperative DVT in the lower limb after minor orthopaedic surgery. The main reason for this is the lack of data in the literature regarding these different DVTs. The studies included in this thesis describe venous function after earlier deep venous thrombosis in upper and lower extremity, assessed by CDU and CSGP. We intended to study how those methods can be used for objective long-term evaluation of venous disease after DVT.

Venous hemodynamics is sometimes described as more complicated than arterial hemodynamics depending on that the overall venous function is influenced by collaterals, obstruction, and function of the calf muscle pump as well as valvular function, i.e. reflux. Further, pathological findings in superficial, deep or perforator systems can in different ways contribute to changes in the venous circulation. The clinical picture may, however, be the same despite many different combinations of obstruction and reflux in these systems.

The clinical signs as well as symptoms stated by the patient in lower and upper limb following DVT are often non-specific and may consist of pain, swelling and functional impairment. With those clinical manifestations it is often of value to confirm or exclude the clinical diagnosis with objective assessment of venous function and morphology (Prandoni et al. 1997a) and to describe the extent of the disease. CDU and plethysmography are non-invasive tests of venous function to help out in this issue.

Venous strain-gauge plethysmography

Before using any new method or new device it is important to evaluate measurements in healthy subjects and to identify the possible influence of confounding factors. This is essential before introducing a method in clinical diagnostic routine, but also in the coherence of research. Such evaluations are available for CSGP for lower, but not for upper extremities (Shi et al. 1992b, Rosfors et al. 1996). In coherence with those studies, we found the device easy to handle and the method achieved all variables presented with a high reproducibility also for the upper extremity. The most commonly used variables (i.e. V, VE and EV_4/V) were independent of age and gender and there was no difference between right and left arm in these values. The coefficient of variation of the plethysmographic variables for the arm was approximately 10 % for healthy subjects as well as for the patients with previous arm DVT. These results are fairly similar to our earlier described methodological variation regarding patients with previous DVT in the lower leg (Rosfors et al. 2001), but somewhat higher than those we found in lower legs in healthy subjects (around 6 %) (own unpublished observations).

For the lower limb, EV_4 should be more than 62 % of the venous volume in healthy controls as well as in symptomatic lower extremities without DVT (Shi et al. 1992a, Rosfors et al. 1996, own unpublished observations). For upper extremities our results demonstrate somewhat lower values in healthy controls, with a normal lower limit for EV_4/V of 0.46.

In study IV concerning lower extremities, EV_4/V was the only variable that was significantly reduced in patients compared with healthy controls, which can indicate that this variable is sensitive to minor residual outflow obstructions.

To our knowledge there are only a few previous plethysmographic studies describing DVT in upper extremities. A study using an older SGP-technique showed values that correlate well with our findings, i.e. decreased VE in 10 patients with previous arm DVT, but they obtained considerable lager variation of the measurements (Lindblad et al. 1990). Another study using SGP and 16 patients with arm DVT showed decreased VE in the acute phase, but not in the follow-up period (Zufferey et al. 1992). A possible explanation to this could be that modern technique is more sensitive in detecting minor degrees of outflow obstruction, but differences regarding the patient material and degrees of disease must also be considered. Also air plethysmography has been used in a study concerning DVT in upper extremities (Gardner et al. 1993). They found reduced venous emptying at a mean follow-up of six months after arm DVT.

The fact that both venous volume and rate of venous emptying were significantly lower in the patient group than in controls demonstrates that this method can be used to characterize venous outflow function in patients with DVT in upper extremities. A reduced outflow capacity even five years after the initial diagnosis of DVT is likely to implicate that this is a sensitive method in detecting venous outflow obstruction, since we reasonably can assume that outflow function was even more decreased during the acute phase of DVT. This assumption is supported by earlier studies showing an increase in venous outflow capacity and venous volume during the first six month following a DVT with computerized SGP for lower extremities (Rosfors et al. 1997, Rosfors & Norén 1999), and for upper extremities using older SGP technique (Zufferey et al. 1992). The finding of still reduced VE and V as a long-term finding following an acute DVT in upper or lower extremities can justify further investigation of patients with persistent symptoms.

Color duplex ultrasound

Color duplex ultrasound imaging provides anatomic, morphologic, and hemodynamic information in patients with both acute and chronic DVT. CDU is often described as the imaging test of choice for diagnosing DVT because the technique is non-invasive, without exposure for radiation or contrast medium and reasonably inexpensive. The technique has high sensitivity and specificity for DVT in the upper as well as in the lower extremities (Prandoni et al. 1997a, Joffe et al. 2002, Lapidus et al. 2006).

A limited number of studies have used CDU to describe outcome after DVT episodes in the upper extremities. The results regarding residual thrombosis and remaining occluded segments after UEDVT do not seem to differ substantially from those reported after DVT in the lower extremities (van Ramhorst et al. 1992), but the relatively few follow-up studies of UEDVT do not allow any reliable comparisons.

The diagnosis of chronic disease in upper extremity is sometimes more difficult than acute venous disease. Recanalized lumens in addition to small caliber veins with non-compressible thickened wall may be seen and highly echogenic structures may be difficult to interpret or may cause acoustic shadowing. Furthermore, collateral veins are often prominent in patients with chronic disease and can compromise the evaluation of flow in the main vein.

Sabeti et al (2003) performed a retrospective study in order to investigate the medium-term clinical and morphological outcome of patients with UEDVT. After a median follow-up of 40 months 48 % of the patients had residual DVT, compared with 58 % in our population. However, one third of the patients in Sabeti's study received systemic thrombolysis, which was found to positively influence the rate of recanalization. Moreover, Petrakis et al (2001) demonstrated that 42 % of the arms

evaluated phlebographically still had occluded segments 15 months following thrombolysis of axillary-subclavian vein thromboses.

In the present studies using CDU in lower extremities post-thrombotic changes and deep venous reflux were common findings. In only a few cases deep venous reflux occurred in segments not involved in the acute episode of DVT, and only a few patients were diagnosed with superficial axial reflux. Many studies have demonstrated that reflux in the superficial venous system of the leg can produce a large range of serious symptoms and signs that previously have been attributed to disease in the deep veins (Labropoulos et al. 1995a and 1995b, Magnusson et al. 2001). Furthermore, Danielsson et al (2003) described that continuous axial reflux is a major contributor to increased prevalence of skin changes or ulcerations compared with segmental deep venous reflux above or below the knee only. Axial deep or superficial reflux were uncommon findings in our series of postoperative DVT mainly limited to calf veins, which possibly is one of the reasons for the low frequency of PTS in our studies.

Segmental deep venous reflux in limbs without morphological signs of previous DVT was found in two ADVT, two SDVT patients and in three controls. This might reflect a normal variation, as has been shown in a cross-sectional survey by Evans et al (1998).

Post-thrombotic syndrome in upper and lower extremities

There is no gold standard test for diagnosing PTS and several recent studies have illustrated that all diagnostic systems have merits and disadvantages (Kolbach et al. 2005). Since precise criteria for PTS have not been established earlier studies have

used various definitions to diagnose PTS. More formal scoring systems have been used in some studies and one of these is the Villalta scale (Kahn 2009b).

For upper extremities more various definitions have been used. Prandoni et al (2004) and Kahn et al (2005) used a modification of the existing lower extremity Villalta scale to diagnose PTS in upper extremity. In the more recent versions this scale assigns points for symptoms of pain, cramps, heaviness, pruritus and paresthesia and clinical signs for edema, prominent veins on arm, prominent veins over shoulder or anterior chest wall, redness, tenderness, dependent cyanosis. This scale has not been formally validated and is also revised to some extent regarding clinical signs compared with the scale we used in Study II.

Few studies have reported on the incidence of PTS following UEDVT and results are difficult to compare due to variations in the definition of PTS, follow-up times, treatment regimen and use of compression stocking. The overall frequency of PTS after UEDVT appears to be in the range of 7 to 46 % (Prandoni et al. 2004, Hingorani et al. 1997, Sabeti et al. 2003, Kahn 2005). In our series of primary UEDVT the most common symptom was swelling of the affected arm, reported by 70 % of the patients. Other frequent findings were pain and reduced strength, discoloration of the skin and distended collateral veins over the shoulder region. It is likely that a number of factors are involved in the expression of this syndrome, including both outflow obstruction and patient-related factors such as degree of physical activity and physical demand.

For the lower extremities, it is considered that 20 to 50 % of patients with previous DVT will develop PTS within 2 years (Shbaklo & Kahn 2008). Prandoni et al (1997b) described a 30 % cumulative incidence of PTS eight years after a first episode of DVT. In the present Study IV mild PTS was found in 11 % of the patients. One reason for the lower frequency of PTS in our patients might be our low rate of only

2 % recurrent ipsilateral DVT, since recurrences are described as one of the most powerful risk factor for development of PTS (Kahn & Ginsberg 2004, Labropoulos et al. 2010b). Another reason is probably the fact that most DVTs were small distal ones with possibly favourable outcome.

Regarding clinical scoring for lower extremities the most common findings in Study III and IV were venous ectasia (22 %) and edema (13 %) in the SDVT group and only venous ectasia (24 %) in the ADVT group. The most commonly reported subjective symptoms were paresthesias and cramps in both groups. Villalta scores for clinical symptoms did not correlate with any objective measure of venous dysfunction. This suggests that symptom scoring in this group of patients might be non-specific and that symptoms in some cases may be related to problems secondary to the surgical procedure rather than being signs of venous disease. The high frequency of calf muscle atrophy in the limbs that were subjected to surgery supports this assumption. However, the reported symptoms did not influence the quality of life, since both groups had a mean score close to the standardized response mean of 50.

Relation between plethysmography and ultrasonography, and postthrombotic disease

The most evident finding in our patients with primary UEDVT was a reduced rate of venous emptying in the arms with earlier DVT compared with the contralateral arm and compared with healthy controls. Thirty-five per cent of the patients had a significant outflow obstruction with values of VE lower then the normal lower limit in our reference material. The CDU demonstrated residual wall abnormalities in most of the patients and there was a clear trend towards lower venous emptying in patients with more advanced post-thrombotic changes. The results showed, however, that other factors than residual DVT can cause reduced VE. Four of 13 patients without

residual DVT had a significant outflow obstruction shown with CSGP, possibly because of stiff vessel walls. Conversely, some patients with residual DVT and remaining occluded veins had VE values within the normal range. This probably shows that development of venous collaterals and the diameters of the patent veins are also of importance for the plethysmographic outcome.

Loss of valvular function is an important factor in the development of PTS after lower-extremity DVT (Killewich et al. 1985, Haenen et al. 2002). However, in patients with previous UEDVT we found no patient with deep or superficial valvular insufficiency in the arms, which shows that loss of valvular function can not be a major part in the development of PTS following UEDVT. This can also explain why PTS in the lower limb, but not in the upper limb, includes more severe manifestations of venous hypertension such as hyperpigmentation and ulcers. In our patients with previous DVT in the lower limb, Villalta scores for clinical signs correlated significantly with plethysmograhic evidence of reflux, which supports the importance of valvular dysfunction regarding development of PTS stated above.

Concerning our patients with lower limb DVT, CDU detected residual post-thrombotic changes in 55 % of the ADVT patients and in 80 % of patients with SDVT. There were no differences between the two groups regarding plethysmographic results and only a few patients had plethysmographic signs of venous dysfunction. Deep venous reflux was more common in SDVT than in ADVT patients. This probably reflects that the extension of the DVT in SDVT patients were lager in the acute phase and caused more damage to the venous valves involved resulting in more extensive reflux at follow-up. There is certainly a large difference in a DVT with more extensive occluding thrombi in two or three vessels in the calf compared with isolated 2 cm thrombi in a deep calf vein segment, but both scenarios represent distal DVTs.

We found no correlations between PTS scoring and CDU findings. This may reflect that CDU technique is able to show subtle abnormalities that do not affect venous pressure and therefore do not lead to significant venous disease.

Conclusions

- Computerised strain-gauge plethysmography can be used in a reproducible way to non-invasively study venous function in the upper extremities. Venous volume and venous outflow in our control group were independent of age and gender. We suggest that these data can be used as reference values.

- Patients with earlier primary upper extremity DVT had significantly reduced venous outflow and residual thrombus was a common finding. Less than one third of the patients had mild-to-moderate PTS according to Villalta scoring. Swelling of the arm was the most common symptom. No patients had recurrent thromboembolic events and we found the clinical outcome following conservative treatment to be relatively benign.

- Deep venous reflux and post-thrombotic changes were more commonly found in patients with earlier symptomatic than in asymptomatic lower extremity DVT. Probably because the symptomatic DVTs are larger. Abnormal pletysmographic results were uncommon and did not differ between the groups, demonstrating that the observed ultrasonographic changes were of minor hemodynamic importance.

- DVT after surgery for rupture of the Achilles tendon consists mainly of distal DVTs and is associated with a low risk for PTS. At seven years follow-up there were few recurrent episodes of DVT. There was no correlation between the Villalta total score and CDU findings or any of the plethysmographic measures of venous function. In general the reported symptoms did not affect quality of life and might partly be related to the surgical procedure.

The present studies concerns studies of venous function and evaluation of clinical sequelae and frequency of PTS in patients with previous primary upper extremity DVT and in patients with postoperative DVT following minor orthopaedic surgery. In general, these studies show that the clinical signs as well as symptoms stated by the patients in these types of DVT are rather non-specific and often consist of pain, paresthesias, cramps, swelling and functional impairment. Therefore, in addition to the clinical examination, objective assessment of venous function and evaluation of the extent of disease are of value. Ultrasonograhy and plethysmograpy are non-invasive tests that can be used for this purpose.

Summary in Swedish

Målsättningen med denna avhandling är att öka kunskapen om långtidseffekter på venfunktionen efter djup ventrombos (DVT) i armar och ben. Ultraljud och datoriserad venpletysmografi är exempel på non-invasiva metoder som idag finns att tillgå för objektiv diagnostik. Med ultraljudsundersökning är det möjligt att kartlägga flödesförhållanden och morfologiska förändringar i kärlväggen. Datoriserad venpletysmografi uppskattar den globala venfunktionen.

DVT har en årlig incidens i Sverige på ca 1-2/1000 och av dessa är cirka 4 % lokaliserade till armarnas vener. Den viktigaste sena effekten av en DVT är kronisk venös insufficiens och utveckling av posttrombotiskt syndrom (PTS). Ofta tar utvecklandet av detta syndrom flera år i anspråk. För att klinisk handläggning av patienten ska kunna planeras och genomföras är en objektiv diagnos av stor betydelse. Detta kan t ex innefatta detaljerad information om sjukdomens omfattning och lokalisation, men också utredning om den globala venösa funktionen. Två olika tillstånd som kan uppträda efter genomgången DVT är reflux (klaff-läckage) pga skadade venklaffar och venös obstruktion orsakad av t ex kvarstående ocklusion, trombrester med partiell rekanalisering eller väggförtjockning. Den venösa hypertensionen som kan uppstå vid dessa tillstånd ger förändringar i mikrocirkulationen och i huden på extremiteten. Kronisk förhöjning av ventrycket ger i regel på sikt lokala hudförändringar som bl a hyperpigmentering, trofiska förändringar, ödem och eventuellt bensår.

Arbete 1: 34 friska försökspersoner inkluderades och med jämn fördelning mellan könen. Som jämförelsematerial inkluderades 32 patienter som insjuknat i primär

armventrombos under perioden 1995-2002. Bägge grupperna undersöktes med datoriserad venpletysmografi och för reproducerbarhetsmätning utfördes proceduren två gånger. Normalvärden på kontrollgruppen kunde beräknas och vid mätning av venvolym och ventömningshastighet fann vi ingen skillnad mellan höger och vänster arm. Vi fann heller ingen inverkan av kön eller ålder. Variationskoefficienten blev cirka 10 %. Resultaten från gruppen med tidigare armventrombos visade lägre venvolym och lägre ventömningshastighet jämfört med kontrollgruppen. Våra resultat visar att denna teknik kan användas för att studera förändringar i armvenernas funktion och de erhållna värdena i kontrollgruppen kan användas som referensvärden för venösa avflödesfunktionen i armarna utan behov av korrektion för ålder eller kön.

Arbete 2: 31 patienter som insjuknat i primär armventrombos och behandlats med antikoagulantia under perioden 1995-2002 inkluderades. Bakgrundsdata samlades in genom journalgenomgång och patientintervjuer. Klinisk grad av posttrombotiskt syndrom (PTS) analyserades genom ett tidigare utvärderat protokoll (Villalta score). Omkrets mättes på bägge armar på samtliga patienter. Trombosarmen undersöktes med ultraljudsteknik för kartläggning av flödesförhållanden och morfologiska förändringar i kärlväggen. Alla patienter undersöktes med datoriserad venpletysmografi för bedömning av venernas avflödesfunktion.

Majoriteten av patienterna (77 %) hade kvarstående besvär från trombosarmen och cirka 30 % hade utvecklat en lätt till måttlig grad av PTS enligt Villalta score. Överarmarnas omkrets var större hos armar med tidigare DVT jämfört med de kontralaterala armarna. 58 % av patienterna hade påvisbara kvarstående trombosrester (ingen hade djup eller ytlig reflux) och 35 % hade venös tömningskapacitet lägre än normalvärdet. Det var en signifikant lägre

ventömningskapacitet i trombosarmen jämfört med den kontralaterala armen. Ventömningskapaciteten tenderade att vara lägre hos patienter där ultraljud visade kvarvarande trombosrester, men det fanns inget säkert statistiskt samband mellan grad av PTS och ultraljudsfynden. Patienter med PTS hade generellt lägre ventömningshastighet än patienter utan PTS.

Arbete 3: Studien omfattar 105 patienter som opererats för hälseneruptur och genomgått postoperativ flebografi och/eller ultraljudsundersökning för diagnostik av djup ventrombos (DVT). Patienterna rekryterades från tidigare studie av postoperativ tromboembolism där inklusionen av patienter påbörjades 2001. Frekvensen DVT i detta material var drygt 40 %. Patienterna genomgick datoriserad venpletysmografi och ultraljudsundersökning. Den del av patientmaterialet som inte hade DVT postoperativt fungerade som kontrollgrupp (n=45). Vidare användes validerade skattningsskalor för tecken till posttrombotiskt syndrom med avseende på klinisk klassifikation och patientens eventuella subjektiva besvär och funktionsnedsättning (Villalta score, CEAP och Quality of Life).

Majoriteten av patienterna hade inga kliniska eller subjektiva symtom talade för venös sjukdom. Vi fann ingen skillnad mellan patient- och kontrollgruppen avseende Villalta score, CEAP klassifikation eller Quality of Life. Ultraljudsmässigt hade 21 av 38 patienter (55 %) i DVT-gruppen kvarstående posttrombotiska förändringar och hos 22 patienter (58 %) kunde djup venös reflux konstateras. Det var ingen signifikant skillnad mellan grupperna avseende ventömningskapacitet eller djup venös reflux tydande på att ultraljudsfynden var av försumbar betydelse för den venösa funktionen.

Arbete 4: 45 patienter med symtomatisk djup ventrombos (SDVT) och 38 patienter med asymtomatisk djup ventrombos (ADVT) efter operation av hälseneruptur efterundersöktes 5 till 9 år efter ingreppet. Uppföljningen omfattade datoriserad venpletysmografi och ultraljudsundersökning. Vidare användes validerade skattningsskalor för tecken till posttrombotiskt syndrom med avseende på klinisk klassifikation och patientens eventuella subjektiva besvär och funktionsnedsättning (Villalta score, CEAP och Quality of Life). En ålders- och könsmatchad kontrollgrupp (n=42) undersöktes med venpletysmografi.

Posttrombotiskt syndrom utvecklades hos 13 % i SDVT-gruppen och i 8 % i ADVT-gruppen, i samtliga fall av lindring grad med Villalta-score 5-9. Djup venös klaffinsufficiens påvisades i högre frekvens hos patienter med SDVT än hos gruppen med ADVT (84 % jämfört med 55 %). Endast ett fåtal patienter hade avvikande pletysmografiska resultat.

Slutsatser

- Datoriserad venpletysmografi kan användas på ett reproducerbart sätt för non-invasiv utredning av venös funktion i armar. Fem år efter djup armventrombos var venvolym och ventömning lägre i en grupp av patienter jämfört med våra friska kontroller.
- Patienter med tidigare primär djup armventrombos uppvisade sänkt ventömning och drygt hälften av patienterna hade kvarvarande trombosrester enligt ultraljud. Svullnad av armen var det vanligaste symtomet och omkring en tredjedel av patienterna hade lätt till måttlig grad av posttrombotiskt syndrom. Det kliniska utfallet hos konservativt behandlade patienter med

tidigare armventrombos var relativt gott och utan betydande grad av posttrombotiskt syndrom.

- Posttrombotiskt syndrom förekommer sällan i efterförloppet av en asymtomatisk djup ventrombos (ADVT) i ben efter operation för brusten hälsena. Vid femårsuppföljning hade mer än hälften av patienterna med asymtomatisk djup ventrombos posttrombotiska förändringar enligt ultraljudsundersökning men ingen påvisbar försämring av den globala venfunktionen.
- Postoperativ djup ventrombos efter operation för brusten hälsena består huvudsakligen av underbenstromboser och är förenad med en låg risk för återkommande episoder av djup ventrombos. Få patienter drabbas av följdtillstånd i venfunktionen. Posttrombotiskt syndrom återfanns hos cirka 10 % av patienterna vid vår sjuårsuppföljning.

Denna avhandling omfattar studier av venös funktion och utvärdering av kliniska symtom och frekvens av posttrombotiskt syndrom hos patienter med tidigare primär trombos i arm och hos patienter med postoperativ trombos i ben efter mindre ortopedisk kirurgi. Generellt visar dessa studier att kliniska fynd samt symtom som anges av patienter vid dessa typer av tromboser är ganska ospecifika och består ofta av smärta, krypningar/stickningar, kramper, svullnad och upplevd nedsatt funktion av extremiteten. Därför är det värdefullt att, utöver den kliniska undersökningen, göra en objektiv bedömning av venös funktion och en utvärdering av förekomst och omfattning av eventuella resttillstånd i kärlen. Ultraljudsundersökning och venös pletysmografi är icke-invasiva metoder som kan användas för detta ändamål.

Acknowledgements

I would like to express my warmest thanks, gratitude and appreciation to everyone who has given me support and encouragement during these years and who made this thesis possible, and with special emphasis to:

Stefan Rosfors, associate Professor at the Department of Clinical Physiology, Södersjukhuset. First and foremost I offer my sincerest gratitude to my principal supervisor whose encouragement, guidance and professional support from the initial to the final level enabled me to develop an understanding of the subject. He has always patiently and generously shared his extensive knowledge in the scientific as well as the clinical field. Without him this thesis would not have been completed or written.

Gerd Lärfars, associate Professor, director of the Department of Internal Medicin, and my co-supervisor for enthusiastic encouragement throughout this project. I highly appreciate that you wanted to contribute with your profound scientific knowledge and clinical experience. Your belief in me and your kindness has meant a lot to me.

Viveka Holmberg, Lic Med Sci, research coordinator at the Department of Clinical Science and Education, Södersjukhuset and my external mentor. For not just being such a wonderful and wise person but also an excellent listener with extensive scientific knowledge. You have given me invaluable support. From now on, I regard you as a dear friend.

Christina Kilander, director of VO Bild and Department of Clinical Physiology, Södersjukhuset, who gave me the opportunity to begin an academic education and allowed me to experience an extraordinary time.

Kerstin Jensen-Urstad, associate Professor and head of Department of Clinical Physiology, Södersjukhuset, for giving me the opportunity to complete this thesis and providing me excellent working conditions. For your professional attitude and constructive criticism of the manuscripts. Your support has been and will always be of great importance to me.

Marie Herlitz Lindberg, head BMA of the Department of Clinical Physiology, Södersjukhuset, for your good leadership and support, for providing me excellent working conditions. I highly appreciate that you contributed with your knowledge and experience in ultrasound examinations. Your kindness and our small talk now and then have meant a lot to me.

Lasse Lapidus, consultant physician at the Department of Orthopaedics, Södersjukhuset and co-author for highly valuable assistance in the studies, for good ideas and cooperation. For the most friendly support and encouragement, and for your quick answers.

Thomas Arnhjort, consultant physician at the Department of Accident and Emergency, Södersjukhuset and co-author, for good ideas and cooperation. Your positive attitude has been very encouraging.

Stefan Svart, engineer at Department of Medical Technology, Södersjukhuset, for never ending patience, helpfulness and for professional assistance with all types of technical development and problems, at all times. Your support as well as your kindness have been crucial for me and the project.

Martin Anderson, consultant physician at the Department of Clinical Physiology, Södersjukhuset, for most valuable advises in the scientific field. Thank you, for being so encouraging and your fantastic enthusiasm has many times given me new energy to move forward.

Carl-Olof Ekman, consultant physician at the Department of Clinical Physiology, Södersjukhuset, who with sharp analyses and bright intellect always encouraged and supported me. You are a living encyclopaedia that allows users at any time.

Tina Levander, study nurse, Department of Orthopaedics, Södersjukhuset, for invaluable and skilful assistance in administrating the patients. Your ability is impressive and it is a pleasure working with you.

Caroline Haneby, vascular technologist at the Department of Clincal Physiology, Södersjukhuset, for skilful contributions with the patient examinations and for pleasant and stimulating collaboration.

All staff at the Department of Clinical Physiology, Södersjukhuset, Stockholm for friendly support and encouragement. Special thanks to all BMA colleagues for coping with the clinical burden when I was off duty to work on this project.

All staff at the Department of Clincal Science and Education, Karolinska Institutet, Södersjukhuset Stockholm. Thank you for all help!

Anita Stålsäter-Pettersson, former doctoral student administrator at the Department of Clincal Science and Education, Karolinska Institutet, Södersjukhuset Stockholm, for professional assistance and fantastic kindness and support.

Katarina Bohm, RN and PhD, Department of Cardiology, for good advice in the scientific field and for your kindness.

To my family and relatives, including Johanna
You are simply the best and I love you all. You are all invited to “Tossene open” next summer. But watch out, I will beat every one of you.

This thesis is to Anton and Elin, my beloved children. You are the sunshine of my life and there is nothing more important than the two of you.

This thesis was supported by Karolinska Institutet, Department of Clinical Physiology at Södersjukhuset, ALF project funding from the Stockholm County Council, Foundation for Coagulation Research, Capio Research Foundation and Swedish Society of Clinical Physiology.

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