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PRIMARY DEEP VEIN THROMBOSIS IN AN UPPER LIMB: A RETROSPECTIVE STUDY WITH AN EMPHASIS ON THE PATHOGENESIS AND LATE SEQUELAE

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PRIMARY DEEP VEIN THROMBOSIS IN AN UPPER LIMB: A RETROSPECTIVE STUDY WITH AN EMPHASIS ON THE PATHOGENESIS AND LATE SEQUELAE

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To Göran, the love of my life

ABSTRACT

Background: Upper extremity deep vein thrombosis (UEDVT) is an uncommon disease with an incidence of 1–11% of all deep vein thrombosis. UEDVT can be classified into two groups, primary and secondary UEDVT. Primary UEDVT includes idiopathic and effort-related UEDVT. Secondary UEDVT is caused by central venous devices, trauma, and cancer. This thesis is focused on primary UEDVT.

Aim: This project emerged from a clinical question when we started to review our guidelines for deep vein thrombosis at the Emergency Department at Södersjukhuset, Stockholm. The overall aim of this thesis was to increase the level of knowledge concerning primary UEDVT.

Patients: Thirty-one patients (23 females, 8 males) with primary UEDVT were enrolled for Papers I. For paper II there was thirty-two patients (23 females and 9 males) included. Fifteen of these patients agreed to participate in the third study, the MRI Study, in which a control group of 15 healthy volunteers was also included. The fourth paper is a retrospective case-control study based on data from the Swedish National Patient Register (NPR) and comprises 25 patients with primary UEDVT.

Methods: In Paper I, the patients were evaluated using interviews, clinical examinations, computerized strain-gauge plethysmography, and color duplex ultrasound (CDU) imaging. The degree of postthrombotic syndrome (PTS) was rated according to the Villalta score. For the second paper, the Villalta score was supplemented with the DASH test (Disability of the arm shoulder and hand). The visual analog scale (VAS) was used to estimate pain and disability. An arm exercise capacity test was performed to evaluate working capacity. Blood samples were taken for analyses of factor V Leiden and common coagulation factors.

In Paper III, the subclavian region (the costoclavicular distance) and vessel area of the subclavian vein were examined using magnetic resonance imaging (MRI). The MRI was performed with the arms in two positions: alongside and elevated. PTS and disability were quantified with the Villalta and DASH scores. The 25 patients in the fourth paper were matched on an individual basis with 474 controls (patients with acute appendicitis) in relation to sex, age at the index point, and the year of the index point. Comorbidity was described as the number of unique ICD codes (diagnoses) registered in the NPR from the index point to the end of year 2011.

Results: *Paper I.* The rate of venous emptying was significantly lower in the arms with DVTs than in the contralateral arms. Fifty-eight percent had a residual thrombus and seventy-five percent of the patients had some morphologic abnormality in the thrombotic vein. There was no statistically significant relationship between the plethysmographic and duplex findings. No significant difference in the relationship between the postthrombotic syndrome score and duplex findings or venous emptying was evident.

Paper II. None of the patients developed malignancies, pulmonary embolism, or recurrent UEDVT. Twenty-eight percent of the patients had mild to moderate PTS according to the scoring instruments. The prevalence of thrombophilia was 40%; the most frequent disorders were the mutation of the gene for factor V Leiden (19%) and elevated fibrinogen (22%).

Paper III. The costoclavicular distance was significantly narrower in the patients than in the controls with the arms alongside the body, but there was a significant difference only in the left arm with the arms elevated. Area of the subclavian vein: on comparing the patients' non-thrombotic arm with that of the controls, there was a significant difference only with the arms in the supine position. Measurements of disability: there was a high correlation between DASH, the Villalta score, and VAS, but there was no correlation between the MRI measurements and the patients' symptoms.

Paper IV. The 25 cases and 474 controls, 48% male and 52% female, had a mean age at the index point of 48 years (range, 20–80, SD 17.5). The mean follow-up time was 8 years (range, 5.7–9). There was no significant difference between patients and controls regarding the frequency of reported unique ICD codes in the NPR when all ICD codes were analyzed together, but there was a significant difference for codes related to symptoms from the blood and blood-forming organs, the endocrine and metabolic systems, disease of the nervous and circulatory systems, and skin and musculoskeletal systems. There was no difference in ICD codes relating to malignancies. The cases had a significantly higher number of healthcare contacts.

Conclusions

- Primary UEDVT is a rather benign disease with a low rate of recurrences, but with a non-negligible proportion of the postthrombotic syndrome.
- Fifty-eight percent had a residual thrombus. Seventy-five percent of the patients had some morphologic abnormality in the thrombotic vein, which was detectable with CDU. The rate of venous emptying was significantly lower in the arms with DVTs than in the contralateral arms.

- There was no correlation between PTS and plethysmography findings, area of the subclavian vein, and morphologic abnormalities detected by CDU.
- The frequency of coagulation disorders was about 40%; the most common disorders in our study population were mutations of factor V Leiden.
- There seemed to be some influence regarding the anatomy of the thoracic outlet and the development of both effort-related and idiopathic UEDVT.
- The rate of malignancies seems to be in line with that of the general population.
- It is extremely important to validate data from the National Patient Register with the medical records especially when there is no unique ICD-code.

LIST OF SCIENTIFIC PAPERS

- I. **Hemodynamic and morphologic evaluation of sequelae of primary upper extremity deep venous thrombosis treated with anticoagulation.**
Persson LM, Arnhjort T, Lärfars G, Rosfors S.
J Vasc Surg. 2006 Jun;43(6):1230-5; discussion 1235.
- II. **Primary deep vein thrombosis in the upper limb: A retrospective study with emphasis on pathogenesis and late sequelae.**
Arnhjort T, Persson LM, Rosfors S, Ludwigs U, Lärfars G.
Eur J Intern Med. 2007 Jul;18(4):304-8.
- III. **The importance of the costoclavicular space in upper limb primary deep vein thrombosis, a study with magnetic resonance imaging (MRI) technique enhanced by a blood pool agent.**
Arnhjort T, Nordberg J, Delle M, Borgis CJ, Rosfors S, Lärfars G.
Eur J Intern Med. 2014 Jul;25(6):545-9. doi: 10.1016/j.ejim.2014.05.005.
Epub 2014 May 27.
- IV. **Primary upper extremity deep venous thrombosis and comorbidity: A population-based nationwide study in Sweden**
Arnhjort T, Lärfars G, Adami J, Järnbert-Pettersson H
(submitted)

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2 LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
ADP	Adenosine diphosphate
APC	Activated protein C
ASA	Acetylsalicylic acid
AT	Antithrombin
BMI	Body mass index
CDU	Color duplex ultrasound
CEAP	Clinical, etiology, anatomy, pathophysiology
CVC	Central venous catheter
DASH	Disability of the arm, shoulder, and hand
DVT	Deep vein thrombosis
FDP	Fibrin/fibrinogen degradation products
GP	Glycoprotein
HRT	Hormone replacement therapy
LEDVT	Lower extremity deep vein thrombosis
LMWH	Low molecular weight heparin
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
NPR	National Patient Register
PA	Plasminogen activator
PAI	Plasminogen activator inhibitor
PE	Pulmonary embolism
PF	Platelet factor
PICCs	Peripherally inserted central venous catheters
PRN	Personal registration number

PSS	Paget-Schrotter syndrome
PTS	Postthrombotic syndrome
TOS	Thoracic outlet syndrome
UEDVT	Upper extremity deep vein thrombosis
VAS	Visual analog scale
VCSS	Venous clinical severity score
VE	Venous emptying
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
VV	Venous volume
vWF	von Willebrand factor

3 INTRODUCTION

Upper extremity deep vein thrombosis (UEDVT) can be classified into two groups, primary and secondary. UEDVT, especially the primary type, is an uncommon disease which mostly affects young to middle-aged patients. This thesis is focused on primary UEDVT.

This project emerged from a clinical question which arose when we started to review our guidelines for deep vein thrombosis at the Emergency Department of Södersjukhuset. The question was “How to handle patients with deep vein thrombosis of the upper extremity?” The first tentative answer was “We do as we do with the legs.” This rather simple and unscientific answer gave rise to further questions and we started to look into the literature on the topic and one of our first findings was that there was no clear answer to our question. There were no consistent answers regarding investigation, examination, and treatment. Some authors advocated such active treatment as thrombolysis, while others considered conventional anticoagulant therapy to be the most suitable.

4 BACKGROUND

4.1 VENOUS THROMBOEMBOLISM

Deep vein thrombosis (DVT) can affect different veins in the body. The incidence of DVT is estimated to be 1.6 per 1000 inhabitants per year for both males and females [1]. The incidence of venous thromboembolism (VTE) increases with age, the highest incidence occurring among women over 85 years of age [2]. Several studies have shown that 40–50% of the patients with symptomatic proximal DVT have ventilation-perfusion lung scan findings associated with a high probability of pulmonary embolism (PE) [3-7].

DVT is not only a severe disease because of the risk for PE, it can also cause long-term sequelae in form of postthrombotic syndrome (PTS) [8]. More than 30 % of all patients with DVT will develop PTS [9].

The most common location of VTE is in the lower extremity with a wide spectrum of severity from a small, limited clot in the calf to marked thrombosis extending into the pelvic veins.

Typical symptoms of DVT are pain and redness or discoloration of the skin, prominent veins, swelling, and tenderness. DVT can also be asymptomatic; the proportion is unknown, but significant. Due to the lack of symptoms, the patient does not seek treatment and the clot is believed to resolve spontaneously [5].

4.1.1 Coagulation and hemostasis

Normal coagulation involves pathways of enzymatic reactions that start as a response to a damaged endothelium. The endpoint is the formation of fibrin, which stabilizes the platelet clot. Both collagen and tissue factor can activate the platelets; see below – the procoagulant system. Simultaneously, the anticoagulant system starts to avoid pathological intravascular coagulation – the anticoagulant system.

Hemostasis is defined as a balance between the two systems or the process that maintains the integrity of the circulatory system after vascular damage [10].

4.1.1.1 Normal coagulation

The procoagulant system

When the endothelium is damaged there will be a contraction of the vessel and formation of an unstable thrombocyte clot, i.e., the primary hemostasis.

There are different ways to activate the platelets. Collagen (the intrinsic pathway) from

damaged endothelium attracts the von Willebrand factor (vWF) which circulates in the blood. This attraction, combined with receptor glycoproteins (GP VI-Ib-V-IX), activates the platelets and causes them to adhere and form a clot, the thrombocyte clot. Tissue factor (extrinsic pathway), normally located inside of the vessel wall, can activate the platelets by forming a complex with factor VIIa, leading to thrombin generation and more platelets being captured on the vessel wall. This second way of platelet activation is independent of the von Willebrand factor.

Inside the platelet are granules which contain several factors and components (adenosine diphosphate [ADP], fibrinogen, FXIII, FV, vWF, serotonin, platelet factor 4 [PF-4] and beta thromboglobulin) which are necessary for homeostasis. ADP is the most important factor for further platelet aggregation, but it also has a role on the thrombocyte membrane aimed at presenting the glycoprotein complex (GPIIb/IIIa). This complex has the function of a fibrin receptor and can attach more platelets. The thrombocytic clot is still permeable and might be flushed away by the bloodstream.

During hemostasis, the prostaglandins are activated, the most important step being the formation of thromboxane A₂, which promotes the aggregation of thrombocytes and also has a contraction effect on the vessel. Acetylsalicylic acid (ASA) has an inhibitory effect on the production of thromboxane A₂.

The clot becomes stable when fibrinogen converts to fibrin. An important step in this process is the formation of activated factor X (FXa). FXa, together with calcium, factor Va, and phospholipids, converts prothrombin to thrombin, which makes the platelets stickier and the thrombocyte clot more stable. Thrombin also generates fibrin out of fibrinogen. Fibrin, together with factor XIII, completes the secondary hemostasis (Figure 1).

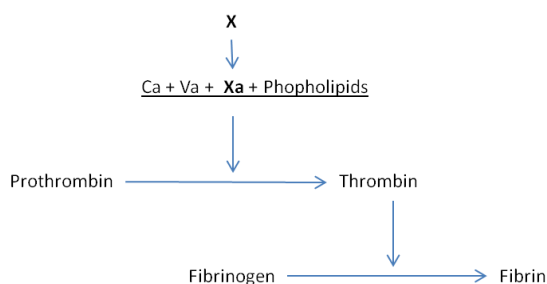


Figure 1. The role of factor X.

Thirteen circulating coagulations factors have been identified and are involved in the complex cascade of various steps to maintain hemostasis. All coagulation factors are synthesized in the liver, except factors V and VIII, which are synthesized in the thrombocytes and the endothelium, respectively. Factors II, VII, IX, and X are vitamin K-dependent.

The coagulation process starts immediately when there is a trauma to a vessel, so as to stop the bleeding. The process can also be triggered by other mechanisms, such as microorganisms and cancer tumors, thereby resulting in pathological intravascular coagulation.

The anticoagulant system

The most important inhibitor of the procoagulant system is protein C, the role of which is to reduce the activity of thrombin and thereby also inhibit the formation of fibrin. Protein C is a vitamin K-dependent pro-enzyme that is slowly activated by thrombin. Activated protein C (APC), together with protein S, degrades the active form of coagulation factors V and VIII (FVa and FVIIIa) and thereby reduces/inhibits the coagulation process. There are also strong specific inhibitors of thrombin, such as antithrombin III (AT III), which also inhibits the activated coagulationsfactors IX, X, XI, and XII.

Fibrinolysis

Fibrinolysis involves thread dissolution - a series of enzymatic reactions leading to the dissolution of fibrin. Fibrinolysis is the most important system for preventing pathological coagulation and thrombus formation. The inactive pro-enzyme plasminogen is activated to form plasmin. Plasmin degrades both fibrin and fibrinogen into fibrin degradation products (FDPs). Plasminogen is activated by plasminogen activators (PAs), tPA and uPA.

tPA is synthesized in the endothelium in both vessels and other tissues. Today tPA is made by a recombinant technique and is used for thrombolytic interventions. uPA is mainly produced in the kidneys and its effect involves keeping the urinary tract free from clots and fibrin precipitates. There is also regulation of the plasminogen activators in the form of two plasminogen activator inhibitors (PAI-1 and PAI-2). The physiological effect of PAI-1 is to moderate the activity of tPA. During pregnancy, the level of PAI-1 is elevated to secure optimal hemostasis. Finally, there is a regulation of plasmin by plasmin inhibitors (Figure 2).

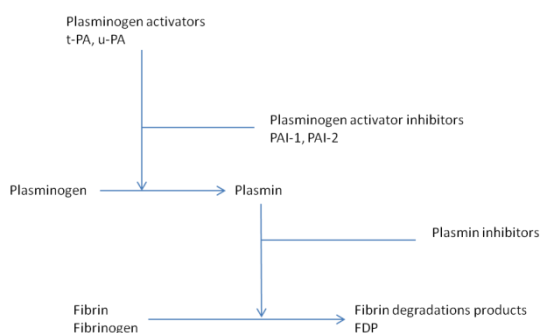


Figure 2. Regulation of fibrinolysis.

Figure 3 shows a schematic picture of the coagulation system.

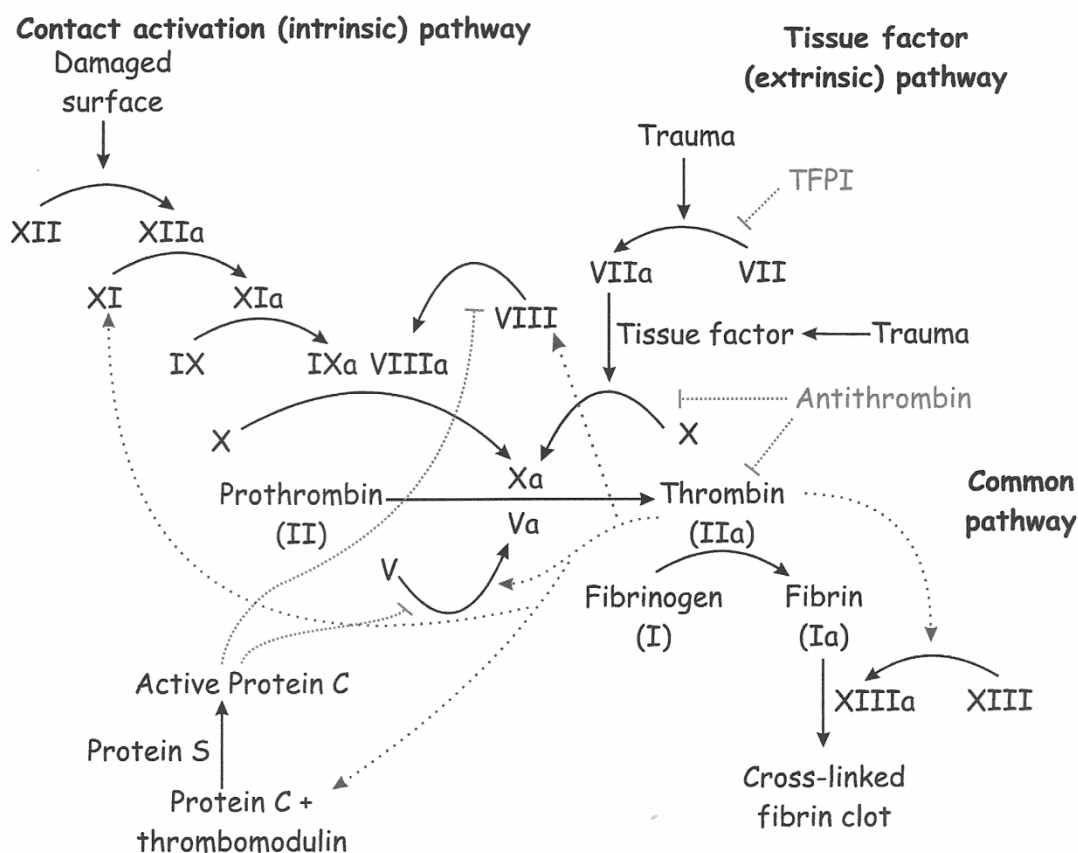


Figure 3. The coagulation system.

4.1.1.2 The hypercoagulable state

In 1884, the German physician, Rudolf Virchow (1821–1902), postulated a triad of events as being the main causes of VTE, i.e., venous stasis and vessel wall abnormalities, such as endothelial dysfunction, in combination with hypercoagulability [11]. There are both acquired and inherited risk factors for VTE.

The acquired risk factors include increasing age, prolonged immobility, major surgery, multiple trauma, prior deep vein thrombosis, chronic heart failure, obesity, and malignancy. Oral contraceptives and hormone replacement therapy (HRT) increase the risk of VTE. The antiphospholipid antibody syndrome and lupus anticoagulans also play an important role in the development of VTE.

Among the inherited factors that contribute to the overall risk of VTE, mutation of the factor V gene (factor V Leiden mutation) constitutes the most prevalent hereditary thrombophilia among the white population in Europe. This mutation causes resistance to

protein C (APC resistance). Mutation of the prothrombin gene, G20210A, also increases the risk of VTE. Furthermore, deficiency of antithrombin (AT, previously referred to as AT-III), protein C, and protein S all increase the risk of VTE.

Elevated levels of coagulation factors VIII, IX, and XI have been linked to an increased thrombotic risk. During the last few decades, some studies have shown that mild to moderate hyperhomocysteinemia can be a risk factor for VTE [11].

4.2 UPPER EXTREMITY DEEP VEIN THROMBOSIS (UEDVT)

Primary axillary-subclavian vein thrombosis was first described by Paget in 1875 and by von Schrotter in 1884, and it was named the Paget-Schrotter syndrome (PSS) by Hughes in 1949 [12]. PSS is most usually seen in the dominant arm of patients who are physically active and it can be provoked by excessive overhead activity [13]. PSS is estimated to have an incidence of 11 out of 100,000 individuals [14].

Thrombosis of the upper extremity is an uncommon disease with an incidence of 1–11% of all DVTs; the figure from different studies varies [15-19].

UEDVT can be classified into two groups, primary and secondary UEDVT.

Primary UEDVT includes idiopathic and effort-related UEDVT and accounts for up to one third of all UEDVTs in some studies [20]. Patients with thoracic outlet syndrome (TOS) and PSS are also classified as primary.

Secondary UEDVT is caused by central venous devices, trauma, and cancer. In large cohort studies on patients with UEDVT, the cancer rate is as high as 22–38% [19, 21-24]. The use of such intravascular devices as central venous catheters (CVCs) [25], peripherally inserted central venous catheters (PICCs) [26], pacemakers [27], and intracardiac defibrillators, secondary UEDVT constitutes an increasing clinical problem. Up to 70% of all UEDVTs are diagnosed in association with the use of CVCs [16]. Among 208 intensive care patients with CVSSs, 33% showed catheter-associated UEDVT [28].

The incidence of primary UEDVT is about 2–11 per 100,000 inhabitants per year [14, 15]. The low incidence compared with lower extremity deep vein thrombosis (LEDVT) is related to both anatomical and physiological differences, such as fewer smaller valves being present in the upper limb [29], shorter veins and therefore less surface to form clots on, and less immobilization of the arm even in bedridden patients [30]. There is also a higher flow rate and less stasis due to gravitational effects in the upper extremity.

Increased fibrinolytic activity has been seen in the endothelium of the upper arm, as compared to the lower arm [31] and on comparing the upper and lower extremities, two studies have shown a higher fibrinolytic activity in the arms [31, 32].

There is also a difference in some endogenous prothrombotic biomarkers (i.e., thrombin-antithrombin, antithrombin activity, prothrombin fragments, and p-selectin) when the blood sample is taken from the leg veins, compared with blood samples from the antecubital vein, which may also contribute to the higher frequency of DVT in the lower limb [33].

Risk factors for VTE also differ between UEDVT and LEDVT. Patients with noncatheter-associated UEDVT have a less pronounced family history of VTE, compared to LEDVT (19% vs. 30%), and are less likely to have undergone major surgery within the last 30 days [19]. Patients with primary UEDVT also tend to be younger and slimmer [34].

The frequency of coagulation disorders varies: two studies comprising 51 and 31 patients, with primary UEDVT have shown rates of 31% and 60%, respectively, for at least one coagulation disorder. The most common disorders were antiphospholipid antibodies and factor V Leiden mutations [35, 36]. The most important genetic risk factors for VTE are the mutation of the genes for FV Leiden mutations and prothrombin G20210A, with incidences in cohorts of thrombosis patients of approximately 30% and 10%, respectively [37]. There is also evidence from case-control studies that the mutation of the genes for both FV Leiden and prothrombin G20210A constitute independent risk factors for UEDVT [21, 38, 39].

Hyperhomocysteinemia has also been discussed as a risk factor for UEDVT, but no conclusive results are found in the literature. One interesting finding is that one of the studies had a two times higher frequency of coagulation disorders in the subgroup comprising non-effort UEDVT [36].

The use of oral contraceptives is a well-known risk factor for LEDVT, but the association does not seem to have the same strength for UEDVT, except for the combination of oral contraceptives and mutation of the genes for prothrombin and factor V Leiden [38]. In contrast, a study by Vayá et al. [39] reports that the use of oral contraceptives may be associated with a six-fold increased risk of suffering from a primary UEDVT. The association of primary UEDVT and oral contraceptives requires further investigation,

4.2.1 Localization of UEDVT and the anatomy of the upper thorax

The proximal veins of the shoulder and arm, the subclavian and axillary veins, are the most usual locations for UEDVT [16, 40, 41].

The thoracic outlet region consists of three anatomical spaces: the interscalene triangle, the costoclavicular space, and the retropectoralis minor spaces [42]. The subclavian vein re-enters the chest in front of the anterior scalene muscle, between the clavicle and the first rib (Figure 4). The thoracic outlet syndrome (TOS) refers to various forms of compression in the thoracic outlet. Compression can be on either nerves or vessels. Compression of both is rare.

Underlying venous TOS is mostly asymptomatic prior to thrombosis. Approximately 5–10% of cases of TOS are vascular [43]. UEDVT can be caused by venous TOS, with the subclavian vein compressed between the clavicle and the first rib.

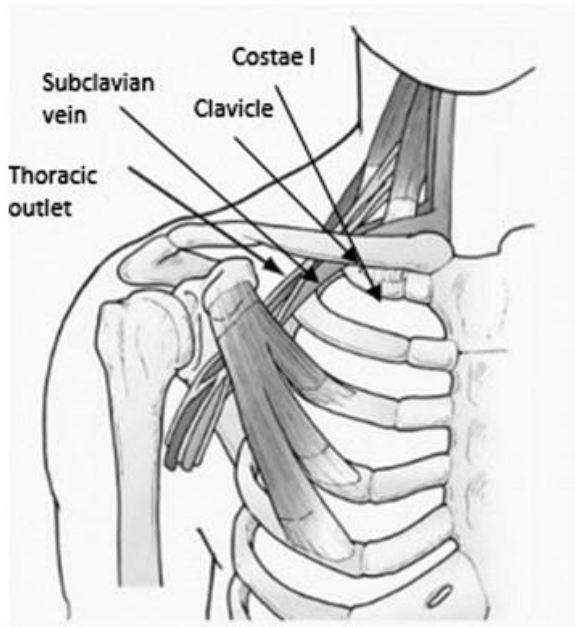


Figure 4. Anatomy of the upper thorax and shoulder.

4.2.2 The literature and primary UEDVT

A recent article by Bleker et al. [44] presents a review of UEDVT. A systematic search of the literature was performed in three databases (MEDLINE, EMBASE, and BIOSIS Previews). Forty-five studies comprising 4580 patients were included; no randomized studies were found. Only 11 studies were prospective and as few as seven had only included primary UEDVT. No meta-analysis was performed due to the heterogeneity of the studies and their design. We have found very few, and small, studies only including primary UEDVT.

4.2.3 Recurrences of VTE and mortality

UEDVT may lead to pulmonary embolism (PE) and the rate ranges approximately from 0 to 20% (mixed material on both primary and secondary UEDVT) [22, 23, 41, 45-51]. PE is more frequent in the lower extremity, up to 50% [2, 3, 7]. The literature states that the frequency of PE in primary UEDVT is lower, but further studies are required to find out the real frequency. One small study (32 patients) [52] comprising only primary UEDVT showed

no pulmonary embolism during the follow-up period of five years.

In their review, Bleker et al. [44] reported an average incidence of recurrent VTE in the included prospective studies (11 studies and 1661 patients) of 5.1% (range 0–13 %) during a follow-up period ranging from 3 to 59 months. The 20 retrospective studies, including 1281 patients, reported recurrent VTE in 9.8% (range 0–26 %), with follow-ups varying from 3 to 62 months. The location of the recurrent VTE was in the upper extremity in 78% of the cases and 21% were PE. One should remember that this report has included “all sorts of UEDVT” (i.e., primary and secondary, including CVC-related UEDVTs). For patients with malignancies, the risk of recurrences was two- to three-fold higher, and patients with CVSs were highly at risk.

Lechner et al. [40] demonstrated, in their study on idiopathic UEDVT, a recurrence rate of VTE of 2% (none of them PE). The likelihood of VTE after five years was stated to be 2% for UEDVT; the same figure for DVT in the lower extremities was 19%.

A study by Martinelli et al. on patients with primary UEDVT reported that patients with thrombophilia are more likely to have symptomatic recurrences than those without, with incidences of 4.4% and 1.6% per year, respectively [38].

There is a striking difference in mortality between primary and secondary UEDVTs. Patients with primary UEDVT are typically young and otherwise healthy, whereas subjects with secondary UEDVT often suffer from chronic diseases. The Computerized Registry of Patients with Venous Thromboembolism (RIETE), an extensive European data registry of consecutive patients with VTE mostly from Spain, Italy, and France, shows that the overall 3-month mortality rate for patients with UEDVT was 11%. The same figure for LEDVT was 7%. For patients with malignancies, the 3-month mortality rate was as high as 28% [53]. In a study from the southern part of Sweden, comprising 63 patients with UEDVT, the mortality during a median of 62 (range 31–117) months was at follow-up 24% for all UEDVTs, 47% for patients with a malignancy, and 14% for other UEDVT patients [54].

4.2.4 Treatment of UEDVT

There are no randomized studies showing optimal treatment for patients with UEDVT and the major clinical guidelines have largely been extrapolated from studies on LEDVT. Current international guidelines recommend low molecular weight heparin (LMWH), followed by vitamin K antagonist (VKA). The incidence of major bleedings was stated in a review paper [44] to be 7.9% for conventional treatment (LMWH and VKA) and 17% for patients receiving systemic thrombolysis. The level of bleeding complications is comparable to that of the treatment of LEDVT; however, the risk of bleeding is higher for patients with

malignancies [55, 56].

The role of thrombolysis has been widely debated and the American College of Chest Physicians (ACCP) guidelines suggest that it may be beneficial for patients with severe symptoms for less than 14 days, good functional status, and a low bleeding risk [57]. Van den Houten et al. [58] presented, in their review article from 2016, evidence that catheter-directed thrombolysis can be added to the therapeutic arsenal. Another study recommends prompt use of catheter-based thrombolytic therapy [59]. However, there are still no randomized studies on the subject and no convincing proof that thrombolytic therapy reduces PTS has been found [60, 61]. Although there is a high risk of relapse in patients with CVCs, it is not recommended to administer prophylactic anticoagulant therapy and recent randomized studies did not show any significant benefit [53].

What is the role of surgery and decompression in the treatment of UEDVT? There is also no clear answer to this question. Lee et al. presented, in their paper from 2000 (22 patients with primary UEDVT), evidence that all patients with primary UEDVT do not need surgical intervention. The study suggests a period of observation with anticoagulant therapy before surgical intervention to detect the patients in need of decompression [62].

4.3 DIAGNOSIS OF VENOUS THROMBOEMBOLISM

4.3.1 Venous contrast phlebography

The traditional objective gold standard for diagnosing DVT is based on ascending contrast phlebography. The sensitivity is 97% and the specificity 95%, compared to autopsy, for LEDVT [63]. Even though phlebography is a diagnostic tool with both high sensitivity and specificity, the test is both uncomfortable for the patient and combined with such associated risks as allergy to contrast agents, renal problems, and the risk that the contrast agent might cause a DVT [64]. Color duplex ultrasonography (CDU) has more and more come to replace venous contrast phlebography.

4.3.2 Color duplex ultrasound (CDU)

During the last 25 years, the hardware technology has improved the quality of CDU dramatically. The method is non-invasive and the risks are negligible. Most laboratories use a list of possible duplex findings to diagnose DVT. The first criterion/finding is the inability to collapse a vein with the pressure from the probe. A meta-analysis has shown this sign to be 95% sensitive and 98% specific for, once again, the lower extremity. Regarding the upper extremity, CDU is an adequate method [65, 66]. There is, however, an acoustic shadow from

the clavicle which limits the visualization of the short segment of the subclavian vein. In addition, it might be difficult to visualize the brachiocephalic and/or the superior caval vein.

4.3.3 D-Dimers

D-dimers are degradation products that result from the action of plasmin on cross-linked fibrin. The use of the blood test has received considerable attention in the past decade. The sensitivity and specificity vary from test to test in studies on LEDVT (Table 1) [67-71].

Table 1. Sensitivity and specificity of different D-dimer tests [67-71].

Method	Sensitivity %	Specificity %
ELISA	96	39
Red blood cell agglutination	88	64
Latex agglutination	87	60

The most sensitive test is the ELISA, but it is also the most expensive and time-consuming D-dimer test. There are also many other conditions that cause elevated levels of D-dimers, such as infection, inflammation, pregnancy, trauma, and post-surgical states.

D-dimer is usually combined with the Wells score, a widely used clinical decision rule for VTE (Table 2).

Table 2. The Wells score for the lower extremities.

Clinical Characteristic	Score
Active cancer	1
Paralyses, paresis, immobilization	1
Recently bedridden or major surgery	1
Localized tenderness of the veins	1
Entire leg swollen	1
Calf swelling	1
Pitting edema	1
Collateral superficial veins	1
Previous DVT	1
Alternative diagnosis at least likely	-2

A Wells score of 2 or higher indicates that DVT is likely [71].

4.3.4 Magnetic resonance imaging (venography)

As for CDU, the quality of magnetic resonance imaging (MRI) has improved during the last decade. It can be enhanced with contrast agents. Absence of imaging of a vein or an intraluminal filling defect indicates the presence of DVT. MRI has a high sensitivity of 97% and a specificity of 100% in studies on the lower extremity [72, 73]. The limitations of MRI include high cost, lack of portability, and MRI cannot be used on some patients with implanted metal devices. MRI has also been shown to be both valuable and usable for mapping the anatomy of the upper region of the thorax [74].

4.3.5 Computerized tomographic venography

Computerized tomographic venography has many of the same advantages as MRI. However, it involves the use of ionizing radiation and of intravenous iodinated contrast agent.

4.4 POSTTHROMBOTIC SYNDROME

The postthrombotic syndrome (PTS) is a common, chronic, and sometimes severe complication of deep venous thrombosis. Twenty to fifty percent of the patients with DVT suffer from PTS [75, 76]. Symptoms of PTS are pain, swelling, edema, varicose veins, and occasional ulcer formation [77]. The symptoms can be intermittent or persistent and tend to improve with resting or elevating the affected limb. PTS is diagnosed on clinical grounds based on the patient's symptoms and signs and is a consequence of venous hypertension, reduced muscle perfusion, abnormal microvasculature function, and increased tissue permeability [78].

Predictors of a risk for PTS after DVT are older age, high BMI, previous ipsilateral DVT, and proximal thrombosis [79]. The best way to prevent PTS is to prevent DVT; therefore, it is important to use thromboprophylaxis in patients at risk [80]. The use of compressive stockings has been widely discussed, but their utility differs from author to author [80-82].

A significant number of patients with UEDVT experience PTS. The frequency ranges from 7% to 46% (weighted mean, 15%) [83] and is, in some studies, as high as 80% [84], but the risk of severe PTS seems to be lower than in LEDVT. Interestingly, there seems to be no correlation between the degree of PTS and TOS. A small study from 2016 including 21 patients with primary UEDVT, 10 of which were considered to have TOS-related UEDVT, showed the same incidence of PTS whether or not the thrombosis was related to TOS [85]. Patients with PTS after UEDVT have a significantly lower quality of life measured with VEINES-QOL (see below) [86].

4.5 PATIENTS' PERSPECTIVE REGARDING THE POSTTHROMBOTIC SYNDROME

As mentioned earlier, about 20–50% of the patients with DVT suffer from PTS after two years. It is important to measure PTS in a standardized manner and follow its development over time.

4.5.1 Scales for measuring PTS

Six clinical scales have been used to define PTS, three of which were developed for chronic venous disease in general: the Widmer classification, Clinical Etiology Anatomy Pathophysiology (CEAP), and the Venous Clinical Severity Score (VCSS). The other three are designed to diagnose PTS after objectively diagnosed DVT: the Brandjes scale, the Ginsberg measurement, and the Villalta scale [87].

- The Widmer scale classifies the patients into three categories of chronic venous disease according to the presence of various clinical signs and five symptoms reported by the patient (pain, heaviness, heat, tension, and tiredness of the limb) [88].
- The CEAP categorizes patients into eight classes of increasing severity with modifiers that reflect the underlying etiology (congenital, primary, or secondary DVT), the anatomic distribution, such as superficial, deep, or perforating veins, and pathophysiologic conditions – obstruction and/or reflux [89].
- The VCSS includes elements of CEAP and other criteria (number, size, and duration of ulcers, use of compression therapy, and only a single symptom, pain) [90].
- The Brandjes scale uses separate subscales to determine whether or not patients have no, mild to moderate, or severe PTS, including items concerning symptoms, signs, and differences in calf circumference [91].
- The Ginsberg scale diagnoses PTS if the patient reports daily leg pain and swelling with duration of at least one month that occurs 6 months or more after the acute DVT and is made worse by standing/walking and relieved by rest or leg elevation. The patient reports whether the symptoms have improved or not since the last assessment. This is a way of attempting to objectify the course of PTS [81].

In addition, there are two scales which have been used by some authors, VEINES-SYM and VEINES-QOL, originally designed for the lower extremity and modified for the upper extremities by replacing the designation “leg” with “arm” [92]. The scales reflect both the patients’ subjective symptoms from the affected limb and how these symptoms affect the activities of daily living [93].

4.5.2 The Villalta postthrombotic scale

As described above, a number of clinical scales have been used for measuring PTS. The Standardization Committee of the International Society on Thrombosis and Haemostasis nowadays recommends the Villalta scale. This scale consists of both the patient’s subjective symptoms and signs found by the clinician (Table 3). The Villalta scale gives a validated

score for assessing PTS [94] in the lower limb and correlates with such quality of life scores as generic disease-specific quality of life (SF-36) [95].

Table 3. Villalta PTS scale.

Symptoms and clinical signs	None	Mild	Moderate	Severe
Symptoms				
Pain	0	1	2	3
Cramps	0	1	2	3
Heaviness	0	1	2	3
Paresthesia	0	1	2	3
Pruritus	0	1	2	3
Clinical signs				
Pretibial edema	0	1	2	3
Skin induration	0	1	2	3
Hyperpigmentation	0	1	2	3
Redness	0	1	2	3
Venous ectasia	0	1	2	3
Pain on calf	0	1	2	3
Venous ulcer	0	1		

A total score of 5 or higher is classified as the presence of PTS and a score of 15 or higher is classified as severe PTS. For upper extremity deep vein thrombosis, several studies have used a modified Villalta scale to diagnose and classify the severity of PTS [83]. This scale has not been validated for the arm, but there is no other validated scale available.

4.5.3 Disability of the arm, shoulder, and hand questionnaire

The disability of the arm, shoulder, and hand (DASH) questionnaire is a validated, standardized, self-administered questionnaire that assesses symptoms and disabilities of the upper extremities by measuring “global” disability from 0 (absent) to 100 (severe). Examples of questions asked concern opening a tight or new jar, writing, doing gardening, making a bed, etc. Answers are given on a five-degree scale ranging from “No difficulty” to “Unable” [96].

4.5.4 Visual analog scale

The visual analog scale (VAS) is a psychometric response scale that can be used in questionnaires. It is a measuring instrument for subjective characteristics or attitudes that cannot be directly measured. When responding to a VAS item, the respondents specify their level of agreement with a statement by indicating a position along a continuous line between two endpoints. In this thesis, VAS was used to estimate pain and disability.

4.6 METHODS FOR ASSESSING VENOUS FUNCTION

4.6.1 Color duplex ultrasound (CDU)

During the past decade, color duplex ultrasound has become the first line of diagnostics for DVT. It is also used to detect chronic venous disease (CVD), including postthrombotic changes in the vessels. The detectable changes are persistent obstruction of the vessel and wall abnormalities, such as wall thickening, reduced lumen, and reduced compressibility [97]. By the use of pulsed Doppler and color flow, the technique also provides information of venous flow and venous reflux [98].

4.6.2 Plethysmography

Venous plethysmography records volume changes in a tissue segment in order to assess venous function. During the 1990s, there began to be less use of plethysmography due to the increasing use of CDU. Plethysmography has been used mostly for examination of the lower limb but there are studies that have used plethysmography for examination of the upper extremity [84, 99].

5 AIM OF THE PRESENT THESIS

The overall aim of this thesis was to increase the existing knowledge of primary UEDVT and, by means of this knowledge, be able to treat future patients more adequately, based on science and proven experience.

The specific aims were:

- To evaluate venous function, late sequelae and PTS in patients with primary UEDVT;
- To identify risk factors for primary UEDVT;
- To find out the level of recurrences;
- To investigate the anatomy of the thoracic outlet in the closeness of the subclavian vein;
- To correlate objective measurements with the patients' subjective symptoms;
- To quantify the comorbidity of patients with primary UEDVT.

5.1 PAPER I

This study was performed to describe venous function, residual morphologic abnormalities, and the occurrence of PTS in patients with conservatively treated primary UEDVT. In addition, the aim was to correlate PTS with color duplex ultrasound and plethysmography.

5.2 PAPER II

The aim of this paper was to examine patients with primary UEDVT with respect to underlying thrombophilic disorders, postthrombotic symptoms, and the rate of complications and recurrences.

5.3 PAPER III

The primary objective of this study was to examine the anatomy of the subclavian region in patients with primary UEDVT with a focus on structural findings that may interfere with the function of the vessel. The secondary objective was to investigate whether there were any correlations between the area of the subclavian vein or costoclavicular distance and symptoms of PTS measured by three different clinical methods (i.e., the Villalta post thrombotic score, DASH, and VAS).

5.4 PAPER IV

Most studies on UEDVT are on mixed material including patients with both primary and secondary UEDVT. Comorbidity is well-described in patients with secondary UEDVT, but we have not found any studies that describe the comorbidity for primary UEDVT.

The aim of this case-control study was to compare comorbidity in patients with primary UEDVT with that of a control group.

6 ETHICS

All studies were approved by the Regional Ethical Review Board in Stockholm and all patients and controls provided their written informed consent (Papers I–III) before inclusion in the studies.

7 STATISTICS

7.1 PAPER I

Data are presented as means and 95% confidence intervals. Differences in the means were tested for statistical significance using two-sided paired or unpaired Student's t tests.

Pearson's or Spearman's correlation analyses were used to explore relationships between different variables. Differences between proportions were analyzed using χ^2 tests. Statistical significance was set at $P < 0.05$.

7.2 PAPER II

Differences in median were tested for statistical significance with the Mann-Whitney U test and the Bonferroni correction was performed. Statistical significance was set at $P < 0.05$.

Spearman's correlation was used to study the relationship between the DASH and Villalta scores.

7.3 PAPER III

A nonparametric test was used because it was difficult to evaluate the distributional assumption due to the relatively small number of observations. Differences between patients and controls were tested using the Mann-Whitney U test. The Wilcoxon signed rank test was used when testing differences within the patient group. Correlation was tested with Spearman's rank correlation. $P < 0.05$ represented a significant difference.

7.4 PAPER IV

Differences in proportions between cases and controls were tested with Fisher's exact test. Differences in the means of healthcare contacts were tested with an independent t test. All tests were two- sided and a P value of <0.05 was considered to be statistically significant.

8 MATERIAL AND METHODS

8.1 PAPER I

8.1.1 Patients

A retrospective search of medical records from Södersjukhuset and Karolinska University Hospital for the years 1992–2002 identified 563 patients diagnosed with UEDVT. All medical records were analyzed according to the underlying disorders and risk factors for UEDVT. Patients with central venous catheters, pacemaker devices, and known malignant disease were excluded from the study and 37 patients were identified with a previous primary UEDVT. Thirty-two patients (23 females, 9 males) agreed to participate in the study (one patient treated with thrombolysis was excluded from paper I but participated in paper II) (Figure 5).

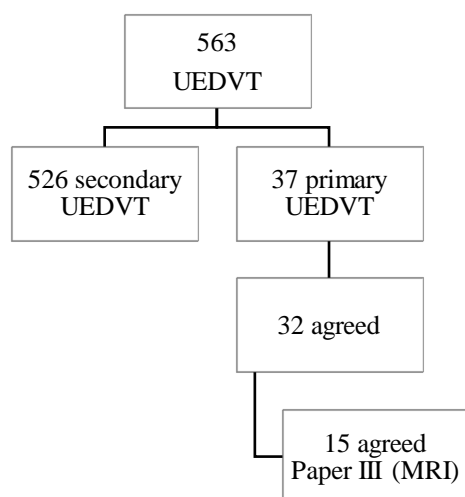


Figure 5. Flow chart for patients included in Papers I–III.

Thirty patients (94%) were diagnosed objectively by contrast venography; 11 of these patients (34%) also had the thrombosis confirmed by CDU and one patient had a computerized tomography for diagnoses. Two patients were diagnosed by CDU only. The localization of the thrombosis was 66% solely in the subclavian vein, 22% in both subclavian and axillary veins, 6% in the subclavian, axillary, and brachial veins, and 6% in the brachial vein alone. In eight (25%) of the patients, the thrombosis also involved the basilic vein.

All patients were treated with LMWH and VKA therapy for 3–6 months. One patient received thrombolysis. All but six patients were investigated with chest X-ray or computerized tomography (CT) to exclude an extra cervical rib; none of the investigated

patients had an extra cervical rib. Six of the UEDVTs were considered to be effort-related according to the medical records, i.e., they had a history of vigorous or unusual exercise within seven days prior to the diagnosis: One patient had carried a heavy bag, two patients had recently started an exercise regimen, one patient had removed old wallpaper, one patient had been working with a drilling machine with elevated arms, and one had worked rigorously shoveling sand in a garden.

The main characteristics of the patients are shown in Table 4. The mean patient age was 45 years at inclusion (range, 21–84) and 23 (71%) were women. The age at diagnosis were 39 years (median) and 40.7 years (mean), (range, 17–77).

Table 4. Main clinical characteristics of the patients included in Studies I–II

Characteristics	
Male/female, n	9*/23
Median age at thrombosis, y (range)	39 (17–77)
Mean age at thrombosis, y (range)	40.7 (17–77)
Positive family history of DVT, n (%)	7 (22)
Smokers, n (%)	6 (28)
Use of oral contraceptives or HRT**, n (%), female	12 (52)
Right arm, n (%)	16 (50)
Dominant arm, n (%)	15 (47)
Effort-related, n (%)	6 (19)

* 8 male in paper I

** Hormone replacement therapy

8.1.2 Methods

All patients were interviewed and examined clinically and the circumference of both arms was measured. This was performed with the patient sitting with the arms in a hanging position, with measurement of the circumference of the forearm and the upper arm 12 cm beneath and above the elbow.

Due to the fact that there is no objective “gold standard” test to diagnose PTS after UEDVT, we used a modified form of the Villalta scale. The patients were asked to rate the severity of each of the five symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and the physician evaluated each of the six signs (edema, prominent veins on the arm, prominent veins on the shoulder or anterior chest wall, redness, tenderness, dependent cyanosis) on a scale of 0 (absent) to 3 (severe). A score of 5 or higher was classified as the presence of PTS

and a score of 15 or higher as severe PTS.

Duplex scanning was performed by a technician with >10 years of experience using the color duplex technique to diagnose DVT. In each patient, the radial, ulnar, brachial, cephalic, basilic, axillary, subclavian, and internal jugular venous segments were evaluated. The occurrence of vessel wall abnormalities, such as wall thickening and a reduced or occluded lumen, was observed, as well as flow in prominent collateral veins, compressibility, and blood flow patterns, to identify postthrombotic changes. Valvular function was evaluated and a reflux duration of >0.5 sec was considered significant.

The duplex findings were classified into four categories:

1. Normal findings.
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 – residual thrombus with occlusion of the lumen, uncompressible lumen, absence of color flow, and blood flow in several prominent dilated collateral veins.

In this thesis, we used a computerized strain-gauge technique modified for the arm to assess venous function [100]. When performing the plethysmography of the upper limb the patient was sitting on a chair and resting the arms on an arm support. Inflatable cuffs were wrapped around the arms and strain-gauge wires were placed on each forearm (Figure 6).

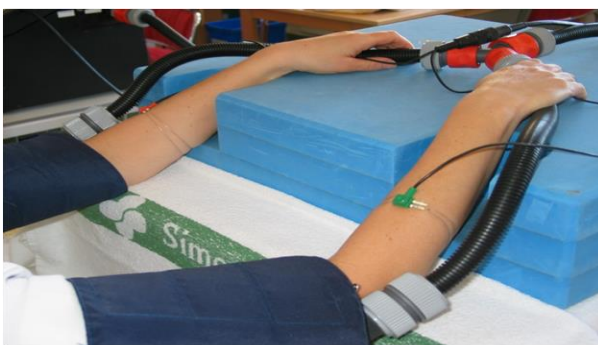


Figure 6. Setup for plethysmography.

Venous occlusion is established by a pressure of 60 mm Hg within the cuffs. To detect when the plateau of the filling phase was reached, we used a capacitance mode which detects when the venous filling is less than 0.1 mL per 100 mL over 20 sec. When the

volume curve plateau is established in both arms the cuff pressure is rapidly released, allowing outflow of the accumulated blood and a fall in the volume curve (Figure 7).

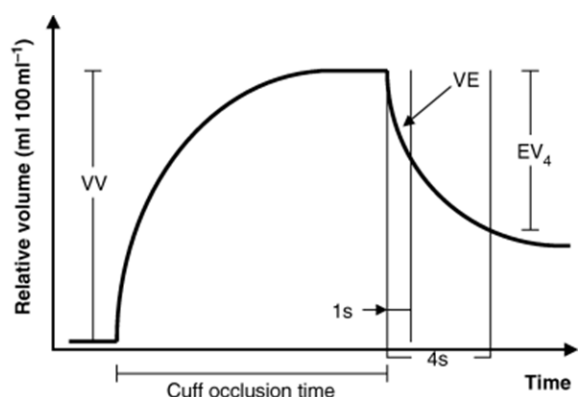


Figure 7. Schematic presentation of the volume curve.

- Venous volume (VV, mL per 100 mL) is the maximum volume change during the occlusion phase.
- Venous emptying (VE, mL per 100 mL per min) describes the outflow rate during the first second after deflation.
- EV_4/VV shows the volume of blood expelled during the initial 4 sec, divided by the maximum VV.

The mean of two determinations was used for each variable.

8.2 PAPER II

8.2.1 Patients

The same patients included in Paper I, plus the one who received thrombolysis, were interviewed with a focus on risk factor diagnostics and treatment.

8.2.2 Methods

The modified Villalta score was used to quantify PTS and the DASH test to assess symptoms and disability of the upper extremity.

To evaluate the working capacity of the upper extremities, an arm exercise tests was used [101] with an increasing work load of 10 W every minute. The test was discontinued when the patient perceived subjectively experienced exhaustion. The test was performed on an electrodynamically braked bicycle ergometer (Rodby 830, Rodby Innovation AB, Hagby, Sweden) adapted for arm exercise (Figure 8).



Figure 8 Setup for arm exercise capacity test.

The circumference of the upper arm and forearm were measured in both arms, before and after exercise. In addition, VAS was used to estimate pain and disability.

Blood samples for the following coagulation factors were taken at diagnosis and/or inclusion in the study: mutation of factor V Leiden, deficiency of protein C and protein S-free, antithrombin, antiphospholipid antibodies, and homocysteine.

Levels of fibrinogen and von Willebrand factor were analyzed at inclusion.

8.3 PAPER III

8.3.1 Patients

The same patients as in Papers I and II were asked to participate in this follow-up study. Fifteen patients, 5 males and 10 females agreed to participate. The major reasons for refusing participation were the use of MRI, contrast agent, and a lack of time and interest. The patients had no concomitant diseases, no previous central venous catheters, and they had all been investigated with a CT scan of the thorax at the index event to exclude cancer-related thrombosis or an extra cervical rib. All UEDVTs were localized in the subclavian vein. Ten patients had their UEDVT in the left arm; only five patients had it in the dominant arm. All primary events were diagnosed by phlebography. The mean time from the thrombotic event to the MRI was 6.9 years (range, 3.6–11.3 years).

A control group of 15 healthy persons without previous UEDVT, matched according to sex, age, and body mass index (BMI), was used. The group was enrolled on a voluntary basis (Table 5).

Table 5. Characteristics of patients and controls included in the study.

Characteristics	Patients	Controls
Male/female, n	5/10	5/10
Smokers, n (%)	3 (20)	1 (7)
Mean age at MRT, y (range)	51 (42–66)	53 (42–70)
Median age at MRT, y, (range)	47 (42–66)	50 (42–70)
Weight, kg, median (range)	69 (56–115)	72 (58–102)
Height, m, median (range)	1.74 (1.62–1.90)	1.72 (1.48–1.88)
BMI, median (range)	24.9 (20.6–31.9)	24.5 (22.6–32.2)
Ethnic origin	All Scandinavian	All Scandinavian

8.3.2 Methods

In the third paper, MRI was used to detect remaining chances such as reduced vessel area or total occlusion of the subclavian vein after UEDVT. In addition, the anatomic structures of the thoracic outlet were visualized. MR imaging was performed on both patients and controls and enhanced by a blood pool contrast agent (10 ml Gadofosveset, 0.25 mmol/mL Vasovist®). Two sets of sequences were performed; the first set of sequences was performed with the arms alongside the body and the second with the arms over the head (hyper-abduction to 120° and external rotation).

The images were analyzed for patency and prevalence of stenosis/occlusion of the subclavian vein and measurements of the costoclavicular space.

The costoclavicular space was measured using a sagittal view. The image in which the first rib was seen with its longest portion was used to measure the costoclavicular distance. The shortest distance between the dorsal portion of the clavicular cortex and the ventral delineation of the cortex of the first rib was measured. The values obtained were derived as a consensus between two observers. All measurements were performed in both positions of the arms. In addition, the width of the subclavian vein was evaluated by means of vessel lumen area measurements in the costoclavicular space. In cases of postthrombotic occlusion (2 patients) and a nondetectable vessel (1 patient), no area measurement was performed; thus, vessel area was calculated for 12 patients.

Postthrombotic syndrome and disability of the upper extremity were once again quantified by two tests: the modified Villalta score and DASH; VAS was also used to quantify pain.

8.4 PAPER IV

8.4.1 National Patient Register

In Sweden, there is a unique possibility of following patients nationally over the years. The National Patient Register (NPR) has collected data on inpatients at public hospitals (the vast majority of hospitals) since 1987 and from 2001 also on outpatient visits, in both public and private healthcare. In combination with the personal registration number (PRN), it is possible to extract data from the NPR even for rare diseases.

8.4.2 Patients

Both in- and outpatients in the NPR who might have had an upper extremity deep vein thrombosis during the years 2001–2011 were traced with the following ICD-10 codes for the diagnoses:

- I80.8 Phlebitis and thrombophlebitis of other sites,
- I80.9 Phlebitis and thrombophlebitis of an unspecified site,
- I82.8 Embolism and thrombosis of other specified veins and,
- I82.9 Embolism and thrombosis of an unspecified vein.

From these data, we identified patients 18 years of age or older. Patients diagnosed with cancer, orthopedic procedures on the shoulder and upper arm, and devices in the vessel within a period of two years before the index point (the first time any of the above DVT codes were registered in the NPR) were excluded in both case and control groups. We assumed that the majority of all important events that could influence the subclavian area were normalized after two years. Therefore, the first index point for inclusion was after 2002. To get a follow-up period of a minimum of three years, only patients with their first thrombotic event reported in the NPR before 2009 were included. Thus, the inclusion period is from the beginning of 2003 to the end of 2008. For patients with more than one thrombotic event, the first one was considered to be the index point.

Unfortunately, there is no exclusive code in the ICD-10 for upper extremity thrombosis. Our hope was that, by choosing the above ICD codes, we would find a great match between ICD-codes reported in the NPR and the presence of UEDVT, but, unfortunately, this was not the case. To validate the register data, 600 patients were randomly selected from a total of 46,349 individuals with thromboembolisms, using the random number generator in IBM SPSS. Their medical records were ordered for review and 520 were handed over. We found 25 cases (5%) with primary upper extremity deep vein thrombosis, all treated with LMWH and VKA; none of the cases involved initial thrombolysis.

8.4.3 The control group

A critical characteristic of subject selection in cohort studies is to have both the exposed and unexposed groups selected from the same source population. In order to have comparable groups, we selected patients with appendicitis as the comparison group. Patients with appendicitis are perceived to reflect the same exposure pattern as the general population, and appendectomy is not related to the causal pathway for the development of UEDVT or any other disease. Therefore, we minimize the risk of bias and confounding

Patients from the NPR with appendicitis were included for the same periods of time as for patients with UEDVT. The following ICD-10 codes were used:

- K35.0 Acute appendicitis with generalized peritonitis,
- K35.1 Acute appendicitis with peritoneal abscess,
- K35.2 Acute appendicitis with generalized peritonitis,
- K35.3 Acute appendicitis with localized peritonitis,
- K35.8 Acute appendicitis, other, and unspecified,
- K35.9 Acute appendicitis, unspecified,
- K36.9 Other appendicitis,
- K37.9 Unspecified appendicitis.

The first time some of these ICD codes were reported in the NPR was considered to be the index point. Ten percent of the controls had more than one registration regarding appendicitis and, for them, the last registration was classified as the index point. These registrations were adjacent in time (less than five days) and were therefore interpreted to be for the same disease episode. For appendicitis, there are specific ICD codes and therefore there was no need for a review of the medical records.

The 25 cases were matched, on an individual basis, with 474 controls who were randomly selected from the individuals who were identical with the cases according to sex, their age at the index point, and the year of the index point. By so doing, the groups were also made comparable for the observation period, the time from the index point to the end of the year 2011.

8.4.4 Comorbidity and healthcare contacts

Comorbidity was described as the number of unique ICD codes (diagnoses) registered in the NPR in each ICD group for cases and controls from the index point to the end of the year 2011. For a better overview, some ICD chapters were merged into study-specific ICD groups (Table 6). The number of healthcare contacts was recorded as the number of admissions to hospital or outpatient visits.

Table 6 . ICD chapters and study-specific ICD groups.

ICD group (study-specific)			ICD code
I	1	Certain infectious and parasitic diseases	A00-B99
II	2	Neoplasms	C00-D48
III	3	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D50-D89
IV	4	Endocrine, nutritional, and metabolic diseases	E00-E90
V	5	Mental and behavioral disorders	F00-F99
VI	6	Diseases of the nervous system	G00-G99
VII–VIII	7	Diseases of the eye and adnexa Diseases of the ear and mastoid process	H00-H59 H60-H95
IX	8	Diseases of the circulatory system	I00-I99
X	9	Diseases of the respiratory system	J00-J99
XI	10	Diseases of the digestive system	K00-K93
XII	11	Diseases of the skin and subcutaneous tissue	L00-L99
XIII	12	Diseases of the musculoskeletal system and connective tissue	M00-M99
XIV	13	Diseases of the genitourinary system	N00-N99

XV	14	Pregnancy, childbirth and the puerperium	O00-O99
XVI	15	Certain conditions originating in the perinatal period	P00-P96
XVII	16	Congenital malformations, deformations, and chromosomal abnormalities	Q00-Q99
XVIII- XXII	17	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	R00-R99
		Injury, poisoning and certain other consequences of external causes	S00-S99 T00-T98 V01-V99
		External causes of morbidity and mortality	W00-Z99
		Factors influencing health status and contact with health services	U00-U49
		Codes for special purposes	U82-U85

9 RESULTS

9.1 PAPER I

This study was performed to describe venous function, residual morphologic abnormalities, and the occurrence of the postthrombotic syndrome in patients with conservatively treated primary upper-extremity deep venous thrombosis and, in addition, to correlate PTS with color duplex ultrasound and plethysmography.

9.1.1 Clinical examination and interview

The patients reported swelling and tension in the thrombotic arm in 71 % (22 patients) especially during and after heavy exercise. Thirty-two percent (10 patients) also reported reduced strength and pain; in addition, they reported distension of the superficial veins and a different skin color. None of the patients had any symptoms in the contralateral arm.

On measuring the circumference of the arm, there was only a significant difference for the upper arm (Table 7).

Table 7. Circumference of the arms.

	Thrombotic arm (mean, cm)	Nonthrombotic arm (mean, cm)	Difference (mean, cm)	P value
Upper arm	30 (24–26)	29 (23–26)	0.9	P <.001
Lower arm	24 (20–31)	24 (19–31)	0.2	ns

Postthrombotic scores ranged from 1 to 9 (median, 3). Twenty-two patients (71%) were classified as having no or minimal PTS (score < 5). The remaining nine patients had mild to moderate PTS (score 5 to 9). Thus, none of the patients had severe PTS (score \geq 15).

9.1.2 Color duplex ultrasound

The duplex findings were classified, as described, into four categories. Eight patients (26%) had normal findings, 5 (16%) had mild changes, 14 (45%) were classified as having moderate-to-severe changes, and 4 (13%) still had an occluded deep venous segment. Eighteen patients (58%) had residual thrombi (Figure 9).

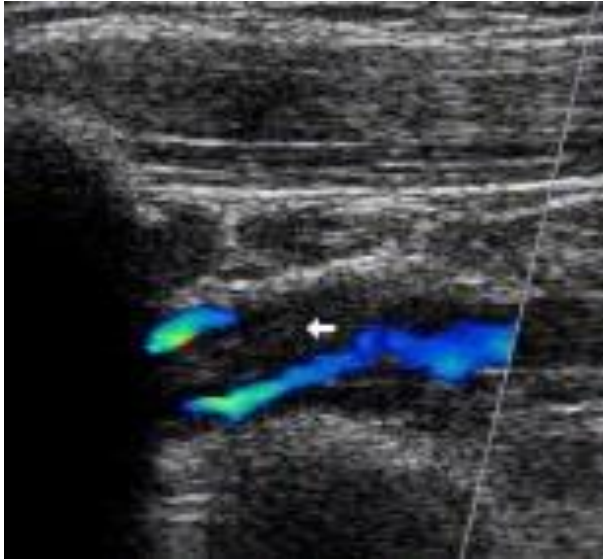


Figure 9. Color Doppler image of the subclavian vein just below the clavicle showing a residual thrombus (arrow) with flow in a partially recanalized lumen.

The study did not show any significant association between the PTS score and duplex findings (category 1 to 4, Spearman's $r = 0.22$).

9.1.3 Computerized strain-gauge plethysmography

The venous emptying, venous volume, and EV4/V were all significantly lower in the arms with a previous DVT than in the contralateral arms ($P < 0.001$). Thirty-five percent of the thrombotic arms had a VE below the lower normal limit of 68 mL/100 mL per min. The lower limit was defined in a previous study by our group as the mean of VE -2SD [102]. Figure 10 shows plethysmographic curves from a patient with a significant outflow obstruction after a right-sided upper-extremity deep vein thrombosis.

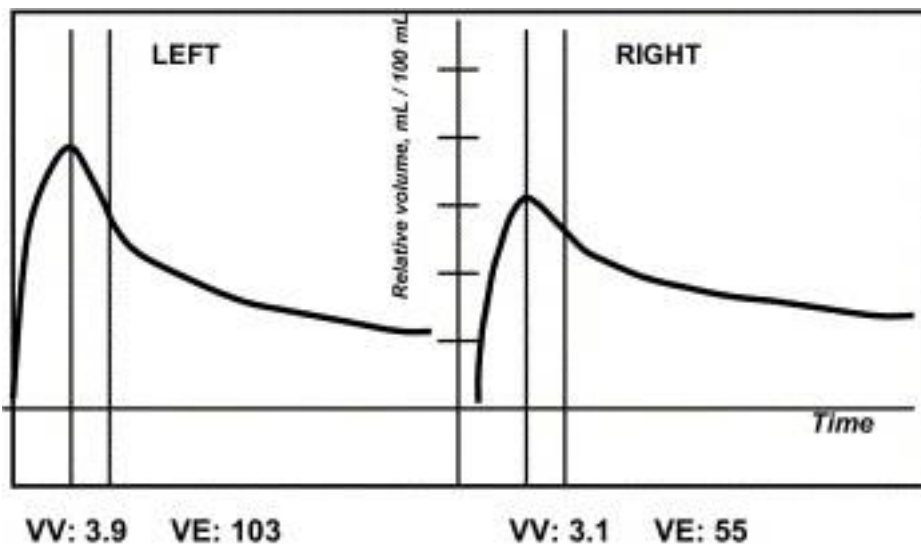


Figure 10. Example of plethysmographic curves from a patient with a significant outflow obstruction after a right-sided upper-extremity deep vein thrombosis.

There was no significant association between plethysmographic and duplex findings, but there was a progressive reduction in venous emptying for each increase in the ultrasonographic degree of postthrombotic changes in the vessel. Patients with PTS generally had lower venous emptying and venous volume values than those without PTS, but these differences were not statistically significant.

In Summary

Forty-two percent of the patients had normal or mild changes in the ultrasonography, 71% were classified as having none or mild PTS. Plethysmography showed reduced venous emptying in the thrombotic arm. There was no significant association between color duplex findings and PTS or between plethysmography and PTS.

9.2 PAPER II

The aim of this study was to examine patients with primary UEDVT with respect to underlying thrombophilic disorders, postthrombotic symptoms, rate of complications, and recurrences.

9.2.1 Coagulation disorder

The prevalence of thrombophilia in our study population was 40% (Table 8), similar to that for LEDVT. Mutation of the gene for factor V Leiden and elevated fibrinogen were the most common coagulation abnormalities. Note that fibrinogen was analyzed without any signs of inflammation for at least two years after the thrombotic event, including one patient with a rheumatic disease. One out of six patients with a factor V mutation was homozygous. A young male, 17 years old, had three different coagulation disorders (deficiency of proteins C

and S and a heterozygote mutation for factor V) without any positive family history. In three patients, there was a slight increase in the D-dimer level at follow-up (0.6–1.13.4 mg/L). Five patients on HRT or oral contraceptives had thrombophilia consisting of one mutation of factor V Leiden and four patients with a slight increase in fibrinogen.

Table 8. Prevalence of thrombophilic abnormalities in the study population, compared to the general population and unselected patients with DVT in the lower limb [11, 103].

Thrombophilic abnormality	Study group n (%)	General Population %	DVT in the lower limb %
Factor V Leiden mutation	6/32 (19)	3.6-6.0	21.0
Antiphospholipid antibodies	1/32 (3)	1-5	
Protein C deficiency	1/31 (3)	0.14-0.5	3.2
Protein S deficiency	1/28 (4)	0.16-0.21	2.2
Hyperhomocysteinemia	0/32		
Antithrombin deficiency	1/32 (3)	0.02-0.17	1.1
Elevated vWF antigen	0/32		
Elevated D-dimer	1/32 (3)		
Elevated fibrinogen	7/31 (22)*		

*Range 4.0–5.2 (normal range, 2.0–4.0)

9.2.2 Villalta postthrombotic score, DASH, VAS, and working capacity

The two questionnaires (modified Villalta and DASH) showed a median value for the modified Villalta score of 3 (range 1–9) and, for DASH, a median value of 6 (range 0–63). Nine patients (28%) were defined as having PTS; the cut-off level for defining PTS is >5 [104].

On the visual analog scale (VAS), the patients estimated remaining pain and disability. The median values were 7 (range 0–95, mean 18) for pain and 9 (range 0–80, mean 20) for disability. No correlation was found between pain and disability or between pain and disability and DASH.

On comparing the results from the two questionnaires DASH and the modified Villalta score, we found a correlation between the two tests ($r = 0.58$, $P < 0.001$) (Figure 11).

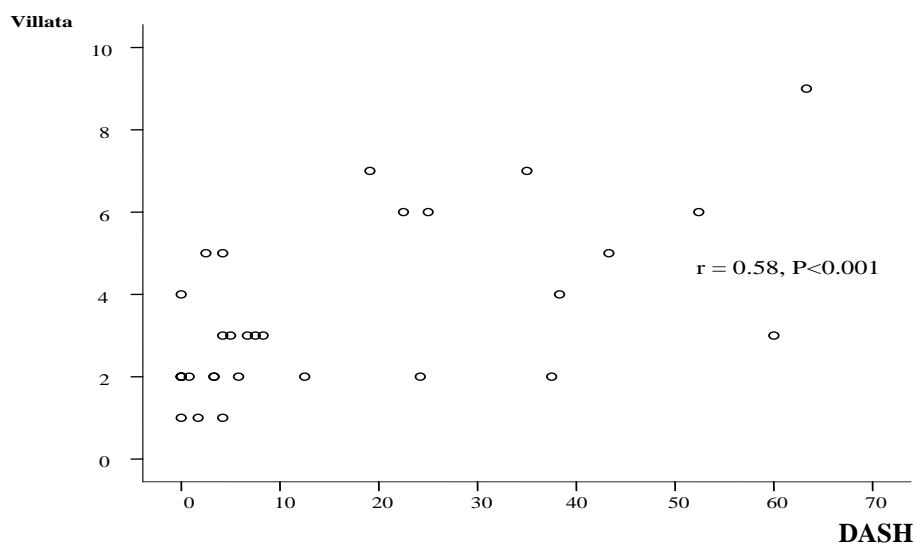


Figure 11. Correlation between Villalta score and DASH.

The patients were divided into two groups with or without PTS according to Table 9. The PTS group had significantly higher DASH scores than the non-PTS group ($P = 0.03$). There was no difference between the two groups according to VAS for pain or disability.

Arm exercise capacity had a median value of 70 W (range, 40–160 W). There was no significant difference in the increase of the arm circumference after the arm exercise test in any of the arms (Table 9). All patients showed increased redness and more prominent veins in the thrombotic arm after the arm exercise test.

Table 9. Functional disability (DASH), increase in arm circumference after exercise, arm exercise capacity test, pain and disability measured by VAS in patients with and without postthrombotic syndrome.

Measure	PTS* (n = 9)	No PTS† (n = 23)	P value
DASH, median	25 (range, 4.2–63.3)	4.2 (range, 0–60)	0.033
Increased circumference, median (cm)	1 (range, 0–1.5)	0.5 (range, 0–2)	ns
Arm exercise capacity, median (W)	70 (range, 40–110)	70 (range, 50–160)	ns
VAS pain (median)	28.5 (range, 3–95)	7 (range, 0–40)	ns
VAS disability (median)	23 (range, 2–56)	7 (range, 0–80)	ns

* Villalta score >4 , †Villalta score ≤ 4 .

9.2.3 Recurrences

None of the patients developed malignancy, pulmonary embolism, or recurrent DVT during the period from diagnosis to inclusion in the study, mean period, 5 years (range, 2–9 years).

In summary, this study supports the view that primary UEDVT is a benign disorder, with a high frequency of PTS (28%), but with a low risk of recurrence. The overall frequency of coagulation disorders was 40%, which is lower than earlier reported.

9.3 PAPER III

The primary objective of this study was to examine the anatomy of the subclavian region in patients with primary UEDVT with the focus on structural findings that may interfere with the function of the vessel. The secondary objective was to investigate whether or not there was any correlation between the area of the subclavian vein or costoclavicular distance and symptoms of PTS measured by three different clinical methods (i.e., the Villalta post-thrombotic score, DASH, and VAS).

9.3.1 Costoclavicular distance

The costoclavicular distance in the right and left arms was significantly narrower in the UEDVT patients than in controls when the arms were held alongside the body and in a hyper-abduction/external rotation position of only the left arm (Table 10).

Table 10. Median values, (range) and P values for differences in measurements (mm) of the costoclavicular distance between patients and controls.

	Alongside			Hyperabduction/external rotation		
	Patients	Controls	P value	Patients	Controls	P value
	<i>Right arm</i>			<i>Right arm</i>		
Costoclavicular distance	12.0 (4.0–14.0)	18.0 (8.8–26.9)	<0.001*	5.0 (3.1–12.0)	7.8 (3.5–16.1)	0.051
	<i>Left arm</i>			<i>Left arm</i>		
Costoclavicular distance	9.0 (6.0–14.0)	16.6 (7.8–28.2)	0.001*	5.0 (3.0–11.0)	8.1 (3.5–16.8)	0.04*
* P values of <0.05 represent a significant difference.						

On comparing the patients' thrombotic and non-thrombotic arms, there was a significant difference with the arms held alongside the body, but not in the supine position (Table 11).

Table 11. Median values (range) and P values for differences in measurements of the costoclavicular distance (mm) between nonthrombotic and thrombotic arms in patients.

	Alongside			Hyperabduction/ext. rotation		
	Non-thrombotic arm	Thrombotic arm	P value	Non-thrombotic arm	Thrombotic arm	P value
Costoclavicular distance	11.0 (6–14)	9.0 (4–14)	0.049*	5.0 (3–12)	5.0 (3–11)	0.35
* P values of <0.05 represent a significant difference.						

9.3.2 Area of the subclavian vein

Three patients were excluded after measuring the area of the subclavian vein due to total occlusion (2 patients) and one patient had a nondetectable vein. There was a significant difference in the vessel area between the thrombotic and nonthrombotic arms in patients in both positions. Ten out of the 12 patients had total compression with no bloodflow in the vessel in the thrombotic arm with the arm held in a hyperabducted and externally rotated position.

Table 12. Median values (range) and P values for differences in measurements of vessel area (mm²) between nonthrombotic and thrombotic arms in patients.

	Alongside			Hyperabduction/ext. rotation		
	Non-thrombotic arm	Thrombotic arm	P value	Non-thrombotic arm	Thrombotic arm	P value
Area of v. subclavia	64.5 (41–112)	24.5 (0–47)	0.005*	9.0 (0–21)	0.0 (0–6)	0.007*
* P value of <0.05 represents a significant difference.						

Regarding the area of the vein between the non-thrombotic arm in patients and controls there was no significant difference when the arms were alongside the body. However, in the position with the arms raised over the head, there was a significant difference between the two groups (Table 13).

Table 13. Median values (range) and P values for differences in measurements of vessel area (mm²) between the nonthrombotic arm of patients and that of controls.

	Alongside			Hyperabduction/external rotation		
	Patient	Controls	P value	Patient	Controls	P value
	<i>Non-thrombotic arm</i>	<i>Right arm</i>		<i>Non-thrombotic arm</i>	<i>Right arm</i>	
Area of v. subclavia	64.5 (41–112)	76.0 (13–128)	0.58	9.0 (0–21)	23.0 (0–88)	0.008*
	<i>Non-thrombotic arm</i>	<i>Left arm</i>		<i>Non-thrombotic arm</i>	<i>Left arm</i>	
Area of v. subclavia	64.5 (41–112)	65.0 (43–118)	0.79	9.0 (0–21)	31.5 (0–67)	0.002*

*P values of <0.05 represent a significant difference.

9.3.3 Villalta postthrombotic score, DASH, and VAS

Eleven patients out of the 15 presented no signs of PTS, four patients showed PTS, two of which had severe PTS according to the modified Villalta test. The mean values for DASH and VAS for pain were 30.4 (0–85) and 44.8 (0–92), respectively. The patients presented almost identical results individually, compared with the previous questionnaire two years earlier, indicating that the symptoms were consistent over the observation period.

There was a high correlation between DASH, the Villalta score, and VAS (Table 14), but no correlation between either the costoclavicular distance or the area of the subclavian vein and the patients' symptoms measured by VAS, the Villalta score, or DASH.

Table 14. Correlation between DASH, VAS, and Villalta score.

		Correlation
DASH	Villalta score	R = 0.925
DASH	VAS	R = 0.951
Villalta score	VAS	R = 0.975

In summary, this study may indicate that there is a relationship between anatomical conditions of the thoracic outlet (i.e., distance from the clavicle to the first rib) and the development of primary UEDVT, both effort-related and idiopathic. Another finding is that there seems to be a low correlation between the degree of obstruction, measured as the area of the subclavian vein and the costoclavicular distance, and PTS.

9.4 PAPER IV

The aim of this case-control study was to compare comorbidity in patients with primary UEDVT with that of a control group.

The 25 cases and 474 controls, 48% males and 52% females, had, at the index point, a mean age of 48 years (range, 20–80; SD, 17.5). The women were slightly older. The mean followup time was 8 years (range, 5.7–9).

9.4.1 Health care contacts

The 25 cases had 561 healthcare contacts (admissions to hospital and outpatient visits) during the follow-up period: a mean of 22 contacts per patient (range, 1–97; SD, 21.7). For the 474 controls, the same figures were 4444 contacts, with a mean of 9 contacts per control (range, 1–260; SD, 16.7). The difference was statistically significant ($P = 0.007$).

9.4.2 Diagnoses/ICD-codes

The numbers of unique ICD codes for cases and controls are presented in Table 15.

On comparing all ICD codes together, there was no difference between the two groups.

For the following ICD chapters, there was a significant difference:

- Diseases of the blood and blood-forming organs ($P = 0.023$)
- Endocrine and metabolic diseases ($P = 0.045$)
- Disease of the nervous system ($P = 0.001$)
- Diseases of the circulatory system ($P = 0.000$)
- Diseases of the skin ($P = 0.049$)
- Diseases of the musculoskeletal system ($P = 0.000$)

To investigate the differences between the two groups, we performed a more in-depth analysis of the ICD chapters with significant differences. In ICD chapter 6 (nervous system), we found, quite surprisingly, that seven of the patients had a ICD codes for symptoms of the brachial plexus or carpal tunnel syndrome, with a frequency of 28%, compared to 1.5% for the controls. The difference in ICD chapter 8 (circulatory system) is explained by the follow-up and monitoring of treatment of the thrombotic event. One patient had a registration for PE close to the thrombotic event. In chapter 12, comprising symptoms from the musculoskeletal system, there is an overrepresentation of ICD codes referring to different diagnoses comprising pain and discomfort in the upper extremity. For ICD chapters 3 (blood and blood organs), 4 (endocrine diseases), and 11 (skin diseases), there was no clear trend with a higher frequency of any ICD code. Most importantly, there was no difference between the two groups for ICD codes relating to malignancies.

Table 15. Number and percent of unique ICD codes for each ICD group for patients and controls from the index point to the end of year.

ICD chapter in ICD-10		Cases		Controls		P value
		n	%	n	%	
1. Certain infectious and parasitic diseases	yes	2	8%	27	6%	0.650
	no	23	92%	447	94%	
2. Neoplasms	yes	4	16%	77	16%	1.0
	no	21	84%	397	84%	
3. Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	yes	3	12%	10	2%	0.023*
	no	22	88%	464	98%	
4. Endocrine, nutritional, and metabolic diseases	yes	5	20%	36	8%	0.045*
	no	20	80%	438	92%	
5. Mental and behavioral disorders	yes	5	20%	39	8%	0.059
	no	20	80%	435	92%	
6. Diseases of the nervous system	yes	8	32%	35	7%	0.001*
	no	17	68%	439	93%	
7-8. Diseases of the eye and adnexa and ear and mastoid process	yes	5	20%	86	18%	0.792
	no	20	80%	388	82%	
9. Diseases of the circulatory system	yes	20	80%	76	16%	0.000*
	no	5	20%	398	84%	
10. Diseases of the respiratory system	yes	3	12%	35	7%	0.426
	no	22	88%	439	93%	
11. Diseases of the digestive system	yes	5	20%	107	23%	1.000
	no	20	80%	367	77%	
12. Diseases of the skin and subcutaneous tissue	yes	8	32%	75	16%	0.049*
	no	17	68%	399	84%	
13. Diseases of the musculoskeletal system and connective tissue	yes	15	60%	113	24%	0.000*
	no	10	40%	361	76%	
14. Diseases of the genitourinary system	yes	5	20%	83	18%	0.787
	no	20	80%	391	82%	
15. Pregnancy, childbirth, and the puerperium	yes	1	4%	25	5%	1.000
	no	24	96%	449	95%	
16. Certain conditions originating in the perinatal period	yes	0	0%	0	0%	1.000
	no	25	100%	474	100%	
17. Congenital malformations, deformations, and chromosomal abnormalities	yes	0	0%	4	1%	1.000
	no	25	100%	470	99%	
18-21. Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified Injury, poisoning, and certain other consequences of external causes External causes of morbidity and mortality Factors influencing health status and contact with health services Codes for special purposes	yes	22	88%	313	66%	0.027*
	no	3	12%	161	34%	
All ICD codes together	yes	24	96%	392	83%	0.099
	no	1	4%	82	17%	

In summary, this study shows that the rate of comorbidity for malignancies was in line with that of the general population and supports our and other authors' opinion that primary UEDVT is a benign disorder; however, the cases had a higher number of healthcare contacts.

10 DISCUSSION

The focus of this thesis is on primary upper extremity deep vein thrombosis, a rare disease. As described in the Introduction, our clinical question was: “How to handle patients with thrombosis of the arm?” What is the most appropriate treatment for our patients with primary UEDVT? A treatment that is based on science and proven experience.

Most previous studies comprise both primary and secondary UEDVT, which considerably complicates the interpretation of the results for primary UEDVT, in particular. In addition, there are very few prospective or randomized studies [44].

The overall aim of this thesis was to increase the present knowledge of primary UEDVT regarding venous function, late sequelae, such as PTS, risk factors, recurrences, and comorbidity. In addition, we also wanted to investigate whether the anatomy of the upper part of the thorax has any role in the development of UEDVT.

10.1 METHODOLOGICAL CONSIDERATIONS

The overall and main limitation of the studies is the small number of enrolled patients. The first three papers comprise 32 to 15 patients with primary UEDVT who were enrolled from 37 patients with primary UEVT that we found in the registers comprising 563 patients with UEDVT from two large hospitals in Stockholm during a period of ten years. This gives us a frequency of primary UEDVT of 7% of all UEDVTs. This is a lower incidence than Bleker et al.[44] describe in their review paper in which they state that one third of all UEDVTs are primary. One explanation of this might be that more than 4500 patients from 45 studies are included. However, the 45 studies were very heterogeneous in terms of study design and study population. Other studies have shown that 20–25% of all UEDVTs are primary [57].

Our intention for the fourth paper was to include a larger number of patients, randomly selected from the NPR data. The hypothesis was that, by selecting the ICD codes, we could achieve a high degree of conformity between the registry data and the patients’ medical records, but, unfortunately, this was not the case. The main reason for this is that there is no unique ICD code for UEDVT. There are unique codes for many other DVTs, but the codes I80.8 (Phlebitis and thrombophlebitis of other sites), I80.9 (Phlebitis and thrombophlebitis of an unspecified site), I82.8 (Embolism and thrombosis of other specified veins), and I8.29 (Embolism and thrombosis of an unspecified vein) are used very frequently for all kinds of VTEs, instead of a more specific ICD code. Another finding is that a “DVT ICD code” is registered when a physician suspects a DVT on clinical grounds and more specific diagnostic examinations, such as CDU or venography conducted the following day, and the DVT

diagnosis can often be written off, while the ICD code remains in the NPR. Therefore, it is extremely important to validate data based on the medical records. One study from Sweden and another from Denmark using the same search method found false positives with a rate of 35–40% [2, 105]. In our study, the frequency of false positives was 95%, the difference being explained by the absence of a unique ICD code for primary UEDVT and by much wider inclusion criteria in the other studies, i.e., all kinds of thromboembolism.

The strength of all four papers is that only patients with primary UEDVT are included and, regarding the first three papers, we have been able to follow the patients over a long period of time: in Papers I and II for a mean period of 5 years (range, 2–9 years) and, in Paper III, for about 7 years (range, 3.6–11.3 years). Another strength of the studies is that all except one of the patients have been treated conservatively, with LMWH and VKA. For all patients, it was the first thrombotic event.

10.2 GENERAL DISCUSSION AND MAIN FINDINGS

10.2.1 Venous function

Plethysmography was used to evaluate venous function. CDU, MRI, and the calculation of the area of the subclavian vein can also be regarded as measures of venous function. CDU can be used to provide both morphologic and hemodynamic information concerning patients with UEDVT [41, 106-108]. CDU has also come to replace phlebography more and more as the first line of diagnostics.

In our study, 58% of the patients had a residual thrombus, which is a higher figure than in a study by Sabeti et al. [60], which showed that 48% of the patients had a residual thrombus after a median follow-up period of 40 months. The difference is largely due to the fact that one third of the patients in their study underwent thrombolysis. Another study on patients with UEDVT and thrombolysis showed similar rates of residual thrombus to those of Sabeti et al. [109]. However, it seems that the frequency of residual thrombus is lower in the arms than in the lower extremities. A study by Johnson et al. [97] on LEDVT shows that only 12% had normal duplex findings after a follow-up period ranging from one to six years. The results regarding the remaining occluded segments of the arm do not seem to differ from those reported after DVT in the lower extremity [110, 111].

Our study did not show any patient with deep or superficial valvular insufficiency in the arms, which suggests that loss of valvular function is of less importance in developing PTS in the arms.

To obtain supplementary data to the morphologic information caught with ultrasonography, plethysmography was performed. The most evident result was that venous volume and venous emptying were significantly lower in the arms with a DVT than in the contralateral arm. Thirty-five percent had a venous emptying less than the lower normal limit, which is calculated as the mean of VE -2 SD, as presented in another study by our group [102]. This result is expected as the majority of the patients had residual vessel wall abnormalities and there was a clear trend toward lower venous emptying in patients with more advanced morphologic changes (Figure 12).

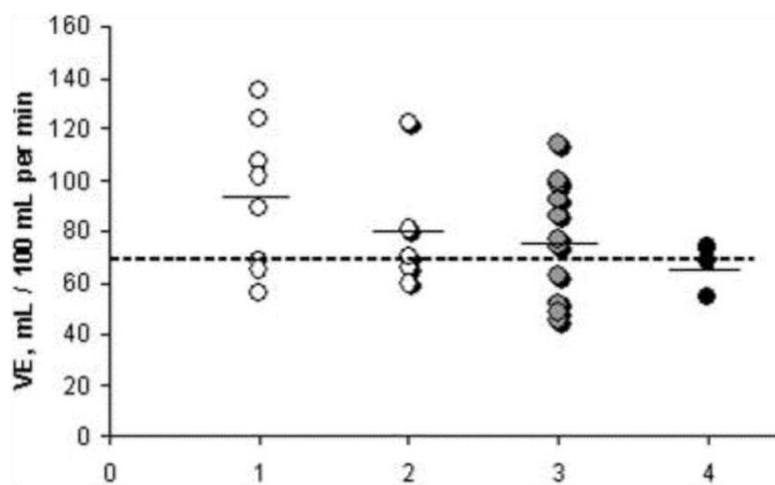


Figure 12. Venous emptying (VE) in relation to duplex category. The duplex categories used were 1, normal; 2, mild changes; 3, moderate-to-severe changes; and 4, occluded. The mean value for VE in each duplex category is indicated, and the lower limit of normality of VE is marked with a discriminating line.

This finding was not significant and can be explained by the small number of patients in each ultrasound category. There are also other factors, such as stiff vessels, that can reduce venous emptying. In our study, four of 13 patients without a residual thrombus had a significant outflow obstruction as shown plethysmographically. Conversely, some patients with residual DVT and a still occluded vessel had normal venous emptying, probably due to the development of collaterals.

In the third paper, we used MRI to explore the anatomy in and around the subclavian vein. Regarding the area of the vein, we found a significant difference between the patients' non-thrombotic arm and that of the controls with the arms raised over the head. This indicates that the anatomy plays a role in thrombus formation in the upper extremity.

10.2.2 Postthrombotic syndrome

The clinical entity of PTS includes a number of symptoms and clinical signs that are difficult to classify adequately. A number of factors are probably involved in the expression of this

syndrome, including both outflow obstruction and patient-related factors such as the degree of physical activity and physical demand.

The frequency of PTS in patients with UEDVT varies in different studies, probably due to heterogeneous study populations (both primary and secondary UEDVT), but also because of the use of different scales to measure the PTS. In this thesis, the modified Villalta scale is used and the same physician has evaluated all patients, also in the follow-up MRI study. There are difficulties in comparing our data with those of other studies because of mixed study populations. Our study showed a frequency of PTS of 28%, which is in line with PTS in patients with LEDVT [112]. One can assume that the frequency of PTS is lower in patients with primary UEDVT, compared to the secondary form; thus, most patients with secondary UEDVT often suffer from other medical conditions, i.e., malignancies, trauma, or indwelling catheters.

The patient group in the third paper had significantly elevated values according to DASH, while the modified Villalta test only showed severe signs of PTS in two patients. This may indicate that DASH, showing the patients' subjective symptoms, is more sensitive than the modified Villalta test for the detection of the disability and discomfort of PTS in UEDVT.

Does PTS affect activities of daily living? Our results and those of others tend to point that way [86, 92]. We found a correlation between DASH and PTS measured with the modified Villalta scale. However, none of the patients reported that they had to change occupation after the thrombotic event, which is also shown in a study by Linblad et al.[15] on patients with primary UEDVT.

It is important to remember that, in our study, the majority of patients suffered only from mild-to-moderate PTS. It is interesting that, for the 15 patients in the follow-up study, the MRI study (two years later) showed almost similar results regarding both the Villalta scale and DASH on an individual basis. This indicates that the remaining symptoms are consistent over time.

In an attempt to further quantify the capacity of the arms, all patients performed an arm exercise test. Unfortunately, it was difficult to discriminate between the influence of PTS of working capacity and overall muscle capacity.

10.2.3 Correlation between PTS and objective findings

As mentioned in the Results section in Paper I, there was no significant association between the PTS score and the duplex findings, category 1 to 4, even though 58% had residual thrombi. Also with regard to plethysmography, the study did not show a statistical significance between PTS and venous function. A recently published study by Czihal et al.

[113] found neither a significant correlation between venous emptying and PTS nor between color duplex ultrasound findings and PTS. This of course raises the question of the cause of PTS. The limited numbers of patients included (31 in our study and 37 in the study by Czihal) limit the possibility of drawing a firm conclusion about factors of importance for the development of PTS. For patients with PTS and an almost normal venous outflow, collaterals play an important role, especially for those with a residual thrombus. Hence, one must consider whether or not color duplex ultrasound and plethysmography are the best methods to objectify PTS or whether the symptoms have an extravascular origin. Some authors have discussed the possibility of obtaining more information from arm volumetry and skin thickness. One can also consider if the Villalta score is the best way to quantify PTS. Further studies are needed.

The third paper comprising MRI confirms the results indicating no association between morphologic changes (i.e., in the area of the subclavian vein) and PTS.

10.2.4 Coagulations disorders

The prevalence of thrombophilia in our study was within the same range as for DVT in the lower extremities and at the same level as in other studies on UEDVT [36]. The most common thrombophilia in our study was the mutation of factor V Leiden. Unfortunately, we do not have the frequency of the mutation of the prothrombin gene; it was not determined in clinical practice when the majority of the patients had their thrombotic event. Interestingly, it seems that a moderate increase in fibrinogen is a common finding in this group of patients. The implication of this finding is unclear and calls for further investigation.

Elevated fibrinogen has been described as a risk factor for arterial thrombosis [114], but there are some studies that have shown an association between elevated levels of fibrinogen and DVT, while others have not [115].

In summary, our findings support the role of coagulation disorders as a risk factor for primary UEDVT.

10.2.5 Recurrences and risk factors

There is a pronounced variability between the recurrence rates, which range from 0% to 26% in different studies. Due to the fact that there are very few studies comprising only primary UEDVT, it is difficult to estimate the “real” frequency of recurrences, but several authors state that the recurrence rate for patients with primary UEDVT “should be lower.”

None of the patients in our study had a recurrent DVT or PE during the observation period, i.e., 5 years in the first two papers and 7 years for the patients who agreed to

participate in the MRI study. For all patients, the VKA treatment was stopped after six months. This is in line with a study by Lechner et al. [40], in which they only included primary VTE and followed 50 patients with primary UEDVT for an average of 59 months and 841 patients with idiopathic lower extremity deep vein thrombosis (LEDVT) for 46 months. Only two patients (4%) in the UEDVT group had a recurrent VTE; for the LEDVT group, the recurrent rate was 15%.

So why is the risk of recurrence in primary UEDVT lower than in both secondary and idiopathic LEDVT?

In some respects, the higher rate of recurrences in the secondary group is explained by the underlying illness that most of these patients suffer from.

The different recurrence rate for idiopathic LEDVT has several explanations and the full picture is not known yet. The risk factors differ: patients with primary UEDVT tend to be slimmer and younger than patients with LEDVT. Both age and an increased BMI are risk factors for VTE. Furthermore, the location of the thrombi may influence the risk of getting a recurrent VTE. As mentioned earlier, the hydrostatic pressure is higher in the leg, there are more valves and, especially in the calf, a lot of muscle veins where the thrombus formation can start. It has also been shown that the fibrinolytic activity is higher in the arms.

The known risk factors for primary UEDVT, as found in our studies and the literature, can be summarized as thrombophilia (especially FV Leiden and the prothrombin mutation) and strenuous exercise with the arms by patients with narrowing of the thoracic outlet. The role of oral contraceptives remains unclear, but there is probably an association, especially when combined with thrombophilia. The use of oral contraceptives and HRT was as high as 52% of the women in our study; this supports the theory that oral contraceptives do play a role. A family history of VTE seems to be lower in patients with UEDVT.

In Papers I–III, the typical patient was a woman (mean age 40) with a sedentary occupation and without any previous exceptional effort. This cannot of course explain the UEDVT, but the influence of one's daily work perhaps calls for further studies. In Paper IV, there was no difference in the sexes, 48% males and 52% females. The study population was also older in Paper IV. Still, the study populations are too small to draw any conclusions.

10.2.6 The anatomy of the upper thorax

Narrowing and compression of the subclavian vein by surrounding structures has been described as risk factors for venous TOS and effort-related UEDVT. In our study, we found a narrowing of the thoracic outlet (costoclavicular distance) in both arms in the patient group when the arms were alongside the body.

Interestingly, only one of the 15 patients was categorized as having effort-related UEDVT. This raises the question of whether external compression of the vein may be a more common cause of UEDVT than previously thought to be. Also, to our knowledge, there have not been any general, standardized questions about unusual and strenuous work with the arms before the thrombotic event. Thus, there probably is a relatively large variation in the meaning of “unusual and strenuous work with the arms,” which can lead to different reported percentages of effort-related UEDVT in different studies.

Our study further shows that the area of the subclavian vein (in the non-thrombotic arm) was smaller when the arm is in a supine position. This confirms the theory that especially working with the arms over the head can be a risk factor for UEDVT.

In summary, the costoclavicular space is narrower in a neutral position in the majority of patients with primary UEDVT than in controls. The importance of the costoclavicular space for developing UEDVT could be one explanation for why women are more exposed to UEDVT than men.

10.2.7 Treatment

All but one of the patients included in our studies were treated with LMWH and VKA; one patient received thrombolysis and was excluded from paper I. We have not found any convincing evidence in the literature that thrombolysis improves the long-term outcome of primary UEDVT. However, the relatively benign clinical outcome of patients with primary UEDVT suggests that a conservative approach is an acceptable choice in most cases and that more aggressive and potentially risky treatment can be an option in selected cases, such as those with extensive thrombosis and severe symptoms.

10.2.8 Comorbidity

This rather small study is, to the best of our knowledge, the first one in which comorbidity has been described in patients with primary UEDVT and compared with that of a control group which has been selected in the same way and can be seen as representing morbidity in the general population. The results in our studies support our theory that primary UEDVT is a rather benign disease. There was no difference between cases and controls in the reported diagnoses of malignancy. There was also no difference between patients and controls in the total unique diagnoses reported in the NPR, but there are differences in some ICD chapters that might be related to the thrombotic event. The cases had, however, a higher number of healthcare contacts than the controls. This can support data from studies on PTS and the reduction of the quality of life [86, 92].

11 CONCLUSIONS

The overall aim of this thesis was to increase the current knowledge of primary upper extremity deep vein thrombosis. Based on the four papers, the following conclusions can be drawn:

- Primary UEDVT is a rather benign disease with a low rate of recurrences, but with a non-negligible proportion of postthrombotic syndromes. The most common symptom is swelling of the arm.
- More than 50% of the patients have residual thrombi and as many as 75% have some morphologic abnormality in the thrombotic vein that is detectable with CDU. The rate of venous emptying was significantly lower in the arms with DVTs than in the contralateral arms.
- There is no correlation between PTS and plethysmographic findings, area of the subclavian vein, and morphologic abnormalities detected by CDU.
- The frequency of coagulation disorders is about 40%, at the level with LEDVT. The most common disorders in our study population are mutations of factor V and elevated fibrinogen.
- There seems to be some influence between the anatomy of the upper thorax, especially the thoracic outlet, and the development of primary UEDVT, both effort-related and idiopathic.
- The rate of comorbidity regarding malignancies seems to be in line with that of the general population.

12 IMPLICATIONS AND FUTURE PERSPECTIVES

This thesis shows that primary UEDVT is a rather benign disease, but with a relatively high rate of postthrombotic discomfort for the patients. The cause of the thrombotic event is still unclear (idiopathic) for some patients. At the first thrombotic event, it is important to examine the patient thoroughly and look for coagulation disorders, listen to the patients' history if there has been any vigorous or unusual exercise prior to the event. We know that malignancy is associated with DVT and therefore has to be ruled out.

The first choice for treatment should be LMVH and VKA, but thrombolysis should be considered for patients with severe symptoms. The best way of preventing PTS is to prevent a new thrombosis and therefore it is important to monitor the anticoagulant treatment accurately.

We, like other researchers, have not found any correlation between objective measurements of venous function and the postthrombotic syndrome. This raises questions about the origin of PTS. The patients report a feeling of heaviness and clumsiness in the affected limb, but we still do not have any objective methods to verify this feeling. Because of the nonassociation between PTS and the venous flow rate, the cause of PTS must be sought elsewhere. Is the cause on an extravenous level or are microcirculation or nervous symptoms involved? All of this requires further investigations.

The next step is to extend the numbers in Paper IV to determine if there is any difference from the general population regarding socioeconomic outcomes. This can be done by searching data on patients with verified primary UEDVT in the LISA register (Longitudinal Integration Database for Health Insurance and Labor Market Studies). This Swedish database integrates existing data from the labor market and educational and social sectors on an individual basis and is updated each year. Another finding is that there is extremely important, in future studies of UEDVT, to validate the PNR data with the medical records due to the fact that there is no unique ICD-code for UEDVT.

Most of all, a prospective study is wanted, but, because of the low incidence of primary UEDVT, there are difficulties in recruiting patients, and it must be done on a national basis.

13 SUMMARY IN SWEDISH

BAKGRUND

Djup ventrombos av den övre extremiteten (UEDVT) är en ovanlig sjukdom med en incidens av 1-11% av alla djupa ventromboser. UEDVT kan delas in i två grupper, primär och sekundär UEDVT.

Primära UEDVT inkluderar idiopatisk och ansträngningsutlöst UEDVT, vilka i vissa studier står för upp till en tredjedel av alla UEDVT. Patienter med thoraxapertursyndrom klassificeras också som primär UEDVT. Sekundär UEDVT orsakas av till exempel katetrar eller pacemakersladdar i venerna. Vidare kan cancer och trauma mot övre extremiteten vara orsak till sekundär UEDVT. I vissa studier av patienter med UEDVT har förekomsten av cancer visat vara sig så hög som 38 %.

Denna avhandling fokuserar på primär UEDVT.

SYFTE

Projektet startade som en klinisk frågeställning när vi skulle revidera vårdprogrammen för djup ventrombos vid vår akutmottagning. Frågan som vi ställde oss var: Hur gör vi med armtromboserna? Det första och på intet sätt vetenskapliga svaret var: Vi gör väl som vi gör med blodpropp i benen. Vid genomgång av tillgänglig forskning fick vi fler nya frågor än svar. Vissa forskare förordade aktiv behandling med trombolys medan andra förespråkade konservativ behandling med lågmolekylärt heparin och vitamin K-antagonist.

Det övergripande syftet med denna avhandling är att öka kunskapen om primär armvenstrombos och genom denna kunskap kunna erbjuda framtida patienter adekvat behandling baserad på vetenskap och beprövad erfarenhet.

PATIENTER

Trettiofyra patienter (23 kvinnor, 9 män) med primär UEDVT rekryterades till studien, alla, utom en patient, behandlade konservativt med lågmolekylärt heparin och vitamin K antagonist. Femton av dessa patienter accepterade senare att delta i den tredje studien, magnet resonans tomografi studien, i vilken också en kontrollgrupp av 15 friska frivilliga nyttjades. Uppföljningsperioden för studie ett och två var 5 år och för studie tre 7 år. Den fjärde studien som är en registerstudie med data från Nationella Patientregistret (NPR) och omfattar 25 patienter med primär UEDVT, alla behandlade konservativt.

METODER

Studie 1. Patienterna utvärderades genom intervjuer, klinisk undersökning, pletysmografi och färgduplex ultraljudsundersökning. Patienternas kvarvarande posttrombotiska symptom skattades med Villalta skalan som både tar hänsyn till patienternas kvarvarande symptom och kliniska fynd.

Studie 2. Som komplement till Villalta skalan användes i denna studie DASH testet, ett frågeformulär som är validerat för att utvärdera funktionen i hand, arm och axel. VAS användes för att värdera smärta och nedsatt funktion. I ett försök att objektivisera arbetsförmågan genomgick alla patienter ett armcykeltest. Blodprover togs för antitrombin, protein C och S-brist, antifosfolipidantikroppar, mutation av faktor V Leiden, fibrinogen, D-dimer, och von Willebrand-faktor-antigen.

Studie 3. Anatomien av övre delen av thorax undersöktes med hjälp av MRI. Avståndet mellan nyckelbenet och första revbenet (det utrymme där v. subclavia passerar) uppmättes. Arealen av v subclavia kalkylerades i samma lokalisation. Bägge beräkningarna gjordes med armarna både längs kroppen och uppsträckta över huvudet. Villalta och DASH genomfördes på nytt.

Studie 4. De 25 patienterna matchades, på individuell basis, med 474 kontroller avseende kön, ålder vid indexhändelse och år för indexhändelse. Genom detta blev grupperna jämförbara även för observationstiden, tiden från indexhändelse till slutet av år 2011. Komorbiditet beskrevs som antalet unika ICD-koder (diagnoser) registrerade i NPR för patienter och kontroller från indexpunkten till slutet av år 2011.

RESULTAT

Studie 1. Ventömningshastigheten var signifikant lägre i armarna med trombos jämfört med den kontralaterala armen ($P < .001$). Femtioåtta procent av patienterna hade kvarvarande trombosrester i kärlet och 74% hade uppvisade någon morfologisk förändring. Det fanns inget statistiskt signifikant samband mellan pletysmografifynd och duplexundersökningen. De flesta (77 %) av patienterna rapporterade kvarvarande symptom i den drabbade armen, vanligaste besväret var svullnadskänsla i armen. Studien visade att det fanns en signifikant skillnad avseende omkretsen av överarmen mellan trombotisk och icke trombotisk arm. Ungefär en tredjedel av patienterna hade utvecklat en måttlig grad av posttrombotiska besvär enligt Villalta skalan. Ingen signifikant relation fanns mellan Villalta poäng och undersökningsfynden med ultraljud. Patienter med posttrombotiska symptom syndrom hade en lägre ventömningshastighet men skillnaden var inte statistiskt signifikant.

Studie 2. Ingen av patienterna utvecklade malignitet, lungemboli, eller återkommande UEDVT. Tjugoåtta procent av patienterna hade milda till måttliga posttrombotiska symptom

enligt Villalta skalan. Förekomsten av trombofili var 40 % och den vanligaste avvikelserna var mutation av genen för Faktor V Leiden. Ett förhöjt fibrinogenvärde noterades också hos 22 % av patienterna.

Studie 3. Avståndet mellan nyckelbenen och första revbenet var mindre hos patienterna när armarna var längs kroppen. Avseende arean av v. subclavia (jämförelse patientens friska arm och kontrollgruppen) fanns det en signifikant skillnad med armarna över huvudet. Det fanns en tydlig korrelation mellan Villalta och DASH men inte mellan Villata/DASH och MRI fynden.

Studie 4. De 25 patienter och 474 kontrollerna, 48 % män och 52 % kvinnor, hade en medelålder vid indextillfället om 48 år (intervall 20-80, SD 17,5). Den genomsnittliga uppföljningstiden var 8 år (intervall 5,7-9 år). Patientgruppen hade signifikant flera hälso- och sjukvårdskontakter jämfört med kontrollgruppen. Det fanns ingen skillnad mellan grupperna avseende komorbiditet när alla ICD koder analyserades tillsammans. Däremot fanns skillnad för vissa kapitel (diagnosområden) av ICD-10. För ICD kapitel 3 (blod och blodbildande organ), 4 (endokrina sjukdomar) och kapitel 11 (hudsjukdomar) fanns det ingen tydlig trend med en högre frekvens av någon ICD-kod för patienterna.

I ICD-kapitel 6 (nervsystemet) hade 7 av de 25 patienterna (28 %) ICD-koder för symptom från plexus brachialis eller karpaltunnelsyndrom, för kontrollerna var motsvarande siffra 1,5 %. Skillnaden i ICD kapitel 8 (cirkulationssystemet) kan förklaras av uppföljning och monitorering av behandlingen av den initiala trombosen. En patient (4 %) patient hade registrerad ICD-kod för lungemboli.

I kapitel 12, innefattande symptom från rörelseapparaten, fanns en överrepresentation av ICD-koder som hänvisar till olika diagnoser med smärta och obehag av den övre extremiteten. Viktigast fyndet var att det inte var någon skillnad mellan grupperna avseende ICD-koder som relaterar till malignitet.

SLUTSATSER OCH DISKUSSION

- Primär UEDVT är en godartad sjukdom med en låg grad av återfall men med en inte försumbar andel posttrombotiska symptom. Det vanligaste symptomet är svullnad av armen. Komorbiditeten avseende cancersjukdomar synes ej var förhöjd
- Sjuttiofyra procent av patienterna har kvarvarande förändringar i kärlet, diagnostiserat med ultraljudsundersökning. Ventömningshastigheten var signifikant lägre i armarna med trombos jämfört med den kontralaterala armen.

- Det finns ingen korrelation mellan graden av posttrombotiska symptom och objektiva mät- och undersökningsmetoder så som pletysmografi, ultraljud eller MRI undersökningsfynd varför orsaken till posttrombotiska besvär måste sökas även utanför vensystemet.
- Frekvensen av koagulationsrubbingar är 40 %.
- Det verkar finnas ett samband mellan anatomin i övre delen av thorax och utvecklandet av UEDVT, både ansträngningsutlöst och idiopatisk.
- För den absoluta majoriteten av patienterna med primär UEDVT är konservativ behandling med lågmolekylärt heparin och vitamin K-antagonist tillräckligt.
- Komorbiditeten avseende cancersjukdomar synes vara i samma nivå som normalbefolkningen
- Det är oerhört viktigt att validera registerdata med patienternas journal, framför allt om det inte finns en specifik ICD kod för den diagnos som skall studeras.

14 LEARNING AND OUTCOMES

This project has been going on for several years, mostly because of a lack of time due to my regular work, first as clinician and later on as the head of the Emergency Department and Chief Medical Officer at our hospital. All the time, my goal was to finalize the project and write my thesis. The work has always been inspiring, even when the manuscripts were rejected, because it has been a way of learning both the subject and the scientific process. I have gained new knowledge on a range of scientific issues such as critical reviews of scientific publications, scientific thinking, hypothesis testing, statistics, writing a scientific paper and, most of all, I have learned to be patient.

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