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Thoracic surgery for improving arterial and venous blood flow in the upper extremity

Frank Hoexum

Thoracic surgery for improving arterial and venous blood flow in the upper extremity.

PhD thesis, Vrije Universiteit Amsterdam, The Netherlands

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The logo for ChipSoft, featuring the word "ChipSoft" in a blue, italicized, sans-serif font. The "C" is underlined with a blue line.

VRIJE UNIVERSITEIT

**THORACIC SURGERY FOR IMPROVING ARTERIAL AND VENOUS BLOOD FLOW
IN THE UPPER EXTREMITY.**

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor of Philosophy aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. J.J.G. Geurts,
volgens besluit van de decaan
van de Faculteit der Geneeskunde
in het openbaar te verdedigen
op vrijdag 8 mei 2026 om 13.45 uur
in de universiteit

door

Frank Hoexum

geboren te Groningen

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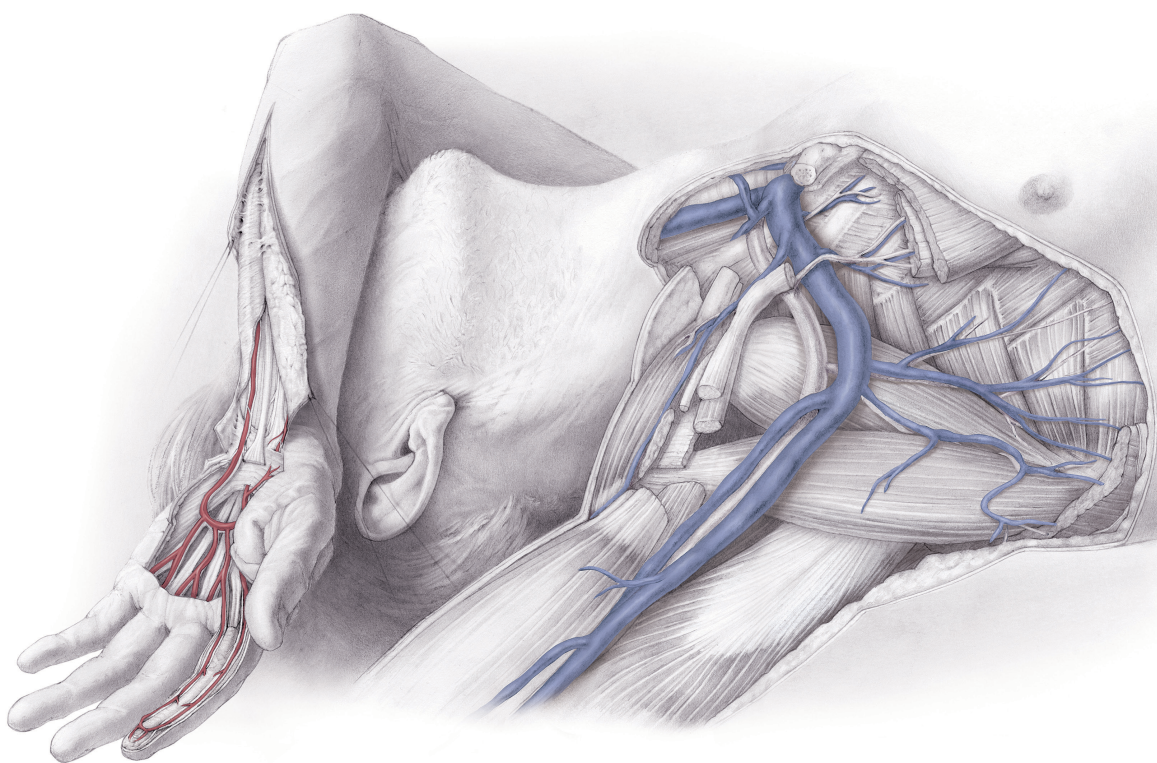
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CHAPTER 1

General introduction and outline of the thesis

GENERAL INTRODUCTION PART I: Thoracic sympathectomy in the management of upper extremity peripheral artery disease (UEPAD).

In contrary to the more common peripheral arterial disease of the lower extremity, atherosclerosis infrequently affects arteries of the upper limb. At the upper limb, the subclavian arteries are affected the most frequent. The epidemiology of subclavian artery stenosis is mostly based on an interarm systolic blood pressure (SBP) difference of more than 10 to 15 mmHg. This definition is poorly sensitive (50%), although highly specific (90%), when compared with angiography.^[1] Based on these definitions, the prevalence of subclavian stenosis is estimated to be approximately 2% in the general population but increases to 9% in the case of concomitant lower extremity artery disease.^[1]

Morbus Raynaud:

Morbus Raynaud is a well-known entity with upper extremity digital ischemia as its main symptom. Maurice Raynaud published his thesis “*De l’asphyxie locale et de la gangrène symétrique des extrémités*” in 1862.^[2] He described a condition triggered by cold or emotional stress characterized by a typical tricolor phenomenon consisting of a pale, cyanotic, and hyperemic phase (figure 1).

Thomas Lewis further divided this phenomenon in Primary Raynaud Disease (PRD) and Secondary Raynaud Phenomenon (SRP).^[3] PRD is characterized by cold hypersensitivity and profound episodic digital colour changes thought to occur as the result of an exaggerated vasoconstrictive response of the digital arteries to cold temperatures, blunt trauma, or emotional stress. By definition, patients with PRD do not have an underlying associated cause for vasospastic events and irreversible tissue injury does not occur from the condition.^[4] In contrast, SRP of the upper extremity is caused by an underlying disorder and the digital ischemia can cause trophic changes, ulceration, and tissue loss. Because of overlapping clinical presentation and aetiology, SRP and UEPAD can be considered to be synonyms for the same disease. A wide variety of causes of SRP are mentioned in the literature and listed in table 1.^[5]

Primary vasospastic disorders are usually benign and require reassurance and conservative measures with avoidance of cold exposure.^[6] Cessation of tobacco use is strongly advised to prevent smoking induced vasoconstriction.^[5] The management and prognosis of SRP depends on the underlying condition and has to be treated if possible. In case of arterial occlusive disease of the upper extremity, surgical or endovascular treatment is often successful. If the cause of the vasospastic disorder cannot be treated, first line of symptomatic management is pharmacological treatment. In general, drug

therapies are started at low dose and increased gradually depending on tolerability and efficacy. Specific reference should be made to potential vasoactive adverse effects such as hypotensive symptoms and vasoactive headache.^[5] Calcium channel blockers are generally considered first-line drug treatment for the management of SRP. A variety of other drugs are available: angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; selective serotonin reuptake inhibitors; topical nitrates; statins; antiplatelet therapy and phosphodiesterase type-5 inhibitors.^[5] Unfortunately there will remain a number of patient in whom these supportive, medical or vascular surgical procedures will not be successful. If all non-operative therapies are unable to relief symptoms or prevent tissue loss, surgery of the sympathetic nerve system can be considered.

Phase 1

A spasm in the afferent arteries results in a decreased blood flow to the skin of the affected limb. The skin subsequently colors pale-white.



Phase 2

Local ischaemia results in the dilatation of the capillaries. An increased concentration of deoxyhemoglobin discolors the blood in the dilated capillaries bluish-purple.



Phase 3

After relaxation of the arterial spasm, the perfusion of the affected limb is restored. The capillaries are supplied with normal oxygen rich blood again. The still dilated capillaries stain the skin red, indicative of hyperemia.

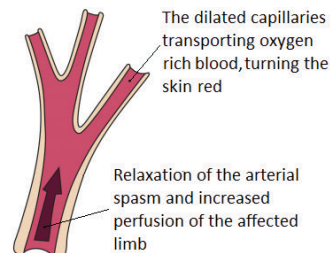
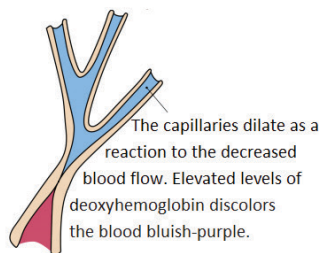
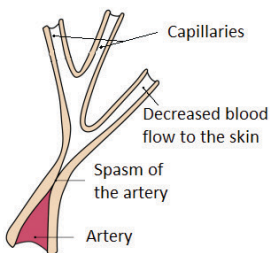


Figure 1. The 3 phases of Morbus Raynaud

Source: combined and modified images from google images

Table 1. Causes of Secondary Raynaud Phenomenon^[5]

Cause of SRP	Underlying aetiology	
Large vessel (usually proximal large-vessel disease, often unilateral symptoms)	• Compressive (e.g. cervical rib) • Neurogenic (thoracic outlet obstruction) • Inflammatory vascular disease (e.g. thromboangiitis, obliterans [Buerger's disease] or large-vessel vasculitis) • Atherosclerosis	
Occupational	Hand–arm–vibration syndrome (vibration white finger)	
Autoimmune rheumatic diseases	• Systemic sclerosis • Systemic lupus erythematosus • Sjogren's syndrome • Mixed connective tissue disease/overlap syndromes • Undifferentiated connective tissue disease • Idiopathic inflammatory myopathies • Vasculitis	
Drug/chemical-related	• Amphetamines • Beta-blockers • Bleomycin • Cisplatin • Clonidine • Cyclosporine • Interferons • Methysergide • Polyvinyl chloride	
Vaso-occlusive disease	• Cold agglutinin disease • Cryoglobulinaemia • Cryofibrinogenaemia • Paraproteinaemia • Malignancy (including as a paraneoplastic phenomenon)	
Other causes and associations	• Carpal tunnel syndrome • Frostbite • Hypothyroidism • POEMS syndrome • Fibromyalgia syndrome	

The autonomic nerve system:[7]

All autonomic functions of the body are regulated by the autonomic nerve system (ANS) (figure 2). The ANS is divided in the sympathetic nerve system (SNS), parasympathetic nerve system (PNS) and enteric nervous system (ENS). The ENS regulates the digestive functions of muscle contraction/relaxation, secretion/absorption, and blood flow. The ENS is self-contained, functioning through local reflex activity, but often receives input from, and provides feedback to, the SNS and PNS.

Activation of the SNS leads to a state of overall elevated activity and attention: the “fight or flight” response. In this process, blood pressure and heart rate increase, glycogenolysis ensues, gastrointestinal peristalsis ceases, etc. The SNS innervates nearly every living tissue in the body. The PNS promotes the “rest and digest” processes; heart rate and blood pressure lower, gastrointestinal peristalsis/digestion restarts, etc.

As mentioned before the SNS enables the body to handle stressors via the “fight-or-flight” response. This reaction primarily regulates blood vessels. Vessels are tonically innervated, and in most cases, an increase in sympathetic signals leads to vasoconstriction. Conversely, elimination of the sympathetic innervation will lead to vasodilatation.

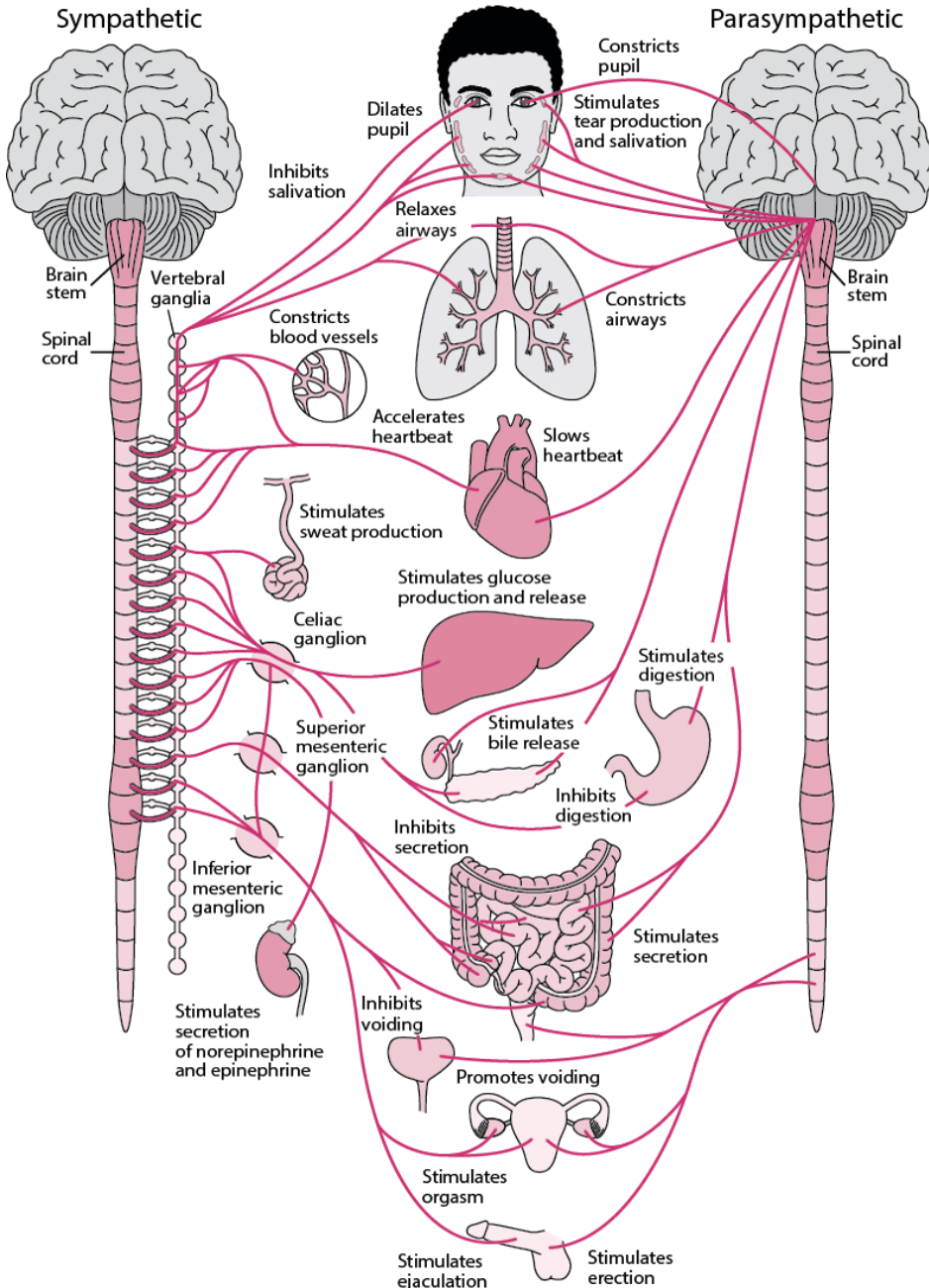


Figure 2. The autonomic nervous system

Source: Merck Manual via: <https://www.merckmanuals.com/home/brain,-spinal-cord,-and-nerve-disorders/autonomic-nervous-system-disorders/overview-of-the-autonomic-nervous-system>

The sympathetic innervation originates from the spinal cord segments T1 through L2. Neurons of the sympathetic nerve system are positioned in the lateral horns of the spinal cord. Preganglionic fibres pass through the white rami communicantes and enter the paravertebral sympathetic chain ganglia. Preganglionic fibres follow one of three different pathways upon entering the paravertebral ganglion (figure 3):

1. Synapse with the ganglion neuron within the same ganglion.
2. Descend or ascend within the sympathetic chain and synapse in an inferior or superior ganglion.
3. Pass through the paravertebral ganglion but don't synapse. It proceeds through one of the splanchnic nerves to synapse within a prevertebral ganglion.

From the paravertebral or prevertebral ganglia postganglionic fibres innervate the end-organs. Transection of the paravertebral thoracic sympathetic chain (thoracic sympathectomy) will eliminate the sympathetic innervation of the end-organs in that specific region.

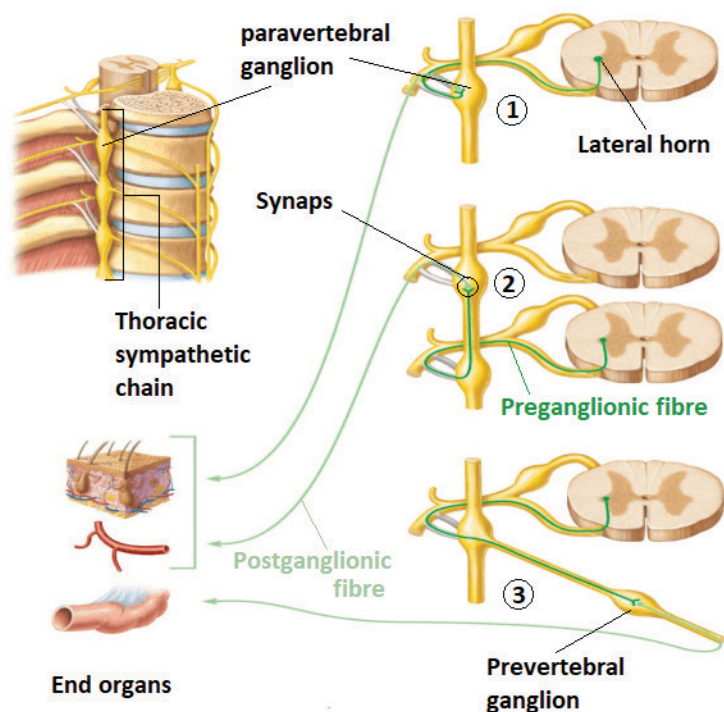


Figure 3. Anatomy of the sympathetic chain

Source: combined and modified images from google images

History of sympathetic surgery:

By the end of the 18th century, the anatomy was fairly well defined. However, the functions of the sympathetic nervous system were not. The first surgeon to operate on the sympathetic nervous system was Alexander of Liverpool who performed a cervical sympathectomy for epilepsy in 1889.^[8] In the years following sympathetic surgery was performed in small numbers in the treatment of epilepsy, exophthalmic goitre, spastic paralysis, glaucoma, hypertension, angina pectoris, vasospastic disorders and peripheral arterial occlusive disease.^[8,9] With the advances in medicine the vast majority of indications is currently considered obsolete. The main indications today are hyperhidrosis and blushing.^[9] For some indications (angina pectoris, vasospastic disorders, and painful conditions) sympathectomy has still a limited application.^[9]

Thoracic sympathectomy (TS) was historically performed using a variety of open procedures; supraclavicular, transthoracic, transaxillary and by a posterior approach.^[10] With the introduction of video assisted thoracic surgery (VATS) a minimal invasive endoscopic thoracic sympathectomy (ETS) procedure was available, resulting in less morbidity.^[11] As mentioned above, by eliminating the sympathetic driven vasoconstriction of the arteries and arterioles, the subsequent vasodilation will lead to an increased arterial blood flow to the of the arm and hand.

AIM AND OUTLINE OF THE THESIS, PART I

The aim of the first part of this thesis was to create more insight in the use, efficacy and results of TS and ETS in the management of PRD/SRP.

In **chapter two** we systematically reviewed the English literature between 1980 and 2010 regarding the outcomes of TS and ETS in the management of PRD and SRP with special attention to ulcer healing and complications. In **chapter three** we extended the search with 10 additional years (1975-2015). The endpoints were identical.

In **chapter four** we evaluated the long-term success, morbidity and overall patient satisfaction of ETS in the management of PRD and SRP in our hospital performed on patients between 1994 and 2009.

in **chapter five** we evaluated the feasibility of a novel Robot-Assisted T2-T5 ramicotomy using the Da Vinci® robot.

GENERAL INTRODUCTION OF PART II: upper extremity deep venous thrombosis (UEDVT)

In contrary to deep venous thrombosis of the lower limbs, UEDVT is uncommon. The estimated incidence of UEDVT is 16 per 100,000 population compared with 91 per 100,000 population for lower extremity deep venous thrombosis.^[12] The majority of UEDVT cases are provoked and secondary to among other things; indwelling lines, pacemaker wires, injury during attempted catheter placement, arteriovenous fistula, paraneoplastic or inflammatory bowel disease and extrinsic pressure from malignancy.^[13] Primary or unprovoked UEDVT is exceedingly rare. Although seldom, it is an important disease affecting often young people and may cause invalidating complaints.

In the year 1875 Sir James Paget published his book “Clinical lectures and essays”.^[14] This book comprised of an assembly of previously published papers regarding his clinical observations. The tenth chapter was devoted to “*Gouty phlebitis*”. Paget describes herein his encounters with patients with “*adhesive phlebitis; the disease in which inflammation of the coats of a vein is associated with clotting of blood in its canal, but not with suppuration or pyaemia*”. In several cases he was unable to establish an underlying cause of the phlebitis. In two cases the upper extremity was affected. The case of a 27 year old regimental servant was described in the Medical Times and Gazette of 13th March 1858 and is probably the first published case in literature of primary upper extremity deep venous thrombosis (figure 4). In accordance with the therapies used at the time, this patients was treated with “*rest in the Hospital, and the occasional application of leeches*”.^[15]

In another case, in a soldier 27 years old, there was great enlargement of all the muscles of the right arm and shoulder, and such fulness of all its subcutaneous veins, and such a feeling of weight and tightness when it hung down, that I supposed the axillary vein must be obstructed. However, with rest in the Hospital, and the occasional application of leeches, the muscles gradually diminished, and the veins became less filled; and finally, during an attack of scarlatina, they returned to nearly their natural state.

Figure 4. The Medical Times and Gazette 13th March 1858

Source: <https://babel.hathitrust.org/cgi/pt?id=hvd.32044103087904&seq=7>

Von Schroetter postulated in 1884 that this entity resulted from direct damage to the vein caused by stretching that occurred from muscular strain. The English surgeon, Hughes, termed the condition Paget-von Schroetter syndrome in 1949, and it has been known by variations of this eponym ever since.^[16]

Paget-Schroetter Syndrome:

Paget-Schroetter Syndrome (PSS) is rare with an estimated incidence of 1-2 per 100,000 individuals per year.^[16,17] The subclavian vein exits the thoracic cavity through a confined opening. The boundaries are composed by the clavicle, the first rib, the costoclavicular ligament and the anterior scalene muscle (figure 5). As mentioned above it is believed that intimal microtrauma of the subclavian vein is caused by external compression at the costoclavicular junction during repetitive motion of the arm which leads to activation of the coagulation cascade and subsequent UEDVT.^[16] Because of this association with repetitive movement the condition is also known as effort thrombosis. Not surprisingly the right arm or dominant arm is effected more often.

Patients with Paget-Schroetter syndrome experience thrombosis related complaints and typically present with sudden onset of an aching discomfort with a feeling of heaviness, swelling, and frequently a reddish-blue discoloration of the affected upper extremity.^[16] A prominent venous pattern consisting of dilated superficial collateral veins over the upper arm, base of the neck, and anterior chest wall develops in many patients (figure 6).

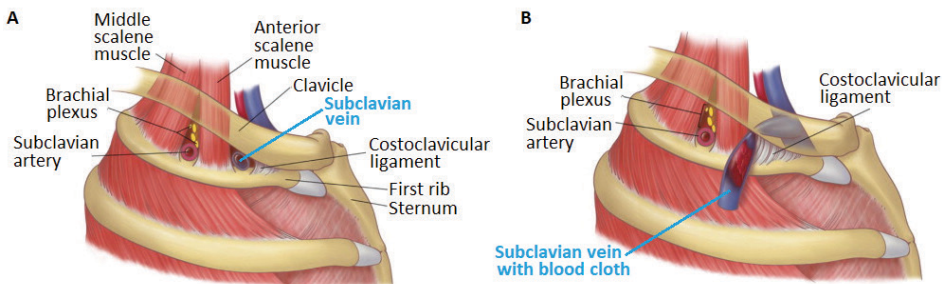


Figure 5. Anatomy at the costoclavicular junction (A). Schematic illustration of a patient with Paget-Schroetter Syndrome (B)

Source: modified from: Urschel et al. ^[18]

Management of Paget-Schroetter Syndrome:

In line with the management of lower extremity deep vein thrombosis (LEDVT), non-operative management of PSS constitutes of oral anticoagulation. Similar to the long-term morbidity of LEDVT are post thrombotic complaints frequently reported after non-operative management.^[19-21] In the effort to reduce these symptoms, catheter directed thrombolysis (CDT) was introduced as adjunct in non-operative management. The aim of CDT is to actively dissolve the blood clot by continuously administering specific lytic drugs into or near the blood clot (figure 7). Several report confirmed the benefit of CDT in lower extremity deep venous thrombosis albeit with an increased risk of bleeding complications.^[22,23]



Figure 6. Venous distension of the left chest in a patient with acute Paget-Schroetter Syndrome
Source: private collection

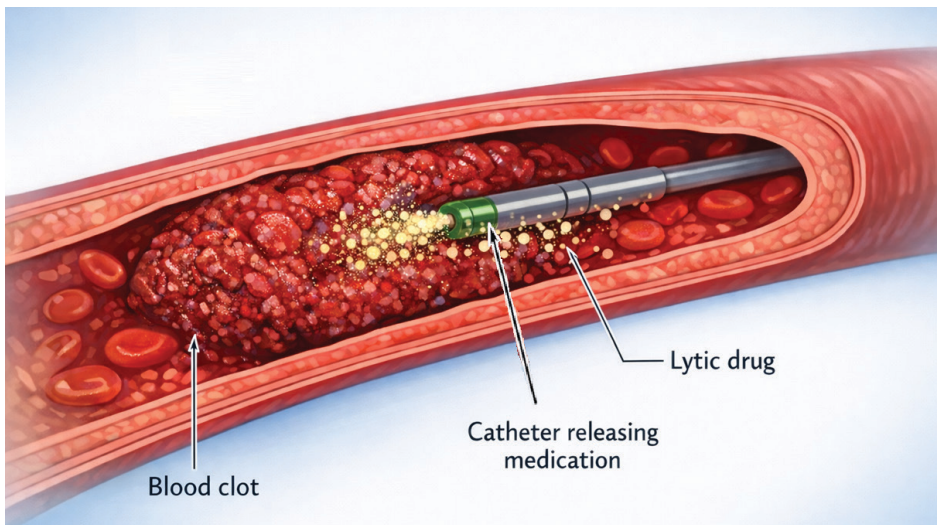


Figure 7. schematic illustration of catheter directed thrombolysis (CDT)
Source: OpenAI, ChatGPT

Because of the compression at the costoclavicular junction being the cause of PSS, surgical management is aimed at decompression of the subclavian vein and thereby eliminating the pathophysiologic cause of the thrombosis. Several surgical procedures are described in literature and all encompass the resection of one of the structures confining the subclavian vein at the thoracic outlet: clavicle, scalene muscle or first rib. First rib resection (FRR) is the preferred surgical procedure for decompression of the thoracic outlet. The aim of this procedure is to remove the most anteromedial part of the osseous part of the first rib. This part of the rib contains the groove sulcus) in which the subclavian vein crosses the first rib and the scalene muscle is attached to the first rib (figure 8).

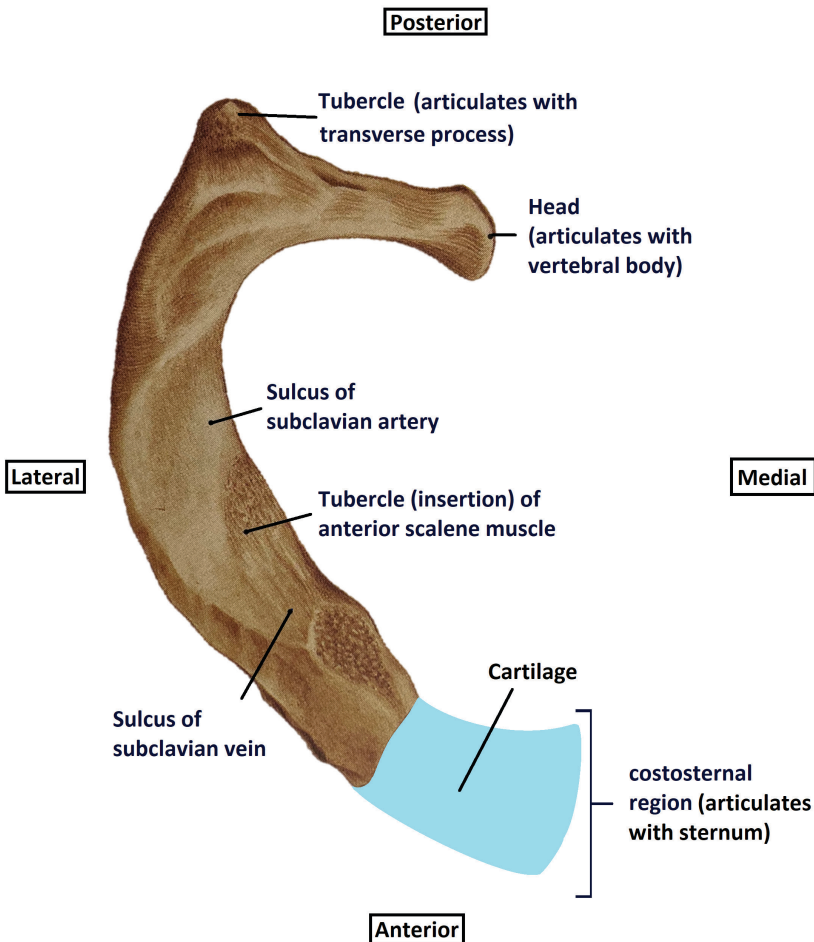


Figure 8. Anatomy of the first rib (right)

Up to this date there is no consensus on the preferred management of Paget-Schroetter syndrome because randomized trials are not available.^[18] The aim of PART II of this thesis was to create more insight in results of non-operative and surgical management of UEDVT and Paget-Schroetter syndrome in particular. An additional chapter was dedicated to a novel Robot-Assisted Transthoracic approach for FRR.

AIM AND OUTLINE OF THE THESIS, PART II

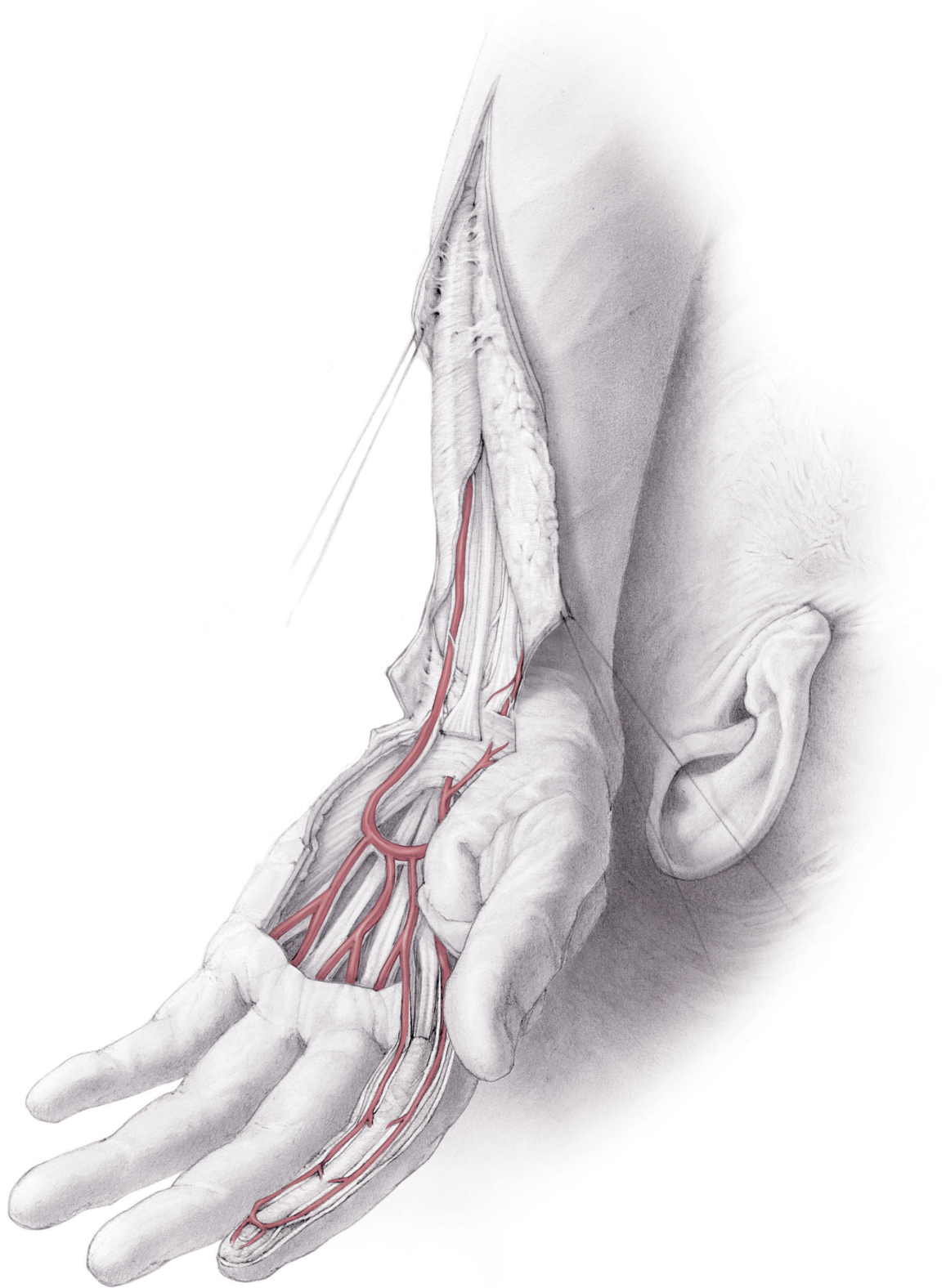
Chapter 6 is a short case report illustrating the clinical presentation of a patient with PSS.

In **chapter 7** we report the functional results of patients treated for PSS in our institution between January 1990 and December 2015. From June 2014 to July 2020 we prospectively analysed all patients undergoing FRR for the management of PSS, the results are presented in **chapter 8**. We reviewed the available literature for the functional outcomes of PSS with special attention to the different management strategies and present our findings in **chapter 9**. In **Chapter 10** provides insight on the outcomes of a new robot-assisted transthoracic approach for first rib resection.

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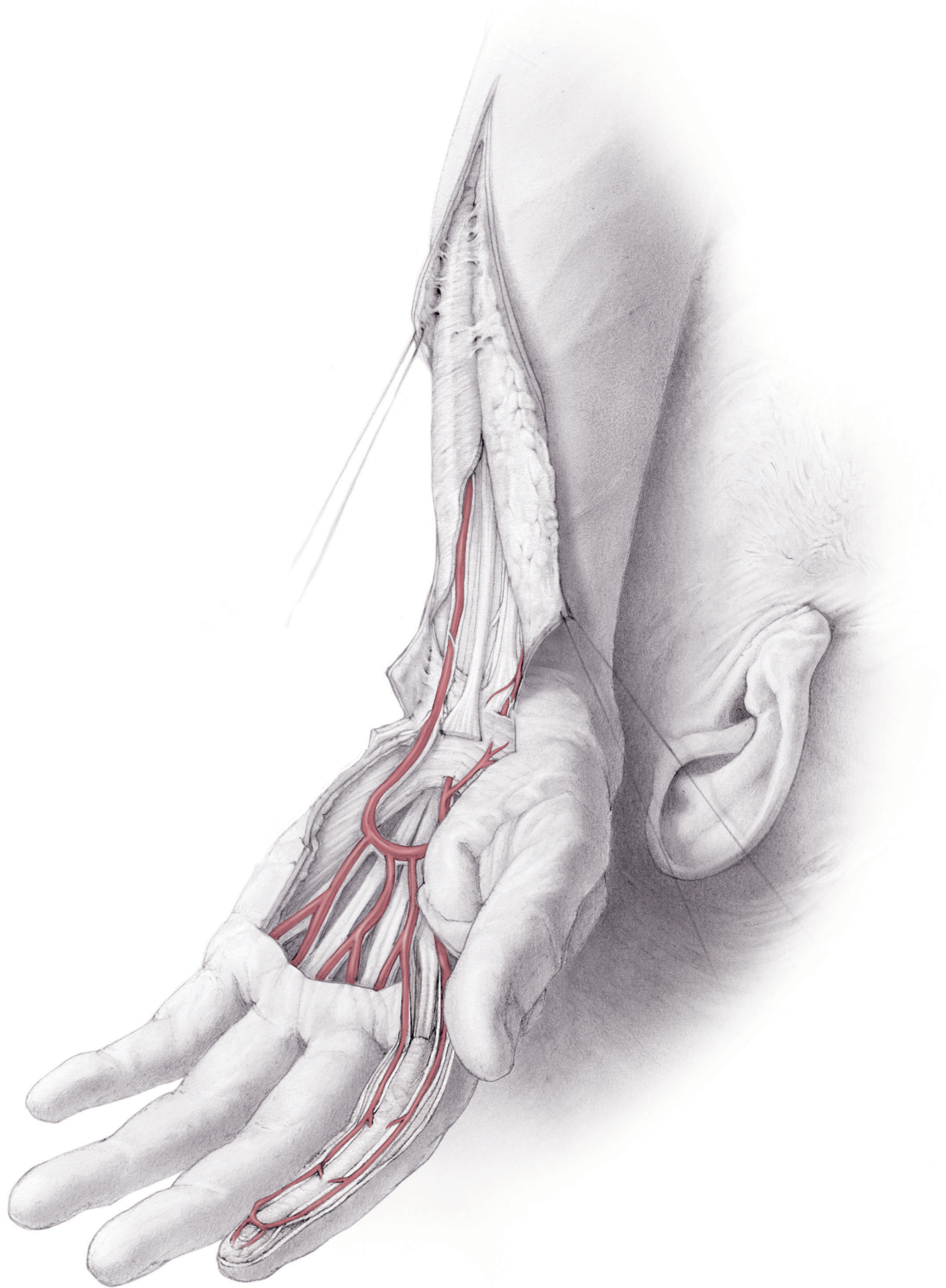
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PART I

Thoracic sympathectomy in the management of upper extremity peripheral artery disease



CHAPTER 2

Thoracic sympathectomy for digital ischemia: A summary of evidence

HME. Coveliers

F. Hoexum

JH. Nederhoed

W. Wisselink

JA. Rauwerda

ABSTRACT

Background: Thoracic sympathectomy is used in the management of a variety of upper limb disorders. We have analyzed the evidence for thoracic sympathectomy in the management of digital ischemia.

Methods: We reviewed the English literature between 1980 and 2010. Our analysis included reports with the clinical end points of relief, recurrence of symptoms or healing of ulcers, or both. Primary Raynaud disease (PRD) and secondary Raynaud phenomenon (SRP) were analyzed separately.

Results: An initial postoperative positive effect was reported in 92% of PRD patients and in 89% of SRP patients. Long-term beneficial effect was 58% for PRD and 89% for SRP. Ulcer healing or improvement was achieved in 95%.

Conclusions: The available evidence suggests that thoracic sympathectomy has a role in the treatment of severe PRD and SRP, albeit with better results in SRP patients than in PRD patients. In case of digital ulceration, thoracic sympathectomy may maximize tissue preservation or prevent amputation.

INTRODUCTION

Reports of the long-term effects of thoracic sympathectomy (TS) or endoscopic thoracic sympathectomy (ETS), or both, in the management of upper limb ischemia are inconsistent, resulting in the lack of consensus and evidence-based recommendations regarding this surgical intervention.¹⁻³ This article provides an overview of the available evidence in the international literature.

METHODS

We systematically reviewed the English literature between 1980 and 2010 using a Medline and Embase search. Keywords used were digital, finger, upper limb, hand, ischemia, vascular occlusive disease, Raynaud, ulcer, emboli, Buerger, and sympathectomy. We also examined the Cochrane database and reference lists of relevant studies. Studies lacking clinical end points of relief, or recurrence of symptoms or healing of ulcers, or both, were excluded. Systematic reviews, small case series (n 5), and letters to the editors were also excluded. Owing to potential differences in outcomes between the underlying disorders, we divided the patients into two groups—primary Raynaud disease (PRD) and secondary Raynaud phenomenon (SRP)—and analyzed them separately.

RESULTS

We included 13 retrospective and 5 prospective studies.⁴⁻²¹ There were no randomized controlled trials. One study was randomized but lacked a control group.¹¹ One article provided data on ulcer healing only.¹⁴ A total of 728 procedures were performed on 580 patients with upper limb ischemia. Short-term follow-up data for relief or recurrence of symptoms were available for 469 procedures and long-term follow-up data for 399 procedures. Outcomes of 123 patients with ulcerations could be analyzed.

Primary Raynaud's Disease:

Nine studies reported outcomes of ETS and TS for PRD. A total of 155 procedures were performed in 114 patients. Postoperative data were available for 151, and long-term results were available for 111 procedures. Initial improvement after ETS was reported in 92% and long-term benefits in 58%. ETS was unsuccessful in alleviating symptoms in 42% of procedures (Table I).

Secondary Raynaud's phenomenon.

Outcomes of TS and ETS for SRP were reported in 17 articles, comprising 511 procedures in 449 patients. Postoperative data were available for 318, long-term results for 288 procedures. Initial improvement after TS and ETS was experienced by 89% of patients. Although the number of patients with an excellent effect decreased, there was a sustained improvement in 89% of procedures at the end of follow-up (Table II).

Table I. Clinical outcome of thoracic sympathectomy (TS) for primary Raynaud disease

Study, ^{reference} year	P (Pts)	Type	Mean FU (range)	Short-term FU (18 m)				Long-term FU (18 months)					
				NA	E	B	S	W	NA	E	B	S	W
Prospective studies													
Claes, ⁷ 1994	18 (9) ^a	ETS	NA (4-48 months)	0	18	0	0	0	0	0	6	12	0
Magneas, ¹⁶ 1987	13 (10)	TS	3,9 years (1-5 years)	0	13	0	0	0	0	2	11	0	0
Retrospective studies													
Thune, ¹⁸ 2006	19 (19) ^b	ETS	40 months (7-114 months)	4	10	1	4	0	19	NA	NA	NA	NA
Matsumoto, ¹⁷ 2002	20 (20) ^b	ETS	62.5 months (NA)	0	18	1	1	0	0	5	14	1	0
Cartier, ⁵ 1999	5 (4) ^a	ETS	NA (NA)	0	5	0	0	0	1	2	0	2	0
Claes, ⁶ 1993	7 (7)	ETS	NA (24-60 months)	0	7	0	0	0	0	0	2	5	0
Adams, ⁴ 1992	12 (6)	ETS	13 months (1-20 months)	0	2	9	1	0	12	NA	NA	NA	NA
Van de Wal, ¹⁹ 1985	35 (25)	TS	8.9 years (2-16 years)	0	0	31	4	0	4	0	18	12	1
Welch, ²⁰ 1984	26 (14) ^a	TS	NA (up to 17 years)	0	0	26	0	0	8	0	4	14	0
Totals, No. (%)	155 (114)			4	73/151 (49%)	68/151 (43%)	10/151 (8%)	0 (0%)	44 (8%)	9/111 (8%)	55/111 (50%)	46/111 (41%)	1/111 (1%)

Table legend: B, Better; E, excellent or symptom free; ETS, endoscopic thoracic sympathectomy; FU, follow-up; NA, not available; P = procedures; Pts = patients; S, same; W, worse.

^aOutcomes given in number of patients, if possible converted to number of procedures.

^bTotal number of procedures available, not specified for primary and secondary Raynaud separately; therefore, assumed as unilateral.

Table II. Clinical outcome of patients with secondary Raynaud phenomenon

Study, ^{reference} year	Procedures (Pts)	Type	Mean FU (range)	Short-term FU (< 18 months)				Long-term FU (> 18 months)					
				NA	E	B	S	W	NA	E	B	S	W
Prospective studies													
El-Samadoni, ¹⁰ 2010	11 (11)	ETS	4.7 days (3-8 days)	0	6	4	1	0	11	NA	NA	NA	NA
Gabrhelik, ¹¹ 2009	50 (50) ^a	PTS	At 7 days and 90 days	0	40	3	7	0	50	NA	NA	NA	NA
Khan, ¹³ 2008	17 (17) ^a	TS	NA (up to 48 months)	0	16	0	1	0	1	11	4	1	0
Claes, ⁷ 1994	10 (5) ^b	ETS	NA (4-48 months)	0	10	0	0	0	0	10	0	0	0
Magneas, ¹⁶ 1987	24 (24)	TS	3.9 years (1-5 years)	0	22	1	0	1	0	20	4	0	0
Retrospective studies													
Thune, ¹⁸ 2006	15 (15) ^c	ETS)	40 months (7-114 months	0	8	6	1	0	15	NA	NA	NA	NA
Matsumoto, ¹⁷ 2002	8 (8) ^c	ETS	62.5 months (NA)	0	7	0	1	0	0	0	6	1	1
De-Giacomo, ⁸ 2002	20 (15) ^b	ETS	33 months (3-71 months)	0	0	20	0	0	5	6	6	3	0
Cartier, ⁵ 1999	6 (6)	ETS	NA (NA)	0	6	0	0	0	0	4	0	2	0
Claes, ⁶ 1993	5 (5)	ETS	NA (24-60 months)	0	5	0	0	0	0	4	0	1	0
Adams, ⁴ 1992	2 (2)	ETS	At 18 months and 25 months	0	1	1	0	0	0	1	1	0	0
Van de Wal, ¹⁹ 1985	36 (31)	TS	8.4 years (1-14 years)	0	0	33	3	0	10	0	20	4	2
Dunant, ⁹ 1985	42 (36) ^b	TS	NA (8-12 months)	42	NA	NA	NA	NA	6	28	8	0	0
Welch, ²⁰ 1984	18 (14)	TS	NA (up to 17 years)	1	8	4	5	0	6	3	5	4	0
Gahhos, ¹² 1984	8 (8) ^a	TS	NA (up to 120 months)	0	5	3	0	0	0	1	0	7	0
Linder, ¹⁵ 1983	150 (129)	TS	NA (12-180 months)	150	NA	NA	NA	NA	30	0	113	5	2
Welling, ²¹ 1981	89 (73)	TS	NA (NA)	0	0	74	15	0	89	NA	NA	NA	NA
Totals, No. (%)	511 (449)			193	134/318 (42%)	149/318 (47%)	34/318 (11%)	1/318 (0%)	223 (31%)	88/288 (31%)	167/288 (58%)	28/288 (10%)	5/288 (2%)

Table legend: B, Better; E, excellent or symptom free; ETS, endoscopic thoracic sympathectomy; FU, follow-up; NA, not available; PTS, percutaneous radiofrequency thoracic sympathectomy; S, same; TS, thoracic sympathectomy; W, worse.

^aNumber of procedures not available, presumed as unilateral in all patients.

^bOutcomes given in number of patients, converted if possible to number of procedures

^cTotal number of procedures available, not specified for primary Raynaud and secondary Raynaud separately, therefore assumed as unilateral

Ulcer healing.

Data on ulcer healing were provided in 12 studies comprising 123 patients. All studies reported an overall positive effect. Ulcer healing was achieved in 81%, improvement in 14%, and sympathectomy had no effect in 2% (Table III). Even when the ulcerations did not completely heal, there was good demarcation of the necrotic areas that allowed maximal preservation of viable tissue.^{8,14}

Table III. Ulcer healing

Study, ^{reference} year	Procedures (Patients)	Type	Mean FU (range)	No. of patients with				
				U	H	I	NE	ND
Prospective studies								
Gabrhelik, ¹¹ 2009	50 (50) ^a	PTS	At 7 and 90 days	3	3	0	0	0
Khan, ¹³ 2008	17 (17) ^a	TS	NA (up to 48 months)	11	10	0	1	0
Claes, ⁷ 1994	28 (14)	ETS	NA (4-48 months)	5	5	0	0	0
Magneas, ¹⁶ 1987	37 (34)	TS	3.9 years (1-5 years)	11	11	0	0	0
Retrospective studies								
Thune, ¹⁸ 2006	52 (34)	ETS	40 months (7-114 months)	8	8	0	0	0
Lee, ¹⁴ 2006	18 (17)	ETS	NA (6-72 months)	12	4	7	1	0
Matsumoto, ¹⁷ 2002	54 (28)	ETS	62.5 months (NA)	7	7	0	0	0
De-Giacomo, ⁸ 2002	20 (15)	ETS	33 months (3-71 months)	11	5	6	0	0
Cartier, ⁵ 1999	11 (10)	ETS	NA (NA)	6	0	4	0	2
Claes, ⁶ 1993	12 (12)	ETS	NA (24-60 months)	5	5	0	0	0
Dunant, ⁹ 1985	42 (36)	TS	NA (8-12 months)	36	36	0	0	0
Welch, ²⁰ 1984	44 (28)	TS	NA (up to 17 years)	8	6	0	0	2
Totals, No. (%)	385 (295)			123	100 (81%)	17 (14%)	2 (2%)	4 (3%)

Table legend: ETS, Endoscopic thoracic sympathectomy; FU, follow-up; H = healing; I = improved; NA, not available; ND = no data; NE = no effect; PTS, percutaneous radiofrequency thoracic sympathectomy; TS, thoracic sympathectomy; U= ulceration;

^a Number of procedures not available, presumed as unilateral in all patients.

Complications and side effects.

Table IV reports the total incidence of adverse effects of surgical sympathectomy of the 18 included studies. Two studies did not show any adverse effects,^{7,14} Others reported that almost all patients experienced side effects.^{17,21} Although side effects frequently occurred, most patients found them only a minor nuisance and did not regret the operation^{4,6}

Table IV. Complications and adverse effects

Complication / adverse effect	TS (n 430)	ETS (n 713)	PTS (n 50)
Thorax: conservative ^a	42	16	0
Thorax: intervention ^b	26	8	1
Neurologic: transient ^c	48 ^d	12	0
Neurologic: permanent ^e	59 ^d	4	0
Compensatory sweating	NA ^f	307	0
Wound healing disorders ^g	45	0	0
Rib fracture	2	0	0
Atrial fibrillation	0	1	0
Dry hands	0	17	0
Stuffy nose	7	0	0

ETS, Endoscopic thoracic sympathectomy; PTS, percutaneous radiofrequency thoracic sympathectomy; TS, thoracic sympathectomy.

^a Pneumothorax, pleural effusion, pneumonia, atelectasis; treatment: conservative and medication.

^b Pneumothorax, hemothorax, pleural effusion; treatment: thoracocentesis, drainage, or rethoracotomy.

^c Horner syndrome, neuralgia, diaphragm/phrenic nerve paresis, eyelid droop, vocal cord paralysis.

^d Linder¹⁵ reported Horner syndrome in almost all patients; however, no number of patients available.

^e Horner syndrome, phrenic nerve paresis/paralysis, neuralgia, scapula alata, eyelid droop, vocal cord paralysis.

^f NA, not available: studies report compensatory sweating without giving an objective number or percentage.

^g Wound infection or wound healing disorders not otherwise specified.

DISCUSSION

Maurice Raynaud published his thesis “Local asphyxia and symmetrical gangrene of the extremities” in 1862. He described a condition triggered by cold or emotional stress characterized by a typical tricolor phenomenon consisting of a pale, cyanotic, and hyperemic phase.²² Thomas Lewis further divided this phenomenon in PRD and SRP.²³ PRD is idiopathic, and SRP is related to an underlying disease. We found a widely diverse array of terms to define the disorders that cause ischemia of the upper extremity. We advocate the use of the Lewis classification to improve uniformity.

We found five prospective studies. One study was randomized, but did not have a control group.¹¹ The remaining studies were retrospective. There is a need for randomized controlled trials to provide more solid, evidence-based recommendations. Three studies mentioned the number of patients included but did not indicate the total number of procedures, and we assumed all procedures were unilateral.¹¹⁻¹³ Five articles described the outcomes for the total of patients, rather than procedures. If conversion to the total of procedures was impossible, we assumed that they were all

unilateral. In 9 of 18 reviewed studies, a thoracoscopic approach was performed; in 8 studies the sympathetic chain was removed through an open technique, and in 1 study percutaneous radiofrequency sympathectomy was performed. The extent of sympathectomy differed substantially among the reviewed articles, ranging cranially from the gray rami of C6 to caudally T5.^{5,16} Nevertheless, most authors performed a sympathectomy at the level of T2 to T4. Several studies pointed out that the second and third thoracic ganglia are responsible for the sympathetic innervation of the hand and that an extension of the sympathectomy beyond these ganglia provided no additional benefit in obtaining the desired reduction of the sympathetic tone of the hand.^{24,25} Three series reported sympathectomy in addition to other interventions. Dunant⁹ performed a first rib resection and thereafter a TS. Magneas¹⁶ combined a similar surgical intervention, a neurovascular decompression, with TS. El Samadoni et al¹⁰ designed a five-stage intervention protocol for intra-arterial recreational drug injection users, who were included in the study. Follow-up ranged from 3 days to 17 years. Eight articles did not provide the mean follow-up, and one study did not mention the range of follow-up. Data collection with objective measurements was obtained in nine reports. Six series used Doppler technology, thermographic equipment, standardized questionnaires, or visual analog scales. In three articles, frequency of oral analgesics intake or frequency of vasospastic attacks were assessed. The other studies did not describe the method of postoperative data collection. In two series, when the patients' palms were noted to be warm and dry postoperatively, this was taken as sufficient evidence to claim a satisfactory clinical response to sympathectomy. Obviously, these subjective end points constitute a major risk for interpretive bias.

Another major point of discussion is the conflicting presentation of adverse effects. Claes⁷ and Lee et al¹⁴ reported no postoperative adverse effects, whereas compensatory sweating was reported in up to 86% of cases by Matsumoto et al,¹⁷ and almost all patients acquired Horner syndrome in Welch's publication.²⁰ We can only assume that adverse effects were not a main focus in some reports and therefore were underreported. This is supported by a recent literature review reporting compensatory sweating in 45% to 98.6% of cases and Horner syndrome in 0% to 6.9%.²⁶ Most authors described the total number of adverse effects without distinguishing between the indication for surgical sympathectomy. Our outcomes concerning the adverse effects are therefore the combined data of all included patients and procedures of the 18 studies.

The long-term effect of TS and ETS in the management of PRD is heavily debated. All of the reviewed articles reported a decrease in effect over time, with a recurrence of symptoms in almost all patients. Recurrence of symptoms typically begins at 6 months after sympathectomy. The cause of this loss of effect is debated: incomplete surgical sympathectomy, reinnervation of the sympathetic pathways, or hypersensitivity of the noradrenergic receptors regulating the precapillary sphincters reacting on very small amounts of circulating catecholamines have all been implicated as factors precipitating recurrence of symptoms.^{2,17}

We found an excellent long-term effect in 8% of patients with PRD, and another 50% of the operated-on patients claimed a beneficial effect of sympathectomy. Although the positive effects were marginal, none of the patients regretted the surgical intervention.^{4,7} The long-term effect of TS is better in patients operated-on for SRP, with 31% having excellent results and 58% having a beneficial effect. This difference with PRD could be explained by the more objective end points for patients with SRP (tissue loss and ulcers) vs the more subjective end points of pain and the tricolor phenomenon in most patients with PRD, because complete healing or significant improvement was achieved in 95% of the patients treated for digital ulceration. In line with this hypothesis, Maga et al²⁷ and Leesman et al²⁸ reported a discrepancy between patient symptoms and objectively measured variables regarding PRD. Another explanation is that sympathectomy for SRP is frequently performed after tissue loss due to embolization or thrombosis of digital arteries, whereby temporary (6 months) vasodilatation of the skin arterioles apparently enhanced the tissue oxygenation enough for wound healing. After healing, less oxygenation is required, and an increase in sympathetic tone has no clinical consequences on the healed wound.

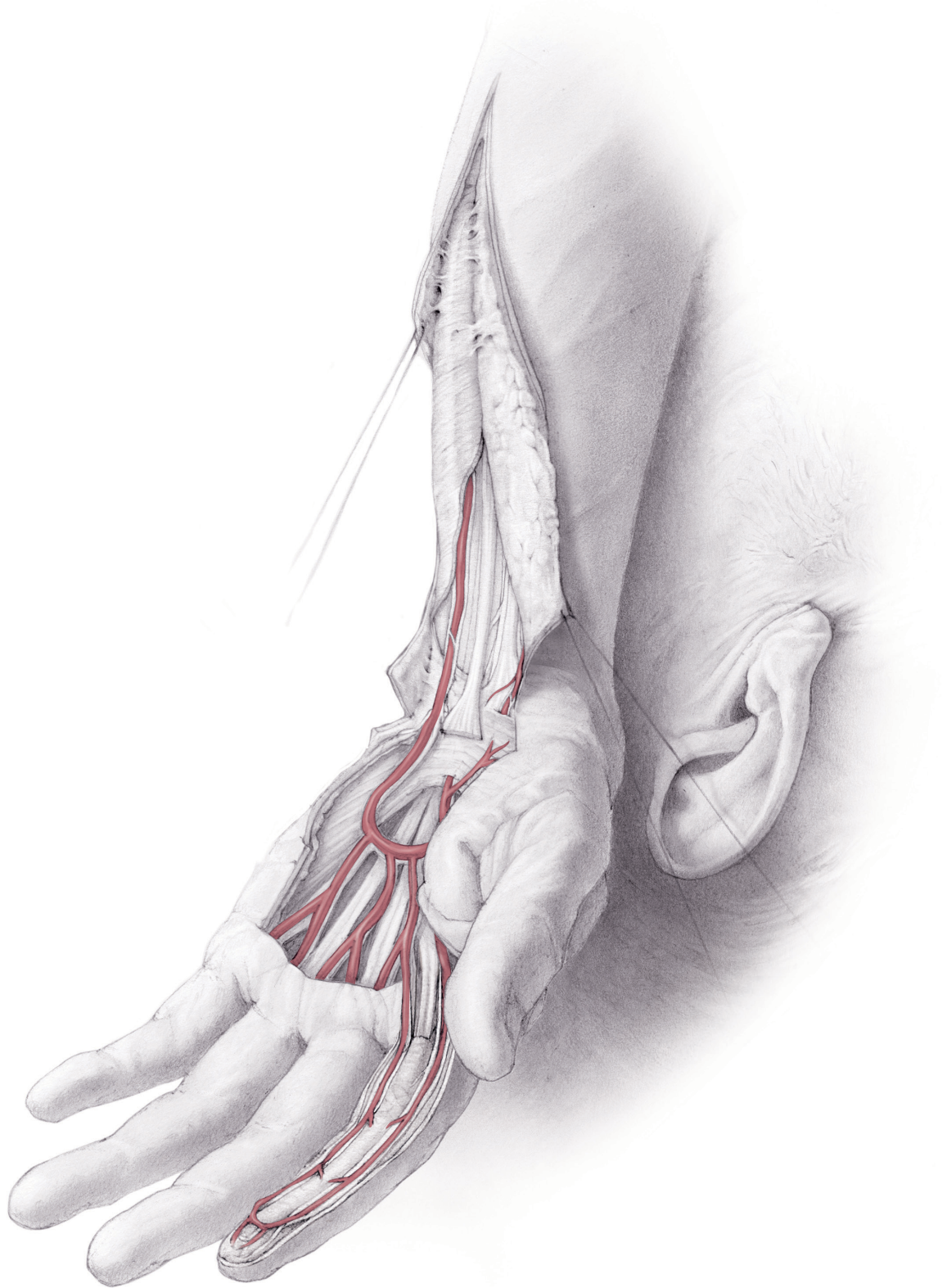
CONCLUSIONS

Despite the many shortcomings in study design, lack of uniformity in terminology and surgical procedures, and absence of hard endpoints, there seem to be benefits of TS in the setting of upper extremity ischemia. In particular, in the management of digital skin ulceration, maximizing tissue preservation, or prevention of amputation was frequently reported. TS appears to have solid long-term results in the treatment of SRP, contrary to PRD, where the benefit in most patients was limited to the first 6 months postoperatively. Nevertheless, due to the minimal invasiveness and low reported incidence of major complications or adverse effects, TS remains a therapeutic option in the treatment of severe PRD and SRP.

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CHAPTER 3

Thoracic sympathectomy for upper extremity ischemia

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ABSTRACT

Introduction: Thoracic sympathectomy is performed in the management of a variety of disorders of the upper extremity. To evaluate the contemporary results of thoracic sympathectomy for upper extremity ischemia a review of the literature was conducted.

Evidence aquisition: We performed a Pubmed, Embase, and Cochrane search of literature written in the English language from January 1975 to December 2015. All articles presenting original patient data regarding the effect of treatment on symptoms or on the healing of ulcers were eligible for inclusion. Individual analyses for Primary Raynaud`s Disease (PRD) and Secondary Raynaud`s Phenomenon (SRP) were performed.

Evidence synthesis: We included 6 prospective and 23 retrospective series with a total of 753 patients and 1026 affected limbs. Early beneficial effects of thoracic sympathectomy were noticed in 63-100%(median 94%) of all patients, in 73-100% (median 98%) of PRD patients and in 63-100% (median 94%) of SRP patients. The beneficial effect was noted to lessen over time. Long-term beneficial effects were reported in 13-100% (median 75%) of all patients, in 22-100% (median 58%) of PRD patients, and in 13-100% (median 79%) of SRD patients. Complete or improved ulcer healing was achieved in 33-100% and 25-67% respectively, of all patients

Conclusions: Thoracic sympathectomy can be beneficial in the treatment of upper extremity ischemia in select patients. Although the effect in patients with PRD will lessen over time, it may still reduce the severity of symptoms. In SRD, effects are more often long-lasting. In addition, thoracic sympathectomy may maximize tissue preservation or prevent amputation in cases of digital ulceration.

INTRODUCTION

Although thoracic sympathectomy is currently an important treatment for palmar and axillary hyperhidrosis, it was historically used in the management of ischemic disorders and causalgia of the upper limb.^[1,2] In 1862, Maurice Raynaud published his thesis, "Local asphyxia and symmetrical gangrene of the extremities," in which he described a condition triggered by cold or emotional stress characterized by a typical tricolor phenomenon consisting of a pale, cyanotic, and hyperemic phase.^[3] Thomas Lewis further divided this phenomenon in Primary Raynaud's Disease (PRD) and Secondary Raynaud's Phenomenon (SRP). PRD is idiopathic whereas SRP is related to an underlying disease (e.g. scleroderma; Buerger's disease or CREST syndrome).^[4] Besides systemic conditions, SRP can be a result of thromboembolic complications resulting from aneurysms of the proximal arteries or trauma. A previous review from our study group showed that thoracic sympathectomy has a positive effect in the vast majority of SRP and PRD patients. Unfortunately, this effect cannot be maintained on longer term for many PRD patients.^[5] Since the previous review was performed more than 5 years ago we wanted to update and expand our review. Here, we present an updated review of the available evidence concerning the efficacy of thoracic sympathectomy in the management of upper extremity ischemic disorders.

METHODS

We performed a systematic search of literature written in English in the online Pubmed, Embase, and Cochrane libraries. To find more studies we expanded the time-span of the search we performed previously.⁵ All articles published from January 1975 to December 2015 presenting original patient data on thoracic sympathectomy in the management of upper limb ischemia were eligible for inclusion. Keywords used were: ischemia, ulcer, Raynaud's, emboli, vascular occlusive disease, finger, digital, hand, upper limb, upper extremity, and sympathectomy. Exclusion criteria were any reports on periarterial and peripheral sympathectomy of the upper limb, case reports or small case series (<5 patients), data regarding re-sympathectomy, letters to the editor without clearly defined outcomes, and published abstracts for scientific congresses. Reference lists of included articles were hand-searched for any missing studies. Relevant studies were selected for full text review based on title and abstract. Data were extracted from the studies using a standardized form. Primary outcomes were short-term and long-term beneficial effect and ulcer healing. Beneficial effect was defined as any improvement of symptoms. Short-term was defined as within 30 days. Long term was defined as 6 months or longer. If possible outcomes for PRD and SRP were analyzed separately. Outcome for combined PRD and SRP was also investigated.

RESULTS

Literature search

Our primary search revealed 569 articles. After excluding duplicate entries, studies on peripheral, lumbar or periarterial sympathectomy, 251 papers were further screened. Based on title and abstract, 163 articles were further excluded. Eighty-eight full-text articles were evaluated and 24 could be included. Hand-searching the reference lists of all included articles revealed 5 additional articles (figure 1).

Compared to our 2011 review, seventeen of the eighteen studies were also included in this review.^[7-9, 12-16, 21, 23-29, 31] One study was excluded because of suspected overlapping patient data.^[35] Twelve additional articles were included in our current review. Expanding our review by 10 years resulted in the inclusion of 4 articles.^[6, 32-34] Combined analysis of both PRD and SRP allowed us to include articles that did not provide separate outcomes for patients with PRD and SRP (n=3)^[19, 20, 22] and those that did not provide the underlying pathology causing upper limb ischemia for all patients (n=2).^[10, 17] Our hand-search of the studies included in the 2011 review revealed two additional articles.^[30, 32] Maga et al.^[11] reported outcomes for all included patients as a group and was excluded in 2011.

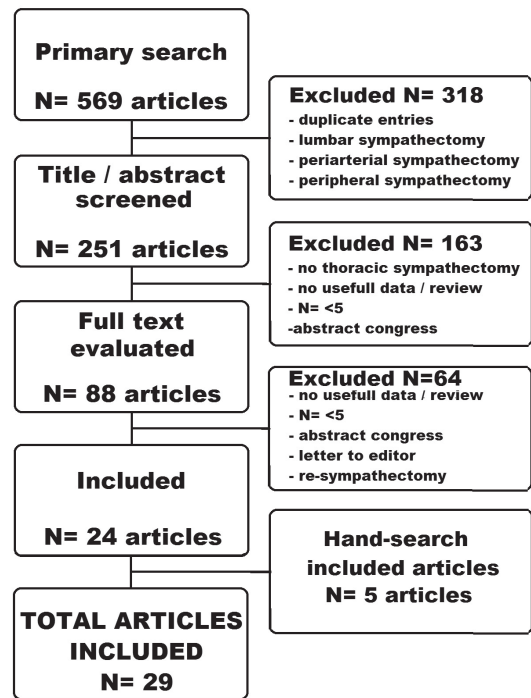


Figure 1. Flow chart literature search

Characteristics of included studies

Prospective randomized controlled trials were not available in the recent English literature. Of all included articles, only one randomized trial was conducted on 50 patients who underwent either percutaneous chemical ablation (n=25) or radiofrequency ablation (n=25) of the thoracic chain without a conservative control group.^[8] Six prospective studies could be found, 23 were retrospective cohort series.
[6,10,12-17, 19-23,25-34]

Indication for intervention

In most studies patients were treated for severe PRD or SRP in which conservative treatment was insufficient for alleviating complaints or ischemia resulted in ulceration or tissue necrosis. Unfortunately, detailed indications for individual patients could not be retrieved.

Technique

Although several surgical procedures were reported, we classified them into three main groups: open thoracic sympathectomy (TS, n= 12 studies / 588 patients)^[9,22,24-29,31-34], endoscopic thoracic sympathectomy (ETS, n= 14 studies / 382 patients)^[6,7,10-16,19-21,23,30], and percutaneous thoracic sympathectomy (PTS, n= 1 study / 50 patients).^[8] Two authors used both ETS and TS.^[17,18] In regards to the surgical procedure of open thoracic sympathectomy, six authors used a transaxillary transthoracic technique.^[17,22,25,29,32-34] Sympathectomy was performed using a supraclavicular procedure in 3 studies.^[9,24,28] An open transthoracic approach was used in 2 articles.^[25,31] Transaxillary extrapleural^[26] or transcervical^[31] procedures were performed in one study each. Two authors did not mention the technique used.^[18,27] Some authors mentioned that they performed an extrapleural procedure in cases with extensive pleural adhesions which led to inadequate visualization.^[17,22] Although the extent of sympathectomy of the included articles ranged from C6 to T5^[16,24], the majority of authors performed T2-T4 sympathectomy.

Clinical endpoints

Nine authors did not mention how long-term follow-up and outcomes were obtained or only vaguely described endpoints (e.g. "all hands were warm and dry").^[10,18,22,23, 26,29,30,33,34] Four studies described more than one modality or measurement method to obtain clinical endpoints.^[7,8,11,14] Objective measurements of outcomes were described in 4 articles and consisted of Doppler ultrasound, laser Doppler flowmetry, infrared thermography and rise of skin temperature.^[8,11,14,31] Visual Analogue Scale (VAS), tissue

ischemia scores or individually-developed scoring systems were used in 7 studies.^[7-9,11,14,17,24] Telephone interviews or mailed questionnaires were the method of follow-up in 11 articles.^[6,8, 15,16, 19-21,23,26,28,32] The use of analgesics was analyzed in 3 studies.^[7,13,14]

Data analysis

Because of the heterogeneity of the included patients, the difference in surgical procedures and the discrepancies in the analysis of therapeutic effect of (E)TS/PTS and clinical endpoint, pooling of data was deemed inappropriate. All outcomes, except ulcer healing, are therefore presented as percentages.

Outcomes; baseline characteristics (table 1)

In total 1026 procedures were performed in 753 patients in the management of upper extremity ischemia (table 1). Gender distribution was slightly in favor of males (n=250, 51.4%) compared to females (n=236, 48.6%). The age of the patients ranged from 14^[7] to 82^[11] years and the mean follow-up of the studies ranged from 4.7 days^[6] to 17 years.^[25] Seven authors presented their data in number of limbs rather than number of patients.^[17,19,20,23,25,31,32] Five articles mentioned the number of patients but did not report the number of procedures, so we assumed that the procedures were all unilateral.^[8,9,18,32,33]

Outcomes (table 2); PRD and SRP combined

Six studies described their outcomes for PRD and SRP in a combined format^[6, 19,20,22] or were analyzed as such since the underlying cause of ischemia was not available for all patients.^[10,17] Thune et al. reported their initial results separately for PRD and SRP, but published the long-term results for both groups together.^[12] Overall, initial follow-up for both PRD and SRP was available in 679 cases, long-term follow-up was available for 605 cases. Early postoperative beneficial effect of thoracic sympathectomy was reported in 63-100%(median 94%). Long-term favorable effects were reported in 13-100% (median 75%) of cases.

PRD

Early postoperative results of patients with PRD were available in 12 studies (n=158), with 9 studies providing long-term outcomes (n=122). Short-term beneficial effect was reported in 73-100% (median 98%). The effect faded over time, but in long-term follow-up there was still noted benefit in 22-100% (median 58%) of cases.

Table 1. Baseline characteristic of included articles

Author	Year	Study design	Patients (procedures)		Type	Sex		Mean age (range)	Follow up Mean (range)
			PRD	SRP		M	F		
Coveliers ^[6]	2015	Retro	6 (9)	29 (36)	ETS	15	20	49 (23-79)	98 (18-198) months
El Samadoni ^[7]	2010	Pros	-	11 (11)	ETS	10	1	30 (18-43)	4.7 (3-8) days
Gabrhelik ^[8]	2009	Pros	-	50 (50) ^a	PTS	5	45	44 (14-67)	At 7 and 90 days
Khan ^[9]	2008	Pros	-	17 (17) ^a	TS	na	na	na	na (up to 48 months)
Moini ^[10]	2008	Retro	-	16 (18)	ETS	8	8	49 (na)	na (at least 1 year)
Maga ^[11]	2007	Pros	25 (50)	-	ETS	7	18	27 (17-49)	5 years
Thune ^[12]	2006	Retro	19 (52) ^c	15	ETS	15	19	50 (23-82)	40 (7-114) months
Lee ^[13]	2006	Retro	-	17 (18)	ETS	15	2	43 (19-69)	na (6-72) months
De Giacomo ^[14]	2002	Retro	-	15 (20)	ETS	13	2	47 (21-72)	33 (3-71) months
Matsumoto ^[15]	2002	Retro	20 (54) ^c	8	ETS	7	21	46 (26-73)	62.5 (na) months
Cartier ^[16]	1999	Retro	4 (5)	6 (6)	ETS	na	na	na	na (na)
Onohara ^{[17] b}	1998	Retro	-	na (21) ^b	14 TS, 7 ETS	17 ^b	4 ^b	na	3 years
Komori ^[18]	1995	Pros	-	13 (13)	7 TS, 6 ETS	12	1	na (28-60)	na (na)
Nicholson ^{[19] b}	1994	Retro	-	na (33) ^b 4(4)	ETS	na	na	na	18 months
Sayers ^{[20] b}	1994	Retro	-	15 (23)	ETS	na	na	na	44.5 (1-75) months
Claes ^[21]	1994	Retro	9 (18)	5 (10)	ETS	8	6	na	na (2-4) years
Lowell ^[22]	1993	Retro	-	14 (20)	TS	6	8	39 (21-61)	na (na)
Adams ^{[23] b}	1992	Retro	6 (12)	2 (2)	ETS	na	na	na	13 (1-20) months
Magneas ^[24]	1987	Pros	10 (13)	24 (24)	TS	na	na	na	3.9 (1-5) years
Van de Wal ^{[25] b}	1985	Retro	25 (35)	31 (36)	TS	42	14	na (20-69)	8.9 (2-16) years
Dunant ^[26]	1985	Retro	-	36 (42)	TS	12	24	na	na (8-12) months
Gahos ^[27]	1984	Retro	-	8 (8)	TS	na	na	na	na (up to 120 months)
Welch ^[28]	1984	Retro	15 (27)	14 (18)	TS	13 ^d	15 ^d	na	na (up to 17 years)
Linder ^[29]	1983	Retro	-	129 (150)	TS	na	na	na	na (12-180) months
Malone ^[30]	1982	Retro	9 (18)	3 (6)	ETS	na	na	na	na (na)
Welling ^{[31] b}	1981	Retro	-	73 (89)	TS	45	28	47 (na)	na (na)
Berguer ^{[32] b}	1981	Retro	4 (4) ^a	6 (6) ^a	TS	na	na	na	10.5 (na) months
Dale ^[33]	1976	Retro	4 (4) ^a	21 (21) ^a	TS	na	na	na	na (na)
Man ^[34]	1976	Retro	1 (2)	14 (21)	TS	na	na	na	na (na)
TOTALS			157 (197)	567 (647)	ETS 418 TS 558 PTS 50	250	236		

Table legend: a= stated as unilateral, b= results only available in number of limbs/procedures rather than patients, c= only data on number of procedures for PRD and SRD together available, d= data of one patient missing, ETS= endoscopic thoracic sympathectomy, F= female, M= male, na= not available, PRD= Primary Raynaud's Disease, pros= prospective, PTS= percutaneous thoracic sympathectomy (chemical or radiofrequency ablation), retro=retrospective, SRP= Secondary Raynaud's Phenomenon, TS= open thoracic sympathectomy

Table 2. Outcomes

Auteur	Jaar	Patients (procedures)	Short term effect				Long term effect			
			% improved		% No effect		% improved		% No effect	
			PRD	SRP	PRD	SRP	PRD	SRP	PRD	SRP
Coveliers ^[5]	2015	6 (9)	29 (36)	63	37	16	53	47	16	16
El Samadoni ^[6]	2010	-	11 (11)	-	82	-	18	-	na	-
Gabrielik ^[7]	2009	-	50 (50) ^a	-	78	-	22	-	na	-
Khan ^[8]	2008	-	17 (17) ^a	-	94	-	6	-	88	-
Moini ^[9]	2008	-	16 (18)	-	100	-	0	-	na	-
Maga ^[10]	2007	25 (50)	-	100	-	0	-	100	-	0
Thune ^[11]	2006	19	(52) ^c	15	73	93	27	7	4	0
Lee ^[12]	2006	-	17 (18)	-	100	-	0	-	na	-
De Giacomo ^[13]	2002	-	15 (20)	-	100	-	0	-	80	-
Matsumoto ^[14]	2002	20	(54) ^c	8	95	88	5	13	0	0
Cartier ^[15]	1999	4 (5)	6 (6)	100	100	0	0	0	50	67
Onohara ^{[16] b}	1998	-	na (21)	-	100	-	0	-	67	-
Dunant ^[17]	1995	-	36 (42)	-	100	-	0	-	na	-
Nicholson ^{[18] b}	1994	na (33)	4(4)	93	7	3	50	50	3	3
Sayers ^{[19] b}	1994	15 (23)	64	36	1	46	55	1	1	1
Claes ^[20]	1994	9 (18)	5 (10)	100	100	0	0	33	100	67
Lowe ^[21]	1993	14 (20)	95	5	0	95	5	0	0	0
Adams ^{[22] b}	1992	6 (12)	2 (2)	92	100	8	0	0	90	100
Magneas ^[23]	1987	10 (13)	24 (24)	100	96	0	4	0	100	100
Van de Wal ^{[24] b}	1985	25 (35)	31 (36)	89	92	11	8	0	58	77
Gahos ^[25]	1984	-	8 (8)	-	63	-	38	-	13	-
Welch ^[26]	1984	15 (27)	14 (18)	100	86	0	14	1	0	22
									62	78
									39	6
									1	1

Table 2. Continued

Auteur	Jaar	Patients (procedures)	Short term effect				Long term effect			
			% improved		% No effect		% improved		% No effect	
			PRD	SRP	PRD	SRP	PRD	SRP	PRD	SRP
Linder ^[27]	1983	-	-	129 (150)	-	na	-	150	-	6
Malone ^[28]	1982	9 (18)	89	100	11	0	0	0	na	9
Welling ^{[29] b}	1981	-	-	73 (89)	-	83	-	17	-	na
Berguer ^{[30] b}	1981	4 (4)	75	83	25	17	0	0	na	4
Dale ^[31]	1976	4 (4)	na	21 (21)	na	na	4	21	25	0
Man ^[32]	1976	1 (2)	100	92	0	7	0	0	na	1

Table legend: a= total procedures not available; stated as unilateral, b= results only available in number of limbs/procedures rather than patients, c= number of patients PRD and SRP available but number of procedures combined, na= not available, PRD= Primary Raynaud's Disease, SRP= Secondary Raynaud's Phenomenon

SRP

Twenty-one studies mentioned short-term therapeutic results of SRP (n=430), 13 authors reported on the long-term results (n=326). An initial favorable effect of thoracic sympathectomy was noticed in 63-100% (median 94%). Even though there was a decline in effect, 13-100% (median 79%) of patients reported long-lasting therapeutic benefit.

Ulcer healing

Data on ulcer healing was reported in 12 studies with a total of 119 cases. Beneficial effect on ulcer healing was reported in 67-100% of cases (Table 3). Even when the ulcers did not completely heal there was good demarcation of the necrosis, which allowed maximal preservation of viable tissue.^[13,14] In contrast to the above-mentioned studies, Gahos^[27] stated that sympathectomy did not prevent formation of new finger ulcers, nor did sympathectomy promote the healing of already established ulcers in his cohort of patients suffering from scleroderma. Unfortunately, no quantitative information was provided in his study.

Table 3. Ulcer healing

Author	year	Ulceration		
		% Complete healing	% Beneficial effect	% No effect
Gabrhelik ^[8]	2009	100	0	0
Khan ^[9]	2008	91	0	9
Thune ^[12]	2006	100	0	0
Lee ^[13]	2006	33	58	8
De Giacomo ^[14]	2002	45	55	0
Matsumoto ^[15]	2002	100	0	0
Cartier ^[16]	1999	0	67	33
Dunant ^[18]	1995	100	0	0
Lowell ^[23]	1993	100	0	0
Magneas ^[25]	1987	100	0	0
Welch ^[28]	1984	75	0	25
Man ^[34]	1976	75	25	0

Complications and adverse effects

Three articles did not report any complications nor side effects from the operation.^[22,27,33] In contrast, Welling reported that almost all patients developed Horner syndrome but did not mention a specific number.^[31] Table 4 summarizes the incidence of complications and adverse effects.

Open thoracic sympathectomy resulted in more complications and adverse events (n= 284, 421 patients / 525 procedures) compared to the ETS group (n= 129, 393 patients / 584 procedures). Especially permanent neurologic and conservative treated thoracic

adverse effects were significant reduced in the ETS group. Minor complications or adverse effects were observed frequently. Despite this, several authors stated that the majority of complications or adverse effects were not severe and only a minor nuisance for the patients.^[15,23,29] Nevertheless, Welch, Sayers, and Thune noted some patients regretted undergoing surgery due to the absence of any long-term benefit and/or experienced disturbing side effects such as severe neuralgia or compensatory sweating (CS).^[12,20,28] Despite the fact that CS is regarded as one of the most common side effects of thoracic sympathectomy, only 10 studies reported CS as an adverse effect.^[6,11,12,15,16,19,20,23,25,26,32] In those studies, CS was reported in 25-86% (median 52%) of patients (table 5).

Table 4. Complications and adverse effects

Complication / adverse effect	TS (n=421 pts / 525 p)	ETS (n= 393 pts / 584 p)	PTS (n=50 pts / 50 p)
Thorax conservative ^a	60	19	0
Thorax intervention ^b	25	17	1
Neurologic permanent ^c	74 ^d	10	0
Neurologic transient ^c	61 ^d	62	0
Wound healing disorder	46	0	1
Other ^e	18	61	8

Table legend: ETS= endoscopic thoracic sympathectomy; p = procedures; PTS= percutaneous thoracic sympathectomy (chemical or radiofrequency ablation), pts = patients; TS= open thoracic sympathectomy; a= pneumothorax, pneumonia, atelectasis, pleural effusion; treatment: conservative and medication b= pneumothorax, hemothorax, pleural effusion; treatment: thoracocentesis, thoracostomy tube or re-thoracotomy

c= Horner syndrome, neuralgia, diaphragm/phrenic nerve paresis, eyelid droop, vocal cord paralysis, scapula alata

d= Linder[27] reported Horner syndrome in almost all patients undergoing open thoracic sympathectomy; however, no number of patients available.

e= dry hands, atrialfibrillation, bradycardia, rhinitis/congestion, rib fracture, pain at puncture site for PTS

Table 5. Compensatory and gustatory sweating

Author	Year	Patients	C/G sweating ETS (%)	C/G sweating TS (%)
Coveliers ^[6]	2011	35	31	-
Maga ^[11]	2007	25	28	-
Thune ^[12]	2006	34	82	-
Matsumoto ^[15]	2002	28	86	-
Cartier ^[16]	1999	35	80	-
Nicholson ^[19]	1994	40	45	-
Sayers ^[20]	1994	34	71	-
Adams ^[23]	1992	26	58	-
Van De Wal ^[25]	1985	56	-	25
Berguer ^[32]	1981	20	-	30

Table legend: C/G = compensatory and/or gustatory; ETS= endoscopic thoracic sympathectomy, pts = patients; TS= open thoracic sympathectomy

DISCUSSION

While the differences of Primary Raynaud's Disease and Secondary Raynaud's Phenomenon were clearly delineated by Thomas Lewis^[4], we found a variety of names and nomenclature used by authors to categorize their patients. We advocate the use of only these two categories. Primary Raynaud's Disease is characterized by cold hypersensitivity and profound episodic digital color changes thought to occur as the result of an exaggerated vasoconstrictive response of the digital arteries to cold temperatures, blunt trauma, or emotional stress. By definition, patients with PRD do not have an underlying associated cause for vasospastic events and irreversible tissue injury does not occur from the condition.^[36] In contrast, SRP ischemia of the upper extremity is caused by an underlying disorder and the digital ischemia can cause trophic changes, ulceration, and tissue loss. A wide variety of causes were mentioned in the included articles. The underlying causes can broadly be divided as: auto-immune or systemic connective tissue disorders, thromboembolic or vascular occlusive disease and trauma including, hypothenar hammer syndrome, intra-arterial recreational drug injection, and frostbite.

The study designs and methodological quality was in some studies moderate. Because of the heterogeneity of the included patients, surgical therapy and evaluation of endpoints , pooling of data was deemed inappropriate. Several authors did not mention how long-term follow-up and outcomes were obtained or only vaguely described endpoints (e.g. "all hands were warm and dry"). Needless to say, this lack of specificity is prone to interpretive bias.

Historically, because of the potential risk of severe complications associated with open thoracic sympathectomy, less invasive procedures were developed. Endoscopic thoracic sympathectomy has been attributed by several authors to Kux who described in 1950 his procedure in the journal "Acta Neurochirurgica Wien."^[37] However Blumberg stated that Hughes published in 1943 a paper in which he described removing the stellate ganglion endoscopically in two cases, and so, he is also believed by some to be the first physician to have used ETS in patients.^[38] This does not diminish the fact that Kux was the first to implement ETS as standard therapy, as he reported in 1978 a case series of 124 ETS procedures performed on 64 patients with palmar and axillar hyperhidrosis.^[39] Two articles in our review used both TS and ETS and they confirmed that ETS has cosmetic advantages of smaller incisions, fewer complications, and fewer adverse effects.^[17,18] Still, severe complications and even deaths have been described in association with ETS.^[40,41] In recent years, even further minimally-invasive treatments are used in the

management of upper extremity ischemia. Percutaneous chemical or radiofrequency ablation were respectively introduced by Reid^[42] and Wilkinson^[43] and further reduce surgical trauma. Only one article could be included in this review who used these techniques.^[8] We have noticed that the focus of many authors shifted to peripheral or periarterial sympathectomy or the use of botulinum toxin injections to treat upper extremity ischemia. Over the period of 2011-2015, only one article presenting results of (E)TS could be included in this review.^[6]

Besides surgical technique, another major topic for discussion is the extent of sympathectomy. The extent of sympathectomy of the included articles ranged from C6 to T5.^[16,24] Lemmens and Cotton reported on the importance of the 2nd and 3rd thoracic ganglia for sympathetic innervation of the hand, thus, more extensive sympathectomy is not necessary for adequate sympathetic denervation of the hands.^[44,45] In line with this concept, the majority of authors performed T2-T4 sympathectomy.

All authors mentioned a decrease of therapeutic effect over time. Several possible explanations are postulated as to why recurrence can occur. Surgical error, re-innervation of the sympathetic pathways, or hypersensitivity of the noradrenergic receptors regulating the pre-capillary sphincters reacting on very small amounts of circulating catecholamines have all been implicated as factors precipitating recurrence of symptoms.^[6] In contrast to these subjective observations by patients, Maga showed that long-term objective measures of palmar perfusion of patients who had undergone sympathectomy because of PRD were comparable to non-patients. Nevertheless, they experienced a 2.8 point increase of complaints according to VAS.^[11] Leesmans also reported on the discrepancy between objective measures and patients' subjective complaints.^[46]

Minor complications and side effects were frequently reported after (E)TS and only three authors did not mention any complications or adverse effects.^[21,27,33] Although the majority of the reported side effects were mild and were only a minor nuisance to patients^[14,22,27], three studies reported patients who regretted the operation because of the side effects.^[12,20,28] We think that the incidence of complications and adverse effects is underreported because only 10 studies provided data on compensatory sweating.^[6,11,12,15,16,19,20,23,25,32] This is in sharp contrast to the consensus that CS is one of the most frequently occurring adverse effects of sympathectomy and is reported in 45.0-98.6% of patients.^[47] CS can result in a dramatically diminished quality of life to such an extent that many patients regret undergoing the operation.^[48]

Recent studies were aimed at reducing the incidence and severity of CS. Robot-assisted procedures have been developed with the possibility to selectively transect the efferent rami communicantes of the thoracic chain.^[48,49] It is postulated that selective transection of the efferent rami communicantes, or ramicotomy, results in less extensive trauma to the sympathetic chain and has shown to result in CS rates of less than 10%.^[48] Selective ramicotomy is more difficult to perform because of the smaller size of the efferent sympathetic nerves compared to the sympathetic chain and its ganglia. With the introduction robot-assisted VATS (video-assisted thoracic surgery) procedures, these disadvantages are minimized. The enhanced optical imaging system, combined with improved maneuverability in a relatively inaccessible working space improves visualization and makes selective ramicotomy feasible and effective.^[48]

In our opinion, the indication for sympathectomy should be reserved for severe PRD, which is unable to be managed with conservative treatment and/or medications. Patient selection and shared decision-making is important. The patient has to be informed about the decreasing therapeutic effect of thoracic sympathectomy over time and the high recurrence rate of symptoms. Recurrence of complaints can occur as soon as 6 months postoperatively. Response to the therapy with improvement of symptoms is difficult to predict beforehand. In the discussion with patients on (E)TS realistic expectations should be made.

In regards to SRP, (E)TS can be of value in the surgical management. Although in our opinion, the results in patients with ongoing autoimmune and/or systemic soft tissue disorders are discouraging, (E)TS still provide benefit by temporarily increasing blood flow to ischemic extremities and thereby optimize ulcer healing. Long-lasting effects cannot be expected in the majority of patients because of the progressive underlying disease which, eventually, will result in recurrent ischemia of the affected extremity. With special regard to the treatment of Buerger's disease, cessation of tobacco use is by far the most important intervention. Sympathectomy can only be used as an adjunct for optimizing ulcer healing and it is ineffective in the long-term if persistent tobacco-use continues.

We believe that the greatest utility of sympathectomy can be expected in patients suffering from a reversible cause of ischemia of the upper extremity, such as thromboembolic complications of trauma, intra-arterial drug injection and atherosclerotic or vascular occlusive disease. Definitive treatment of the underlying cause of ischemia (i.e. eliminating the source of emboli, restoring patency of occluded arteries by thrombectomy or catheter-directed thrombolysis and re-establishing

optimal perfusion with (endovascular) revascularization of the affected limb), combined with the vasodilatation of the microcirculation caused by thoracic sympathectomy in these patients, can result in very good success rates. Prospective trials of sufficient methodological quality are needed to provide evidence based recommendation for the future.

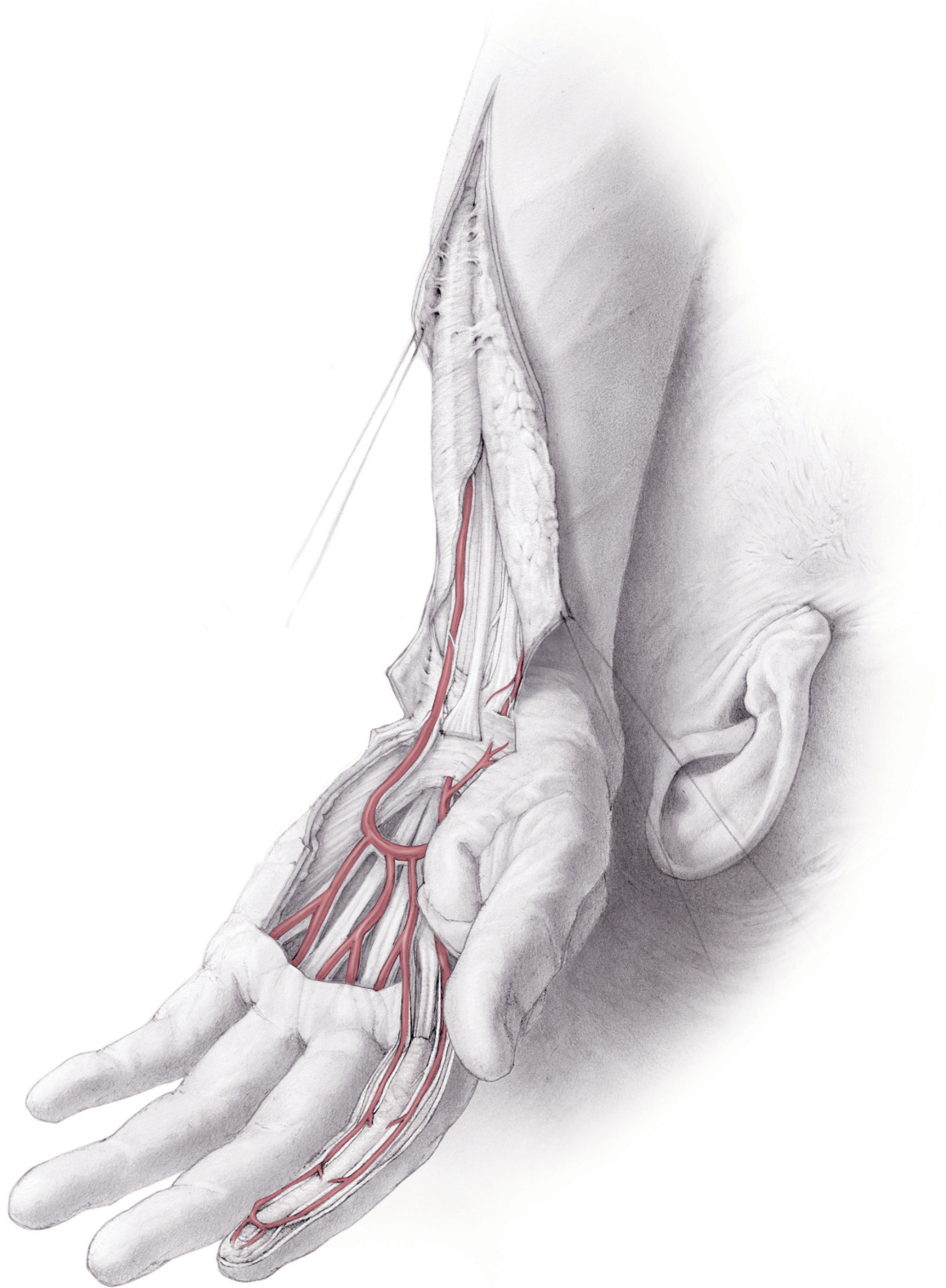
CONCLUSION

Thoracic sympathectomy in selected patients can be of benefit in Primary Raynaud's Disease as well as Secondary Raynaud's Phenomenon. Unfortunately, only cohort studies were found and no prospective randomized controlled studies have been performed, so results reported in the literature have to be interpreted with caution. While effective in short term the effect of (E)TS/PTS decreases over time in some patients, especially in case of PRD recurrence rates are high. Despite this, the severity of the recurrent symptoms may be less severe in some patients. Careful patient selection and realistic expectations are essential to optimize patient satisfaction. In SRP, the long-term effects are slightly better. SRP caused by chronic or progressive (autoimmune) disorders have a worse prognosis compared to patients with SRP caused by an underlying reversible vascular disorder such as thromboembolic, vascular occlusive, or posttraumatic ischemic disease. With the option of minimally invasive techniques (with low complication rates and only mild adverse effects), thoracic sympathectomy should be considered a valuable adjunct in the management of severe upper

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CHAPTER 4

Endoscopic Thoracic Sympathectomy for Upper Limb ischemia: A 16 year follow-up in a single center

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ABSTRACT

Introduction: The aim of our study was to evaluate the long-term results of Endoscopic Thoracic Sympathectomy (ETS) in the management of upper limb ischemia (ULI).

Methods: We retrospectively reviewed the records of all consecutive patients who underwent ETS for ULI between January 1994 and May 2009. A standardized questionnaire was used to evaluate the long term success, morbidity and overall patient satisfaction.

Results: Thirty-five patients (20 female, mean age 49 years (range 23-79)) underwent bilateral (n=9) and unilateral (n=27) ETS procedures, respectively. Six patients had Primary (idiopathic) Raynaud Disease. Twenty-nine patients had upper limb ischemia secondary to systemic disorders (n=12), embolic disease (n=10), occlusion of the arteries of the arm (n=5) or hypothenar hammer syndrome (n=2). Tissue loss at time of surgery was present in nineteen patients. Short term beneficial effects were reported by 12 patients (63%). Eleven of the 35 patients experienced a total of 13 complications or adverse events, whereof 11 were minor or transient. Limb salvage was unsuccessful in three patients because of major amputations (n= 2) or severe functional impairment (n=1). Necrotectomies or minor amputations without functional impairment were performed in 9 patients. Medium or long term follow up (mean 98 months (range 18-198) was available in 19 out of 22 living patients(86%). Long term beneficial effects were reported by 10 (53%). Overall patient satisfaction was 56%. Compensatory sweating was experienced by 11 patients (58%).

Conclusion: Although the long-term efficacy of ETS in our study was moderate (53%), due to its low invasiveness ETS is a valuable option in the management of ULI.

INTRODUCTION

Endoscopic thoracic sympathectomy (ETS) is widely used in the management of patients with hyperhidrosis.^[1-3] Vasospastic and ischemic disease of the upper limb is a less common indication for surgery on the thoracic sympathetic chain.^[4, 5] Short term results and side effects are well-known and have been reported extensively in literature. Long term follow up of the results and side-effects are rare.^[5] Compensatory sweating (CS) is the most frequently occurring side effect. It varies in level, extent and intensity and plays a major role in patient's dissatisfaction with the operation. CS seems to be unavoidable, untreatable and is often considered to be the price that patients have to pay for the treatment of their (ischemic) complaints.^[6-9] We retrospectively surveyed the long term results of patients with upper limb ischemia (ULI) who were managed by ETS in our department from January 1994 to May 2009. The aim of our study was to evaluate the long term success, overall patients' satisfaction and morbidity, in particular CS.

METHODS

Data collection

Medical charts of all patients undergoing ETS for treatment of ULI in a single center from January 1994 to May 2009 were reviewed. Collected data included patient's age and gender, indication for surgery, whether the procedures were unilateral or bilateral, operation time, length of hospital stay, peri-operative complications and side effects. All patients underwent routine office follow up at 6 weeks. To evaluate the long-term results a questionnaire was performed by telephone. To standardize patient response, the questionnaire was designed to include single words or numbers or categorical options rather than free text.^[appendix 1] We integrated the Hyperhidrosis Disease Severity Scale(HDSS) in our questionnaire. This is a validated disease specific scale that provides a qualitative measure of the effect of patient's symptoms on their daily activities.^[10,11] the effect of symptoms on daily activities is graded in order of severity from 1 to 4; (1) sweating is hardly noticeable and never interferes with daily activities; (2) sweating is tolerable and sometimes interferes with daily activities; (3) Sweating is barely tolerable and frequently interferes with daily activities; (4) sweating is intolerable and always interferes with daily activities

Operative technique

Endoscopic Thoracic Sympathectomy, both unilateral and bilateral, was preferably performed in a single stage procedure under general anesthesia. Airway and Low-volume-high-frequency mechanical ventilation was secured by endotracheal intubation

using a single or double-lumen tube. Patients were placed in a lateral, prone or supine position depending of the surgical procedure or preference of the attending surgeon. The procedure was performed through three or four thoracoscopic trocars, one of 10mm in diameter was placed in the 5th intercostals space at the midaxillary line and two 5mm trocars in the 4th intercostals space at the anterior and posterior axillary line. If necessary an additional 5mm trocar was placed. We used a 30° videothoracoscope (Olympus, Hamburg, Germany) and electrocautery. The mediastinal pleura opened and the sympathetic chain was identified. We resected by diathermy the sympathetic trunk from T2 to T4. A 16 French chest tube was inserted into the chest during closure and removed 24 hours postoperative.

RESULTS

Between January 1994 and May 2009 a total of 45 sympathectomies were performed on 35 patients in 9 bilateral and 27 unilateral procedures. All patients were referred to our department after conservative treatment was unsuccessful. Our study population consisted of 15 males and 20 females with an average age at the time of surgery of 49 years (range 23-79). Six patients had Primary (idiopathic) Raynaud Disease. Twenty-nine patients had ULI secondary to systemic disorders (N=12), embolic disease (N=10), occlusion of the arteries of the arm (N=5) or hypothenar hammer syndrome (N=2). Tissue loss at time of surgery was present in nineteen patients, none of these patients had Primary Raynaud Disease. ^[table 1] Mean procedure duration was 93 minutes (range 35-340). Conversion to open thoracic sympathectomy was needed in 4 patients, due to suboptimal visualization (n=3) and venous hemorrhage (n=1).

Table 1. Patient characteristics.

Indication	Pts	M / F	ETS	P	Limb salvage		
					Tissue Loss ^a	Major amputation	Minor amputation
Primary Raynaud disease	6	2 / 4	9	7^b	0	0	0
Secondary ischemia:	29	13 / 16	36	29	19	3	9
Systemic disorders ^c	12	4 / 8	18	12	7	1	5
Emboli, stenosis or aneurysms	10	5 / 5	11	10	8	1	3
Arterial occlusion of the arm	5	2 / 3	5	5	4	1	1
Hypothenar hammer syndrome	2	2 / 0	2	2	0	0	0
TOTAL	35	15 / 20	45	36	19	3	9

Table legend: ETS = Endoscopic Thoracic Sympathectomy, F = Female, M = Male, P = procedures, Pts = patients ^a = necrosis or ischemic ulcers at time of sympathectomy, ^b = One bilateral sympathectomy performed in two unilateral procedures, ^c = scleroderma, CREST syndrome, polyarthritis nodosa, M. Sjögren, etc

Table 2. additional surgical interventions in 35 patients

Combined surgical interventions	Number
Lost to follow up:	
ETS + amputation / necrotectomy	4
ETS + revascularisation	2
ETS + trombectomy (2x) + revascularisation (2x)	1
Follow up:	
ETS + first rib and cervical rib resection	2
ETS + first rib resection	1
ETS + skin biopsy	1
TOTAL	11

Table legend: ETS = Endoscopic Thoracic Sympathectomy

Eleven procedures were combined with additional surgical interventions. ^[Table 2] The average hospital stay was 11 days (range 2-57). Eight patients experienced postoperative neuralgia, of which four could not be managed during the admission. Four patients were seen after discharge in the outpatient clinic by an anesthesiologist because of persistent neuralgia, of those only two patients had prolonged complaints of neuralgia (>6 months). Four patients had a delayed removal of their chest tube (> 24 hours postoperative) and are therefore considered as having a prolonged pneumothorax. Although it deviated from our postoperative protocol, it had no clinical consequences. The length of hospital stay was not prolonged by the delayed removal of the chest tubes in either of cases. One patient noticed a slight ptosis after the ETS procedure. ^[table 3]

Table 3. Complications / adverse events experienced in 35 patients

Complications / adverse events	Number	Intervention
Inter costal neuralgia:	8	Oral or local analgetics / cryoablation or intercostal block of intercostals nerves
<i>managed during admission</i>	4	
<i>Complaints <3 months</i>	2	
<i>prolonged complaints > 3months</i>	2	
Prolonged pneumothorax ^a	4	Delayed removal chest tube ^b
Partial Horner syndrome / ptosis	1	none
TOTAL	13	

Table legend: ^a = more than 24 hours, ^b = without clinical consequences, i.e no delayed discharge

Limb salvage was unsuccessful in three patients because of major amputations (N= 2) or severe functional impairment (N=1, loss of all fingers at the level of the proximal interfalangeal joints). Necrotectomies or minor amputations or without severe functional impairment were performed in 9 patients. ^[table 1] During the follow up period 13 patients died. One patient died during the admission due to a stroke which could not be attributed

to the ETS. One patient could not be traced because he emigrated, one patient did not want to participate and in one case the interview was unreliable due to a language barrier. Follow up data was therefore available in 19 cases (54% of the total cohort, 86% of all living patients).^[table 4] Mean follow up was 93 months (range 18-198 months). Postoperative beneficial effects were reported by 12 patients (63%). During the follow up period 11 patients (58%) reported a change of complaints over time. Nine patients reported a deterioration of their complaints. In four cases the symptoms became more severe, three patients had less complaints and in two cases the complaints returned to their pre-operative level. Two patients reported an improvement of their symptoms. Long-term beneficial effect of ETS was reported in 10 cases (53%). Patient satisfaction was consistent with 56%. CS was reported by 11 patients (58%) and graded using the Hyperhidrosis Disease Severity Scale. Three patients graded their CS as barely tolerable, five as tolerable and three as never noticeable. Four patients experienced a change in intensity of their CS. In 2 cases each there was respectively an improvement or deterioration of their CS.

Table 4. results questionnaire

Pt.	M/F	Age (y)	post-operative	Change effect	Long-term	FU (m)	exp. result	CS	Change CS	HDSS	Satisfaction
1	M	55	Better	Yes	Better	198	Yes	No	-	(1)	Yes
2	F	24	Better	Yes	Worse	177	No	Yes	Better	(1)	No
3	M	51	Excellent	No	Excellent	173	Yes	Yes	None	(3)	Yes
4	F	44	Same	Yes	Worse	164	No	Yes	Worse	(3)	No
5	M	36	Better	No	Better	157	Yes	Yes	None	(3)	Yes
6	M	46	Better	Yes	Worse	139	No	Yes	Worse	(2)	No
7	F	52	Same	No	Same	96	No	No	-	(1)	No
8	F	25	Better	No	Better	94	Yes	No	-	(1)	Yes
9	F	45	Same	Yes	Better	92	Yes	Yes	None	(1)	No
10	M	44	Same	Yes	Worse	88	No	Yes	None	(2)	No
11	F	60	Same	Yes	Better	86	No	Yes	None	(2)	Yes
12	F	22	Same	No	Same	81	Yes	Yes	None	(2)	No
13	M	45	Same	No	Same	78	No	Yes	Better	(1)	No
14	F	52	Better	No	Better	57	Yes	No	-	(2)	Yes
15	F	40	Excellent	Yes	Same	56	Yes	Yes	None	(2)	Yes
16	F	60	Better	Yes	Same	52	Yes	No	-	(1)	Yes
17	M	39	Excellent	No	Excellent	35	Yes	No	-	(1)	Yes
18	F	28	Excellent	Yes	Better	27	Yes	No	-	(1)	Yes
19	F	29	Better	Yes	Better	18	Yes	No	-	(1)	Yes

Table legend: CS = Compensatory sweating, exp. = expected, FU = follow up, m = months, Pt = patient, y = years, - = not applicable. HDSS = hyperhidrosis Disease Severity Scale:

- (1) sweating is hardly noticeable and never interferes with daily activities
- (2) sweating is tolerable and sometimes interferes with daily activities
- (3) Sweating is barely tolerable and frequently interferes with daily activities
- (4) sweating is intolerable and always interferes with daily activities

DISCUSSION

ETS is considered a safe and effective treatment for hyperhidrosis palmaris and axillaris.^[1-3] However, this is frequently offset by the development of disturbing side effects, especially compensatory sweating. In the long term the side effects can seriously reduce patient satisfaction and be a cause of regretting the operation.^[3,6,9] Although our recent summary of evidence suggest that there could be a benefit of ETS in the management of ULI, solid evidence based recommendations are still lacking up to this date.^[5] We studied retrospectively the data of 35 patients who had undergone an ETS between 1994 and 2009 in the management of ULI.

The lost to follow up of the total cohort was 46% and mainly due to mortality (13 patients = 37%). The majority of patients died years after their sympathectomy and it is therefore highly unlikely that the thoracic sympathectomy is related to their deaths. Besides the death of one patient during the admission, three patients died in the first year (2, 3 and 4 months). In all three cases progression of their underlying disease was the cause of death, not the recent surgical intervention. This high mortality rate in our study population can partially be explained by the relative old age of these 13 individuals (mean 59 years, range 36-79) compared to the mean age of the total study population (49 years). Furthermore we assume that the overall health of patients suffering from ischemic complaints is worse compared to an age controlled group and with it the life-expectancy should be adjusted.

In 10 patients ULI was caused by peripheral embolisation due to proximal arterial pathology (costoclavicular compression, aneurysms of the subclavian artery, stenosis of subclavian artery or an aortic coarctation). Another 5 patients had an occlusion of the brachial and or ulnar/radial artery. In these cases often the thoracic sympathectomy was performed in addition to arterial revascularisation or angioplasty to create a maximal vasodilatation of the capillaries to limit the extend of skin necrosis and ischemia of the fingers.

For upper limb ischemia or vasospastic disorders 53% of patients reported a long-term beneficial effect of thoracic sympathectomy. Nine patients (47%) reported a deterioration of their complaints over time. This phenomenon of diminishing of the effect of ETS is not uncommon. Incomplete surgical sympathectomy, reinnervation of the sympathetic pathways or hypersensitivity of the noradrenergic receptors regulating the precapillary sphincters reacting on very small amounts of circulating catecholamines have all been implicated as factors precipitating recurrence of symptoms.^[12,13]

There was a relative high incidence of neuralgia and postoperative chest pain (8 patients = 23%) probably caused by the 10 mm diameter trocar at the fifth intercostal space. It is a bothersome adverse event not uncommon after thoracic sympathectomy. Nicholson et al ^[4] reported a similar incidence. However it's in the vast majority merely a temporary nuisance. Only two patients suffered a prolonged period of pain. All other patients could be managed with oral analgetic and / or cryo-ablation of the intercostals nerve. None of the patients reported pain during the interview. Reducing the size of the trocars would possible reduce the incidence of chest pain.

The incidence and severity of compensatory sweating in literature varies, it is reported up to 93-97%.^[6,9,14] We used the validated Hyperhidrosis Disease Severity Score to establish the long-term incidence and severity of CS. In our study CS was reported by 11 patients (58%) One female had complaints of sweating that she attributes to hot flushes as part of the menopause she's currently going through and not as a side effect of the operation. In 3 cases (27%) the compensatory sweating was barely tolerable (HDSS 3). Thirty-six percent off patients experienced a change in severity of the CS. In two cases the CS deteriorated and in 2 cases there was an improvement. The two patients who suffered from deterioration all described their CS still as tolerable (HDSS 2), Although debated in literature our results suggest that there is a change severity of CS in time. Compensatory sweating is a frequently occurring side effect with a strong impact in the social domain and probably strongly affecting patient satisfaction.

Our results (63% short term and 53% long term benefit) of the ETS in the treatment of ischemia of the upper extremity are less favorable than those described in the literature.^[5] Several possible factors can be identified. In the first place only the outcomes of small cohorts are available in literature. It is well know that only small differences in patient characteristics can produce substantial changes in percentages in small cohorts. Furthermore we used subjective endpoints and an interview to determine the long term results. This can result in bias due to errors in recollection of complaints at time of surgery. On the other hand, objective long term analyses also do have limitations. Maga et al^[15] and Leesman et al^[16] reported a discrepancy between patient symptoms and objectively measured variables.

CONCLUSION

Although the long-term efficacy of ETS in the management of upper limb ischemic disorders in our study was 53%. Its minimal invasive character makes ETS worthwhile in the management of upper limb ischemic disorders especially in addition to prior revascularization or angioplasty.

APPENDIX (1) QUESTIONNAIRE

1) Symptoms of reduced blood flow to the arms, hand and fingers can occur in several ways. What symptoms did you experienced before the operation? (Multiple answers possible)

- ☐ Skin discoloration of finger(s) and / or hand
- ☐ Pain in the finger(s) and / or hand
- ☐ Poor healing wounds / ulcers on finger(s) or hand

2) Where did you experience these symptoms?

- ☐ [number] finger(s) of the left hand
- ☐ [number] finger(s) of the right hand

3) Did the symptoms occurred continuous or paroxysmal?

- ☐ Continue (proceed to question 5)
- ☐ Paroxysmal

4) How often did you suffer from these attacks

- ☐ daily
- ☐ weekly
- ☐ monthly

5) The aim of the operation was to reduce your symptoms. To what extent did this actually happened?

- ☐ Excellent effect, I had no complaints
- ☐ Good effect, I had fewer complaints compared to before surgery
- ☐ No effect, I had the same complaints compared to before surgery
- ☐ Negative effect, I had more complaints compared to before surgery

6) Did the complaints have returned / got worse over the years?

- ☐ No, the complaints are still at the same level as just after surgery
(proceed to question 8)
- ☐ Yes, the symptoms have returned / worsened over the years

7) Your current symptoms are compared prior to operation?

- ☐ Less intense
- ☐ Same
- ☐ More severe

8) Did you noticed any side-effect(s) or adverse event(s) of the operation?

- ☐ Yes
- ☐ No (proceed to question 10)

9) Which side-effect(s) or adverse event(s) of the operation did you experienced?

.....

.....

10) Had the operation had the expected result?

- ☐ Yes
- ☐ No

11) One of the major side effects of thoracic sympathectomy is compensatory sweating. The ability to sweat on the operated side of your body can be impaired due to the surgery. The unaffected side of the body can produce more sweat as a compensatory mechanism. Was this the case in your situation?

- ☐ Yes, on the unaffected side I tend to sweat more compared to prior to surgery
- ☐ No, I do not sweat more on my unaffected side after I had surgery
(proceed to question 13)

12) Did you noticed any change in severity of compensatory sweating?

- ☐ No, it is still at the same level compared to the postoperative period
- ☐ Yes, I'm now sweating more compared to the postoperative period
- ☐ Yes, I'm sweating less compared to the postoperative period

13) How can you best describe the overall pattern of sweating?

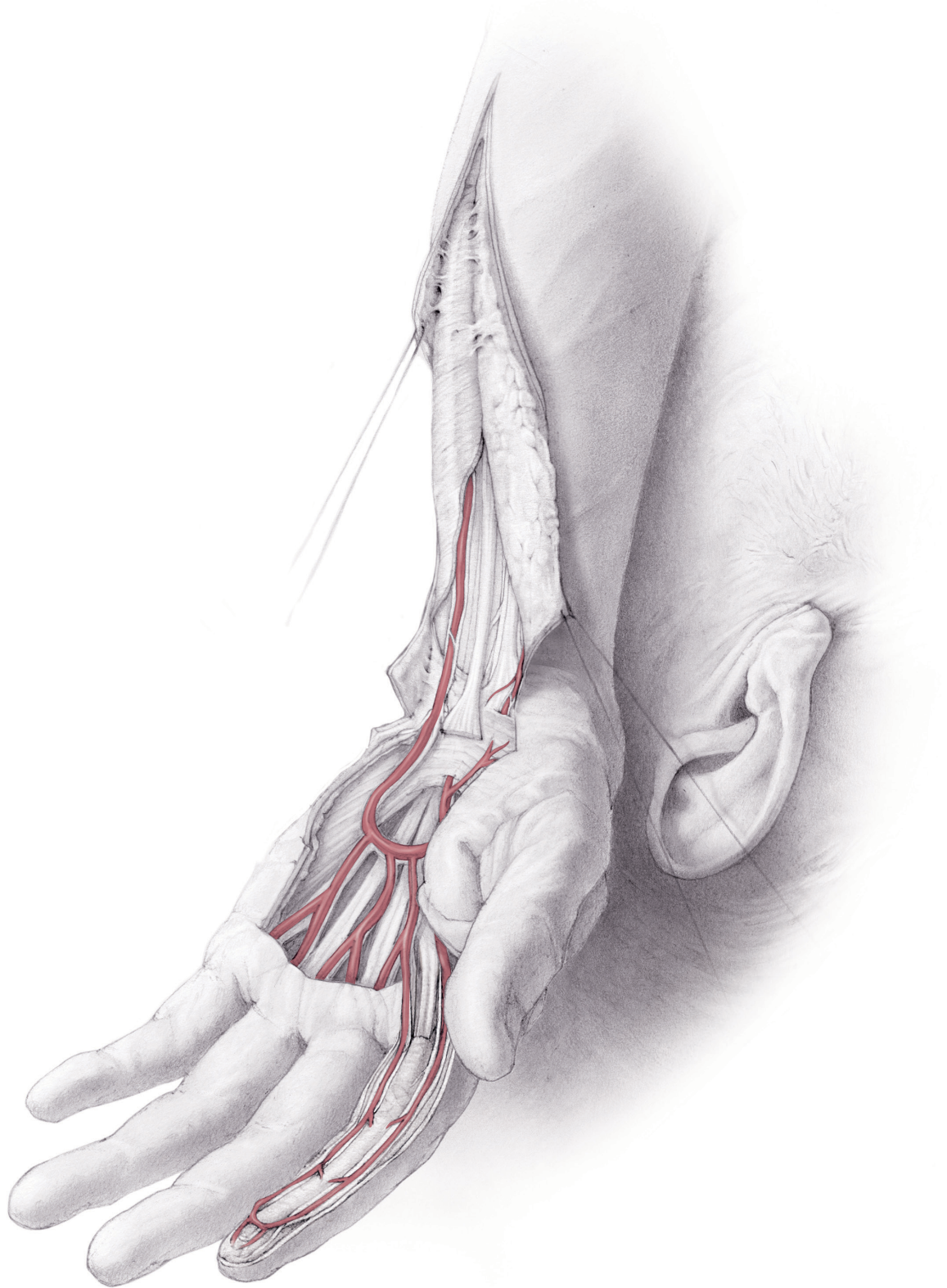
1. My sweating is hardly noticeable and never interferes with daily activities
2. My sweating is tolerable and sometimes interferes with daily activities
3. My Sweating is barely tolerable and frequently interferes with daily activities
4. My sweating is intolerable and always interferes with daily activities

14) Are you satisfied with the current situation regarding the complaints for which you had surgery?

- ☐ Yes, I'm satisfied
- ☐ No, I'm not satisfied

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CHAPTER 5

Robot-assisted ramicotomy: Evaluation in a swine model

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ABSTRACT

Background: To evaluate the feasibility of robot-assisted thoracoscopic T2–T5 ramicotomy.

Methods: In 5 pigs, a robot-assisted thoracoscopic T2–T5 ramicotomy was performed, followed by T2–T5 sympathectomy 10 min later. Ramicotomy and sympathectomy times, and core (esophageal) and surface (left front foot) temperatures, were monitored and recorded.

Results: The procedure was successfully completed in all 5 animals. In all cases, the sympathetic chain remained intact. No major hemorrhage occurred. The mean operating time for T2–T5 ramicotomy from incision until transsection of the last efferent ramus was 34 min (32–40). After completion of the ramicotomy, a total T2–T5 sympathectomy was performed, with a mean duration of 7 min (4–12). Mean core temperature before the operation was 37.6 °C (36.7–38.0). Mean surface temperature before the operation was 34.2 °C (33.3–35.5). Ten minutes after completion of the ramicotomy, temperatures stabilized. Mean postramicotomy core temperature was 37.4 °C (36.3–38) and mean postramicotomy surface temperature was 35.4 °C (33.9–37). Mean postsympathectomy temperatures were: core 37.3 °C (36.1–38) and surface 35.8 °C (33.8–37.1).

Conclusion: Robot-assisted thoracoscopic T2–T5 ramicotomy is feasible and effective in a porcine model.

INTRODUCTION

Primary palmar hyperhidrosis is caused by the excessive secretion of the eccrine sweat glands. The etiology is unknown. Endoscopic thoracic sympathectomy at T2–T4 is a well-established minimally invasive, safe and effective treatment for this disorder [1, 2]. Complications such as Horner syndrome, radial paresthesia, dysesthesia of the arm and hyperesthesia/ pain at the incision site/thorax are relatively rare (2.4–8.4%). However, the most frequent side effect is compensatory hyperhidrosis with an incidence reported in the recent literature of up to 93% [3, 4]. Gustatory sweating (38%) and phantom sweating (38.6%) are also fairly common. Compensatory hyperhidrosis seems to be quite acceptable to most of the patients; severe compensatory sweating, though, can result in a dramatically decreased quality of life in such a way that even a successful outcome of the operation may result in a patient regretting the intervention due to the severe compensatory sweating [5–7]. In order to limit the incidence of compensatory hyperhidrosis, some surgeons perform only a ramicotomy as opposed to removing the sympathetic bundle or performing a sympathicotomy. This procedure encompasses the selective division of the efferent rami communicantes of the sympathetic chain. Ramicotomy shows the lowest rate of compensatory hyperhidrosis and the lowest rate of Horner's syndrome [8]. However, a selective thoracic ramicotomy is not easily accomplished by conventional thoracoscopy and questions have been raised concerning the effectiveness of this technique [9–12]. The DaVinci® three-dimensional optical imaging system enhances visualization and the endowrist technology promotes telemanipulation of soft tissue structures in a relatively inaccessible working space. The immediate effectiveness of surgery of the thoracic sympathetic nervous system can be monitored by measuring the ipsilateral hand temperature during the actual operation. A +1 °C increase in hand temperature in the first minutes after sympathectomy is an indication of a successful intervention [13, 14]. The aim of this study was to examine the feasibility of robot-assisted thoracoscopic T2–T5 efferent ramicotomy. This procedure has the potential of providing relief to patients with upper extremity hyperhidrosis and significantly lowering the rate of debilitating compensatory sweating.

MATERIALS AND METHODS

Five female Yorkshire pigs weighing a mean 92 kg (82–98) were obtained from a single vendor and underwent a 5-day preoperative conditioning period. All animals underwent the same operative procedure in 5 consecutive experiments. Experiments were conducted using the guidelines published in the Guide for the Care and Use of Laboratory Animals (NIH publication 85–23, revised 1985). The study protocol was

approved by our institution's Animal Care and Use Committee (code: HK 04-01V1). The animals were sedated with intravenous fentanyl (5 µg/kg) and etomidate (0.25 mg/kg) before endotracheal intubation. A mixture of intramuscular ketamine (10 mg/kg), midazolam (0.2 mg/kg) and atropine (0.01 mg/kg) was administered, and general anesthesia was continued with intravenous fentanyl (5 µg/kg/h), midazolam (0.125 mg/kg/h) and pancuronium (0.20 mg/kg/h) and inhaled isoflurane (2.4%). Tidal volume was initially set at 15 ml/kg and the respiratory rate was 17 breaths/min. These initial parameters were modified after serial blood gas measurements to keep the pCO₂ between 25 and 35 mm Hg and the pH within normal limits. There was no selective single lung ventilation but high-frequency, low-volume ventilation. Right-sided jugular venous and carotid arterial accesses were obtained prior to the procedure. The electrocardiogram, blood pressure, blood gasses, urine output and transcutaneous oxygen saturation were monitored throughout the entire procedure. At operation, ramicotomy and sympathectomy times and core (esophageal) and surface (left front foot) temperatures were monitored. The pigs were placed in a left lateral position. A 12-mm port was introduced in the 9th intercostal space of the left thorax, and the 0° robot thoracoscope was introduced. Under direct visualization, two 5-mm dissecting ports were inserted in the 5th and 6th intercostal space. An additional 12-mm port was placed into the 8th intercostal space for a fan retractor. After insertion of the thoracoscope in the left thoracic cavity, the pleura overlying the sympathetic chain was opened from the second rib on towards the 6th rib. The sympathetic chain runs parallel to the spine at the level of the costovertebral joint of the rib and connects the different ganglia from which the rami communicantes efferentes originate and run along with the ribs. The lung was then gently retracted by the fan retractor. The sympathetic chain was identified and all the efferent rami communicantes from T2 to T5 were interrupted and removed for 2 cm laterally. Great care was taken to preserve the integrity of the sympathetic chain.

After completion of the ramicotomy, the various temperature variables were observed for a 10-min period. A complete T2–T5 sympathectomy was then performed with temperatures continuing to be monitored. The pigs were euthanized afterwards with an overdose of potassium chloride, and an autopsy was performed to study the effectiveness of the sympathetic chain resection

RESULTS

The procedure was successfully completed in all 5 animals. In all cases the sympathetic chain remained intact during ramicotomy. No major hemorrhage occurred. The mean operating time for T2–T5 ramicotomy from incision until transection of the last efferent ramus was 34 min (32–40). Ramicotomy increased the surface temperature significantly from 34.2 °C (33.3–35.5) before the operation to 35.4 °C [33.9–37; $p = 0.043$, Wilcoxon-Paired Rank test (twosided)] at 10 min when temperatures had stabilized. The mean core temperature before operation was 37.6 °C (36.7–38.0) and decreased by 0.2 °C to 37.4 °C (36.3–38) after ramicotomy. After completion of the ramicotomy, a total T2–T5 sympathectomy was performed, with a mean duration of 7 min (4–12). Mean postsympathectomy temperatures were: core 37.3 °C (36.1–38) and surface 35.8 °C (33.8–37.1; $p = 0.08$; fig. 1 , 2). The effective resection of T2–T5 sympathetic ganglia was confirmed at autopsy

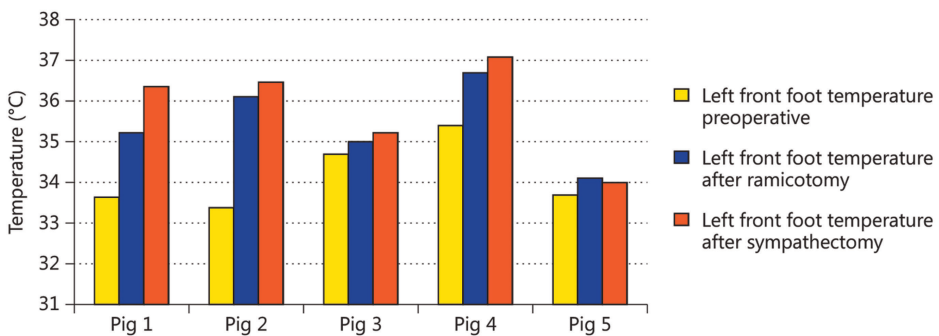


Fig.1. evaluation of surface temperature. Left front foot temperature before surgery (yellow), 10 minutes after ramicotomy (blue) and after subsequent sympathectomy (orange).

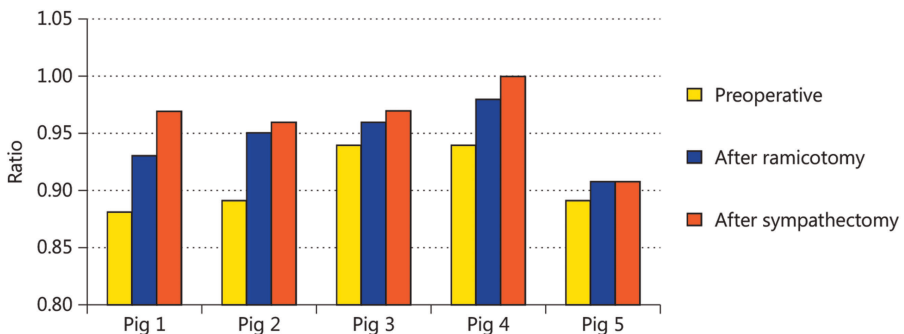


Fig.2. Ratio of surface temperature to core temperature before surgery (yellow), 10 minutes after ramicotomy (blue) and after subsequent sympathectomy (orange)

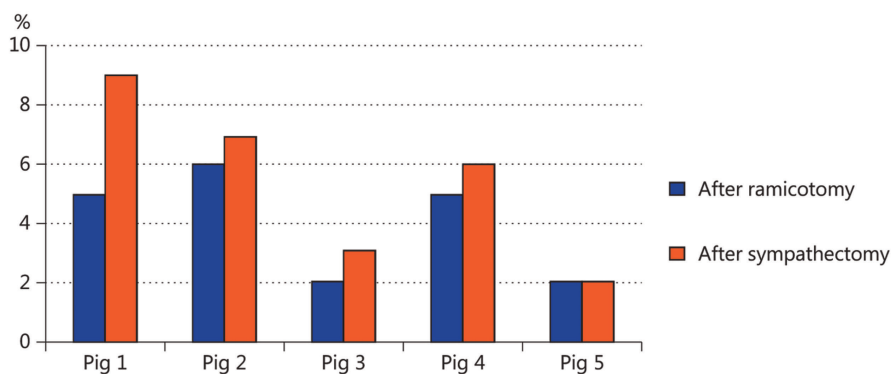


Fig.3. Percentage change in the surface/core temperature ratio compared to the ratio preoperative, for ramicotomy (blue) and subsequent sympathectomy (orange).

DISCUSSION

Surgery of the sympathetic nervous system has a long history and is characterized by an evolution in indications correlating with the evolution in surgical techniques and the understanding of the physiology and anatomy of the sympathetic nervous system. The optimal technique has remained a subject of controversy because the conventional endoscopic thoracic sympathectomy and sympathicotomy procedures often result in overdryness of the enervated area and irreversible compensatory hyperhidrosis [10]. Criteria for a successful thoracic sympathectomy are: a high rate of hyperhidrosis relief combined with a low rate of recurrence, and a low rate of compensatory and gustatory hyperhidrosis. The technique of dividing sympathetic rami communicantes while preserving the thoracic sympathetic ganglia and nerve chain (ramicotomy) was first introduced by Wittmoser [8], which was later reported by Gossot et al. [11]. Gossot et al. reported a lower rate of compensatory sweating but a higher recurrence rate (5%) in an 11-month follow-up study. The outcome could be improved by broadening the area of resection to 2 cm laterally of the sympathetic cord. A longer section of the rami communicantes is removed, which includes aberrant connections and sometimes the Kuntz nerve. An additional advantage to this procedure is a residual relative humidity of the hands after ramicotomy, thus avoiding overdryness of the hands [10]. Drawbacks to thoracoscopic ramicotomy are a longer operating time and an increased possibility of accidental injury to the intercostal vessels [11]. Therefore, ramicotomy is not easily accomplished by conventional thoracoscopy [9–12]. Ramicotomy is a more selective and physiological treatment of essential hyperhidrosis than sympathectomy or sympathicotomy. The enhanced visualization of the Da Vinci® three-dimensional optical imaging system combined with the improved agility of the endowrist system promotes

the telemanipulation of soft tissue structures in a relatively inaccessible working space [10, 15]. By using the advantages of the Da Vinci® system and by broadening the area of transection to 2 cm laterally of the sympathetic cord, we overcome the drawbacks mentioned before and aim to make robotic ramicotomy accepted as the method of choice for the treatment of essential hyperhidrosis. We chose to perform the procedure only at the left sympathetic chain in the porcine models due to anatomical reasons: the pig has an accessory apical right bronchus which prevents adequate thoracoscopic exposure of the right sympathetic chain. Mean operating time from incision until transection of the last efferent ramus for a robot-assisted T2–T5 ramicotomy was 34 min (32–40), which is comparable to times for unilateral thoracoscopic sympathectomy T2–T5. We measured the temperature of the surface of the left front foot as a parameter for the immediate effectiveness of the operation. In humans, an increase of 1 °C in the hand temperature indicates a successful intervention. The correlation between a rise in temperature at the innervated areas and the relief of hyperhidrosis at those areas can be explained by the three physiological functions of the sympathetic nerve system: the vasomotoric, the sudomotoric and the pilomotoric function. By transecting the efferent rami communicantes, the sympathetic function is inhibited resulting in vasodilatation of the superficial arterioles to the skin causing an increase in local surface temperature, a decrease in core temperature and a decrease in sweat production. This is congruent with our results. The increase of the mean surface temperature by 1.2 °C from 34.2 °C (33.3–35.5) to 35.4 °C (33.9–37) is significant ($p = 0.0043$) using the Wilcoxon-paired rank test (two-sided) and suggests a successful intervention. The maximum possible increase of surface temperature ($\Delta\text{Tempmax}$) is the surface temperature after sympathectomy (T_{ss}) compared to the skin temperature before intervention (T_{spre}). The $\Delta\text{Tempmax}$ is calculated by subtracting the T_{spre} from the T_{ss} . The skin temperature after ramicotomy rises compared to the $\Delta\text{Tempmax}$ with an average of 76% (57, 87, 60, 77 and 100%). This is even further evident when the decrease of core temperature is also taken into account by examining the mean surface temperature/mean core temperature ratio. The ratio after ramicotomy rises by 5% from 90 to 95% (fig. 2). After ramicotomy, we observed a progression of the temperature towards a plateau within the first 5 min. That is why we measured the postramicotomy temperature after 10 min. After the ramicotomy, we completed the intervention and performed a T2–T5 sympathectomy by removing the nerve chain and ganglia. Interestingly, we noticed an additional increase in surface temperature of 0.4 °C from 35.4 °C (33.9–37) to 35.8° [33.8–37.1; $p = 0.08$, Wilcoxon-paired rank test (two-sided); fig. 1]. The mean surface temperature/mean core temperature ratio increased by an additional 1% (96%; fig. 3).

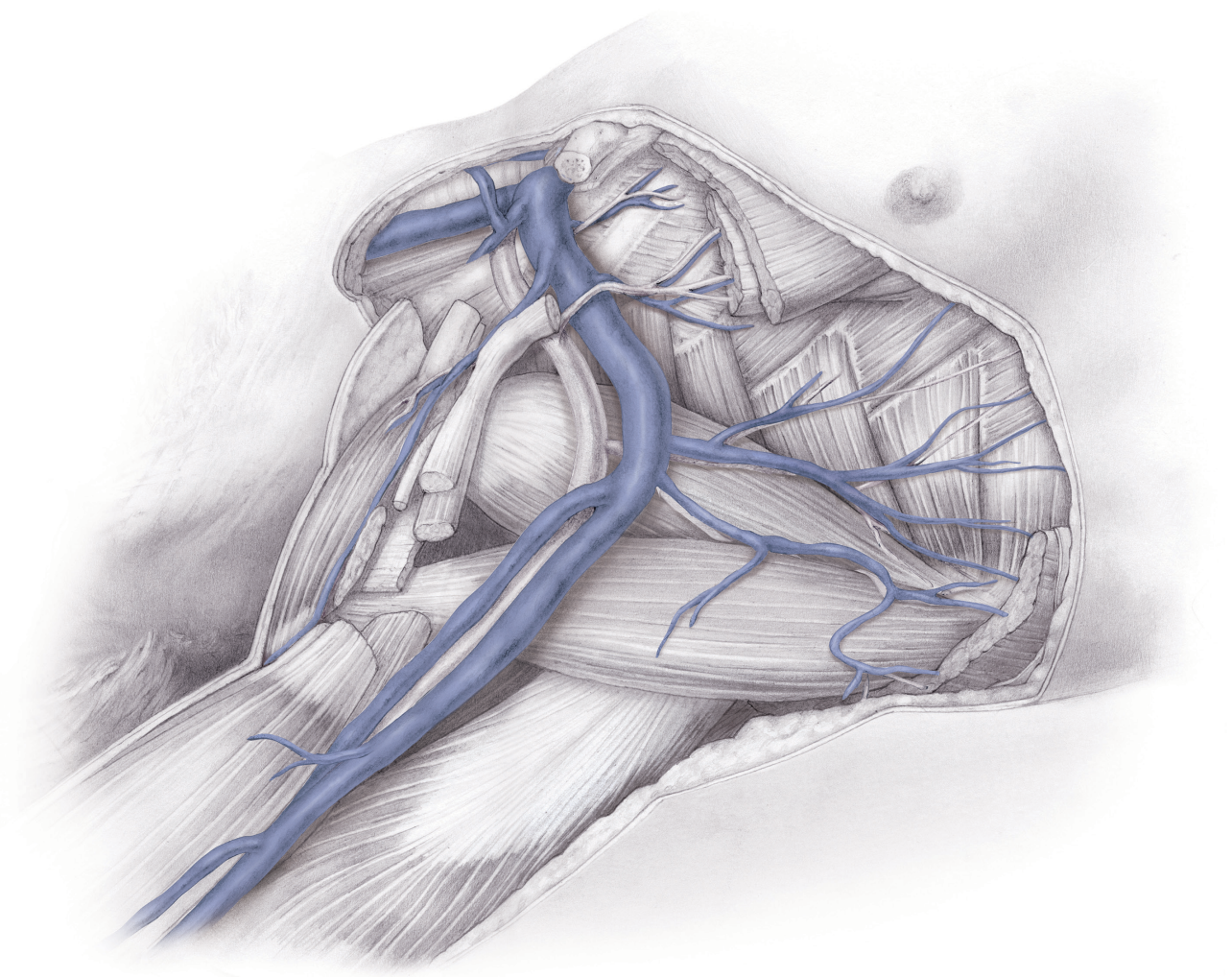
This tendency towards a rise in the surface temperature of the palms after ramicotomy and upon completion of the sympathectomy could suggest that there could be still some degree of residual humidity in the palms. This could indicate that ramicotomy is a more selective and physiological treatment of essential hyperhidrosis than sympathectomy or sympathicotomy because it may prevent overdryness of the enervated zones. The long-term recurrence rate of hyperhidrosis, the incidence of compensatory sweating, the incidence of Horner syndrome and postoperative pain could not be determined in this swine model and will be examined in a prospective clinical study.

CONCLUSION

Robot-assisted thoracoscopic T2–T5 ramicotomy is feasible and effective in a swine model. The use of the Da Vinci® robot enables us to perform this operation, which is not easily accomplished by conventional thoracoscopy, in a safe and controlled manner within a reasonable operation time. More prospective clinical data need to be collected to show robot-assisted thoracoscopic ramicotomy is acceptable as the method of choice for the treatment of disabling essential hyperhidrosis.

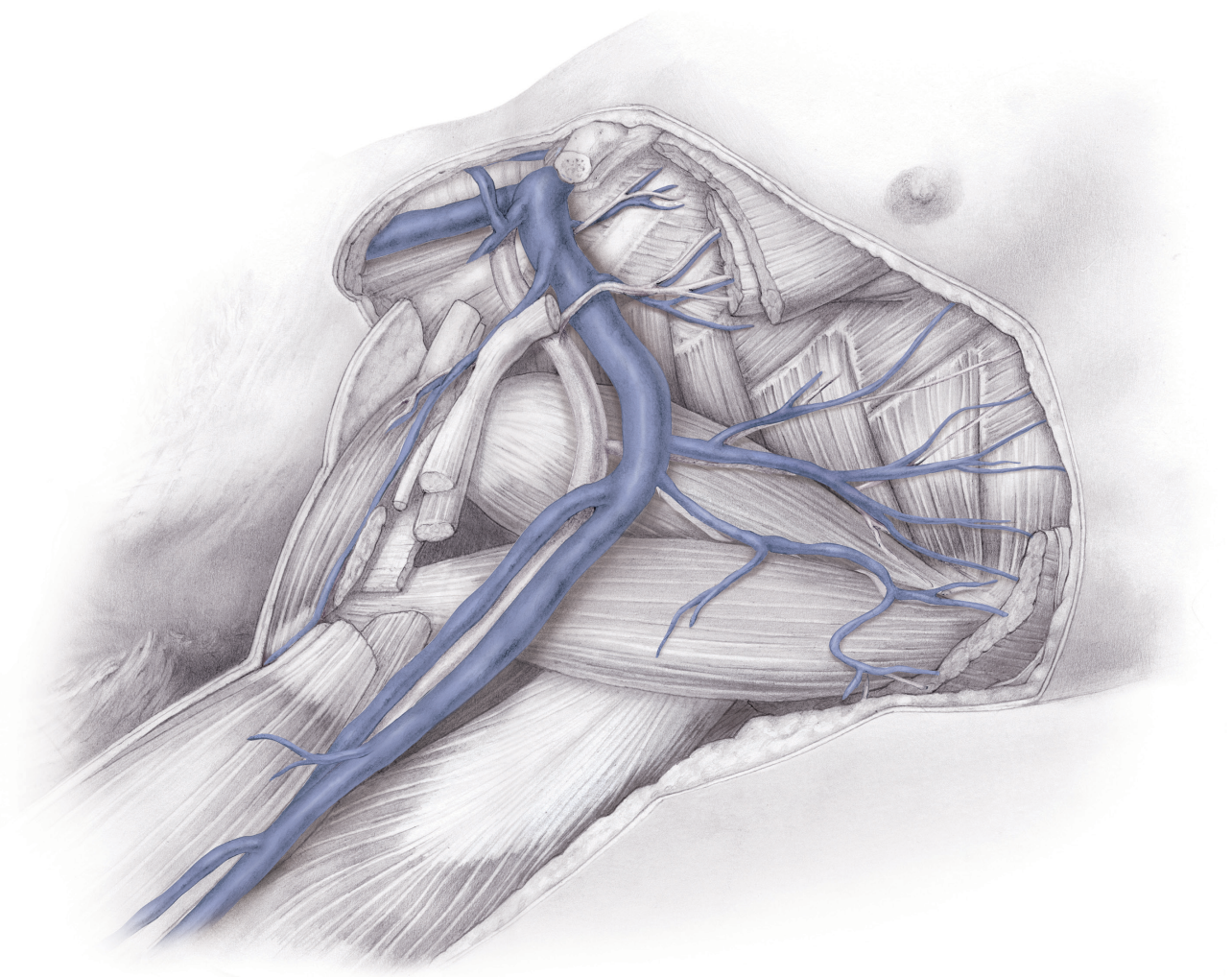
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PART II

Upper extremity deep venous thrombosis



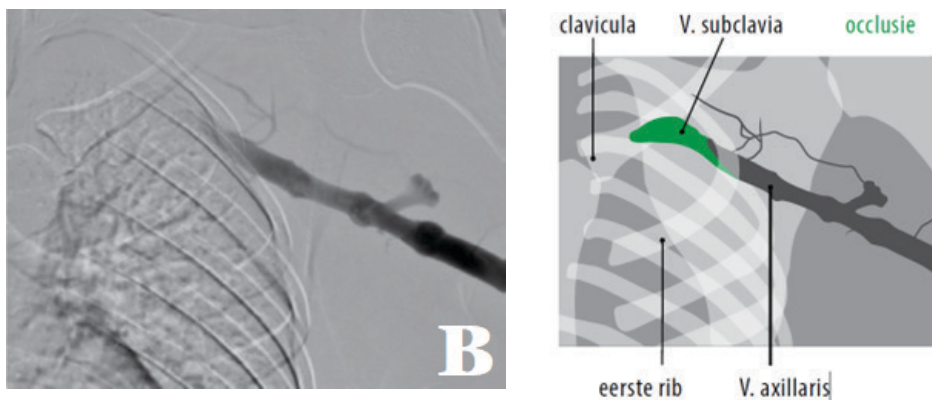
CHAPTER 6

Diagnose in beeld

F. Hoexum

KK. Yeung

W. Wisselink



FIGUUR (a) Foto van de borstkas van patiënt. Er is duidelijke venetekening zichtbaar ter hoogte van de linker borstspier en schouder. (b) Flebogram toont occlusie van de linker V. subclavia ter hoogte van de costo-claviculaire overgang.

DIAGNOSE IN BEELD

Een sportieve man met een gezwollen arm

Casus

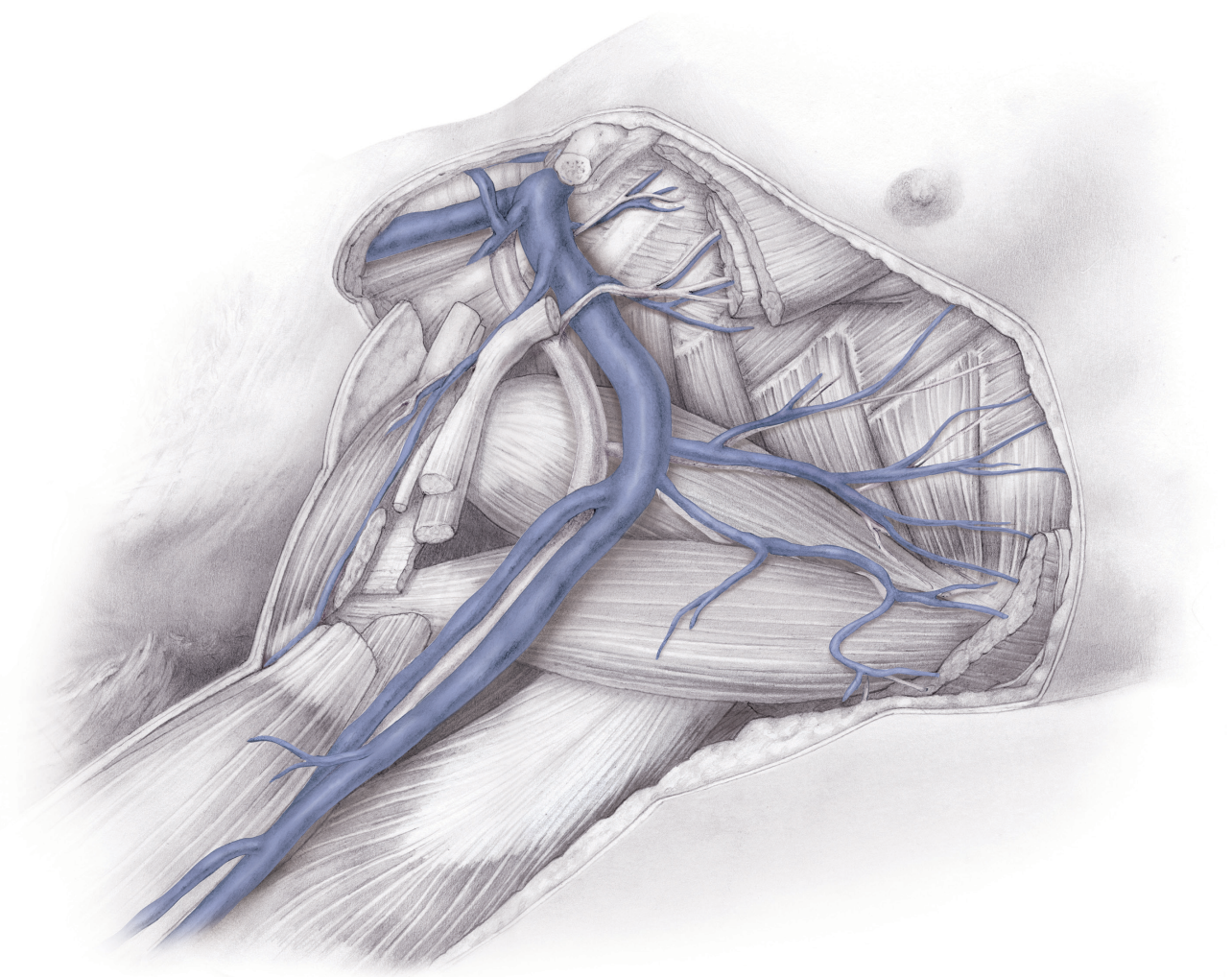
Een 28-jarige man werd door zijn huisarts naar onze SEH verwezen vanwege een acuut gezwollen linker arm. De avond daarvoor had hij intensief gefitnest. Zijn arm was niet pijnlijk en hij had geen risicofactoren voor diepveneuze trombose. Bij lichamelijk onderzoek zagen wij een sportieve man met een gezwollen, blauw-paarsgekleurde linker arm. Opvallend was de veneuze stuwing met duidelijke venetekening op zijn linker arm, borstspier en schouder (figuur a). Duplex-onderzoek en flebografie toonden een trombotische occlusie van de linker V. subclavia ter hoogte van de costo-claviculaire overgang (figuur b), wat de diagnose 'syndroom van Paget-Schroetter' bevestigde.

We begonnen met trombolysen en na 36 h was de linker V. subclavia weer doorgankelijk. Vanwege enige wandonregelmatigheden verrichtten we daarna percutane transluminale angioplastiek. Na aanvang van behandeling met acenocoumarol ontsloegen we hem naar huis. Na 4 weken kwam hij terug voor een robotgeassisteerde transthoracale resectie van de eerste rib. Het postoperatieve herstel verliep ongecompliceerd, waarna we patiënt opnieuw behandelden met acenocoumarol voor de duur van 6 maanden. Daarna deed zich geen recidieftrombose voor. Patiënt ervoer geen enkele beperking in zijn dagelijks functioneren en kon het sporten volledig hervatten. Het syndroom van Paget-Schroetter is zeldzaam. Het treft vooral jonge, sportieve mensen en wordt ook wel inspanningsgebonden trombose of 'effort'-trombose genoemd.

Een proactieve behandeling met trombolysen gevolgd door een eerste-ribresectie resulteert mogelijk in betere resultaten dan conservatieve therapie met orale anticoagulantia, maar hiervoor ontbreekt vooralsnog bewijs uit gerandomiseerd onderzoek. Wij pasten een nieuwe robotgeassisteerde techniek toe, maar de standaardbenadering voor een eerste-ribresectie is transaxillair.

Diagnose

Paget-Schroetter Syndroom



CHAPTER 7

Long-Term outcomes of Non-operative and Surgical Management of Paget-Schroetter Syndrome

F. Hoexum

V. Jongkind

HME. Coveliers

W. Wisselink

KK. Yeung

ABSTRACT

Purpose: In Paget-Schroetter Syndrome (PSS) subclavian vein thrombosis is caused by external compression of the subclavian vein at the costoclavicular junction. PSS can be treated non-operatively, surgical or with a combination of treatments. Non-operative management consist in most cases of anticoagulation (AC) or catheter directed thrombolysis (CDT). With surgical management decompression of the subclavian vein is performed by resection of the first rib. No prospective randomized trials are available to determine if non-operative or surgical management is superior. We report our long term outcomes of both non-operative and surgical treated patients.

Materials and methods: We retrospectively analyzed all patients with PSS who were treated between January 1990 and December 2015. Patients were divided based on primary non-operative or primary surgical therapy. Long-term outcomes regarding functional outcomes were assessed by questionnaires using the “disability of the arm, shoulder and hand” (DASH) questionnaire, a modified Villalta score and a disease specific question regarding lifestyle changes.

Results: In total 91 patients (95 limbs) were included. Seventy patients (73 limbs) were treated non-operative, 21 patients (22 limbs) surgical. Questionnaires were returned by 67 patients (70 limbs). Mean follow-up of was 184 months (range 43-459). All functional outcomes were better in the surgical group compared to the non-operative treated group (DASH general 3.11 vs. 9.86; DASH work 0.35 vs. 11.47; DASH sport 5.85 vs. 17.98 and modified Villalta score 1.11 vs. 3.20 points). Surgical treated patients were more likely to be able to continue their original lifestyle and sports activities (84% vs 40%, $p = 0.005$). Patients with recurrence of thrombosis, or the need for surgical intervention after primary non-operative management reported worse functional outcomes.

Conclusion: surgical management of PSS with immediate CDT followed by FRR leads to excellent functional outcomes with low risk of complications. The results of non-operative management in our non-matched retrospective comparative series were satisfactory, but resulted in worse functional outcomes and more patients needing to adjust their lifestyle compared to surgical treated patients.

INTRODUCTION

Paget-Schroetter Syndrome (PSS) is effort induced subclavian vein thrombosis and can be classified as a separate entity within the venous thoracic outlet syndromes (vTOS). PSS can be treated non-operatively, surgical or by a combination of treatments. Non-operative treatment can be anticoagulation, catheter directed thrombolysis (CDT) or other comparable catheter based therapies. Surgical therapy is aimed to prevent recurrence of thrombosis and consist of decompression of the subclavian vein by resection of the first rib after patency is restored with AC or CDT. Currently, there is no consensus on the optimal management of PSS.^[1] Published reports are predominantly retrospective in design and limited by short follow-up and/or not well documented functional outcomes. Therefore, we investigated the long-term functional outcomes of both non-operative and surgical treated patients with PSS.

METHODS

Approval for this research was obtained from the Medical Ethics Review. Our institutional Research Data Platform provided all patients diagnosed with upper extremity deep venous thrombosis (UEDVT) during the period 1-1-1990 and 31-12-2015 using financial and medical coding information from the departments of surgery and Internal Medicine. An additional search identified all patients who underwent first rib resection (FRR) during the same period. All identified patients were screened for the diagnosis of PSS. PSS was defined as UEDVT without any secondary cause: active malignancy, central intravenous line, pace maker leads, pregnancy, hormonal hyper stimulation during fertility treatment, related to arterial-venous fistula in chronic kidney disease or trauma. The medical files of all patients with PSS were further reviewed. All patients eligible for inclusion were contacted by phone and were asked to participate in this study. If patients were willing to participate, informed consent forms and the following questionnaires were sent by mail. Overall functional outcomes were assessed using the validated Disabilities of the Arm, Shoulder and Hand questionnaire (DASH).^[2] Post thrombotic complaints were self-assessed with a 7-point modification (symptoms only) of the Villalta score [supplemental document 1]. Additional information regarding any changes in life style or sporting activity was obtained with a disease specific question [supplemental document 2]. Patients were reminded several times to return their questionnaires. All patients who did not returned their questionnaires before April 1st 2021 were considered not willing to participate in this study.

Statistical analysis: Descriptive statistics were used for analysing patients' characteristics. Statistical analysis was performed using SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). DASH scores and Villalta scores of both groups were compared with a Mann-Whitney U test. The disease specific question

was analysed with a Chi-square test. A p-value of 0.05 or less was considered statistically significant. A 10-point DASH difference was considered a minimal important change.^[3]

RESULTS

In total of 94 patients were identified (98 limbs, 52 males, 60 right-sided, mean age 33 years (range 16-63)). Two patients were excluded because they were included in our robot assisted transthoracic first rib resection case series as reported previously.^[4] One patient was excluded because he received no treatment at all. In 76,9% (70/91 patients, 73 limbs) of all patients a non-operative treatment was instituted as the initial management of their first PSS episode. Twenty-one patients (22 limbs) were treated with catheter directed thrombolysis (CDT) followed by first rib resection (FRR). Twenty-four patients (non-operative n=21, surgical n=3) were lost to follow-up (untraceable n=11, did not return their questionnaires n=7, did not want to participate n=5, deceased n=1). Questionnaires were returned by 73,6% of patients (67/91), reporting on 70 limbs.

Outcome non-operative treatment. *[table 1]*

In total 70 patients (73 limbs) were treated non-operative with anticoagulation (AC, n=43) or CDT followed by AC (n=30). In 8 limbs (11.0%, CDT n=4, AC n=4) initial therapy was unsuccessful in restoring patency. Of the remaining 65 limbs, recurrent thrombosis was reported in 26 (40.0%). Median time to recurrence was 32.4 months (range 0,5-168). Eventually 20 limbs underwent surgical decompression (27.4%), at a mean interval of 19 months (range 6-168 months). Forty-nine patients returned the questionnaires corresponding with 51 limbs and were further analysed (AC n=32, CDT n=19). Mean follow-up was 175 months (range 43-459 months). Mean DASH scores were: General 9.86 (sd 12.81, range 0-56.7); Work module 11.47 (sd 19.85, range 0-68,8); Sport module 17,98 (sd 23.06, range 0-87,5). Mean modified Villalta score was 3.20 (sd 3.18, range 0-12) with fifteen out of 51 patients (29,4%) scored 0 points which corresponds with the absence of any post-thrombotic complaints. Sixty percent of patients (30/50, 20 moderate, 10 severe) altered their normal daily living or sporting routine to adjust for physical limitations after their PSS episode. A perfect minimum score of 0 points at both questionnaires and no alterations needed in daily activities was reported in 6/52 (11,5%) treated limbs. No statistical nor clinical relevant difference was seen between patients receiving AC or CDT as primary management. Of the 20 patients who underwent FRR because of recurrent or persistent complaints, 10 needed a venous reconstruction. Patients who needed surgical treatment after failed non-operative treatment more often had to make lifestyle adjustments (11/14 vs 19/36, p=0.004). Although also a trend was seen regarding a worse General DASH, Work related DASH and Villalta scores, this was not statistically significant.

Table 1. Patient characteristics and management

N=	Primary non-operative treatment			Primary surgical treatment			Total		
Patients	70			21			91		
Limbs	73			22			95		
Male / Female (limbs)	38 (39) / 32 (34)			11(12) / 10(10)			49 (51) / 42 (44)		
Mean age (range)	32.8 years (16 – 63)			32.6 (18 - 63)			32.8 (16 – 63)		
Side right / left	44 / 29			14 / 8			58 / 37		
	Y	N	?	Y	N	?	Y	N	?
Dominant side	28	24	21	10	9	3	38	33	24
Pre-existing symptoms	6	42	25	0	19	3	6	61	28
Smoking	16	34	23	8	11	4	24	45	27
Oral contraceptive use*	14	9	11	7	3	0	21	12	11
Coagulopathy	6	40	27	0	16	6	6	56	33
Effort induced	25	20	28	9	7	6	34	27	34
AC / CDT	43 / 30			0 / 22			43 / 52		
CDT unsuccessful	4			1			5		
CDT unsuccessful	4			1			5		
No recanalization with AC	4			na			4		
Recurrence of thrombosis	26 (9 CDT, 17 AC)			1**			27		
Time to recurrence (range)	32.40 months (0.5 – 168)			4 (na)			31.35 months (0.5 – 168)		
FRR	20			22			42		
Venous reconstruction	10			0			10		

Table legend: AC = anticoagulation; CDT = catheter directed thrombolysis; FRR = first rib resection; N = no; na = not applicable; N= = numbers of patients; Y = yes; ? = unknown; * females only; **in waiting time before FRR managed with CDT and immediate FRR

Outcome surgical management: [table 1]

Twenty-one patients (22 limbs) were treated with catheter directed thrombolysis followed by scheduled FRR. Two patients didn't want to participate in this study, one patient was untraceable. Median time between PSS and FRR was approximately 4 months (122 days, range 24-731). The transaxillar approach was used in all but one patient in which a paraclavicular approach was used because a venous reconstruction was performed in the same procedure. Mean operation time was 86,2 minutes (range 55-160 minutes). Median hospital stay for FRR was 4 days (range 1-10 days). Mean follow-up was 206 months (range 60-370 months). Mean general DASH scores was 3.11 (range 0-30), mean work related DASH score was 0.35 (range 0-6.3) and mean sport related DASH score was 5.86 (range 0-37.5). Mean modified Villalta score was 1,11 (range 0-5). Alterations in their normal daily living or sporting routine to adjust for physical limitations after their PSS was reported by 15,8% of patients (3/21, 2 moderate, 1 severe). More than half of all patients (11/21) had a perfect minimum score of 0 points at both questionnaires and were able to maintain their daily activities as before their episode of PSS.

Non-operative versus surgical management:[table 2]

All functional outcome were in favour of surgical management; General DASH module (-6.75 points, $p = 0.005$), DASH Work module (-11.12 points, $p = 0.013$); DASH Sports module (-12.12 points, $p = 0.057$); Villalta score (-2.09 points, $p = 0.006$). Surgical treated patients were more often able to maintain their pre-existent functional and sporting activities (40% vs 85%, $p = 0.005$).

Complications^(table 3)

Two complications were observed related to CDT. Hemoptysis in one patient and a vaginal bleeding in another patient warranted cessation of CDT and prevented complete restoration of flow in the subclavian vein. No further treatment was instituted at the patient's requests. No other CDT related adverse events were reported. Information regarding postoperative complications after FRR could be retrieved in 38 of 42 FRR (non-operative $n=18$, surgical $n=20$). In total 27 complications or adverse effects of FRR were recorded in 19/38 procedures (11/18 non-operative, 8/20 surgical). No Clavien-Dindo grade IV (life threatening) or grade V (death) complications were observed.

Table 2. Functional outcome

	Primary non-operative management	Primary surgical management		Non-operative: success**	Non-operative: recurrence	Non-operative: surgery
	n= 52	n= 20		n= 22	n= 16	n= 14
Patients						
Mean follow-up (range)	175 months (43-459)	206 months (60-370)		141 months (43-270)	180 months (56-330)	223 months (89-459)
Functional outcome						
DASH general	n= 51	n= 19	MW-U,	n= 22	n= 16	n= 13
Mean (range)	9.86 (0 - 56.7)	3.11 (0 - 30.0)	$p = 0.005^*$	7.02 (0 - 27.7)	8.90 (0 - 34.2)	16.58 (0 - 56.7)
DASH work	n= 46	n= 18	MW-U,	n= 20	n= 22	n= 12
Mean (range)	11.47 (0 - 68.8)	0.35 (0 - 6.3)	$p = 0.013^*$	5.63 (0 - 43.8)	13.47 (0 - 62.5)	15.11 (0 - 68.8)
DASH sport	n= 40	n= 16	MW-U,	n= 18	n= 18	n= 11
Mean (range)	17.98 (0 - 87.5)	5.86 (0 - 37.5)	$p = 0.057$	21.19 (0 - 87.5)	11.12 (0 - 62.5)	17.64 (0 - 43.8)
Villalta score	n= 51	n= 19	MW-U,	n= 21	n= 24	n= 14
Mean (range)	3.20 (0 - 12)	1.11 (0 - 5)	$p = 0.006^*$	2.33 (0 - 5)	3.21 (0 - 12)	4.43 (0 - 9)
Life style change	n= 50	n= 19	χ^2	n= 21	n= 23	n= 14
No	20 (40%)	16 (85%)	$P = 0.005^*$	11 (52%)	9 (39%)	3 (21%)
Some	20 (40%)	2 (10%)		9 (43%)	9 (39%)	4 (29%)
Severe	10 (20%)	1 (5%)		1 (5%)	5 (22%)	6 (50%)

Table legend: DASH = disability of the arm, shoulder and hand questionnaire, MW-U = Mann-Whitney U test, n = number, p = probability value, χ^2 = chi-squared test, * = statistical significant, # = clinical relevant, ** = No recurrence nor surgical intervention needed

Table 3. Complications of First Rib Resection

Complications		Primary non-operative management	Primary surgical management	Total
		n= 18 FRR*	n= 20 FRR*	38
Pneumothorax (conservative)	C-D 1	n= 0	n= 1	n= 1
Surgical site infection	C-D 1	n= 1	n= 0	n= 1
Urinary retention	C-D 1	n= 0	n= 1	n= 1
Hypoesthesia (conservative)	C-D 1	n= 0	n= 2	n= 2
Atelectasis (conservative)	C-D 1	n= 2	n= 0	n= 2
Transient scapula alata (conservative)	C-D 1	n= 2	n= 0	n= 2
Transient neuralgia (conservative)	C-D 1	n= 1	n= 1	n= 2
Bleeding / hematoma (conservative)	C-D 1	n= 2	n= 1	n= 3
Epipleural hematoma / pleural effusion (conservative)	C-D 1	n= 3	n= 0	n= 3
Hemothorax / pleural effusion (drainage)	C-D 3a	n= 1	n= 0	n= 1
Pneumothorax (drainage)	C-D 3a	n= 1	n= 1	n= 2
Removal steel sternal fixation wire [‡]	C-D 3b	n= 1	n= 0	n= 1
Surgical correction hypertrophic scar [‡]	C-D 3b	n= 1	n= 0	n= 1
Hemothorax (thoracotomy / VATS)	C-D 3b	n= 2	n= 0	n= 2
Bleeding (exploration)	C-D 3b	n= 2	n= 1	n= 3
Total		n= 19	n= 8	n= 27 [§]

Table legend: C-D = Clavien-Dindo grade, * in 2 FRR complications were unknown, [§] 27 Complications registered in 19 (11 non-operative, 8 surgical) out of 38 first rib resections, [‡] Performed in same procedure, correction hypertrophic scar not the indication for surgery

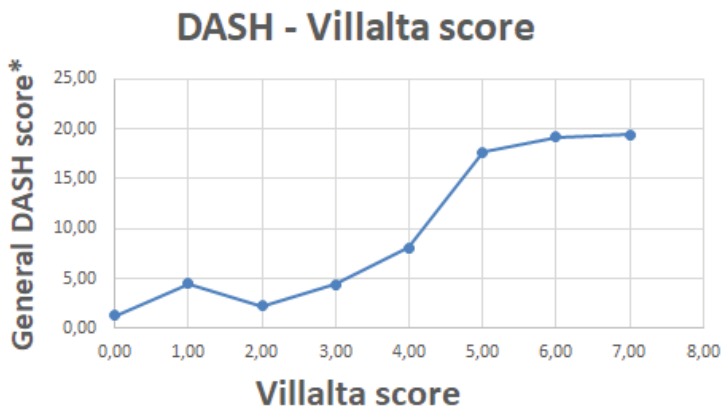


Figure 1. Relation DASH and Villalta score

* mean DASH scores based on ≥3 cases

DISCUSSION

Our study provides insight in long-term functional outcome after non-operative and surgical management of PSS. Surgical treatment results in better DASH scores and modified Villalta scores. Furthermore, surgical treated patients are less often required to change their daily activities. All DASH scores of surgical treated patients and the General DASH scores of non-operative treated patients are comparable to the normative population.^[5] The work and sport related DASH scores of non-operative treated patients are worse.^[6] Patients treated with non-operative therapy have a substantial risk of persistent complaints or recurrence of PSS and frequently undergo FRR eventually. In our series persistent occlusion (n=8) or recurrence (n=26) was reported in 46.6% (34/73). Twenty patients did undergo FRR (27.4%), which is in line with the rates reported by others in literature^[6] Failure of non-operative treatment results in worse functional outcomes.^[table 2]

Our recurrence rate (26/73, 35,6%) after non-operative treatment is high compared to the recurrence rate reported in literature of 23%.^[6] A possible explanation may be that our institution serves as a referral centre and therefore the possibility of selection bias is present. This may also lead to worse functional outcomes. Patients with the need for surgical intervention after failed non-operative management have the worst outcomes. Venous reconstruction is often needed resulting in a more extensive procedure. The risk for postoperative complications is much higher compared to the FRR performed in the surgical group (61% vs 40%).^(table3)

The stereotypical case presentation in literature is an adolescent male athlete experiencing sudden complaints after strenuous physical exercise. This image is not entirely reflected in this series, gender distribution is nearly 1:1 with 46,2% female patients. Physical activity was reported in our series in 56%. The average age in our series was 32.8 years but it ranged from 16 to 63 years. Primary care physicians and emergency medical staff therefore need to have a high index of suspicion in any patient with a swollen upper extremity. Besides the before mentioned possible inclusion bias, several methodological shortcomings have to be addressed. Because of the retrospective design of this study, we have no information about the severity of complaints before the initiation of treatment. Furthermore, we do not have data on which ground there was chosen for non-operative or surgical management. A substantial part of our patients were referred from other hospitals, we don't know exactly why they were referred for further management. Therefore, due to the possibility of unobserved confounders we have to be cautious not to overvalue our results. Also, data about patency at

last follow-up is lacking. A large proportion of our patients were referred from other institutions and after our management the follow-up was frequently carried out by the referring hospitals. It is well known that there is a lack of association between venous hemodynamics, venous morphology and post thrombotic complaints.^[7,8] In line with this discrepancy several authors mention patients with a complete occlusion without any complaints.^[9-12] Patient reported outcome measures (PROM's) are therefore the most important modality to evaluate treatment success. Although we do see a correlation between the DASH and Villalta scores (figure 1) we did also see a remarkable incoherency in our series. The non-operative treated patient with the worst modified Villalta score (12 points) had a better than average General DASH score (8.3 points) and reported no alterations in his daily activities.

Although we do acknowledge the conceptual superiority of surgical management with immediate recanalization with CDT followed by scheduled FRR, we have to point out that a substantial part of all non-operative treated patients are experiencing none to minimal complaints. In our series 67% of non-operative treated patients had a DASH score of ≤ 10 and can be therefore be grades as good to excellent. This has to be taken into account, when advising patients which management is most appropriate for their specific case. Shared decision making is essential in the management of PSS.

CONCLUSION

Surgical management of PSS with immediate CDT followed by FRR leads to excellent functional outcomes with low risk of complications. The results of non-operative treatment in our non-matched retrospective comparative series were satisfactory, but resulted in worse functional outcome and more patients needing to adjust their lifestyle.

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SUPPLEMENTAL DOCUMENT 1: MODIFIED VILLALTA SCORE

Please tick one box per question that best fits your complaints

In what extend did you experience pain in your affected arm in the last week?	☐ No pain ☐ Mild pain ☐ Moderate pain ☐ Severe pain
In what extend did you experience cramps in your affected arm in the last week?	☐ No cramps ☐ Mild cramps ☐ Moderate cramps ☐ Severe cramps
In what extend did you experience heaviness in your affected arm in the last week?	☐ No heaviness ☐ Mild heaviness ☐ Moderate heaviness ☐ Severe heaviness
In what extend did you experience tingling sensations in your affected arm in the last week?	☐ No heaviness ☐ Mild heaviness ☐ Moderate heaviness ☐ Severe heaviness
In what extend did you experience itching in your affected arm in the last week?	☐ No heaviness ☐ Mild heaviness ☐ Moderate heaviness ☐ Severe heaviness
In what extend was your arm swollen / did you experience edema of your affected arm in the last week?	☐ No swelling /edema ☐ Mild swelling /edema ☐ Moderate swelling /edema ☐ Severe swelling /edema
In what extend is the skin of your affected arm red or brown discolored?	☐ No red or brown skin discoloration ☐ Mild red or brown skin discoloration ☐ Moderate red or brown skin discoloration ☐ Severe red or brown skin discoloration
In what extend are the veins enlarged in your affected arm?	☐ No enlarged veins ☐ Mild enlarged veins ☐ Moderate enlarged veins ☐ Severe enlarged veins

SUPPLEMENTAL DOCUMENT 2 - DISEASE SPECIFIC QUESTION:

After the occurrence of the thrombosis, to what extent have you adjusted your lifestyle, daily activities and sports practice in order to experience as few complaints as possible in your right/ left arm? *(choose one of the three options below, choose the one that best applies to you)*

- ☐ I have made no adjustments and use my left arm just like before the thrombosis.

I still exercise / could exercise as before the thrombosis.

- ☐ I had to make some adjustments. I spare my left arm with heavy physical activity.

I exercise / could exercise but not as intensively as before the thrombosis.

- ☐ I have made clear adjustments. I had to make choices in my work and/or sports. I can no longer practice the work I did before or my sport as before the thrombosis

SUPPLEMENTAL DOCUMENT 3. RAW DATA

Table 1. patients with follow up / response

Case	Gender	Age (years)	Follow-up (months)	Affected side	Affected side Dominant	Pre-existing symptoms	Smoking	Oral contraceptive	Known clotting disorder	Effort induced	Primary management	Primary management successful	Recurrence of thrombosis	time to re-thrombosis	FRR	Venous reconstruction	Time to FRR (months)	Complications	DASH score (0-100)			Modified Villalta score (0-21)	Life-style adjustments
																			G	W	S		
1	F	21	459	R	Y	Y	Y	Y	Y	Y	AC	Y	Y	168	Y	N	168	?	25,8	0	43,8	7	S
2	F	44	178	L	N	Y	Y	N	Y	Y	AC	Y	Y	2	Y	N	6	pneumothorax	21,7	0	12,5	7	M
3	F	40	235	R	Y	N	N	N	Y	Y	AC	Y	Y	6	Y	Y	10	hematoma, hemothorax (VATS)	0	0	0	0	N
4	M	29	311	R	N	Y	N	X	Y	Y	CDT	Y	Y	23	N/?	N	X	X	10,8	56,3	25	7	X
5	M	19	244	R	Y	N	Y	X	N	N	CDT	Y	Y	4	Y	Y	88	none	31,7	62,5	X	9	S
6	M	33	228	L	N	N	Y	X	N	Y	CDT	N	X	#	N/?	N	X	X	3,3	0	0	0	N
7	F	19	208	L	N	N	N	Y	N	Y	AC	Y	Y	10	Y	Y	13	removal steel sternal wire, resection hypertrophic scar	0	0	0	0	N
8	F	16	270	R	Y	N	N	N	N	Y	CDT	Y	N/?	X	N/?	N	X	X	17,5	0	25	5	M
9	M	23	111	L	Y	?	?	X	?	?	CDT	Y	N/?	X	N/?	N	X	X	11,7	12,5	87,5	4	S
10	M	24	330	L	N	N	N	X	N	N	CDT	Y	Y	1	N/?	N	X	X	5,8	0	0	3	M
11	M	41	74	L	N	N	N	X	N	Y	CDT	N	X	#	N/?	N	X	x	0	0	0	1	N
12	F	36	56	R	N	N	N	Y	N	N	AC	N	X	#	N/?	N	X	x	0	X	X	0	M
13	F	32	123	R	Y	N	N	Y	N	Y	AC	Y	N/?	X	N/?	N	X	x	12,5	X	X	5	M
14	F	49	130	R	N	N	N	Y	N	N	AC	Y	N/?	X	N/?	N	X	x	0	0	X	0	N
15	M	51	130	R	Y	N	N	X	N	N	CDT	Y	Y	0,5	N/?	N	X	x	5	0	X	0	M
16	M	48	108	R	Y	N	N	X	N	N	CDT	Y	N/?	X	N/?	N	X	x	5	0	25	1	M

Table 1. Continued

Case	Gender	Age (years)	Follow-Up (months)	Affected side	Affected side Dominant	Pre-existing symptoms	Smoking	Oral contraceptive	Known clotting disorder	Effort induced	Primary management	Primary management successful	Recurrence of thrombosis	time to re-thrombosis	FRR	Venous reconstruction	Time to FRR (months)	Complications	DASH score (0-100)			Modified Villalta score (0-21)	Life-style adjustments
																			G	W	S		
17	F	38	165	R	N	N	N	N	N	Y	AC	Y	N/?	X	N/?	N	X	X	0	0	0	2	N
18	M	40	217	R	Y	N	Y	X	?	N	AC	N	X	#	N/?	N	X	X	5,8	12,5	0	4	M
19	F	16	232	L	N	?	?	?	?	?	AC	Y	N/?	X	N/?	N	X	X	24,2	43,8	62,5	X	X
20	F	20	185	R	Y	N	Y	Y	N	Y	AC	Y	N/?	X	Y	N	11	X	X	X	X	6	S
21	F	19	190	R	Y	?	N	?	N	N	AC	Y	N/?	X	Y	Y	22	X	13,8	12,5	43,8	5	M
22	F	45	126	L	N	?	Y	N	N	N	AC	Y	N/?	X	Y	Y	16	pleural effusion, atelectasis	56,7	68,8	X	8	S
23	F	28	108	R	Y	N	N	Y	?	N	CDT	Y	N/?	X	N/?	N	X	X	11,7	12,5	56,3	4	M
24	M	18	173	R	Y	N	N	X	N	Y	AC	Y	N/?	X	N/?	N	X	X	2,5	0	0	3	N
25	M	28	224	L	N	Y	Y	X	N	N	AC	Y	Y	42	Y	Y	60	X	0	0	0	0	M
26	M	20	430	L	Y	N	N	X	N	Y	CDT	Y	Y	132	Y	N	137	scapula alata (transient)	1,7	0	0	2	N
27	F	25	147	R	N	N	N	Y	Y	N	AC	Y	N/?	X	N/?	N	X	X	1,7	0	X	4	M
28	M	20	253	R	Y	N	N	X	N	Y	AC	Y	Y	14	N/?	N	X	X	7,5	0	37,5	3	S
29	M	30	134	L	N	N	N	X	N	Y	CDT	Y	N/?	X	N/?	N	X	X	0	0	0	0	N
30	M	40	166	R	Y	Y	N	X	N	N	0	Y	N/?	X	Y	Y	80	hematoma, hemothorax (VATS)	4,2	0	18,8	6	M
31	F	40	179	R	Y	Y	N	N	N	Y	AC	Y	Y	24	N/?	N	X	X	25,8	37,5	X	9	M
32	M	35	62	R	Y	N	N	X	N	Y	CDT	Y	N/?	X	N/?	N	X	X	5	0	12,5	4	M
33	M	50	180	L	N	N	N	X	N	N	AC	Y	N/?	X	N/?	N	X	X	4,2	0	6,3	0	N
34	M	27	131	R	Y	N	Y	X	N	?	CDT	Y	N/?	X	N/?	N	X	X	0,8	0	0	0	N

Table 1. Continued

Case	Gender	Age (years)	Follow-Up (months)	Affected side	Affected side Dominant	Pre-existing symptoms	Smoking	Oral contraceptive	Known clotting disorder	Effort induced	Primary management	Primary management successful	Recurrence of thrombosis	time to re-thrombosis	FRR	Venous reconstruction	Time to FRR (months)	Complications	DASH score (0-100)			Modified Villalta score (0-21)	Life-style adjustments
																			G	W	S		
35	M	44	135	R	Y	N	N	N	N	N	AC	Y	N/?	X	N/?	N	X	X	8,3	0	25	1	M
36	M	47	101	L	N	N	N	N	N	N	AC	Y	Y	94	N/?	N	X	X	34,2	58,3	62,5	6	M
37	M	32	43	L	N	N	N	Y	?	N	AC	Y	N/?	X	N/?	N	X	X	1,7	12,5	0	3	N
38	M	43	79	R	Y	N	Y	X	N	Y	AC	Y	Y	3	N/?	N	X	X	8,3	37,5	X	12	N
39	M	47	90	L	N	N	Y	X	?	?	AC	N	X	#	N/?	N	X	X	6,3	6,7	X	2	N
40	F	43	269	L	N	N	Y	Y	N	Y	CDT	Y	Y	2	N/?	N	X	X	5,8	X	0	0	N
41	M	29	115	R	N	N	Y	X	N	?	CDT	Y	N/?	X	N/?	N	X	X	0	0	0	0	N
42	M	27	100	L	N	N	N	X	N	Y	AC	Y	N/?	X	N/?	N	X	X	0,8	0	0	2	N
43	F	22	103	L	N	N	N	Y	N	Y	AC	Y	N/?	X	N/?	N	X	X	16,7	31,3	43,8	5	M
44	M	22	101	L	N	N	N	X	N	Y	AC	Y	N/?	X	N/?	N	X	X	2,5	0	37,5	1	M
45	F	38	154	R	Y	N	Y	Y	Y	Y	CDT	N	X	#	N/?	N	X	vaginal bleeding during CDT	12,5	25	18,8	4	M
46	M	53	129	R	Y	N	Y	X	N	?	AC	Y	N/?	X	Y	N	39	X	9,2	X	31,3	1	S
47	M	36	159	R	Y	N	Y	X	N	Y	AC	N	X	#	N/?	N	X	X	0	0	0	0	S
48	M	40	147	R	Y	N	N	X	N	?	AC	Y	N/?	X	N/?	N	X	X	0	0	0	0	N
49	M	18	263	R	Y	N	N	X	N	Y	AC	Y	Y	12	Y	N	16	Bleeding (re-operation) pleural effusion (thoracosentesis)	0	0	0	0	S
50	F	21	246	R	N	N	Y	Y	N	N	AC	Y	Y	108	N/?	N	X	X	1,7	0	0	1	N
51	F	47	269	R	Y	N	Y	N	Y	N	AC	Y	N/?	X	N/?	N	X	X	27,7	X	X	5	N
52	F	24	89	R	Y	N	N	Y	N	N	CDT	Y	N/?	X	Y	N	3	scapula alata, apical pleural effusion/hematoma	50,8	37,5	43,8	11	S

Table 1. Continued: patients 53-71: primary surgical treated patients

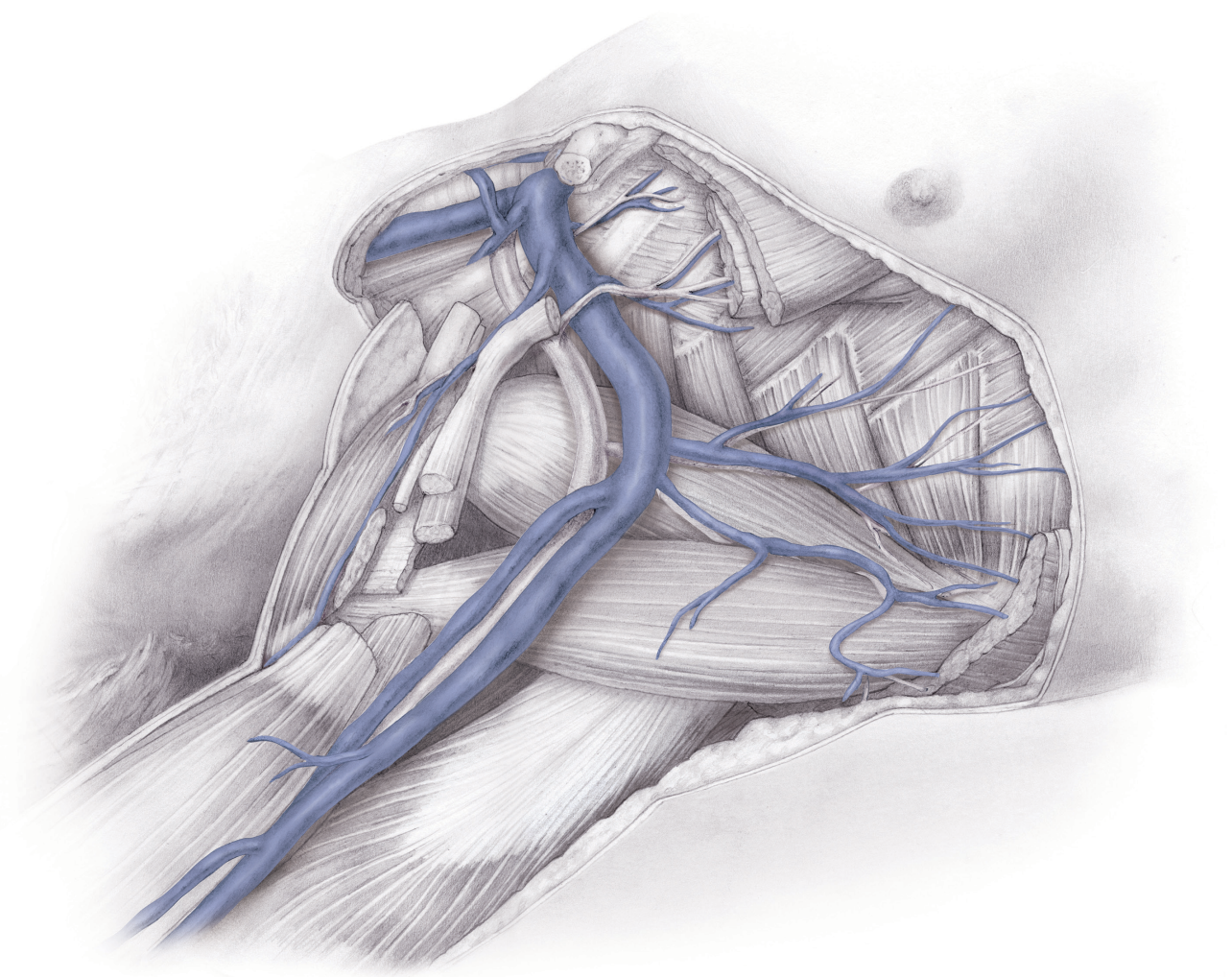
Case	Gender	Age (years)	Follow-Up (months)	Affected side	Affected side Dominant	Pre-existing symptoms	Smoking	Oral contraceptive	Known clotting disorder	Effort induced	Primary management	Primary management successful	Recurrence of thrombosis	time to re-thrombosis	FRR	Venous reconstruction	Time to FRR (months)	Complications	DASH score (0-100)			Modified Villalta score (0-21)	Life-style adjustments
																			G	W	S		
53	M	31	192	L	N	N	N	X	N	Y	CDT	Y	N	X	Y	N	20	none	0	0	X	0	N
54	F	50	192	L	N	N	Y	N	?	N	CDT	Y	N	X	Y	N	6	none	7,5	X	0	0	N
55	F	32	211	R	N	N	Y	Y	N	Y	CDT	Y	N	X	Y	N	8	none	0	0	0	0	N
56	F	41	152	R	N	N	N	N	N	N	CDT	Y	N	X	Y	N	1	bleeding, conservative	6,7	0	25	2	M
57	F	26	297	R	Y	N	Y	N	N	N	CDT	Y	N	X	Y	N	2	none	0	0	0	0	N
58	F	46	153	R	Y	N	Y	N	N	N	CDT	Y	N	X	Y	N	4	none	3,3	0	X	5	N
59	M	26	306	L	N	N	X	N	Y	Y	CDT	Y	N	X	Y	N	2	Urine retention	0	0	0	0	N
60	M	24	194	L	N	N	Y	X	N	Y	CDT	Y	N	X	Y	N	3	None	0,8	0	0	0	N
61	F	39	136	R	Y	N	N	N	Y	Y	CDT	Y	N	X	Y	N	4	Neuralgia	5	6,3	25	4	M
62	F	24	130	L	N	N	Y	N	Y	Y	CDT	Y	N	X	Y	N	6	intercostobrachial hypoalgesia	0	0	0	0	N
63	M	32	370	R	Y	N	N	X	N	?	CDT	Y	N	X	Y	N	3	Unknown	0	0	0	0	N
64	F	25	79	R	1	N	Y	Y	N	Y	CDT	Y	N	X	Y	N	5	hypoalgesia	0	0	X	0	N
65	M	18	286	R	N	N	Y	X	?	?	CDT	N	N	X	Y	N	3	none	0	0	0	0	N
66	M	21	254	L	Y	N	Y	X	?	?	CDT	Y	Y	4	Y	N	6	none	0	0	0	2	N
67	F	44	90	R	Y	N	N	Y	N	N	CDT	Y	N	X	Y	N	7	none	30	0	37,5	4	S
68	M	23	322	R	N	N	X	N	N	N	CDT	Y	N	X	Y	N	3	Bleeding (re-operation)	2,5	0	0	0	N
69	M	27	340	R	Y	N	Y	X	N	N	CDT	Y	N	X	Y	N	3	None	0	0	0	0	N
70	F	18	60	R	Y	N	N	Y	N	Y	CDT	Y	N	X	Y	N	1	pneumothorax (drain)	2,5	0	6,3	3	N
71	M	41	150	R	Y	N	N	X	N	Y	CDT	Y	N	X	Y	N	5	pneumothorax	0,8	0	0	1	N

Table legend: AC = anticoagulation (LMWH / heparin /OAC /DOAC), CDT = catheter directed thrombolysis, F = female, FRR = first rib resection, gray, M = male (gender) or Moderate (life style adjustment), N = no, X = not applicable, Y = yes, ? = unknown, # = no recanalization with AC or CDT not successful, red = bilateral patients

Table 2. patients without follow up / response

Case	Gender	Age (years)	Affected side	Primary management	Primary management successful	Recurrence of thrombosis	time to re-thrombosis	FRR	Venous reconstruction	Time to FRR (months)	Complications of FRR
72	M	24	R	AC	Y	Y	72	Y	Y	75	?
73	F	32	R	CDT	Y	Y	2	N/?	N	X	x
74	M	22	R	AC	Y	Y	18	Y	Y	31	x
75	M	31	L	CDT	N	X	#	N/?	N	X	Hemoptysis during CDT
76	M	61	L	CDT	Y	N/?	X	N/?	N	X	X
77	F	41	L	CDT	Y	N/?	X	N/?	N	X	X
78	F	17	R	AC	Y	N/?	X	Y	N	12	X
79	F	18	R	AC	Y	N/?	X	N/?	N	?	?
80	F	37	L	AC	Y	N/?	X	N/?	N	?	?
81	M	28	R	AC	Y	N/?	X	Y	Y	10	epileural hematoma, atelectasis. Hemothorax (thoracotomy)
82	M	43	L	CDT	Y	N/?	X	N/?	N	X	x
83	F	17	L	CDT	Y	Y	10	N/?	N	X	x
84	M	33	L	AC	Y	Y	58	N/?	N	X	x
85	F	32	R	AC	Y	Y	13	N/?	N	X	x
86	M	35	R	CDT	Y	N/?	X	Y	N	13	None
87	F	31	R	AC	Y	Y	6	N/?	N	X	x
88	M	24	L	AC	Y	Y	15	N/?	N	X	x
89	M	22	R	CDT	Y	N/?	X	Y	N	19	Bleeding (re-operation)
90	F	39	R	CDT	Y	N/?	X	N/?	N	X	X
91	M	50	R	CDT	Y	N/?	X	N/?	N	X	X
92	M	63	L	CDT	Y	Y	3	N/?	N	X	X
93	M	18	R	CDT	Y	N/?	X	Y	N	3	None
94	M	63	L	CDT	Y	N/?	X	Y	N	13	None
95	M	48	L	CDT	Y	N/?	X	Y	N	24	?

Table legend: AC = anticoagulation (LMWH / heparin /OAC /DOAC), bold = primary surgical treated patients, CDT = catheter directed thrombolysis, F = female, FRR = first rib resection, M = male, N = no, X = not applicable, Y = yes, ? = unknown, # = no recanalization with AC or CDT not successful,



CHAPTER 8

Functional outcome of patients undergoing primarily or on-demand first rib resection for Paget-Schroetter Syndrome; a prospective case series

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ABSTRACT

Objectives: In Paget-Schroetter Syndrome (PSS) subclavian vein thrombosis is caused by external compression of the subclavian vein at the costoclavicular junction. Prompt treatment with catheter directed thrombolysis (CDT) and subsequent primarily first rib resection (P-FRR) can be performed. Alternatively, non-operative treatment can be initiated, reserving on-demand FRR (OD-FRR) for patients with residual complaints and/or recurrent thrombosis. Comparative studies investigating functional outcome are lacking. Our objective was to prospectively objectify the functional outcomes of patients who required OD-FRR and patients undergoing P-FRR using the standardized DASH questionnaire.

Methods: All patients scheduled to undergo P-FRR or OD-FRR were asked to participate in this study. Pre-operative and postoperative functional outcomes were recorded with the “disabilities of arm, shoulder and hand” (DASH) questionnaire. All data regarding the surgical procedure, outcome and complications were recorded prospectively.

Results: from June 2014 to July 2020 a total of 24 patients (P-FRR n=10, OD-FRR n= 14) were included. Mean General DASH scores at 12 months was 6.5 for P-FRR and 21.6 for OD-FRR. Complications (n=20) were reported in 12 patients (P-FRR n= 5, OD-FRR n= 7). Performing venous reconstruction or patch was associated with an increased risk of postoperative complications (87,5% vs. 31.3%). Patency at mean follow up of 12.4 months was 80%. Recurrence of thrombosis was more frequent in the OD-FRR group (0/8 vs 4/12) and was associated with worse postoperative DASH scores (9.4 vs 43.5). 46% of patients who received OD-FRR reported improved general DASH at 12 months versus 70% of patients who received P-FRR.

Conclusions: DASH scores of patients treated with P-FRR after one year are excellent. Patients requiring OD-FRR reported less favorable DASH scores. Elaborate surgery with venous reconstruction is more often required during OD-FRR and is associated with an increased risk of complications. Recurrence of thrombosis is more frequent after OD-FRR and results in worse functional outcomes.

INTRODUCTION

Paget-Schroetter Syndrome (PSS) is a distinct entity within the venous thoracic outlet syndrome (vTOS) in which thrombosis of the subclavian vein is caused by external compression of the subclavian vein in the thoracic outlet at the costoclavicular junction. [1] PSS can be treated non-operatively, surgically or by a combination of treatments. Non-operative treatment includes anticoagulation (AC), catheter directed thrombolysis (CDT) or other comparable catheter based therapies. Surgical management is aimed to prevent recurrence of thrombosis and to achieve good functional outcome on the long term. Surgery consists of decompression of the subclavian vein by first rib resection (FRR) and, if indicated, combined with venous reconstruction. Surgical decompression is preceded by CDT in most cases. Currently, there is no consensus on the optimal management of PSS.[2] Published reports are predominantly retrospective in design, have only short follow up, and assessment of functional outcomes is often not well reported. In recent years the surgical management of PSS has become increasingly popular with CDT as initial therapy followed by elective primary FRR (P-FRR). Failure of non-operative management may warrant FRR to alleviate recurrent or chronic complaints and can be classified as On-Demand FRR (OD-FRR).

Our recent review and meta-analysis supports the surgical management of PSS, although more than half of patients treated non-operatively were symptom free at last follow up. [3] This raises the question if it would be safe to explore a non-operative management first and if necessary cross over to a surgical treatment if non-operative management fails. Therefore the results of OD-FRR need to be investigated. Our objective was to describe the functional outcomes of patients who required OD-FRR and patients undergoing P-FRR using the Disabilities of the Arm, Shoulder and Hand questionnaire (DASH).[4]

METHODS

Approval for this research was obtained from the Medical Ethics Review Committee of the Amsterdam Medical Centers.

Institutional protocol non-referred patients

Patients with suspected PSS were evaluated with duplex ultrasound. In the case of a negative ultrasound, but a high clinical suspicion, venography was performed. In patients with proven PSS both surgical and non-operative treatment options were discussed with the patient and the decision to initiate a specific treatment was made using shared decision-making. Within the shared decision making phase the opinion of the patient was decisive. Non-operative management consisted of a vitamin K antagonist or Direct

Oral Anticoagulant (DOAC) for the duration of 6 months. Surgical management consisted of CDT followed by anticoagulation, elective P-FRR on short term and 3 months of postoperative anticoagulation (vitamin K antagonist or DOAC). Non-operatively treated patients received clinical follow up without standard imaging of venous patency. In case of recurrent complaints after initial non-operative management imaging was obtained and OD-FRR was offered if indicated. In case of static stenosis or occlusion of the subclavian vein, venous reconstruction was considered. In primarily surgical treated patients venous patency was assessed after FRR with duplex or venography. In case of persistent residual stenosis a percutaneous transluminal angioplasty (PTA) was performed. The use of intravenous stents was only considered in patients with persistent stenosis after serial PTA's without sufficient results.

Institutional protocol referred patients

Depending on the initial therapy performed in the referring hospital the management was tailored to the needs and preference of the patients. Patients with complaints after initial non-operative management (AC or CDT) were offered OD-FRR. In case of static stenosis or occlusion of the subclavian vein, venous reconstruction was considered. Patients without complaints after initial therapy were counselled and offered both non-operative management or P-FRR as described above.

Patient selection and study design

All patients diagnosed with PSS who were scheduled for FRR between June 2014 and July 2020 for FRR were eligible for inclusion. After obtaining informed consent patients were enrolled pre-operatively and filled out the baseline standardized Disabilities of the Arm, Shoulder and Hand questionnaire (DASH). At 3, 6 and 12 months postoperatively this DASH questionnaire was send by mail to participants for postoperative evaluation. Data regarding patient characteristics, initial management of PSS, success of initial management and recurrence of thrombosis before FRR were retrospectively recorded from their medical files. Data regarding the surgical procedure, postoperative hospital stay, complications, recurrence of thrombosis and patency were prospectively recorded. Eight patients who underwent robot assisted transthoracic first rib resection were also included in our previously published case series on this technique.[1] Various surgical techniques were used tailored to the specifics of the patients. After successfully restoring patency using AC or CDT, with or without additional PTA, a robot-assisted transthoracic, transaxillary or infraclavicular approach was used. No intra-operative venography was used. In case of persistent stenosis after initial non-operative management a paraclavicular

(combined infra- and supraclavicular) or Molina[5] approach was used because of the need for venous reconstruction. All asymptomatic patients who were subsequently scheduled to undergo first rib resection within 6 months after initial management of PSS were appointed to the P-FRR group. All patients with PSS who were treated initially non-operatively with anticoagulant therapy and were scheduled to undergo first rib resection after 6 months or because of persistent complaints were appointed to the OD-FRR group.

RESULTS

During the study period 26 patients underwent FRR for management of PSS. Two patients were excluded. In one patient no pre-operative DASH score was available. The other patient withdrew informed consent during the study period. Patient characteristics, management and outcomes are presented in supplement document table 1 for the two groups. Supplement document tables 2 and 3 provides the data on individual patients. Half of the patients were referred from other institutions. No cervical ribs were identified in this cohort. In 7 patients (29,2%) an osseous anomaly was reported. Acute PSS was diagnosed in 23 patients. In 10 patients FRR was primarily scheduled after initial management, in 14 patients FRR was performed on demand because of persistent complaints or recurrence of thrombosis. More information regarding both treatment groups are presented in the figure 1.

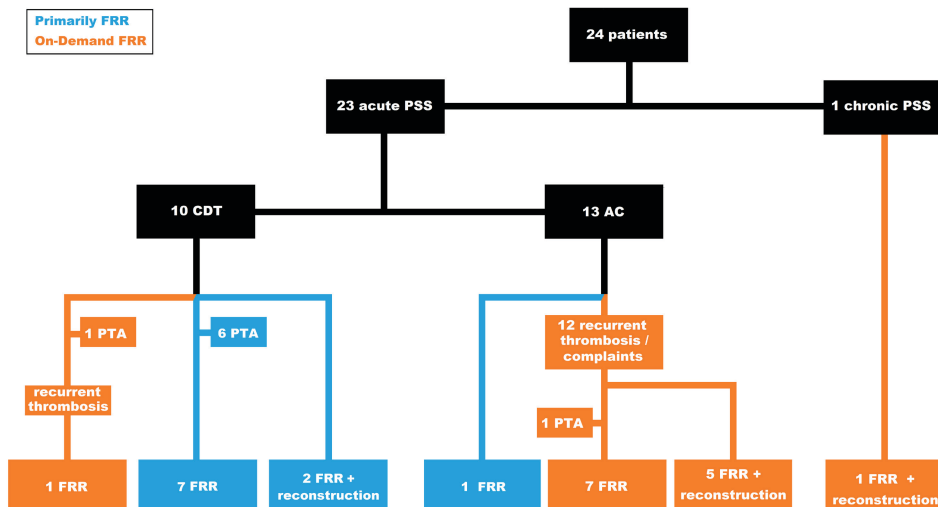


Figure 1. Flow chart management

Figure legend: Legend: AC = anticoagulation, CDT = catheter directed thrombolysis, FRR = first rib resection, PSS = Paget-Schroetter Syndrome, PTA = percutaneous transluminal angioplasty

Primarily first rib resection

All 10 patients (7 males, mean age 31.3 years) presented with acute PSS. Median time from onset of complaints to start treatment was 3 days (range 0 – 37 days). Initial management of PSS was CDT in 9 patients and AC in 1 patient. CDT was successful in 8/9 patients. Mean duration of CDT was 47.6 hours (range 21-72). Recanalization of the subclavian vein was achieved in the patient treated with AC. Additional pre-operative percutaneous transluminal angioplasty (PTA) was performed in 5 patients. Median time to P-FRR was 86 days (range 14 - 166). No patients experienced recurrence of thrombosis between initial therapy and P-FRR. Three different approaches were used for FRR: Robot assisted transthoracic n= 4; transaxillary n= 4 and paraclavicular n=2. Additional procedures were performed in 2 patients (venous reconstruction n=1, venous patch n=1). Mean operation time was 117 minutes (range 44 – 283). In 1 robot –assisted procedures conversion to a transaxillary approach was necessary because an osseous anomaly prevented transthoracic transection of the first rib. No other intraoperative complications were seen. Mean hospital stay was 2.9 days (range 1-6). Five patients (50%) reported 8 complications requiring 4 re-interventions (Clavien-Dindo grade ≥ 3) in 3 patients.[table 1] One patient required post-operative PTA without placement of an intravenous stent. Postoperative DASH questionnaires were returned in 73% (22/30). Mean DASH scores decreased over time with a General DASH score at 12 months of 6.5, corresponding with excellent overall function.[table2, figure 2] Seventy percent (7/10) of patients reported a better (lower) general DASH score at 12 months compared to pre-operative. Objective follow up was available in 8 patients (duplex n=5, venography n=3) with a mean time from P-FRR of 11.3 months (range 1-35 months). All 8 patients had a patent vein at follow up, with only one patient needing postoperative PTA.

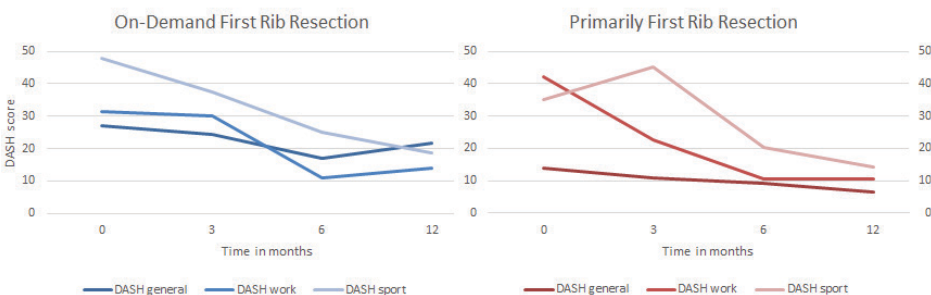


Figure 2. DASH scores of On-Demand and Primarily First Rib Resection

Figure legend: DASH = Disabilities of the Arm, Shoulder, and Hand Questionnaire

Table 1. Complications of first rib resection

Complication	Treatment	Clavien-Dindo grade	FRR	
			P (n=5)	OD (n=7)
Hematoma	Conservative	1	1	
Scapula alata	Conservative	1	1	
Phrenic nerve injury	Conservative	1		1
Neuropathy arm	Conservative	1		1
Influenza infection	Conservative	1		1
SSI donorsite SVG	AB, opening wound bedside	2		1
Pneumonia	Antibiotic treatment	2	2	1
Hemothorax / pleural effusion	Pleurocentesis	3a		2
Thrombosis subclavian vein	thrombosuction + PTA	3a	1	
Bleeding intercostal artery	Coiling	3a		1
Epipleural hematoma	Pleurocentesis	3a		1
Chyleous leakage	thorac duct embolization	3a	1	
Hematoma	evacuation	3b		1
Hemothorax / rebleeding	re-exploration / VATS	3b	2	2
Totals			8	12

Table legend: FRR = first rib resection OD = on-demand, n= number, P = primarily, PTA = percutaneous transluminal angioplasty, SSI = surgical site infection, SVG = saphenous vein graft, VATS = video assisted thoracic surgery

Table 2. Functional outcome, DASH scores

DASH SCORE	Overall		P-FRR		OD-FRR		Patent SCV at last follow up		Occluded SCV at last follow up	
	n=24		n=10		n=14		n=16		n=4	
Pre-operative										
General	n=24	21.6	n=10	14.0	n=14	27.0	n=16	18.7	n=4	33.1
Work	n=17	35.7	n=7	42.0	n=10	31.3	n=12	29.7	n=2	40.6
Sport	n=14	43.3	n=5	35.0	n=9	47.9	n=10	35.0	n=2	78.2
3 months										
General	n=10	18.7	n=5	10.8	n=7	24.2	n=6	18.8	n=3	29.6
Work	n=10	26.3	n=5	22.5	n=5	30.0	n=6	17.7	n=2	37.5
Sport	n=10	40.6	n=4	45.3	n=6	37.5	n=5	40.0	n=2	53.2
6 months										
General	n=13	12.8	n=7	9.2	n=6	17.1	n=8	8.5	n=3	27.9
Work	n=10	10.6	n=5	10.4	n=5	10.8	n=7	5.7	n=2	20.9
Sport	n=10	23.1	n=4	20.3	n=6	25.0	n=6	15.6	n=3	37.5
12 months										
General	n=23	15.1	n=10	6.5	n=13	21.6	n=15	9.4	n=4	43.5
Work	n=19	12.2	n=9	10.4	n=10	13.8	n=12	8.9	n=3	25.0
Sport	n=19	16.7	n=8	14.1	n=10	18.8	n=14	15.2	n=2	34.4

Table legend: all DASH scores are mean values. DASH = disabilities of arm shoulder and hand questionnaire, FRR = first rib resection, n = number, OD = on demand, P = primarily, SCV = subclavian vein

On-Demand first rib resection

Fourteen patients (6 males, mean age 32.9 years) underwent OD-FRR. Thirteen patients had presented in the past with acute PSS as their index event and were treated non-operatively. Median time from onset of complaints to start initial treatment was 3,5 days (range 0–428). Initial management of PSS with AC was instituted in 12 patients (successful recanalization in 8), in 1 patient CDT was performed to restore patency. Additional percutaneous transluminal angioplasty (PTA) was performed in 2 patients. One patient did not receive any initial treatment because of prolonged chronic complaints. Median time from the index event and OD-FRR was 427 days (range 208 days - 15 year). Seven patients experienced 8 episodes of recurrence of thrombosis between initial therapy and OD-FRR and were treated with AC (n=7) and CDT (n=1). Five different approaches were used for FRR: Robot assisted transthoracic n= 5; Molina n= 4; transaxillary n= 2; paraclavicular n=2; infraclavicular n= 1. An additional venous reconstruction because of persistent occlusion or severe stenosis was performed in 6 patients. Mean operation time was 198 minutes (range 74 – 563). In 3 robot –assisted procedures conversion to a transaxillary approach was necessary. In one patient an osseous anomaly prevented transthoracic transection of the first rib. In another case, conversion was performed because of a peroperative bleeding. In the last patient selective ventilation of one lung was not tolerated prohibiting and transthoracic approach and necessitating conversion. In one patient multiple per-operative occlusions of the venous reconstruction occurred necessitating revisions resulting in a prolonged operation time (563 minutes). Mean hospital stay was 5.1 days (range 1-12). Seven patients (50%) reported 12 complications requiring 7 re-interventions (Clavien-Dindo grade ≥ 3) in all 7 patients.[table 1] Three patients required post-operative PTA with stent placement in one. Postoperative DASH questionnaires were returned in 62% (26/42). Mean DASH scores decreased over time with a General DASH score at 12 months of 21.6, corresponding with a satisfying overall function.[table 2, figure 2] Forty-six percent (6/13) of patients reported a better (lower) general DASH score at 12 months compared to pre-operative. Objective follow up was available in 12 patients (duplex n=8, venography n=3, CT venography n=1) with a mean time from OD-FRR of 13.2 months (range 2-26 months). Eight patients had a patent vein at follow up, two patients had received postoperative PTA, four patients had occlusion of the vein.

DISCUSSION

Our prospective case series underlines the current concept that surgical management of PSS consisting of CDT followed by scheduled P-FRR leads to excellent results with a mean general DASH score of 6.5 at 12 months. This score is equivalent to the normative values in the general population.[6] The DASH scores of patients requiring OD-FRR in our series was 21.6. This score is worse compared to the normative values in the general population (age 30-39: normative DASH score males 5; females 8). [6] Only 46% of patients needing OD-FRR reported better general DASH scores at 12 months compared to their pre-operative baseline scores. In the P-FRR group 70% of the patients reported better general DASH scores at 12 months compared to pre-operative. OD-FRR more often had to be combined with additional revascularization to restore patency. This resulted in more complications. In 50% of patients who underwent OD-FRR a complication that necessitated a reintervention was recorded. Complications needing reinterventions were reported in 30% of patients in the P-FRR group.

Currently there is no definitive consensus on the best management of PSS because randomised trials are lacking.[2] In correspondence with the management of lower extremity DVT, non-operative treatment is based on (oral) anticoagulation which facilitates secondary recanalization and/or increased outflow through collateral veins, CDT is in some cases used as an adjunct in restoring patency. Surgical management is focussed on immediate restoring patency of the native subclavian and/or axillary vein with catheter based therapies (i.e. catheter directed thrombolysis, thrombosuction or pharmacomechanical thrombolysis/thrombectomy) and preventing recurrent thrombosis by eliminating the external compression of the subclavian vein at the costoclavicular junction by the first rib. Multiple case series have shown a high percentage of persistent complaints or risk of recurrent thrombosis in non-operative treated patients,[7-9] although a forgiving course is also reported by several authors. [10-12] Our recent review and meta-analysis supports the surgical management of PSS, although more than half of patients treated non-operatively were symptom free at last follow up.[3] Because of this lack of consensus, management strategies will differ between institutions and patients. Of the 11 referred PSS patients, 9 were treated with AC as initial therapy. In contrary 7 out of 12 patients who presented themselves in our institutions received CDT as first therapy after shared decision making. In our opinion immediate initiation of CDT after diagnosis of acute PSS will ensure early recanalization of the subclavian vein. This early recanalization of the subclavian vein could prevent the formation of collateral veins, and subsequently maintain high flow through the native

axillary and subclavian veins. This could lead to a decreased risk of recurrent thrombosis even if residual venous wall irregularities persist. The results of Phadke et al. are in line with this hypothesis; patients with high-grade collateralization had more repeat interventions compared to patients with low-grade collateralization.[13] Some authors agree with the possible beneficial role of CDT,[14-16] others couldn't find a superior result with CDT compared to AC as primary therapy.[17,18] Our recent meta-analysis supports the use of CDT.[3] Because of the conflicting evidence, objective counselling and shared decision making are essential to provide each individual patient tailored therapy to his or her preferences.

Residual venous wall irregularities found at the regular venograms during CDT were noted in almost all patients. This necessitated a pre-operative PTA in 7 patients in our series. Only 1 patient treated with AC had undergone venography and required PTA because of persistent venous wall irregularities. It is not recommended to use intravenous stents before surgical decompression because of the risk of stent related re-thrombosis and complications.[19-22] Recurrent thrombosis after initial therapy was diagnosed in 7 patients. No recurrent thrombosis was seen in the P-FRR group. All our recurrent thrombosis were diagnosed in patients in which OD-FRR was performed after AC as initial management.

Patients in the OD-FRR had more often post thrombotic sequelae like persistent occlusion or severe stenosis which necessitated more elaborate surgery. In chronic occlusion restoration of adequate outflow of the arm was less successful and surgical revascularisation was more often indicated. This resulted in longer operation time and more complications.

Occlusion at last follow up was diagnosed in 20% (4/20). All these patients had AC as initial therapy. The incidence of recurrence of thrombosis or persistent occlusion after surgical management of PSS vary in literature and ranges in series with adequate numbers of patients from 0% (0/126)[23] to 36% (13/36).[24] In our series patients with an occluded subclavian vein at follow up had worse functional outcomes. This relation between patency and complaints is not always clear. It is well known that there is a lack of association between venous hemodynamics, venous morphology and postthrombotic complaints.[25,26] In line with this discrepancy several authors mention patients with a complete occlusion without any complaints.[12,24,27,28] We advocate therefore the use of PROMS and focussing on the functional outcome of the therapy, rather than endpoints like patency or incidence of recurrence.

An osseous anomaly of the first rib was described in 7 patients (29.2%). Bone anomalies are not an uncommon cause in TOS although the association of vTOS with bone anomalies is still debated in literature. Weber et al. reported 115 anomalies in 400 patients (29%) with an anatomical variation concerning the first rib in 10 patients ($10/400 = 2,5\%$, 9% of all anomalies).[29] Weber et al. stated that only 4% of all venous TOS cases were associated with a bone anomaly.[28] In contrary Gharagozloo et al. compared 7 first ribs from human cadavers with 15 resected first ribs of patients with PSS and found in all 15 patients with PSS a bony tubercle that corresponded to the area of the subclavian vein groove.[30] They proposed the pathogenesis of this bony tubercle as the cause of PSS.[24] Furthermore a significantly increased width of the vertebral and sternal end of the first rib on postero-anterior chest and antero-posterior C-spine radiographs was reported by Chang et al. in 32 patients undergoing TOS related surgical decompression compared to 30 control patients.[31]

Strengths and weaknesses of this study

Reports comparing the outcomes of acute and chronic PSS are scarce, prospective reports are exceedingly rare and reports providing subjective functional outcomes using PROMS are lacking. Our pre- and postoperative DASH scores over time give valuable insight in the changes of complaints experienced by patients. The difference in DASH scores does cross the threshold for a minimal important difference of 10 points.[32]

Several limitations have to be taken into account when interpreting our results. Our cohort is of limited size. This is a common finding in series presenting data on PSS with the majority of case series presenting on 10 to 40 patients.[3] Centralization and/or collaboration in research projects is essential to increase the knowledge on this entity. Statistical analysis and comparison of the P-FRR and OD-FRR groups was deemed inappropriate because of the assumed heterogeneity of both groups. This was mainly caused by the difference in initial therapy as well in the surgical procedures. The lack of consensus on best treatment led to different initial therapy, not only in referred patients but also in our non-referred participants. After counselling, patients may opt non-operative management which may lead to a satisfying result. If non-operative treatment is unsuccessful some patients will require further surgical management. These more chronic cases of PSS will present with a variety of anatomical alterations which need tailored surgical management. Individual surgeons will perform FRR with revascularisation of the subclavian vein by different approaches as anatomical lesions will impose.

Despite the heterogeneity in this cohort, this series can be seen as a reflection of common practice of referred patients from other institutions with unsuccessful primary management of PSS.

CONCLUSION

Our prospective case series underlines the current concept that surgical management of PSS consisting of CDT followed by scheduled P-FRR leads to excellent results. Unlike the DASH scores of patients undergoing OD-FRR, mean DASH score of P-FRR were equivalent to the normative values of the general population. After failure of non-operative treatment, venous reconstruction was more often necessary in patients with recurrence of thrombosis or persisting complaints and was associated with an increased risk of complications. All patients managed with P-FRR had a patent subclavian vein at last follow up. In 33% of the patients who needed OD-FRR an occluded subclavian vein was recorded at last follow up. The DASH scores of these patients were less favourable. Further research, preferably prospective and randomised, is needed to confirm the claimed superiority of primarily invasive management of PSS.

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SUPPLEMENT DOCUMENT 1

Supplement table 1. Patient characteristics, management and outcomes of the P-FRR and OD-FRR groups

Patient characteristics and risk factors	P-FRR	OD-FRR
Sex		
- Male	7	6
- female	3	8
Age	31.3 (21-48)	32.9 (20-53)
Referred	3/10	9/14
Right side	5/10	10/14
Effort induced	7/8	8/12
Smoking	3/10	3/13
OC use	2/3	5/8
Cervical rib	0/10	0/14
Bone anomaly	4/10	3/14
Management	P-FRR	OD-FRR
Median time to start treatment	3 (0-37) days	4 (0-428) days
Initial therapy		
- AC	1	12
- CDT	9	1
Success initial therapy	9/10	9/14
Pre-op PTA	5/10	2/14
Median time to FRR	86 (14-166) days	427 (208-5715) days
Recurrence or persistent occlusion before FRR	0/10	11/14
Approach FRR		
- Transaxillar	4	2
- Robot assisted	4	5
- Paraclavicular	2	2
- Molina	0	4
- infraclavicular	0	1
Venous reconstruction	2/10	6/14
Mean OR time	117 (44-283) minutes	198 (74-563) minutes
Mean hospital stay	2.9 (1-6) days	5.1 (1-12) days
Post operative PTA	1/10	3/14
Post operative stent	0/10	1/14
complication	5/10	7/14
Outcomes	P-FRR	OD-FRR
Recurrence	0/10	6/14
Functional outcome		
- Pre-op DASH	14 (1-55)	27 (0-81.7)
- DASH 3 months	10.8 (6.7-18.3)	24.2 (0.8-67.2)
- DASH 6 months	9.2 (0.8-16.7)	17.1 (0.8-47.3)
- DASH 12 months	6.5 (0-22.4)	21.6 (0-65.5)
Follow up imaging	8/10	12/14
time between FFR and last imaging	11.3 (1-25) months	13.2 (2-26) months
Patent subclavian vein	8/8	8/12
stenosis	0/8	3/8

Supplement table 2. Patient characteristics and treatment of the individual patients.

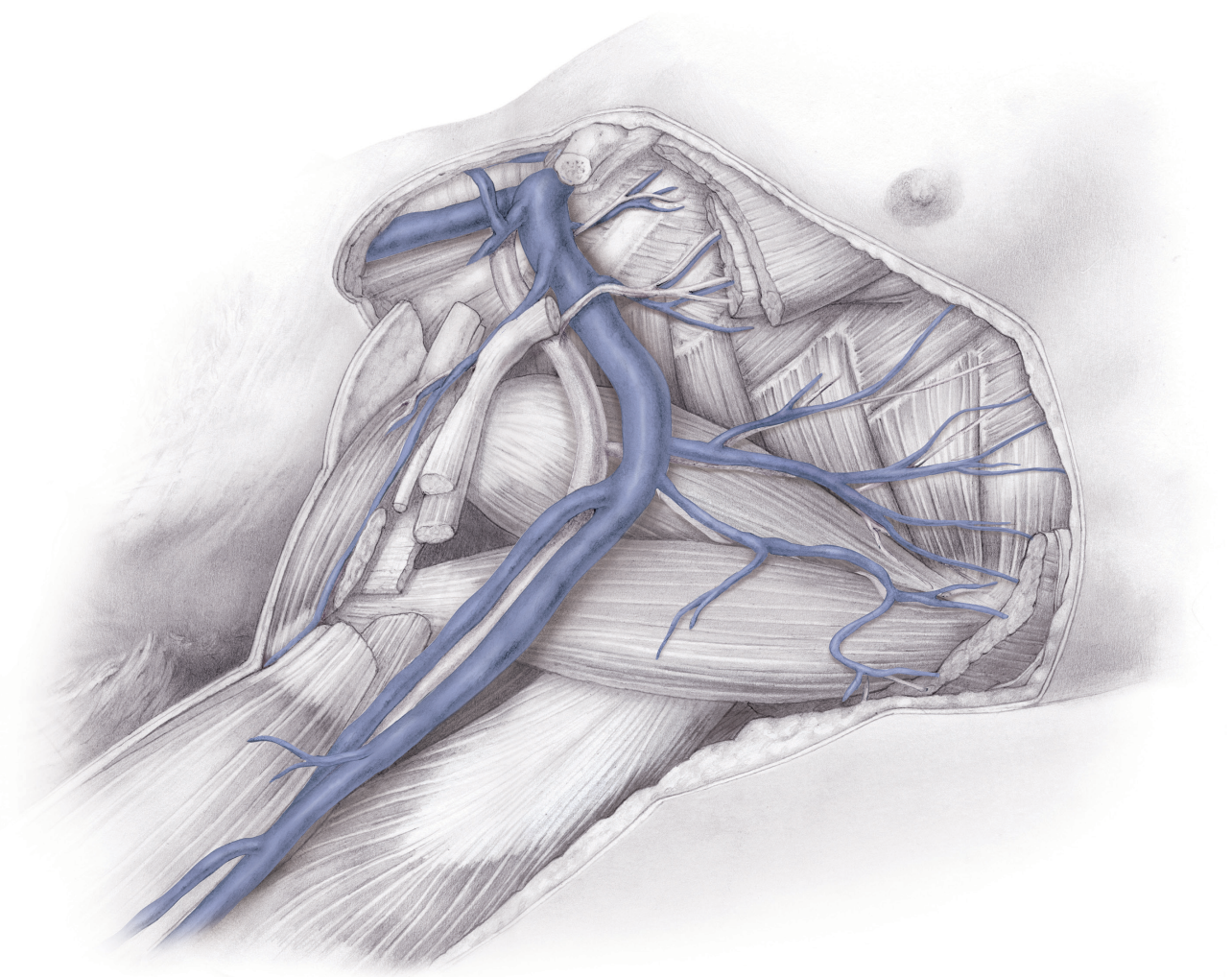
Pt	FRR P / OD	Sex	Age	Ref.	side	Effort induced	Activity	Smoking	OC Use*	Cervical rib	Time to start therapy (d)	Initial therapy	CDT duration (hr)	Pre-op. PTA	Time to FRR (d)	Recurrence before FRR (treatment)	Approach FRR	Venous Recon-struction	OR time (m)	Bone Anomaly	Hospital stay (d)	Post-op. PTA
1	P	M	22	Y	L	Y	Ballroom dancing	Y	n.a.	N	5	CDT	48	N	110	N	RAT	N	130	N	3	N
2	P	M	39	N	R	?	Unknown	N	n.a.	N	3	CDT	72	Y	166	N	RAT*	N	166	Y	4	N
3	P	M	28	N	L	Y	Fitness	N	n.a.	N	0	CDT	41	Y	154	N	RAT	N	88	N	2	N
4	P	F	24	N	L	?	Unknown	Y	Y	N	4	CDT	21	N	84	N	RAT	N	96	Y	3	N
5	P	M	21	N	R	Y	Fitness	N	n.a.	N	1	CDT	44	Y	30	N	TA	N	55	Y	3	Y
6	P	M	26	Y	L	Y	Overhead lifting	N	n.a.	N	1	CDT	48	Y	37	N	TA	N	71	N	1	N
7	P	M	38	Y	R	Y	Painting	Y	n.a.	N	37	CDT	34	Y	88	N	TA	N	44	N	1	N
8	P	F	41	Y	R	N	n.a.	N	N	N	10	AC	n.a.	N	118	N	TA	N	56	Y	2	N
9	P	M	48	N	L	Y	Painting, plastering	N	n.a.	N	3	CDT	72	N	14	N	PC	Y	283	N	6	N
10	P	M	26	N	R	Y	Overhead tiling	N	n.a.	N	1	CDT	24	N	44	N	PC	Y (patch)	181	N	4	N
11	OD	F	23	Y	R	Y	Fitness	N	Y	N	3	AC	n.a.	N	320	N	RAT	N	120	N	4	N
12	OD	F	44	Y	L	?	Unknown	?	N	N	0	AC	n.a.	Y	763	Y, 2x (AC)	RAT*	N	131	N	8	N
13	OD	F	23	Y	R	N	n.a.	Y	Y	N	6	AC	n.a.	N	426	Y (AC)	RAT	N	102	N	7	N
14	OD	M	50	Y	R	Y	Ballroom dancing, weight lifting	Y	n.a.	N	0	AC	n.a.	N	5715	Y (CDT)	TA	N	80	N	3	N
15	OD	F	20	Y	R	N	n.a.	N	Y	N	3	AC	n.a.	N	1170	Y (AC)	RAT*	N	88	Y	1	N
16	OD	F	53	N	R	?	Unknown	N	Y	N	0	CDT	41	Y	762	Y (AC)	RAT*	N	180	Y	2	Y
17	OD	M	21	Y	L	N	n.a.	N	n.a.	N	7	AC	n.a.	N	728	N	TA	N	74	N	3	Y + Stent
18	OD	M	24	Y	R	Y	Fitness	N	n.a.	N	428	None	n.a.	N	428	n.a.	MO	Y	251	N	8	N
19	OD	F	46	N	L	Y	Fitness	N	N	N	1	AC	n.a.	N	217	n.a.	MO	Y	254	N	7	N
20	OD	F	26	Y	R	N	n.a.	N	Y	N	7	AC	n.a.	N	334	Y (AC)	MO	Y	259	N	4	N
21	OD	F	37	N	R	Y	Triathlete	N	N	N	121	AC	n.a.	N	208	N	PC	Y	255	N	4	N
22	OD	M	24	Y	R	Y	Fitness	N	n.a.	N	4	AC	n.a.	N	1180	N	MO	Y	309	Y	12	N
23	OD	M	46	N	L	Y	Repetitive assembly line work	Y	n.a.	N	11	AC	n.a.	N	325	n.a.	PC	Y	563+	N	7	N
24	OD	F	23	N	R	Y	Intensive labor	N	Y	N	0	AC	n.a.	N	224	Y (AC)	IC	N	108	N	2	Y

Legend: AC = anticoagulation, CDT = catheter directed thrombolysis, d = days, F = female, FRR = first rib resection, hr = hours, IC = infraclavicular, L = left, M = male, m = minutes, MO = Molina, N = no, n.a. = not applicable, OC = oral contraceptive, OD = on demand, OR = operation, p = primarily, PC = paracervical, PSS = Paget-Schroetter syndrome, Pt = patient, PTA = percutaneous transluminal angioplasty, R = right, RAT = robot assisted transthoracic, ref. = referred patient, SVG = saphenous vein graft, TA = transaxillary, Y = yes, ? = unknown, ¥ = conversion to TA approach, † = multiple occlusions venous reconstruction during procedure, * = females only

Supplement table 3. Management and outcomes of individual patients

Pt	Treatment PSS	FRR P/ OD	DASH pre-op			DASH 3 months			DASH 6 months			DASH 12 months			Last imaging modality	patent stenosis	PTA
			G	W	S	G	W	S	G	W	S	G	W	S			
1	CDT => FRR	P	1,7	0,0	25,0	7,5	6,3	37,5	6,0	8,3	25,0	13,3	43,8	50,0	24,8	Y	N
2	CDT+PTA => FRR	P	10,0	50,0	-	x	x	x	10,0	6,3	-	7,5	18,8	25,0	8,8	Y	N
3	CDT+ PTA => FRR	P	3,3	6,3	12,5	x	x	x	0,8	0,0	0,0	0,0	0,0	0,0	2,1	Y	N
4	CDT => FRR	P	9,5	-	-	6,7	0,0	-	x	x	x	8,3	0,0	-	10,3	Y	N
5	CDT => FRR	P	6,7	25,0	12,5	18,3	25,0	43,8	16,7	12,5	31,3	6,7	6,3	12,5	1,1	Y	N
6	CDT => FRR	P	20,8	100,0	100,0	8,3	75,0	50,0	1,7	-	25,0	0,0	0,0	0,0	NI	n.a	n.a
7	CDT (no success) => FRR	P	15,0	25,0	-	13,3	6,3	50,0	13,3	25,0	-	22,4	25,0	-	NI	n.a	n.a
8	AC => FRR	P	16,4	-	-	x	x	x	15,8	-	-	5,0	-	25,0	4,3	Y	N
9	CDT => FRR + VR	P	1	-	25	x	x	x	x	x	x	0	0	0	35,3	Y	N
10	CDT => FRR + venous patch	P	55,2	87,5	-	x	x	x	x	x	x	1,7	0	0	4,0	Y	N
11	AC => complaints => FRR	OD	10,0	18,8	43,8	x	x	x	0,8	0,0	0,0	0,8	0,0	0,0	3,6	Y	N
12	AC => 2x recurrence => PTA => FRR	OD	31,7	50,0	-	46,4	62,5	-	47,3	41,7	37,5	65,5	50,0	-	23,5	N	n.a.
13	AC => recurrence/complaints => FRR	OD	81,7	-	-	x	x	x	x	x	x	x	x	x	18,0	Y	N
14	AC => recurrence => CDT => FRR	OD	23,3	-	56,3	17,5	-	25,0	22,3	-	37,5	23,3	25,0	31,3	2,2	N	n.a.
15	AC => recurrence => AC => FRR	OD	5,0	-	0,0	0,8	-	0,0	x	x	x	2,5	0,0	18,8	NI	n.a	n.a
16	CDT => recurrence* => AC => FRR	OD	12,9	25,0	-	9,5	12,5	25,0	7,8	0,0	12,5	13,3	12,5	18,8	2,3	Y	Y
17	AC => complaints => FRR	OD	26,2	62,5	56,3	67,2	62,5	93,8	x	x	x	59,2	-	43,8	9,2	Y	N
18	Chronic PSS => FRR + VR	OD	31,7	37,5	75,0	3,3	0,0	0,0	x	x	x	0,0	0,0	0,0	10,4	Y	N
19	AC => chronic occlusion => FRR + VR	OD	45,5	43,8	-	x	x	x	x	x	x	6,7	25	-	NI	n.a	n.a
20	AC => chronic occlusion => FRR + VR	OD	36,7	31,25	100	25	12,5	81,3	14,2	0	37,5	30,8	0	37,5	25,1	D	N
21	AC => FRR + VR => occlusion => thrombectomy	OD	14,7	12,5	87,5	x	x	x	10	12,5	25	1,7	6,3	0	17,0	D	Y
22	AC => complaints => FRR + VR	OD	0	0	0	x	x	x	x	x	x	0	-	0	26,2	D	N
23	AC => FRR + VR	OD	40,5	-	-	x	x	x	x	x	x	54,3	-	-	9,9	CT	N
24	AC => recurrence => FRR	OD	18,5	31,3	12,5	x	x	x	x	x	x	23,3	18,8	37,5	10,6	D	Y

AC = anticoagulation, CDT = catheter directed thrombolysis, CT = computed tomography, D = duplex ultrasound, DASH = disabilities of arm, hand and shoulder questionnaire, FRR = first rib resection, G = general section, m = months, N = no, n.a. = not applicable, NI = no imaging, PSS = Paget-Schroetter syndrome, Pt = patient, PTA = percutaneous transluminal angioplasty, S = sports section, V = venogram, VR = venous reconstruction, W = work section, x = not available, Y = yes, - = optional section not filled out, * = recurrence in waiting time because FRR postponed due to analysis long nodule,



CHAPTER 9

Management of Paget-Schroetter Syndrome: a systematic review and meta-analysis

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ABSTRACT

Objective: Currently, there is no consensus on the optimal management of Paget-Schroetter syndrome (PSS). The objective was to summarise the current evidence for management of PSS with explicit attention to the clinical outcomes of different management strategies.

Data Sources: The Cochrane, PubMed, and Embase databases were searched for reports published between January 1990 and December 2021.

Review Methods: A systematic review and meta-analysis was conducted following PRISMA 2020 guidelines. The primary endpoint was the proportion of symptom free patients at last follow up. Secondary outcomes were success of initial treatment, recurrence of thrombosis or persistent occlusion, and patency at last follow up. Meta-analyses of the primary endpoint were performed for non-comparative and comparative reports. The quality of evidence was assessed using the GRADE approach.

Results: Sixty reports were included (2 653 patients), with overall moderate quality. The proportions of symptom free patients in non-comparative analysis were: anticoagulation (AC), 0.54; catheter directed thrombolysis (CDT) + AC, 0.71; AC + first rib resection (FRR), 0.80; and CDT + FRR, 0.96. Pooled analysis of comparative reports confirmed the superiority of CDT + FRR compared with AC (OR 13.89, 95% CI 1.08 - 179.04; $p = .040$, I^2 87%, very low certainty of evidence), AC + FRR (OR 2.29, 95% CI 1.21 - 4.35; $p = .010$, I^2 0%, very low certainty of evidence), and CDT + AC (OR 8.44, 95% CI 1.12 - 59.53; $p = .030$, I^2 63%, very low certainty of evidence). Secondary endpoints were in favour of CDT + FRR.

Conclusion: Non-operative management of PSS with AC alone results in persistent symptoms in 46% of patients, while 96% of patients managed with CDT + FRR were symptom free at end of follow up. Superiority of CDT + FRR compared with AC, CDT + AC, and AC + FRR was confirmed by meta-analysis. The overall quality of included reports was moderate, and the level of certainty was very low.

INTRODUCTION

Venous thoracic outlet syndrome (VTOS) is caused by external compression of the subclavian vein in the thoracic outlet at the costoclavicular junction. If compression and outflow obstruction of the subclavian vein leads to acute, effort induced, thrombosis this is called Paget-Schroetter Syndrome (PSS).^[1] PSS is uncommon with an incidence of approximately 0.5-1 per 100,000 people per year.^[2] Patients who perform physical strenuous labour (e.g. overhead work) and athletes are especially at risk.^[3] Although PSS only seldom threatens the survival of the limb it can cause serious and invalidating complaints. Treatment can be divided in non-operative and surgical management. Non-operative treatment is subdivided in anticoagulant therapy and endovenous catheter based therapies. Vitamin-K antagonist or direct oral anticoagulation is most frequent used as anticoagulant therapy. Catheter based therapies consists of a variety of endovenous techniques to resolve or remove the clot from the subclavian vein. Catheter directed thrombolysis (CDT) is at this date most frequently used. Surgical management consists of decompressive surgery of the subclavian vein. First rib resection (FRR) is most commonly used. FRR is in most cases preceded by catheter based therapy or anticoagulation. There is no consensus on the best management of PSS. Our objective was to provide a comprehensive overview of the available evidence regarding the management of PSS in the literature from 1990 to the present using the PRISMA 2020 guidelines^[4] and summarize outcomes with a meta-analysis. Main questions we wanted to address were: which management strategy results in the best functional outcome?; can we demonstrate that adding CDT improves functional outcomes? and is CDT followed by FRR superior to treatment with AC alone?

MATERIALS AND METHODS

In December 2021 The medical databases Embase, PubMed and the Cochrane Database of Systematic Reviews were searched from January 1990 to December 2021. All articles, written in the English language, presenting original and well documented data on outcomes of human patients ($N \geq 10$) with first episodes of Paget-Schroetter syndrome/ (effort induced) primary upper extremity deep venous thrombosis were included. For this review we have focused on the clinical outcome of the different treatment groups. We have not aimed to compare in detail treatment techniques; diagnostic work-up; post interventional medication or follow up. The search strategy and in- and exclusion criteria are provided in **supplementary document 1**. Two independent researchers (FH, MH) separately selected the reports for inclusion extracted data and assessed the quality of included reports, discrepancies were resolved by discussion with a third

investigator (VJ). The reference lists of all included reports were hand-searched to retrieve additional reports.

Data extraction

All relevant data was extracted from the included reports using a standard template and managed in Microsoft Excel 2016 (Microsoft corporation, Redmond, WA, USA). The complete list of all parameters that were extracted is accessible in **supplementary document 1**. The primary outcome was “symptom free at last follow up”. For the purpose of meta-analysis, patients were regarded as symptomatic unless they were graded as symptom free by matching one of these descriptions: Villalta / PTS score 0 points, DASH <20 points (the normative DASH score in healthy individuals ranges from 5 (20-29 year) to 36 points (>80 years)), “excellent”, “symptom free”, “asymptomatic”, “no PTS”, “complete relief”, or “good” (only if this was the best possible reported outcome in the study), or. The secondary outcomes were: success of initial treatment; recurrence of thrombosis or persistent occlusion and patency at last follow up. Success of initial treatment was scored if authors stated that initial therapy was successful in recanalization of the subclavian vein, restoring outflow of the arm, if resolution of the clot was achieved, or a similar description was used to state that the thrombotic occlusion was remedied. Recurrence of thrombosis was scored if thrombosis reoccurred after initial restoration of outflow. Persistent occlusion was scored if all therapies were unable to achieve clot resolution or restoration of blood flow through the occluded subclavian vein. Patency at last follow up was scored if authors stated that the subclavian vein was open at last follow up, that no recurrence was noted or a similar statement was provided. All 16 first authors of the reports in which relevant data on clinical outcome was only available for the total cohort and not specified for subgroups were contacted (ResearchGate, e-mail, LinkedIn) and asked for additional data for these subgroups. Five authors responded and three of them were able to provide the requested additional data.

Quality assessment

The quality of the included reports was assessed based on the quality assessment tool for case series reports formulated by the National Heart, Lung, and Blood Institute (Bethesda, Maryland, United States of America). The quality of the reports was graded as “good”, “fair” or “poor” for all nine topics and results in an overall score. Additionally a certainty of evidence was established, using the methodology developed by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) working group

^[5] A summary of findings table was generated using the GRADEpro online platform

(<https://www.gradepro.org>). The process of assessing the quality of the included reports and establishing the certainty of evidence using the GRADE-recommendations is specified in detail in **supplementary document 2**.

Statistical analysis

For patient characteristics descriptive statistics were used. A pooled proportion of symptom free patients at last follow up was performed with RStudio (RStudio Team (2020). RStudio: Integrated Development Environment for R. RStudio, PBC, Boston). A meta-analysis was performed using a general linear mixed model. The results were displayed as weighed proportions with corresponding 95% confidence intervals (95% CI's). A meta-analysis of the reports comparing multiple treatment protocols was performed with Cochrane's Review Manager (Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020). Pooled results were displayed as Odds Ratio's (OR) and corresponding 95% CI's. Heterogeneity was assessed using the I^2 -statistic. I^2 was interpreted using the Cochrane methodology: 0% - 40%: might not be important; 30% - 60% may represent moderate heterogeneity; 50% - 90% may represent substantial heterogeneity; and 75% - 100% may represent considerable heterogeneity..^[6] A fixed effects model was used, if heterogeneity was deemed not important ($I^2 = 0 - 40\%$). Otherwise a random effects model was applied. ^[7]The Chi-square test was used to assess statistical significant (p-value of $<.050$) differences between the incidences of secondary outcomes provided by all reports(IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp, USA).

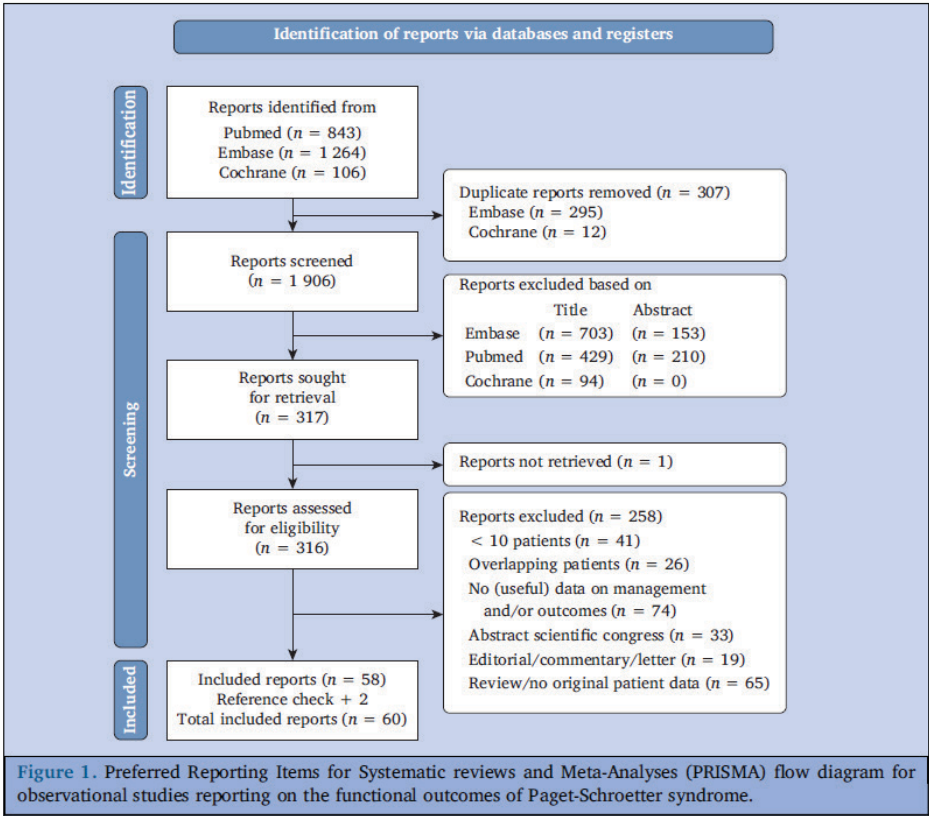
RESULTS

After full text review of 316 reports, 58 reports could be included. The reference check revealed 2 additional reports, adding the total to 60 included reports in this review.^[8-67] 258 assessed reports had to be excluded because of various reasons as depicted in the flow chart in figure 1.

General study design

All details concerning the study design are provided in **supplementary Table S1**. No randomised trials were available. Only 4/60 reports had a prospective design. With the exception of one report from Israel, all reports were presented by institutions in North America (n=39) or Europe (n=20). In 19 reports (15 surgical, 4 non-operative) a single treatment was used in all reported patients, all other reports described multiple treatments. Seven institutions published more than one report that could be included

(2 to 4 reports). Four of these reports had overlapping patients. Because these reports presented different outcomes they were all included as elaborated in **supplementary document 1**. The mean time span of patient inclusion in the reports was 10.6 years (median 8.2, range 3 - 50 years). The average number of included patients per report was 48.3 (median 27.5, range 10 – 608 patients), resulting in an average of 4.6 patients included per year (median 3.2, range: 0.9 - 19.1 patients/year).



Quality assessment

The overall quality of the included reports was moderate with only 9 reports graded as “good” (fair n = 43, poor n = 8). Further details per report regarding quality score are provided in **supplementary Table S1**. The comparability of included patients was often limited and reports did not always described an uniform, fully detailed study population (i.e. chronic and acute patients were combined). Furthermore reports frequently omitted information regarding statistical analysis, risk factors or causative events leading to PSS. In a fair amount of reports it was not possible to trace back the

functional outcomes to specific patients or interventions, because of incomplete display of results. The majority of the included reports did not statistically analyse their data and in multiple reports, functional outcomes were paraphrased as excellent, symptom free, good, fair, poor or in other subjective results.

Patient characteristics

All data regarding patient characteristics are provided in **supplementary Table S2**. In total 2653 patients were identified in the 57 reports presenting original patients. Gender distribution was balanced (n= 2489, male 52.6%, female 47.4%). Mean age was 31.6 year (n = 2559, range 11 - 86 years). Paediatric cases (≤ 15 years old) and patients over 60 years of age were reported in 11 reports. Additional patient characteristics and risk factors were frequently unavailable (percentage unknown: 42.8% - 85.1%). In approximately two-thirds of patients the complaints were effort induced (65.3%, 577/884), right sided (65.8%, 564/857) or affecting the patient's dominant side (69.0%, 394/571). Cervical ribs were identified in 5.6% (78/1404). Pulmonary embolism was infrequent (4.9%, 74/1523). The prevalence of thrombophilia in the included reports in our review varied from 0%^[8,9,23,25,38,50] to 55.6% (10/18)^[10], with an average of 11.5% (112/977).

Management

Reports presented data on non-operative (n = 7), surgical (n = 36) or both non-operative and surgically treated patients (n = 17). Forty-one reports presented data of two to five different treatment arms. Non-operative treatment consisted in the vast majority of AC alone or CDT followed by AC. Only 4 reports presented patients who were treated with percutaneous pharmacomechanical^[16,23] or surgical thrombectomy^[21,36,60] as initial invasive therapy and were assigned to the CDT cohort for descriptive analyses but were kept out from the meta-analysis of primary and secondary endpoints. In 98.1% (2146/2185) of the surgically treated patients FRR was performed to decompress the thoracic outlet. Scalenelectomies, medial claviclelectomies, decompression by resection of osseous exostoses or other/unknown surgical procedures were described in 39 patients and were left out from the meta-analysis.

Primary and secondary outcomes and meta-analysis.

Outcomes and meta-analysis of reports on non-operative management.

Non-operative treatment was reported in 24 reports including 465 patients (AC n = 240, CDT + AC n = 203, CDT alone n = 17 and 5 other or no treatment) (**supplementary Table**

S3) Mean age of non-operative treated patients was 37.2 years (AC 38.9 and CDT + AC 35.4 years). Adjunctive percutaneous transluminal angioplasty (PTA) was performed in 43.1% (66/153) and stent placement in 4.2% (8/191) of patients. Mean follow up of the reports on non-operative treatment was 45 months (range 2 - 324 months). The proportion of symptom free patients at last follow up from non-comparative analysis were: AC .54 and CDT + AC .71 (**Table 1**). Three reports comparing AC with CDT + AC were pooled (31 vs. 37 patients). Meta-analysis showed an OR of 2.71 (95% CI.86 – 8.61; $p = .09$, $I^2 = 24\%$) of being symptom free at last follow-up (**Figure 2**). All patients reported by *Grassi et al.* and *Lee et al.* were symptom free at last follow-up. An OR could not be estimated in these studies and were therefore not included in meta-analysis.^{47,67} GRADE certainty of evidence summarizing these three reports was considered 'very low' (**Table 2**). There was no statistical significant difference regarding the secondary endpoints when comparing AC with CDT + AC; success of initial treatment (77.8% (14/18) vs. 90.8% (178/196), $p = .081$); recurrence of thrombosis or persistent occlusion (18.8% (9/48) vs. 28.6% (36/126), $p = .19$); patency at last follow up (65.4% (34/52) vs. 75.5% (74/98), $p = .19$). (**supplementary Table 4**)

Table 1. Meta-analysis of observational evidence on the management of Paget-Schroetter syndrome using a generalised linear mixed model. The functional outcome was specified as being symptom free at last follow up. The functional outcome improved with increasingly invasive therapy, from 0.54 in anticoagulation (AC) alone to 0.96 in patients treated with catheter directed thrombolysis (CDT) followed by first rib resection (FRR)

Treatment	Reports	Patients – n	Symptom free patients – n	Weighted pooled proportion (95% CI)	I^2 – %
AC	10	180	80	0.54 (0.17 – 0.88)	58
CDT + AC	13	150	108	0.71 (0.44 – 0.88)	1
AC + FRR	14	171	115	0.80 (0.56 – 0.93)	0
CDT + FRR	31	1 284	1 199	0.96 (0.91 – 0.98)	25

CI = confidence interval; I^2 = statistic for heterogeneity.

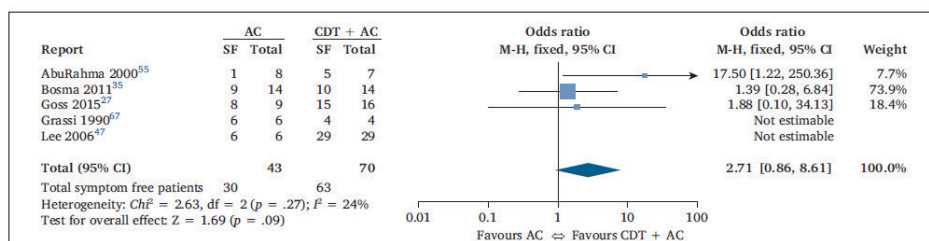


Figure 2. Forest plot of comparison for five reports on functional outcomes of anticoagulation (AC) vs. catheter directed thrombolysis (CDT) + AC in the management of Paget-Schroetter syndrome. Outcome: symptom free at last follow up in 113 patients. No statistical difference could be detected between the two patient groups, indicating that the superiority of using CDT as an adjunct in non-operative management is not proven. SF = number of symptom free patients; M-H = Mantel-Haenszel analysis; CI = confidence interval.

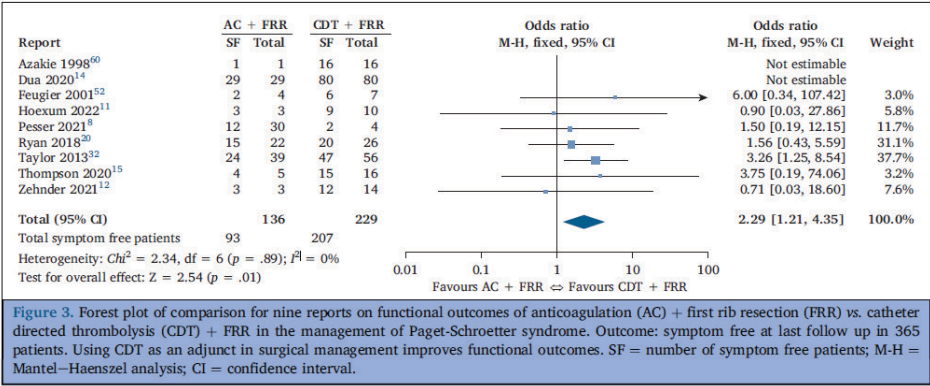
Table 2. Summary of findings table of pooled observational studies comparing functional outcomes of different treatments in patients with Paget-Schroetter syndrome. Functional outcome was defined as being symptom free at last follow up. The quality of evidence was graded using the system developed by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group

Certainty assessment							Patients – n	Effect		Certainty	Importance	
Studies – n	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute (95% CI)			
CDT + AC compared with AC												
5	Observational studies	Serious	Not serious	Serious	Serious	None	CDT + AC: 63/70 (90.0%)	AC: 30/43 (69.8%)	OR 2.71 (0.86 – 8.61)	164 more per 1 000 (33 fewer – 254 more)	⊕○○○ (Very low)	Important
CDT + FRR compared with AC + FRR												
9	Observational studies	Serious	Serious	Very serious	Not serious	None	CDT + FRR: 207/229 (90.4%)	AC + FRR: 93/136 (68.4%)	OR 2.29 (1.21 – 4.35)	148 more per 1 000 (40 more – 220 more)	⊕○○○ (Very low)	Important
CDT + FRR compared with CDT + AC												
6	Observational studies	Very serious	Serious	Serious	Serious	None	CDT + FRR: 46/54 (85.2%)	CDT + AC: 21/42 (50.0%)	OR 8.44 (1.12 – 59.53)	394 more per 1 000 (45 more – 483 more)	⊕○○○ (Very low)	Important
CDT + FRR compared with AC												
4	Observational studies	Very serious	Very serious	Serious	Serious	None	CDT + FRR: 569/615 (92.5%)	AC: 20/59 (33.9%)	OR 13.89 (1.08 – 179.04)	538 more per 1 000 (17 more – 650 more)	⊕○○○ (Very low)	Important

CI = confidence interval; CDT = catheter directed thrombolysis; AC = anticoagulation; OR = odds ratio; FRR = first rib resection.

Outcomes and meta-analysis of reports on surgical management (supplementary table 4 - 6).

Surgical management was reported in 53 reports including 2208 patients (AC + FRR n = 351, CDT + FRR n = 1699, FRR alone /other n = 158). Mean age of surgically treated patients was 29.8 years (AC + FRR: 29.3 and CDT + FRR 29.9 years). Recanalization was more often reported after CDT (91.2%, 726/796) compared to AC (78.3%, 72/92). Additional stent placement prior to surgical decompression was only reported in 14 patients (1.6%, 14/856). In 2055 FRR's the approach was described: transaxillary 62.5%, infraclavicular 13.1%, supraclavicular 6.3%, robot assisted 5.4%, paraclavicular 5.2% and thoracoscopic 3.2%. Additional surgical interventions (i.e. revascularization, AV-fistula) were reported in 9.2% (191/2065). Postoperative adjunctive PTA was performed in 36.0% (444/1233) with adjunctive stent placement in 5.6% (63/1125). Mean follow up of the reports on surgical management was 38 months (range 0 - 316 months). The proportion of symptom free patients at last follow up from non-comparative analysis were; AC + FRR .80 and CDT + FRR .96 (**Table 1**). Seven reports comparing AC + FRR with CDT + FRR were pooled (106 vs. 133 patients). Meta-analysis showed a significant OR of 2.29 (95% CI 1.21 – 4.35; $p = .01$, $I^2 = 0\%$) of being symptom free at last follow-up (**Figure 3**). The patients reported by *Azaki et al.* and *Dua et al.* were all symptom free at last follow-up. An OR could not be estimated in these studies and were therefore not included in meta-analysis.^{14,60} GRADE certainty of evidence summarizing these seven reports was considered 'very low' (**Table 2**). Success of initial treatment (96.0% (679/707) vs. 91.8% (179/195), $p = .015$) and patency at last follow up (95.9% (534/557) vs. 78.2% (81/103), $p < .001$) were superior for patients treated by CDT + FRR versus AC + FRR. Recurrence of thrombosis or persistent occlusion did not differ significantly (6.8% (33/483) vs. 11.1% (12/108), $p = .13$).



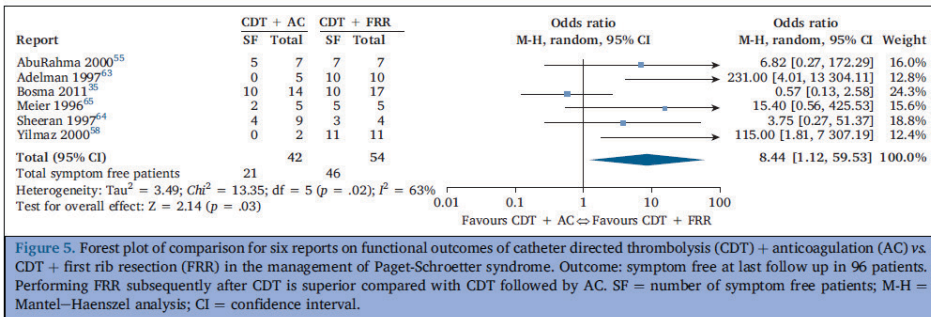
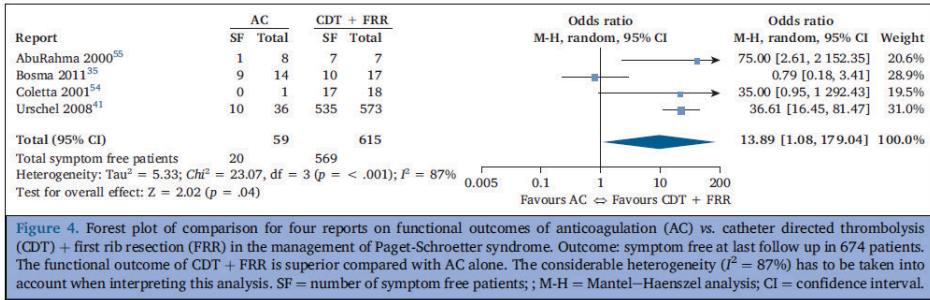
Meta-analysis of non-operative vs. surgical management

Anticoagulation vs. catheter directed thrombolysis followed by first rib resection

Pooled comparative analysis of four reports showed a significant odds of being symptom free when treated with CDT + FRR compared to treatment with AC alone (OR = 13.89, 95% CI 1.98 – 179.04, $p = .04$). Considerable heterogeneity was present ($I^2 = 87\%$). (figure 4). GRADE certainty of evidence summarizing these four reports was considered ‘very low’ (Table 2). Secondary endpoints were in favour of CDT + FRR: success of initial treatment (77.8% (14/18) vs 96.0% (679/707), $p < .001$); recurrence of thrombosis or persistent occlusion (18.8% (9/48) vs 6.8% (33/483), $p = .004$); patency at last follow up (65.4% (34/52) vs 95.9% (534/557), $p < .001$)(supplementary Table S4).

Catheter directed thrombolysis followed by anticoagulation vs. catheter directed thrombolysis followed by first rib resection

Six reports were included for meta-analysis comparing CDT + AC with CDT + FRR (42 vs. 54 patients). OR was 8.44 of being symptom free when receiving CDT + FRR compared to CDT + AC (95% CI 1.20 – 59.53; $p = .03$, $I^2 = 63\%$) (figure 5). Secondary endpoints were in favour of CDT + FRR: success of initial treatment (90.8% (178/196) vs. 98.6% (679/707), $p = .003$); recurrence of thrombosis or persistent occlusion (28.6% (36/126) vs. 6.8% (33/483), $p < .001$); patency at last follow up (75.5% (74/98) vs. 95.9% (534/557), $p < .001$) (supplementary table S4).



Anticoagulation vs anticoagulation followed by first rib resection, and catheter directed thrombolysis followed by anticoagulation vs. anticoagulation followed by first rib resection.

Due to the limited amount of reports (≤ 2) analysing both treatment groups, meta-analyses of AC vs. AC + FRR and CDT + AC vs. AC + FRR were not performed. With the exception of the secondary endpoint recurrence of thrombosis or persistent occlusion in favour of AC + FRR compared to CDT + AC (11% (12/108) vs 29% (36/126), $p = < .001$), none of the secondary endpoints were statistically different (**supplementary Table S4**).

SENSITIVITY ANALYSIS

In order to investigate the possible negative influence of qualitatively poor reports, we additionally performed the analyses of the pooled proportions without these 8 lowest-scoring reports. The pooled proportions symptom free patients were comparable: AC .66, CDT + AC .67, AC + FRR .81 and CDT + FRR .97. Meta-analyses of comparative reports showed an corresponding OR of 2.86 ($p = .007$) for AC + FRR vs CDT + FRR. The other OR were identical (AC vs. CDT + AC and CDT + AC vs CDT + FRR) or impossible because of limited remaining reports (≤ 2 ; AC vs. CDT + FRR).

Complications

Information regarding complications or adverse effects were presented in just over half of the reports (total 33 reports, FRR related $n = 23$; FRR + CDT related $n = 9$, CDT related $n = 1$). No mortality was reported. In total 208 complications were noted in 1145 procedures (**supplementary Table S7**). Postoperative pneumothorax was most frequent ($n = 86$) followed by bleeding complications ($n = 39$; major 19 (needing surgical management), minor 10 (managed non-operatively), unknown 10), (transient) neurologic complications ($n = 31$), hemothorax ($n = 26$) and chylous leakage ($n = 10$). The need for interventions ($n = 46$) or reoperation ($n = 35$) was limited. Only 10 reports presented data on adverse events during catheter based therapy resulting in 11 reported complications in 244 procedures (4.5%), including pulmonary embolism, venous injury requiring surgery, hematoma and allergic reaction (**supplementary Table S8**).

DISCUSSION

This review illustrates the available literature of the last 32 years concerning the treatment of Paget-Schroetter Syndrome. Sixty retrospective and prospective cohort studies could be included. Meta-analysis was possible, showing that CDT followed by FFR is by far the most reported treatment and leads to excellent clinical outcome in almost all patients (96%) with a low risk of reported complications. Other treatments are less often reported and have less favourable outcome, although direct comparison between the various treatments should be done with caution.

Conservative treatment using AC alone leads to good functional outcome in 54% of patients, leaving many with unsatisfactory results. Data from this systematic review is not suitable for in debt analysis on predictors for excellent or poor clinical outcome after AC alone. Large prospective studies are needed. Data from the current meta-analysis suggests that there is no clear benefit of CDT in combination with non-operative management with AC, which is in line with current guidelines.^[68]

For this meta-analysis functional outcome was chosen as primary outcome. Objective evaluation of patients can be difficult in PSS because previous studies showed that venous hemodynamic or residual morphological abnormalities are not associated with poor functional outcome after UEDVT.^[59,69] In a large cohort study no difference in DASH scores for patients with patent, stenosed or occluded veins could be found.^[32] In fact, several authors reported on patients who were symptom free or experiencing only minimal complaints despite occluded subclavian veins.^[51,67] While PSS is not limb threatening, functional outcome is the most important outcome measure for patients.

This should preferably be measured using a validated score.

Several techniques can be used to perform FRR. Because of the low number of patients per study, sub analysis of the different surgical techniques was deemed not appropriate. Nevertheless, statistical heterogeneity for functional outcome after FRR was low, suggesting that specific technique used for decompression might be of less importance. Future studies should analyse the best surgical technique. We demonstrated a possible beneficial effect of CDT in patients undergoing first rib resection. Compared to AC, CDT has the potential benefit of early cloth lysis, increased success of initial treatment and shorter lysis time. These advantages could potentially lead to better functional outcomes as is seen in the non-comparative analysis. In the comparative analysis there was a significant difference noted. As is pointed out in the ESVS guideline^[68] CDT is most effective when performed in the first two weeks after development of UEDVT. Time between event and start of CDT was often not reported in the included studies and consequently could not be used for meta-analysis. Inclusion of UEDVT existing longer than 2 weeks could potentially influence results. Delay in diagnosis and treatment could be important despite treatment strategy. The functional outcomes of chronic patients or patients in which initiation of treatment is delayed are worse.^[8,41,70] In chronic patients CDT is often unsuccessful or not even attempted. In our experience surgical procedures for chronic cases, decompression is frequently combined with venous revascularization techniques (endoflebectomy or interposition grafting) entailing more extensive surgery with longer operating times and associated with increased complication rate and morbidity and less favourable functional outcome (data to be published). This is also the experience of other centers.^[71] The use of intravenous stents is not advised because of a high risk of complications, especially when placed before surgical decompression has been achieved.^[53,65,72-76]

Notable is the low number of patients included in almost all studies. As is known from literature and from the results of this review multiple therapeutic strategies are possible with varying outcomes. Concentration of treatment of this rare disease might benefit patients. Cooperation of research groups seems essential to progress our understanding of the disease, optimal treatment strategies and best selection of patients.

Limitations

Almost all reports were retrospective case series often reporting on a limited number of patients and at risk for possible inclusion bias. For example the difference in age between surgical and non-operative treatment may be indicative for inclusion bias. No randomized

controlled trials were found. As mentioned before the overall quality of the included reports was moderate. The vast majority of reports did not provide all relevant data as described in the 2016 reporting standards of the Society for Vascular Surgery for venous thoracic outlet syndrome.^[77] Especially the secondary endpoints were often not available for all patients; success of initial treatment 42.3% missing, recurrence of thrombosis or persistent occlusion 46.5% missing and patency at last follow up 45.1% missing. Data regarding primary patency, primary assisted or secondary patency was not available. Functional outcome reporting was frequently not consistent and from many reports outcomes could not be retrieved for quantitative analysis. Furthermore there may be unobserved confounders. Baseline severity scores of patients were not available. Complications were scarcely reported and may be underreported. Meta analyses comparing CDT + FRR vs. AC and CDT + FRR vs CDT + AC displayed considerable heterogeneity. This was caused by *Bosma et al.*, reporting an opposite effect to the detriment of patient treated with CDT + FRR in contrast to the other reports.³⁵ This opposite effect could have been caused by the subjective manner in which functional outcomes were reported in all reports, possibly inducing variation between studies. *Bosma* and colleagues provided functional outcomes in more detail then other reports. The relatively strict reporting of persisting symptoms might have led to less symptom free patients in the CDT + FRR group in this report. Also, this report was the only European study, in contrast to three American studies. While secondary risk factors of effort thrombosis were not fully reported by *Bosma et al.* (i.e. previous trauma, smoking, oral contraceptive use) patient inclusion criteria seemed comparable to the other reports. However, given the retrospective nature of all reports, substantial differences between included patients might still be present, leading to the considerable heterogeneity in this meta-analysis. these results should therefore be interpreted with caution. GRADE certainty of evidence was overall 'very low'. The results from this systematic review and meta-analysis should therefore be interpreted with caution.

CONCLUSION

Non-operative management of PSS with AC alone results in persistent symptoms in 46% of patients, while 96% of patients managed with CDT + FRR are symptom free at the end of follow up. Superiority of CDT+FRR compared to CDT+AC and AC+FRR was confirmed by meta-analysis. Large prospective studies are urgently needed to identify patients with good outcome after conservative management. Ideally, randomized controlled trials are performed to clarify the exact place of thrombolysis and first rib resection in treating PSS. In the meantime, concentration of care for patients and cooperation in research on PSS might benefit patient outcome.

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SUPPLEMENTAL DOCUMENT 1

Search strategy

PUBMED search

((((((((((((venous thoracic outlet syndrome) OR paget-schroetter) OR effort thrombosis) OR subclavian vein thrombosis)) AND ((management) OR therapy))) AND (((((anticoagulation) OR anticoagulants)) OR thrombolysis) OR ((first rib resection) OR decompression)))) AND (((“1990/01/01”[PDat] : “2019/12/31”[PDat]) AND Humans[Mesh] AND English[lang])) AND Humans[Mesh] AND English[lang])) AND (“1990/01/01”[PDat] : “2021/11/30”[PDat]) AND Humans[Mesh] AND English[lang])) NOT case report[Title]

EMBASE search

(‘venous thoracic outlet syndrome’ OR ‘paget schroetter’ OR ‘upper extremity deep vein thrombosis’ OR (‘axillo subclavian’ AND vein AND thrombosis) OR (‘subclavian axillary’ AND vein AND thrombosis) OR (effort AND thrombosis)) AND (‘conservative treatment’ OR ‘conservative therapy’ OR ‘conservative management’ OR ‘anticoagulant’ OR ‘anticoagulation’ OR ‘decompression’ OR ‘thrombolysis’ OR ‘first rib resection’) AND [english]/lim AND [humans]/lim AND ([embase]/lim OR [medline]/lim) AND [1-1-1990]/sd NOT [30-11-2021]/sd NOT line:ti NOT cancer:ti NOT neurogenic:ti NOT malignancy:ti NOT catheter:ti NOT pacemaker:ti NOT review:ti NOT ‘case report’:ti NOT ‘COVID’:ti

Cochrane Search

(venous thoracic outlet syndrome OR paget-schroetter OR effort thrombosis OR subclavian vein thrombosis) AND (anticoagulation OR anticoagulants OR thrombolysis OR first rib resection OR decompression). Date limit 01-01-1990 till 30-11-2021

Inclusion and exclusion criteria

Inclusion

All articles; written in the English language, published between 01-01-1990 and 30-11-2021, presenting original and well documented data on outcomes of human patients (N= ≥ 10) with first episodes of Paget-Schroetter syndrome / (effort induced) primary upper extremity deep venous thrombosis.

Exclusion

- no data on primary and secondary endpoints
- only data presented on secondary endpoints “primary patency” and/or “recurrence” without data on secondary endpoint “patency at latest follow up” or primary endpoint “functional outcome”
- All articles that reported on secondary (all causes, except coagulopathy) * or specific on recurrent upper extremity deep venous thrombosis after failed management
- no original data:
 - reviews, meta-analysis, guidelines, management protocols
 - overlapping patients reported in multiple articles (same hospital and same time period,
 - except when presenting different data regarding different subject/outcome**)
 - Not well documented outcomes
 - data presented briefly in letters, comments or in abstracts of oral presentations on scientific congresses
 - data presented in vague terms as; “all patients benefitted from the procedure”, “Excellent-fair-poor” without details about the way this was scored, etc...
 - articles focused on other outcomes (cost, hospital stay, lysis time etc) and briefly mention clinical outcomes

* cancer/malignancy, (systemic) disease, trauma, catheter/pacemaker/ICD/etc intravenous wires, hormonal stimulation, pregnancy.

**If studies from the same institution reported on patients during the same period we excluded the study which contributed the least to our review. An exception was made in case the papers reported on different outcomes in the same patient population. We did take the possible overlapping patients in account in determining total reported patients and used the data of different reports during different analyses.

Data extracted from included articles

Data extracted regarding study design and parametric data

- Name 1st author
- Year of publication
- Study design (retrospective, prospective, randomized)
- Name of institution performing the research
- Location (city and country) of institution performing the research
- inclusion period / number of years of inclusion
- total patients included
- Number of patients per year included

Data extracted regarding patients characteristics

- Number of patients
- Number of affected limbs
- Gender
- Age
- Affected side
- Affected side dominant or not
- presence of a pulmonary embolism
- Current smoker
- Oral hormonal contraceptive use (females only)
- Previous thrombosis
- Hypercoagulability
- Presence of a cervical rib
- Complaints effort induced

Data extracted regarding management:

- Initial management;
 - None
 - anticoagulation (heparin, LMWH warfarin, DOAC, etc)
 - endovascular or surgical intervention (thrombolysis / catheter directed thrombolysis /
 - pharmamechanical thrombectomy / surgical thrombectomy / etc)
- Time to start treatment
- Adjunctive PTA with or without the use of an intravenous stent

- Successful recanalization after initial therapy / primary patency
- period of anticoagulation
- Rethrombosis before surgery (surgery group only)
- Surgical approach first rib resection (surgery group only)
- Other surgical decompressive interventions (surgery group only)
- Revascularisation (surgery group only)
- Postoperative PTA with/without stenting (surgery group only)
- follow up
- Recurrence or persistent occlusion
- secondary patency or open at latest follow up
- Clinical outcome symptom free or not at last follow up

Data extracted regarding Complications:

- All complications reported in the included articles

SUPPLEMENTAL DOCUMENT 2

Quality assessment, GRADE and general study design

Quality assessment

Based on the Quality assessment tool for case series from the National Heart, Lung and Blood Institute, Bethesda, MD, The United States of America

Available at: <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>

Criteria
1. Was the study question or objective clearly stated?
2. Was the study population clearly and fully described, including a case definition?
3. Were the cases consecutive?
4. Were the subjects comparable?
5. Was the intervention clearly described?
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?
7. Was the length of follow-up adequate?
8. Were the statistical methods well-described?
9. Were the results well-described?

Elaboration of the questions, papers graded by the following characteristics:

1. Was the study question or objective clearly stated?.
- Good (2pt) The aim of the study is explicitly mentioned in the abstract or introduction.
- Fair (1pt) In the abstract or introduction there is outlined which information is presented in the report
- Poor (0pt) No goal nor study objective is stated

2. Was the study population clearly and fully described, including a case definition?

- Good (2pt) Yes, explicitly mentioned: years, institutions/hospitals, deep vein thrombosis vs McCleery's syndrome. Excluded patients described. Data regarding risk factors provided. Imaging available and diagnostic workup described. Clearly defined effort thrombosis, Paget-Schroetter Syndrome or primary deep vein thrombosis
- Fair (1pt) data and or institution/hospital not clearly mentioned but can be traced back. Unclear thrombosis, stenosis. Risk factors incomplete described. No clear explanation which imaging used.
- Poor (0pt) No years, no patient characteristics, only vTOS mentioned without possible subgroup analysis possible.

3. Were the cases consecutive?

- Good (2pt) Yes and explicitly mentioned in the manuscript.
- Fair (1pt) not explicitly mentioned in the manuscript, but "all patients within the study period"
- Poor (0pt) no information available

4. Were the subjects comparable?

- Good (2pt) Yes, all patients had unprovoked or effort induced thrombosis. All other underlying causes were explicitly mentioned and described by the authors. Clear subdivision in acute and chronic cases
- Fair (1pt) varying causes for primary upper extremity deep venous thrombosis (effort induced, trauma, chronic or acute). No clear division possible regarding the data on outcomes.
- Poor (0pt) underlying cause not mentioned

5. Was the intervention clearly described?

- Good (2pt) Yes. Initial therapy described for all patients. OAC, heparin or CDT. Adjunctive PTA or not. For all patients information whether surgical decompression was performed or not and if it was the case which surgical technique.
- Fair (1pt) Management for groups available but not able to track down individual management per patient. Interventions described (thrombolysis, stent, PTA, decompression) but not the technique used.
- Poor (0pt) no clear data available

6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?

- Good (2pt) primary and secondary outcomes described. Objective endpoints: patency, validated questionnaires. All patients had the same follow up
- Fair (1pt) primary and secondary outcomes not fully described. patency as outcome without mentioning the way it was objectified or objectified in different ways. Follow up not clear
- Poor (0pt) No or insufficient data available. Only subjective endpoints

7. Was the length of follow-up adequate?

- Good (2pt) mean > 36 months
- Fair (1pt) mean > 12 months, minimum > 3 months
- Poor (0pt) - mean < 12 months
- mean > 12 months but shortest follow up less than 3 months
- follow up not clear

8. Were the statistical methods well-described?

- Good (2pt) Yes, clearly elaborated in section methods.
- Fair (1pt) described in methods but not specified which statistic program or tests
- Poor (0pt) no information regarding statistical analysis

9. Were the results well-described?

- Good (2pt) clearly described. Full data on every patient / subgroup useful for analysis.
Objective outcomes.
- Fair (1pt) outcomes for total group. Not specified for the subgroups
- Poor (0pt) outcomes not objective (only excellent, good, fair, poor). Follow up time not known

Color code



Overall quality score

System of assigning overall quality score:

Total quality scores can range from 0 (low quality) to 18 (high quality)

Overall quality was graded as poor (0-8 points), fair (9-13 points) or good (14-18 points)

Color code



GRADE

classification, workflow

Assessing risk of bias

- Not serious Overall populations both groups clearly defined (secondary causes of VTOS excluded), no significant differences in prognostic factors (smoking, oral contraception, hypercoagulability). No differences in underlying causes (trauma, cervical rib, repetitive movements), acute and chronic patients separately described. Follow up: mean >36 months and no or little differences in follow-up (time points: within 6 months) and clearly defined per group.
- Serious Overall populations not completely defined. Several differences in prognostic factors, underlying causes, or not completely defined. Acute and chronic presentation in both groups, but different presentations not separately described. Follow up: > 12 months, minimum > 3 months.

Very serious Population not specifically Paget-Schroetter syndrome. Basic characteristics including prognostic, underlying cause, acute and chronic patients not defined or very serious differences. Substantial differences in follow up (mean follow up > 1 year difference, different measurement instruments between groups or follow-up not clearly reported per intervention group). Follow up: mean < 12 months or minimum < 3 months.

Inconsistency

Not serious substantial overlap of CI's, small variances, Chi square test for heterogeneity non-significant, $I^2 < 40\%$,
Serious Marginal overlap of CI's, large variances, Chi square test for heterogeneity non-significant + $I^2 = 40-75\%$
Very serious Overall minimal overlap of CI's, very large variances, Chi square test for heterogeneity significant, $I^2 > 75\%$

Indirectness of evidence

Not serious Underlying causes (previous trauma, cervical rib, repetitive movements) clearly defined. No differences in acute and chronic between groups. Interventions clearly described, fitting and comparable between groups (OAC, surgical approach, PTA, CDT). The same, objective outcome measures between groups with same follow-up (DASH, Villalta score). Direct comparison between interventions or outcomes for every patient described separately.
Serious Varying cause for effort thrombosis or not all underlying causes clearly described. Interventions comparable, but not clearly described which additional treatments. Surgical procedure not clearly described. Variations in follow-up length for outcome measurements, variation in measurement tools between groups. Interventions not directly compared or comparable with each other (just reporting of series). Semi-subjective outcome measures ('symptomfree').

Very serious No definitions of underlying causes. No risk factors. Chronic or acute not described, or differences per intervention group in underlying causes, risk factors or chronic vs acute. No clear data about interventions or interventions between groups not comparable (other surgical approaches, other AC regime, other radiological interventions). Different measurement tools used between groups, subjective outcome measurements ('good' function), or not clear how functional outcomes were measured. Large difference in follow-up (>1 year) or follow up not specified per intervention group.

Imprecision

Not serious OIS is met + 95% CI excludes no effect (RR = 1 is excluded)
 Serious If IOS is not met (except population > 2000 patients). Is IOS is met, but 95% includes no effect (RR =1) when 95% fails to exclude important benefit or harm (RR < 0.5 or > 1.5)
 Very serious When there are very few events and CIs around both relative and absolute estimates of effect, that include both appreciable benefit and appreciable harm (RD -250 and + 250 included)

Other factors

Publication bias

Not found	Symmetrical funnel plot
Strong suspicion	Asymmetrical funnel plot

Strong effect

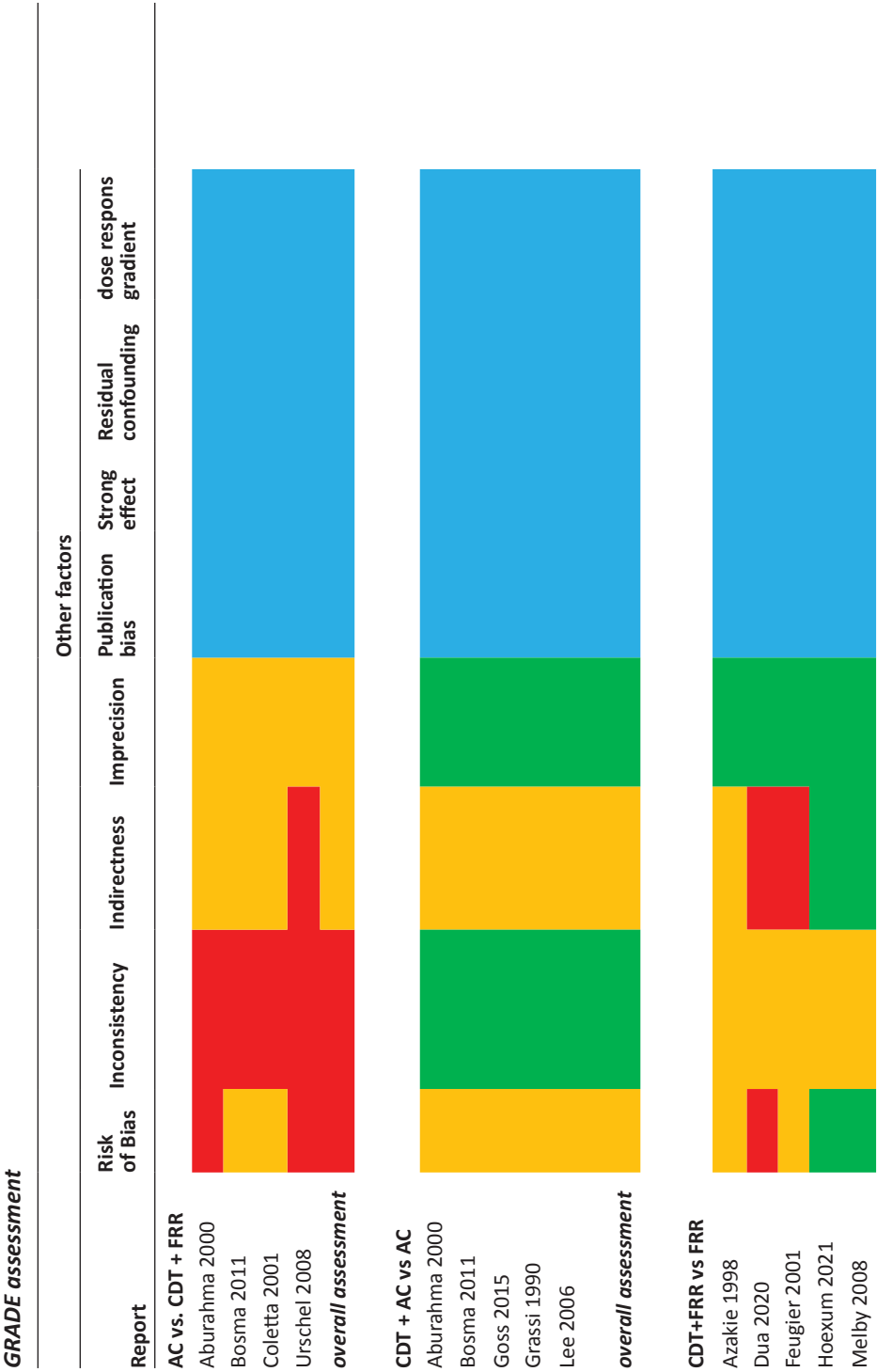
RR not < 0.5 or > 2.0 in all comparisons so 'no' for strong effect in all comparisons.

Rating residual confounding

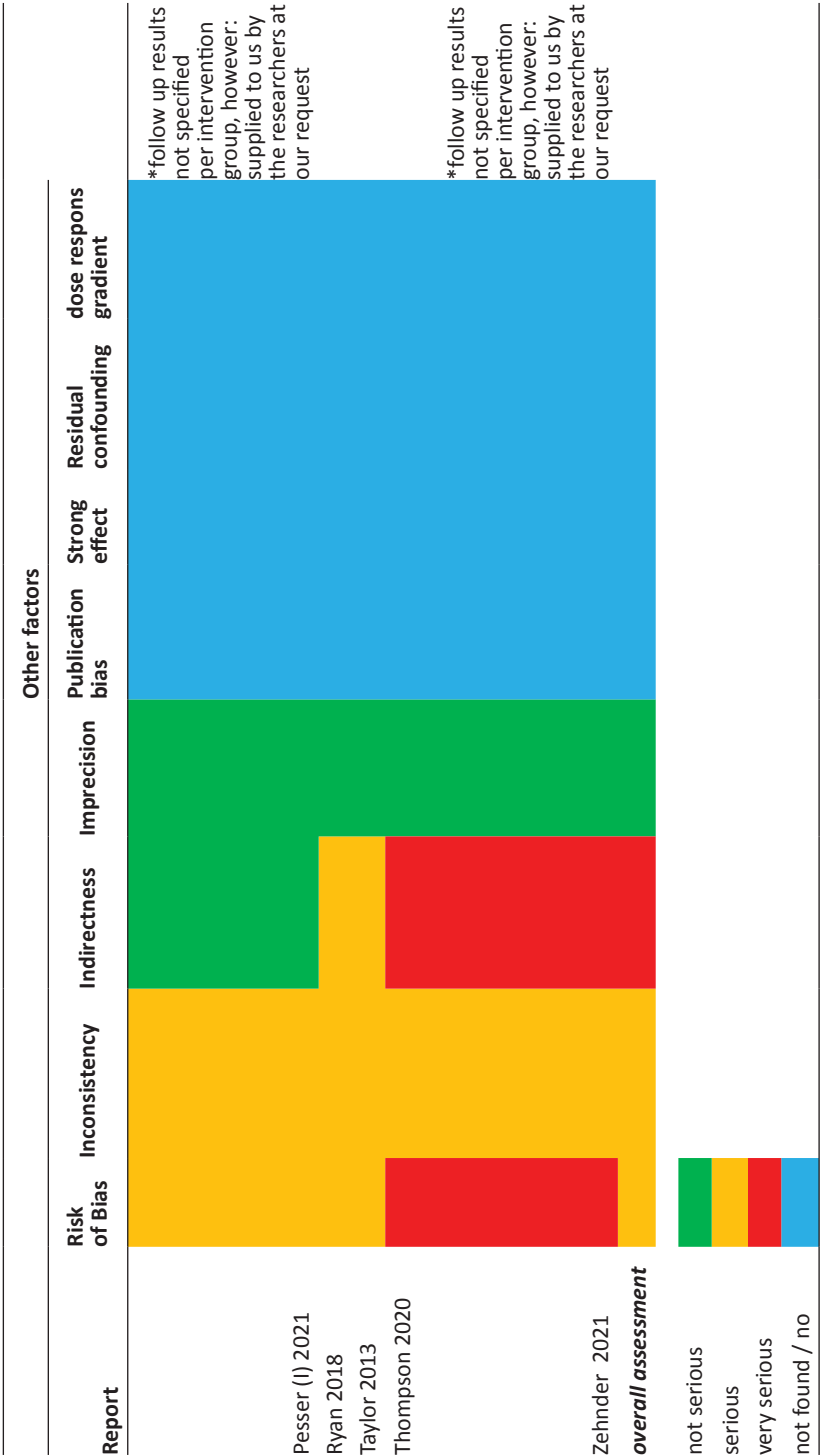
All comparisons have been rated down in previous assessments, so no additional rating down for residual confounding has been done.

Rating dose-response gradient

All comparisons have been rated down in previous assessments, so dose-response gradient has not been graded additionally.



GRADE assessment Continued



Catheter directed thrombolysis in addition to anticoagulation compared to anticoagulation for Paget-Schroetter syndrome					
Patient or population: Paget-Schroetter syndrome					
Intervention: catheter directed thrombolysis in addition to anticoagulation					
Comparison: anticoagulation					
Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with anticoagulation	Risk difference with catheter directed thrombolysis in addition to anticoagulation
Functional outcomes (Functional outcomes) assessed with: Symptomfree at last follow-up	113 (5 observational studies) ^{1,2,3,4,5}	⊕○○○ Very low ^{1,2,3,4,5,a,b,c,d,e,f}	RR 1.05 (0.86 to 1.28)	698 per 1.000	35 more per 1.000 (98 fewer to 195 more)
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio					
GRADE Working Group grades of evidence					
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.					
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.					
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.					
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.					
Explanations					
a. Incomplete definition of risk factors and aetiology of Paget-Schroetter syndrome in 5/5 reports]					
b. Follow-up of separate intervention groups not reported or differences in follow-up length in 3/5 reports					
c. Incomplete definition of study population in 4/5 reports					
d. Acute or chronic presentation unclear in 1/5 report					
e. Subjective description of outcome measurement in 2/5 reports					
f. Interventions not directly compared with each other, just reporting of series in 1/5 report					

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Surgical management consisting of catheter directed thrombolysis followed by first rib resection compared to non-operative management with anticoagulation for Paget-Schroetter syndrome

Patient or population: Paget-Schroetter syndrome

Intervention: catheter directed thrombolysis followed by first rib resection

Comparison: anticoagulation

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	Risk difference with surgical management consisting of catheter directed thrombolysis followed by first rib resection
Functional outcomes (Functional outcomes) assessed with: Symptomfree at last follow-up	674 (4 observational studies) ^{1,2,3,4}	⊕○○○ Very low ^{1,2,3,4,a,b,c,d,e,f,g,h,i,j,k}	RR 2.47 (0.86 to 7.09)	339 per 1.000	498 more per 1.000 (47 fewer to 2.064 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

- a. Underlying causes of Paget-Schroetter syndrome incompletely defined in 2/4 reports
- b. Risk factors of Paget-Schroetter syndrome not defined in 2/4 reports
- c. Acute and chronic presentation with Paget-Schroetter syndrome not clearly defined in 2/4 reports
- d. Total follow-up not specified per intervention in 2/4 reports
- e. Risk factors of Paget-Schroetter syndrome incompletely described in 1/4 reports
- f. Underlying causes of Paget-Schroetter syndrome not defined in 1/4 report
- g. Significant chi-square test for heterogeneity (chi-square = 16.13, P < 0.001) and I-square = 81% (heterogeneity may be substantial)
- h. Specific additional interventions (i.e. PTA, stenting) could not be linked to specific functional outcomes in 1/4 report
- i. Subjective description of outcomes in 3/4 reports
- j. Intervention groups not directly compared, patient series described in 1/4 reports
- k. The optimal information size criterion is met, however 95% CI includes RR = 1, as well as RR = 7.09

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Catheter directed thrombolysis followed by first rib resection compared to anticoagulation followed by first rib resection for Paget-Schroetter syndrome

Patient or population: Paget-Schroetter syndrome

Intervention: catheter directed thrombolysis followed by first rib resection

Comparison: anticoagulation followed by first rib resection

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with first rib resection	Risk difference with catheter directed thrombolysis followed by first rib resection
Functional outcomes assessed with: Symptomfree at last follow-up	397 (10 observational studies) ^{1,2,3,4,5,6,7,8,9,10}	⊕○○○ Very low ^{1,2,3,4,5,6,7,8,9,10}	RR 1.09 (0.91 to 1.31)	697 per 1.000	63 more per 1.000 (63 fewer to 216 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

- a. Risk factors of Paget-Schroetter syndrome not defined in 8/10 reports
- b. Underlying causes of Paget-Schroetter syndrome incompletely defined in 8/10 reports
- c. Total follow-up not specified per intervention in 6/10 reports
- d. Interventions described, but functional outcomes after specific radiologic interventions not traceable in 4/10 reports
- e. Population not specifically defined as patients with Paget-Schroetter syndrome in 3/10 reports
- f. Acute and chronic presentation with Paget-Schroetter syndrome not clearly defined in 5/10 reports
- g. Underlying causes of Paget-Schroetter syndrome not defined in 2/10 reports
- h. Follow-up mean < 36 months in 1/10 report
- i. Substantial overlap of 95% CI's, but significant heterogeneity (Chi square for heterogeneity: P < 0.01; I square = 67%)
- j. Interventions not directly compared with each other in 3/10 reports
- k. No clear data about additional radiological interventions in 1/10 report
- l. Subjective description of outcomes in 5/10 reports
- m. Different surgical procedures described, but not traceable to specific intervention groups in 1/10 report

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Author(s): Hoexum F, Hoebink M, Coveliers HME, Wisselink W, Jongkind V, Yeung KK.
Question: Catheter directed thrombolysis in addition to anticoagulation compared to anticoagulation for Paget-Schroetter syndrome
Bibliography: Hoexum F, Hoebink M, Coveliers HME, Wisselink W, Jongkind V, Yeung KK. Management of Paget-Schroetter Syndrome: a systematic review and meta-analysis.

Certainty assessment		No of patients		Effect		Certainty		Importance				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anticoagulation catheter directed thrombolysis in addition to anticoagulation	Relative (95% CI)	Absolute (95% CI)			
Functional outcomes (assessed with: Symptomfree at last follow-up)												
5 ^{1,2,3,4,5}	observational studies	serious ^{1,2,3,4,5,a,b,c,d}	not serious	serious ^{1,2,3,4,5,a,b,c,d,e,f}	not serious	none	63/70 (90.0%)	30/43 (69.8%)	RR 1.05 (0.86 to 1.28)	35 more per 1,000 (from 98 fewer to 195 more)	⊕○○○ Very low	IMPORTANT

CI: confidence interval; RR: risk ratio

Explanations

- a. Incomplete definition of risk factors and aetiology of Paget-Schroetter syndrome in 5/5 reports
- b. Follow-up of separate intervention groups not reported or differences in follow-up length in 3/5 reports
- c. Incomplete definition of study population in 4/5 reports
- d. Acute or chronic presentation unclear in 1/5 report
- e. Subjective description of outcome measurement in 2/5 reports
- f. Interventions not directly compared with each other, just reporting of series in 1/5 report

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Author(s): Hoexum F, Hoebink M, Coveliers HME, Wisselink W, Jongkind V, Yeung KK.
Question: Catheter directed thrombolysis in addition to anticoagulation compared to anticoagulation for Paget-Schroetter syndrome
Bibliography: Hoexum F, Hoebink M, Coveliers HME, Wisselink W, Jongkind V, Yeung KK. Management of Paget-Schroetter Syndrome: a systematic review and meta-analysis.

Certainty assessment							Effect	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations					
							No of patients	non-operative management consisting with anticoagulation	surgical management of catheter directed thrombolysis followed by first rib resection		
Functional outcomes (assessed with: Symptomfree at last follow-up)											
4 ^{1,2,3,4}	observational studies	very serious ^{1,2,3,4,abc,def}	very serious ^{1,2,3,4,g}	serious ^{1,2,3,4,abc,def,h,i}	serious ^{1,2,3,4,k}	none	569/615 (92.5%)	20/59 (33.9%)	RR 2.47 (0.86 to 7.09)	⊕○○○ Very low	498 more per 1,000 (from 47 fewer to 1,000 more)
IMPORTANT											

CI: confidence interval; **RR:** risk ratio

Explanations

a. Underlying causes of Paget-Schroetter syndrome incompletely defined in 2/4 reports

b. Risk factors of Paget-Schroetter syndrome not defined in 2/4 reports

c. Acute and chronic presentation with Paget-Schroetter syndrome not clearly defined in 2/4 reports

d. Total follow-up not specified per intervention in 2/4 reports

e. Risk factors of Paget-Schroetter syndrome incompletely described in 1/4 reports

f. Underlying causes of Paget-Schroetter syndrome not defined in 1/4 report

g. Significant chi-square test for heterogeneity (chi-square = 16.13, P < 0.001) and I-square = 81% (heterogeneity may be substantial)

h. Specific additional interventions (i.e. PTA, stenting) could not be linked to specific functional outcomes in 1/4 report

i. Subjective description of outcomes in 3/4 reports

j. Intervention groups not directly compared, patient series described in 1/4 reports

k. The optimal information size criterion is met, however 95% CI includes RR = 1, as well as RR = 7.09

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Question: catheter directed thrombolysis followed by first rib resection compared to anticoagulation followed by first rib resection for Paget-Schroetter syndrome
Bibliography: Hoexum F, Hoebink M, Coveliers HME, Wisselink W, Jongkind V, Yeung KK. Management of Paget-Schroetter Syndrome: a systematic review and meta-analysis.

Certainty assessment			No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	first rib resection	Absolute (95% CI)
							thrombolysis followed by first rib resection	Relative (95% CI)
Functional outcomes (assessed with: Symptom free at last follow-up)								
10 ^{1,2,3,4,5,6,7,8,9,10}	observational studies	serious ^{1,2,3,4,5,6,7,8,9,10,a,b,c,d,e,f,g,h}	serious ^{1,2,3,4,5,6,7,8,9,10,a,b,c,d,e,f,g,h,i,j,k,l,m}	very serious ^{1,2,3,4,5,6,7,8,9,10,a,b,c,d,e,f,g,h,i,j,k,l,m}	not serious	none	99/142 (69.7%)	RR 1.09 (0.91 to 1.31)
							233/255 (91.4%)	63 more per 1,000 (from 63 fewer to 216 more)
								⊕○○○ Very low
								IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

- a. risk factors of Paget-Schroetter syndrome not defined in 8/10 reports
- b. Underlying causes of Paget-Schroetter syndrome incompletely defined in 8/10 reports
- c. Total follow-up not specified per intervention in 6/10 reports
- d. Interventions described, but functional outcomes after specific radiologic interventions not traceable in 4/10 reports
- e. Population not specifically defined as patients with Paget-Schroetter syndrome in 3/10 reports
- f. acute and chronic presentation with Paget-Schroetter syndrome not clearly defined in 5/10 reports
- g. Underlying causes of Paget-Schroetter syndrome not defined in 2/10 reports
- h. Follow-up mean < 36 months in 1/10 report
- i. Substantial overlap of 95% CI's, but significant heterogeneity (Chi square for heterogeneity: P < 0.01; I square = 67%)
- j. Interventions not directly compared with each other in 3/10 reports
- k. no clear data about additional radiological interventions in 1/10 report
- l. subjective description of outcomes in 5/10 reports
- m. Different surgical procedures described, but not traceable to specific intervention groups in 1/10 report

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SUPPLEMENTARY TABLES

Supplementary table S1. general study design and quality assessment.

Author	Ref.	Year	INSTITUTION		INCLUSION				QUALITY ASSESSMENT***										
			Study design	Name	City	Country *	Period	Years	Patients	Patients a year	Criteria								Overall score
											1	2	3	4	5	6	7	8	
Pesser	8	2021	R	Catharina Hospital	Eindhoven	NL	2015-2019	5	36	7.2	2	1	0	2	2	1	2	2	13
Pesser	9	2021	R	Catharina Hospital	Eindhoven	NL	2015-2019	5	10	2.0	1	1	1	2	2	2	2	2	14
Silverberg	10	2021	R	Chaim Sheba Medical Center	Tel Hashomer	IL	2007-2019	13	18	1.4	1	1	2	2	2	0	1	12	
Hoeum	11	2021	R	Amsterdam University Medical Centers	Amsterdam	NL	7-2012 / 5-2016	3.9	13	3.3	1	2	1	1	2	1	0	2	12
Zehnder	12	2021	R	Cantonal Hospital of Winterthur / Bern University Hospital / Kantonsspital Luzern	Winterthur, Bern, Lucerne	CH	1-2015 / 7-2021	6.5	19	2.9	1	0	2	0	1	1	0	1	8
Bozzay	13	2020	R	Walter Reed National Military Medical Center / Temple University Hospital	Bethesda / Philadelphia	US	12-2010 / 11-2017	7	30	4.3	2	2	1	1	0	2	1	12	
Dua	14	2020	R	Massachusetts General Hospital / Stanford Hospital and Clinics	Boston / Stanford	US	2000 / 2018	19	109	5.7	2	0	1	0	2	2	1	2	12
Thompson	15	2020	R	Naval Medical Center / Santa Barbara Cottage Hospital	San Diego / Santa Barbara	US	2008-2016	9	23	2.6	2	1	1	1	1	0	2	1	10
Fairman	16	2020	R	Hospital of the University of Pennsylvania	Philadelphia	US	1-2007 / 12-2018	12	125	10.4	2	1	1	1	1	0	1	1	9
Madden	17	2019	R	Pennsylvania Hospital	Philadelphia	US	(1)1993 - (12)2018	26	51	2.0	2	1	0	2	2	2	2	2	14
Kumar	18	2019	R	Nationwide Children's Hospital	Columbus, Ohio	US	(1)2010 - (12)2017	8	22	2.8	2	1	1	1	2	2	2	1	13
Gharagozloo	19	2019	R	University of Central Florida	Florida	US	(1)2010 - (12)2015	6	83	13.8	1	1	2	0	2	1	2	2	13
Ryan	20	2018	R	The Ohio State University College of Medicine	Columbus, Ohio	US	(4)2000 - (12)2013	13.75	48	3.5	2	1	0	1	0	0	2	0	7
Mahmoud	21	2018	R	Helsinki University Hospital	Helsinki	US	01-2006 / 12-2013	8	60	7.5	2	1	2	2	2	1	1	2	14
Stuck	22	2016	R	Bern University Hospital	Bern	CH	2010 - 2015	6	23	3.8	2	1	0	1	2	1	1	1	10
Kärkkäinen	23	2016	P	Kuopio University Hospital	Kuopio	FI	(10)2010 - (12)2014	4.25	22	5.2	2	2	1	2	2	1	2	2	16
Siracuse	24	2015	R	New York-Presbyterian Hospital / Boston Medical Center	New York / Boston	US	7-2005 / 2-2014	8.67	33	3.8	2	1	2	2	2	0	0	1	12
Hawkins	25	2015	R	Brigham & Women's Hospital	Boston	US	(2)2007 - (4)2014	7.25	30	4.1	2	1	1	1	2	1	2	1	13
Riera-Mestre	26	2016	R	Universitat Internacional de Catalunya	Barcelona	ES	2008 - 2014	7	21	3.0	2	1	0	2	0	2	1	0	9
Goss	27	2015	R	St. Luke's-Roosevelt Hospital Center	New York	US	1994 - 2014	11	27	2.5	1	1	0	1	2	2	0	1	9
Trenor	28	2015	R	Boston Children's Hospital	Boston	US	(01)2003 - (12)2013	11	21	1.9	2	2	1	1	1	0	0	1	9

Supplementary table S1. Continued

Author	Ref.	Year	Study design	INSTITUTION		INCLUSION			QUALITY ASSESSMENT**											Overall score
				Name	City	Country *	Period	Years	Patients	Patients a year	Criteria									
											1	2	3	4	5	6	7	8	9	
Abulararage	29	2014	R	The Johns Hopkins Hospital	Baltimore	US	(8)2003 - (12)2011	8.33	159	19.1	2	1	1	0	1	2	0	2	1	10
Chandra	30	2014	R	Stanford University Medical Center	Stanford	US	2000 - 2013	14	14	1.0	2	1	1	0	1	1	2	1	10	
Elivène	31	2014	R	Saint Roch Hospital, University Hospital of Nice	Nice	FR	(1)1978 - (1)2013	35	33	0.9	2	1	2	2	2	2	2	2	17	
Taylor	32	2013	R	Royal Devon and Exeter Hospital	Exeter	GB	1995 - 2011	16	117	7.3	2	1	1	0	1	2	0	2	11	
Barnford	33	2012	R	St George's Vascular Institute	London	GB	(1)2002 - (12)2009	8	33	4.1	2	1	1	1	2	1	1	1	12	
Chang	34	2012	R	The Johns Hopkins Hospital	Baltimore	US	12-2003 / 11-2009	5.9	84**	14.2	2	1	1	0	2	2	1	2	13	
Bosma	35	2011	R	Onze Lieve Vrouwe Gasthuis / Amsterdam University Medical Centers	Amsterdam	NL	1994 - 2008	15	45	3.0	2	1	2	1	2	2	2	2	16	
	R																			
Skalikca	36	2011	R	General University Hospital / First Faculty of Medicine of Charles University	Prague	CZ	(1)2001 - (12)2007	7	73	10.4	2	1	2	0	1	2	2	1	12	
	Guizzo	37	2010	R	The Johns Hopkins Hospital	Baltimore	US	07-2003 / 05-2009	5.9	103**	17.5	2	1	1	1	2	1	0	2	10
Stone	38	2010	R	Dartmouth-Hitchcock Medical Center	Lebanon	US	1988 - 2008	21	36	1.7	2	1	1	0	1	2	2	2	12	
De Léon	39	2009	P	The Johns Hopkins Hospital	Baltimore	US	(10)2003 - (12)2007	4.25	56**	13.2	1	1	1	0	1	2	0	2	8	
Molina	40	2009	R	University of Minnesota Medical Center	Minnesota	US	(7)1985 - (5)2008	22.9	126	5.5	0	1	1	0	2	2	0	2	10	
Urschel	41	2008	R	Baylor University Medical Center	Dallas	US	"last 50 years"	50	608	12.2	2	0	0	1	1	0	0	0	4	
Melby	42	2008	R	Washington University School of Medicine / Barnes-Jewish Hospital	Washington / St Louis	US	(01)1997 - (1)2007	10	32	3.2	1	1	1	2	1	2	2	1	12	
	Cordobes-Gual	43	2008	P	Son Dureta University Hospital	Mallorca	ES	(1)1998 - (12)2005	8	14	1.8	2	1	1	1	2	2	2	13	
Doyle	44	2007	R	University of Rochester Medical Center	Rochester	US	1996 - (6)2006	10.5	34	3.2	2	1	1	0	2	2	1	2	13	
Gelabert	45	2007	R	UCLA Gonda (Goldschmied) Vascular Center	Los Angeles	US	1993 - 2002	10	30	3.0	2	2	2	1	2	0	2	1	14	
Shebel	46	2006	R	University of Southern California Center for Vascular Care	Los Angeles	US	2003 - 2005	3	14	4.7	2	1	1	1	1	0	0	1	8	
	Lee	47	2006	R	Stanford University Medical Center	Stanford	US	(6)1996 - (8)1995	9.17	35	3.8	2	1	2	1	2	2	2	2	16
Persson	48	2006	R	Stockholm Söder Hospital	Stockholm	SE	1995 - 2002	8	31	3.9	2	1	1	0	2	0	2	2	12	
Fassiadi	49	2005	R	Maidstone hospital	Kent	GB	(5)1995 - (1)2004	8.75	24	2.7	2	1	1	0	1	0	0	0	5	
Pupka	50	2003	R	Wroclaw University Medical center	Wroclaw	PL	1991 - 2002	12	22	1.8	1	1	1	1	2	1	0	1	9	
Lokanathan	51	2001	R	Vancouver General Hospital	Vancouver	CA	1989 - 1998	10	28	2.8	2	1	1	0	1	2	0	1	10	
Feugier	52	2001	R	Edouard Herriot Hospital	Lyon	FR	(1)1991 - (12)1999	9	10	1.1	2	1	1	1	1	2	0	2	11	
Kreienber	53	2001	R	Albany Medical Center Hospital	Albany	US	1994 - 2000	7	23	3.3	2	1	2	1	1	2	2	0	12	

Supplementary table S1. Continued

Author	INSTITUTION		INCLUSION				QUALITY ASSESSMENT***													
	Ref.	Year	Study design	Name	City	Country *	Period	Years	Patients	Patients a year	Criteria								Overall score	
											1	2	3	4	5	6	7	8		9
Coletta	54	2001	R	Naval Medical Center	San Diego	US	(11)1992 - (1)1999	6.25	19	3.0	1	1	0	2	1	1	0	1	8	
Aburahma	55	2000	R	Charleston Area Medical Center	Charleston	US	(1)1987 - (12)1996	10	23	2.3	1	1	0	1	2	2	1	1	10	
Green	56	2000	R	University of Rochester Medical Center	Rochester	US	1990 - 1998	9	11	1.2	2	1	0	2	2	0	2	12		
Lee	57	2000	R	Stanford University Medical Center	Stanford	US	(6)1996 - (6)1999	3	13	4.3	2	1	0	1	2	1	0	1	9	
Yilmaz	58	2000	R	Amsterdam University Medical Centers	Amsterdam	NL	(1)1983 - (10)1997	14.83	24	1.6	1	1	1	2	2	2	0	1	12	
Héron	59	1999	R	Broussais Hospital	Paris	FR	(4)1980 - (11)1998	18.58	54	2.9	2	1	2	1	0	1	2	0	1	10
Azakie	60	1998	R	University of California San Francisco Medical center	San Francisco	US	1977 - 1997	21	21	1.0	2	1	1	1	2	1	0	1	10	
Lee	61	1998	R	Brigham & Women's Hospital	Boston	US	1988 - 1996	8	11	1.4	1	1	2	1	1	1	0	1	9	
Beygui	62	1997	R	Stanford University Medical Center	Stanford	US	1987 - 1994	8	13	1.6	2	1	1	1	1	0	0	1	8	
Adelman	63	1997	R	New York University Medical Center	New York	US	(11)1991 - (2)1995	3.25	18	5.5	2	1	1	2	1	1	0	1	10	
Sheeran	64	1997	R	Hartford Hospital	Hartford	US	(1)1992 - (6)1996	4.5	14	3.1	2	1	1	0	2	1	0	2	9	
Meier	65	1996	R	Yale-New Haven Hospital.	New Haven	US	(10)1992 - (12)1995	3.16	10	3.2	2	1	1	1	2	0	0	1	9	
Machleder	66	1993	P	University Medical Center UCLA	Los Angeles	US	(3)1985 - (10)1991	6.5	50	7.7	2	1	2	1	2	1	1	1	14	
Grassi	67	1990	R	Brigham & Women's Hospital	Boston	US	"5 year period"	5	11	2.2	1	1	1	0	2	2	1	0	2	10

Table legend: R= retrospective, ref. = reference, P= prospective, * = ISO-3166-1 ALPHA-2 abbreviation of country names, ** = not included in the calculation because of overlapping patients, *** = for grading system see supplementary document 2

Supplementary table S2. patient characteristics

Author	Ref.	Year	P	Gender	Age		Side	Dominant side	PE	RISK FACTORS												Cervical		Effort induced													
					Li	M				F	Range			Smoking	Contraceptive use			Previous thrombosis			Hypercoagulability				rib												
											mean	min	max		R	L	?	Y	N	?	Y	N	?			Y	N	?	Y	N	?	Y	N	?			
Pesser	8	2021	36	16	20	0	33	16	57	21	17	0	14	10	14	0	0	36	0	0	36	0	0	36	0	2	34	0	12	24	0						
Pesser	9	2021	10	6	4	0	34	22	59	3	7	0	0	10	0	0	10	0	0	10	0	0	4	1	9	0	0	10	0	0	10						
Silverberg	10	2021	18	0	15	3	0	29	16	46	0	0	18	11	7	0	0	18	0	0	18	0	0	3	0	18	0	0	18	0	18						
Hoexum	11	2021	13	8	5	0	32.9	20	54	9	4	0	0	13	0	13	0	6	7	0	3	2	0	0	0	13	0	13	0	6	7	0					
Zahnder	12	2021	19	19	13	6	0	na	na	15	4	0	18	1	0	0	19	0	0	19	1	0	5	1	18	0	0	19	0	5	0	14					
Bozay	13	2020	30	30	24	6	0	32.1	na	na	0	0	30	0	0	30	0	0	30	0	0	6	0	0	30	1	29	0	0	30	0	30					
Dua	14	2020	109	Na	55	54	0	30.1	na	na	0	0	109	0	0	109	0	109	0	0	109	0	0	54	0	109	0	0	109	0	109	0	109				
Thompson	15	2020	21	Na	0	0	21	na	na	0	0	21	0	0	21	0	0	21	0	0	21	0	0	21	0	21	0	0	21	0	0	21					
Fairman	16	2020	123	125	54	69	0	28.4	12	64	0	0	123	13	120	0	0	123	0	0	69	0	0	69	0	123	0	123	3	120	0	0	123				
Madden	17	2019	51	na	23	28	0	36.7	na	na	36	15	0	0	51	0	0	51	2	49	0	0	0	28	0	0	51	0	0	51	0	0	51				
Kumar	18	2019	22	na	10	12	0	16.3	13.5	18.2	0	0	22	12	5	4	18	0	1	21	0	3	9	0	0	22	8	14	0	0	22	19	3	0			
Gharagozloo	19	2019	83	na	49	34	0	24	na	na	0	0	83	0	0	83	0	83	0	0	83	0	0	34	0	83	5	78	0	0	83	0	83				
Ryan	20	2018	48	na	0	0	48	na	na	0	0	48	0	0	48	0	0	48	0	0	48	na	na	0	0	48	0	0	48	0	0	48	0	48			
Mahmoud	21	2018	60	na	26	34	0	29	16	54	41	19	0	0	60	1	59	0	0	60	0	0	34	9	51	0	10	50	0	0	60	0	45	15	0		
Stuck	22	2016	23	na	17	6	0	39	na	na	13	10	0	0	23	0	0	23	0	0	23	0	0	6	2	21	0	0	23	0	23	14	9	0			
Kärkkäinen	23	2016	22	na	14	8	0	37	16	62	0	0	22	0	0	22	4	18	0	5	17	0	2	6	0	3	19	0	0	22	0	0	22				
Sirouse	24	2017	33	na	20	13	0	35	na	na	0	0	33	0	0	33	0	33	1	32	0	1	12	0	0	0	33	2	31	0	0	33	0	21	12	0	
Hawkins	25	2015	30	na	13	17	0	29.5	17	52	24	6	0	23	5	2	0	30	0	0	30	0	0	17	0	0	30	0	30	0	0	30	0	30			
Riera-Mestre	26	2016	21	na	10	11	0	34.9	na	na	0	0	21	0	0	21	0	21	0	21	0	0	21	0	0	21	3	18	0	0	21	0	0	21			
Goss	27	2015	27	na	12	15	0	39.9	24	71	0	0	27	0	0	27	0	27	0	27	0	0	15	3	24	0	3	0	24	0	0	27	8	19	0		
Trenor	28	2015	21	na	11	10	0	16	11	18	0	0	21	0	0	21	0	21	1	20	0	2	8	0	0	21	4	17	0	0	21	0	13	8	0		
Abularagge	29	2014	159	na	74	85	0	31.7	na	na	0	0	159	0	0	159	17	142	0	22	137	0	0	85	0	0	159	15	60	84	0	0	159	0	159		
Chandra	30	2014	14	14	13	1	0	18.8	15	24	14	0	0	14	0	0	14	0	14	0	14	0	1	0	0	14	0	14	0	14	0	14	0	14			
Elkène	31	2014	33	33	17	16	0	34	14	53	10	23	0	20	13	0	0	33	11	22	0	0	0	16	1	0	32	0	0	33	0	0	33	13	20	0	
Taylor	32	2013	117	na	52	65	0	32	15	68	0	0	117	85	32	0	15	80	22	25	92	0	0	0	65	2	115	0	1	116	0	5	90	22	99	23	0

Supplementary table S2. Continued

Author	Ref.	Year	P	Li	Gender	Age		Side	Dominant side			PE	RISK FACTORS										Cervical rib			Effort induced											
						Range			Smoking	Contraceptive use			Previous thrombosis		Hypercoagulability						Y	N	?	Y	N	?											
						min	max			R	L		?	Y	N	?	Y	N	?	Y							N	?	Y	N	?						
																																M	F	?			
Barnford	33	2012	33	na	19	14	0	37.9	22	67	22	11	0	0	33	1	32	0	12	11	0	0	14	0	0	33	2	31	0	0	33	0	0	33			
Chang	34	2012	84	na	42	42	0	na	na	0	0	84	0	0	84	0	0	84	0	0	84	0	42	0	0	84	10	74	0	0	84	0	0	84			
Bosma	35	2011	45	na	28	17	0	40	18	63	26	19	0	0	45	0	0	45	0	0	45	0	17	0	0	45	2	43	0	1	44	0	0	45			
Skalikla	36	2011	73	na	33	40	0	36	na	na	0	0	73	0	0	73	2	71	0	0	73	21	19	0	0	73	23	50	0	2	71	0	0	73			
Guizzo	37	2010	103	110	53	50	0	31.5	16	54	0	0	103	0	103	0	0	103	0	103	0	0	50	0	0	103	8	95	0	1	102	0	75	4	30		
Stone	38	2010	36	na	24	12	0	30	17	51	30	6	0	0	36	0	0	36	3	33	0	0	12	0	0	36	0	36	0	0	36	0	0	36			
De Léon	39	2009	56	na	31	25	0	na	na	na	0	0	56	0	0	56	0	0	56	0	0	56	0	0	25	0	56	4	24	39	0	0	56	0	0	56	
Molina	40	2009	126	na	69	57	0	28.9	na	na	96	30	0	0	126	0	0	126	0	0	126	0	57	0	0	126	0	0	126	0	0	126	0	0	126		
Urschel	41	2008	608	626	301	307	0	32	16	51	0	0	608	0	0	608	0	608	0	0	608	0	0	307	0	0	608	0	0	608	62	564	0	0	608		
Melby	42	2008	32	na	29	3	0	20.3	16	26	26	6	0	28	4	0	1	31	0	0	32	0	3	0	32	0	32	0	32	0	32	0	32	0	0	32	
Cordobes-Gual	43	2008	14	na	5	9	0	na	na	na	0	0	14	0	0	14	0	14	0	0	14	0	9	0	0	14	0	14	0	0	14	0	0	14			
Doyle	44	2007	34	na	0	0	34	33	18	69	0	0	34	0	0	34	0	34	0	0	34	na	na	na	0	0	34	0	34	0	0	34	17	17	0		
Gelabert	45	2007	30	na	13	17	0	32	na	na	0	0	30	0	0	30	0	30	0	30	1	29	0	2	15	0	0	30	1	29	0	0	30	0	0	30	
Shebel	46	2006	14	na	7	7	0	32	16	58	8	6	0	0	14	0	0	14	0	0	14	0	7	0	0	14	2	12	0	1	13	0	12	2	0		
Lee	47	2006	35	na	20	15	0	32	16	61	22	13	0	23	12	0	0	35	0	0	35	0	15	0	0	35	0	35	0	0	35	25	10	0			
Persson	48	2006	31	na	9	22	0	45	21	84	16	15	0	15	16	0	0	31	0	0	31	12	10	0	0	31	0	31	0	25	6	14	17	0			
Fassiadis	49	2005	24	na	8	16	0	46	21	80	0	0	24	0	0	24	0	24	0	8	15	0	4	12	16	4	20	0	5	14	5	0	0	24	4	20	0
Pupka	50	2003	22	23	13	10	0	na	17	42	13	10	0	13	10	0	0	22	0	0	22	2	8	0	0	22	0	22	0	0	22	11	11	0	0		
Lokanathan	51	2001	28	na	20	8	0	36	na	na	0	0	28	23	5	0	0	28	0	0	28	0	8	0	28	0	0	28	16	12	0	0	28	16	12	0	
Feugier	52	2001	10	11	8	2	0	30.5	18	45	6	5	0	8	3	0	0	10	0	0	10	0	2	0	0	10	0	10	0	0	10	11	0	0	0		
Kreienber	53	2001	23	na	11	12	0	30.3	18	58	11	12	0	11	12	0	0	23	0	0	23	0	12	3	20	0	3	20	0	0	23	7	16	0	0		
Coletta	54	2001	19	21	0	19	na	na	na	na	na	0	19	0	0	19	0	19	0	19	0	na	0	na	0	19	0	19	0	19	0	19	0	0	19		
Aburahma	55	2000	23	na	21	2	0	35.3	15	55	18	5	0	0	23	0	0	23	0	0	23	0	2	0	0	23	0	23	0	0	23	0	23	0	0	23	
Green	56	2000	11	na	9	2	0	28.5	18	43	0	0	11	0	0	11	0	11	0	0	11	0	2	0	2	0	11	0	11	0	11	0	11	0	0	11	

Supplementary table S2. Continued

Author	Ref.	Year	P	Li	Gender		Age		Side		Dominant side	PE	RISK FACTORS										Cervical rib		Effort induced																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																											
					M	F	?	min	max	R			L	?	Y	N	?	Y	N	?	Y	N	?	Y	N	?	Y	N	?	Y	N	?																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																				
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Table legend: data presented as n or percentage. Blue = Not included in totals because of bias in inclusion criteria, F= Female, Green= data presented as number of affected limbs, not number of patients, L = left, Li = Limbs, M= Male, max= maximum, min= minimum, N= No; na= not available, NR= number, P= patients, PE= pulmonary embolism, R= right, Red = not included in totals because of overlapping data, Y= Yes, ?= unknown

Supplementary table S3. Non-operative treatment.

Author[ref]	ref	Management	P	Time to start treatment [mean], (range)	First (endovascular) treatment				Anticoagulation			FU (m)		Success of initial treatment	Recurrence of thrombosis or persistent occlusion				Open at last FU				Symptom free at last FU										
					AC		CDT	PTA	Stent			Y	N		?	min	max	Y	N	?	Y	N	?	Y	N	?	Y	N	?				
					Y	N			Y	N	?																			Y	N	?	
Silverberg	10	CDT+AC	18	[4d] (1-4)	0	18	4	14	0	18	0	18	0	0	26-520	109	37	176	16	2	0	3	15	0	0	18	14	4	0	0			
Stuck	22	CDT+AC	23	[3.5 d]	0	23	19	4	0	23	0	23	0	0	12-26	12	na	na	23	0	0	6	17	0	21	2	0	15	8	0	0		
Kärkkäinen	23	PMT+AC	4	18<2w,4.2-4w	0	4	4	0	0	4	0	4	0	0	8-12	20.5	16	24	4	0	0	0	4	0	4	0	0	0	0	4	0		
Riera-Mestre	26	AC	21	na	21	0	-	-	-	-	21	0	0	33	46.5	na	na	na	0	0	21	1	20	0	0	21	17	4	0	0	0		
Goss	27		25	[15d] (1-210d)	9	16	0	16	0	16	0	25	0	0	37	54.3	2	219	16	0	9	0	0	25	23	2	0	23	2	0	0	0	
Taylor	9	AC	9	na	9	0	-	-	-	-	9	0	0	37	na	na	na	na	0	0	9	0	0	9	na	na	na	8	1	0	0	0	
	16	CDT+AC	16	na	0	16	0	16	0	16	0	16	0	0	37	na	na	na	16	0	0	0	0	16	na	na	na	15	1	0	0	0	
	32	AC	22	na	22	0	-	-	-	-	22	0	0	na	na	na	na	na	0	0	22	0	0	22	0	0	22	0	0	22	0	0	
	35		28	na	14	14	0	0	14	0	14	0	28	0	x	13	na	na	na	13	1	14	1	27	0	0	28	19	9	0	0		
Skallicka	14	AC	14	na	14	0	-	-	-	-	14	0	x	13	52	na	na	na	0	0	14	1	13	0	0	0	14	9	5	0	0	0	
	14	CDT+AC	14	na	0	14	0	0	14	0	14	0	x	13	49	na	na	na	13	1	0	0	14	0	0	0	14	10	4	0	0	0	
	36		31	na	12	19	0	0	19	0	19	0	31	0	13-26	48	na	na	31	0	0	0	22	9	19	3	9	13	9	0	0	0	
		AC	12	na	12	0	-	-	-	-	12	0	0	13-26	na	na	na	na	12	0	0	na	na	na	na	na	na	na	na	na	na	na	
Urschel	40	CDT+AC	19	na	0	19	0	0	19	0	19	0	0	13-26	na	na	na	na	19	0	0	na	na	na	na	na	na	na	na	na	na	na	
		AC	53	na	36	17	0	0	17	0	0	36	17	0	na	na	na	na	0	0	53	0	0	53	0	0	53	10	43	0	0	0	
Doyle	36	AC	36	<6w	36	0	-	-	-	-	36	0	0	na	na	na	na	na	0	0	36	0	0	36	0	0	36	10	26	0	0	0	
	17	CDT	17	na	0	17	0	0	17	0	17	0	0	na	na	na	na	na	0	0	17	0	0	17	0	0	17	0	17	0	0	0	
	2	CDT+AC	2	na	0	2	0	0	2	0	2	0	0	26-?	na	na	na	na	0	2	0	0	2	0	2	0	0	2	0	0	2	0	0
	47		35	na	6	29	17	12	0	2	27	0	35	0	Na	54	2	110	28	1	6	8	27	0	34	1	0	35	0	0	0	0	
Persson	6	AC	6	na	6	0	-	-	-	-	6	0	0	23	na	na	na	na	0	0	6	0	6	0	6	0	6	0	6	0	0	0	0
	29	CDT+AC	29	na	0	29	17	12	0	2	27	0	29	0	23	na	na	na	28	1	0	8	21	0	28	1	0	29	0	0	0	0	0
	48	AC	31	na	31	0	-	-	-	-	31	0	0	13-26	60	24	108,00	0	0	31	0	0	31	0	0	27	4	0	0	31	0	0	
	49		24	na	23	1	0	0	1	0	1	0	24	0	Na	na	na	na	na	0	24	0	0	24	0	0	24	14	8	2	0	0	
Lokanathan	23	AC	23	na	23	0					23	0	0	na	na	na	na	na	0	0	23	0	0	23	0	0	23	na	na	na	na	na	
	1	CDT+AC	1	na	0	1	0	0	1	0	1	0	0	na	na	na	na	na	0	0	1	0	0	1	0	0	1	na	na	na	na	na	
51		28	[5.5d], (1-100)	2	25	12	13	0	0	25	0	27	1	0	na	34.8	2	96,00	25	0	3	3	8	17	9	2	17	19	2	7	0	0	

Supplementary table S3. Continued

[Author][ref]	Management	P	Time to start treatment [mean], (range)	First (endovascular) treatment					Anticoagulation			FU (m)		Success of initial treatment			Recurrence of thrombosis or persistent occlusion			Open at last FU			Symptom free at last FU							
				AC		PTA	Stent			Y	N	?	Time (w)	range	mean	Y	N	?	Y	N	?	Y	N	?	Y	N	?			
				Y	N		?	Y	N																			?		
-	1	na		0	0	-	-	-	-	0	1	0	na	na	na	na	na	0	0	1	0	0	1	0	0	1	na	na	na	
AC	2	na		2	0	-	-	-	-	2	0	0	13-?	na	na	na	na	0	0	2	0	0	2	0	0	2	na	na	na	
CDT+AC	25 ^y	na		0	25	12	13	0	0	25	0	0	13-?	na	na	na	na	25	0	0	3	8	14	9	2	14	na	na	na	
Coletta	54	AC	1	na	1	0	-	-	-	-	1	0	0	na	na	na	na	0	1	0	1	0	0	0	1	0	0	1	0	0
Aburahma	55	Na	15	Na	8	7	2	5	0	2	5	0	8	0	7	na	na	7	0	8	2	5	8	6	9	0	6	9	0	0
AC	8	[3.7d]		8	0	-	-	-	-	-	8	0	0	13-52	na	12	na	0	0	8	0	0	8	1	7	0	1	7	0	0
CDT+AC	7	[3.4d]		0	7	2	5	0	2	5	0	0	0	7	na	na	12	na	7	0	0	2	5	0	5	2	0	5	2	0
Yilmaz	58	CDT+AC	5	na	0	5	0	0	5	0	5	0	0	12	na	na	na	na	0	0	5	0	0	5	0	0	5	0	2	3
Héron	59	AC	48	na	48	0	-	-	-	-	48	0	0	na	60	3	324	0	0	48	0	0	48	0	0	48	23	25	0	0
Beygui	62	CDT+AC	5	<14d	0	5	0	5	0	5	0	5	0	na	na	na	na	4	0	1	0	0	5	0	0	5	5	0	0	0
Adelman	63	na	8	na	1	7	0	8	0	0	8	0	1	0	7	na	na	na	5	2	1	4	3	1	4	3	1	0	5	3
AC	1	na		1	0	-	-	-	-	-	1	0	0	na	na	na	na	na	0	0	1	0	0	1	0	0	1	0	0	1
CDT+AC	7	na		0	7	0	7	0	0	7	0	0	7	na	na	na	na	5	2	0	4	3	0	4	3	0	0	5	2	0
Sheeran	64	CDT+AC	9	(1-14 d)	0	9	3	6	0	0	9	0	0	13	28.9	18	36	9	0	0	4	5	0	0	9	4	5	0	0	0
Meier	65	CDT+AC	5	na	0	5	4	1	0	4	1	0	5	0	13	na	na	na	5	0	0	3	2	0	3	2	0	2	3	0
Machleder	66	CDT+AC	14	na	0	14	0	0	14	0	0	14	0	0-52	36	7	84	5	9	0	0	0	14	4	9	1	5	8	1	
Grassi	67	na	10	na	6	4	1	3	0	0	4	0	10	0	24	22.4	12	36	5	4	1	9	0	1	0	9	1	10	0	0
AC	6	na		6	0	-	-	-	-	-	6	0	0	24	21.3	18	36	2	3	1	6	0	0	0	6	0	6	0	0	0
CDT+AC	4	na		0	4	1	3	0	0	4	0	4	0	24	24	12	36	3	1	0	3	0	1	0	3	1	4	0	0	0
Totals	465			240	224	66	87	72	8	183	34	433	18	14	45.1	2	324	196	22	247	45	155	265	154	47	294	230	182	53	53
%				43.1	56.9	32.0	4.2	95.8	15.1	96.0	4.0	3.0						89.9	10.1	53.1	22.5	77.5	57.0	76.6	23.4	56.8	55.8	44.2	11.4	11.4

Table legend: AC = anticoagulation; CDT = catheter directed thrombolysis; d= days; FU= follow up; Green= data presented as number of affected limbs, not number of patients; max= maximum; min= minimum; N= no; na= not available; P = patients; PMT = pharmacomechanical thrombectomy; PTA = percutaneous Transluminal Angioplasty; ref = reference; w= weeks; Y= yes; - = not applicable; ?= unknown; x= 2 patients underwent FRR.

Supplementary table S4. Secondary endpoints

Secondary endpoint	Versus	CDT+AC	χ^2	AC+FRR	χ^2	CDT+FRR	χ^2
Success of initial treatment	AC	14/18	178/196	14/18	179/195	14/18	679/707
	CDT+AC			178/196	179/195	178/196	679/707
	AC+FRR					179/195	679/707
Recurrence of thrombosis or persistent occlusion	AC	9/48	36/126	9/48	12/108	9/48	33/483
	CDT+AC			36/126	12/108	36/126	33/483
	AC+FRR					12/108	33/483
Open at last follow up	AC	34/52	74/98	34/52	81/103	34/52	534/557
	CDT+AC			74/98	81/103	74/98	534/557
	AC+FRR					81/103	534/557

Table legend: AC = anticoagulation; CDT = catheter directed thrombolysis; FRR = first rib resection; χ^2 = chi-square test; p= probability

Supplementary table S5. Surgical management 1.

Author	ref	Management	p	Mean time to start treatment [range]	PRE-OPERATIVE TREATMENT					Recurrence					SURGICAL MANAGEMENT										POSTOPERATIVE INTERVENTIONS							
										Successful CDT / / Symp.																						
					AC	CDT	? / O	PTA	Stent	Y	N	?	Y	N	?	Y	N	?	TA	SC	IC	PC	T	R	? / O	Y	N	?	Y	N	?	
Pesser	8		36	88 weeks	30	4	2	4	32	0	0	36	0	32	4	0	32	0	4	36	0	0	0	0	36	0	33	3	0	5	31	0
		AC+FRR (chronic)	30	na	30	0	0	na	na	na	na	na	na	na	na	na	na	na	30	0	0	0	0	30	0	na	na	na	na	na	na	
		CDT+FRR (chronic)	4	na	0	4	0	na	na	na	na	na	na	na	na	na	na	na	4	0	0	0	0	4	0	na	na	na	na	na	na	
		FRR (chronic)	2	na	0	0	2	na	na	na	na	na	na	na	na	na	na	na	2	0	0	0	0	2	0	na	na	na	na	na	na	
Pesser	9	CDT+FRR	10	(1d)	0	10	0	2	8	0	0	10	0	10	0	0	10	0	10	0	0	0	0	10	0	10	0	0	0	10	0	
	11		13	na	3	10	0	0	13	2	11	0	13	0	3	10	0	0	0	0	0	0	13	0	13	0	2	11	0	1	12	0
Zehnder		AC+FRR	3	na	3	0	0	0	3	0	3	0	3	0	0	3	0	0	0	0	0	0	3	0	3	0	0	3	0	0	3	0
		CDT+FRR	10	na	0	10	0	0	10	2	8	0	10	0	3	7	0	0	0	0	0	10	0	10	0	2	8	0	1	9	0	
			19	na	0	19	0	18	1	0	2	17	0	19	0	0	0	19	0	0	0	0	19	0	19	0	7	12	0	6	11	2
		AC+FRR	4	na	4	0	0	na	na	na	na	na	na	4	0	0	0	4	0	0	0	0	4	0	4	0	na	na	na	na	na	na
Bozzay		CDT+FRR	15	na	0	15	0	na	na	na	na	na	15	0	0	0	15	0	0	0	0	15	0	15	0	na	na	na	na	na	na	
	13		30	20<14d, 10>14<28d	17	13	0	0	13	0	13	0	12	1	17	12	1	17	0	15	15	0	0	1	29	0	13	0	17	3	27	0
Dua		AC+FRR	17	na	17	0	0	x	x	x	x	x	0	0	17	0	0	17	0	9	8	0	0	na	na	na	na	na	na	na	na	na
		CDT+FRR	13	na	0	13	0	0	13	0	13	0	12	1	0	12	1	0	0	6	7	0	0	na	na	na	na	na	na	na	na	na
			109	na	29	80	0	0	109	0	0	109	0	0	109	0	0	109	0	54	55	0	0	0	0	109	0	0	109	0	109	0
		AC+FRR	29	na	29	0	0	X	X	29	0	0	29	0	0	29	0	0	29	0	19	10	0	0	0	0	29	0	0	29	0	29
Thompson		CDT+FRR	80	na	0	80	0	0	80	0	0	80	0	0	80	0	0	80	0	35	45	0	0	0	0	80	0	0	80	0	80	0
	15		21	na	5	16	0	0	21	0	21	0	21	0	0	21	0	0	21	21	21	0	0	0	21	0	0	0	21	7	14	0
		CDT+FRR (acute)	13	na	0	13	0	0	13	0	13	0	0	0	13	0	0	13	0	13	13	0	0	0	13	0	0	0	13	4	9	0

Supplementary table S5. Continued

Author	ref	Management	P	Mean time to start treatment [range]	PRE-OPERATIVE TREATMENT										SURGICAL MANAGEMENT										POSTOPERATIVE INTERVENTIONS																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																															
					AC					CDT					PTA					Stent					Successful CDT / / Symp. Recanalization with AC					Recurrence restenosis / no recanalization before surgery					FRR					VR					PTA					Stent																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
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Supplementary table S5. Continued

Author	ref	Management	p	Mean time to start treatment [range]	PRE-OPERATIVE TREATMENT						Recurrence Successful CDT / / Sympt. Recanalization with AC						SURGICAL MANAGEMENT										POSTOPERATIVE INTERVENTIONS						
					AC		CDT		PTA		Stent		FRR		VR		PTA		Stent														
					Y	N	?	Y	N	?	Y	N	?	Y	N	?	Y	N	?	Y	N	?	Y	N	?								
Trenor	28	CDT + FRR	21	4d [0-32]	0	19	2	18	1	2	0	21	0	19	0	2	0	21	0	0	0	21	0	0	21	0	0	21	0				
	Abularagge	29		159	na	84	75	0	45	30	0	3	72	0	95	64	0	0	159	159	0	0	0	159	0	95	63	1	0	158	1		
		AC + FRR	78	na	78	0	0	x	x	x	x	x	x	na	na	na	0	0	78	78	0	0	0	0	78	0	na	na	0	0	78	0	
		CDT + FRR	81	na	0	81	0	45	36	0	3	78	0	na	na	na	0	0	81	81	0	0	0	0	81	0	na	na	0	0	81	0	
Chandra	30		14	[1-60]	1	13	0	0	13	0	0	13	0	13	0	0	14	0	0	0	14	0	0	14	0	6	8	0	0	14	0		
		AC + FRR	1	na	1	0	0	x	x	x	x	x	x	0	0	1	0	0	0	1	0	0	0	1	0	na	na	0	1	0	0		
		CDT + FRR	13	na	0	13	0	0	13	0	0	13	0	13	0	0	13	0	0	13	0	0	13	0	na	na	0	na	na	0	13	0	
Elkène	31		33	na	20	3	10	0	3	0	3	0	3	0	28	5	0	5	28	0	25	0	8	0	1	32	0	0	33	0	33	0	
		AC + FRR	20	na	20	0	0	x	x	x	x	x	x	x	15	5	0	5	15	0	na	0	na	0	0	20	0	0	20	0	20	0	
		CDT / other + FRR	13	<10d	0	12	1	0	0	13	0	0	13	13	0	0	13	0	na	0	na	0	na	0	0	1	12	0	0	13	0	13	0
Taylor	32		95	na	39	55	0	2	54	0	0	56	0	42	14	39	22	34	39	90	5	0	0	0	0	95	0	25	47	23	0	0	95
		CDT (<2w) + FRR	41	4,3d	0	41	0	0	0	41	0	0	41	29	12	0	17	24	0	38	3	0	0	0	0	41	0	na	na	0	0	41	0
		CDT (>2w) + FRR	15	7,5d	0	15	0	0	0	15	0	0	15	13	2	0	5	10	0	14	1	0	0	0	0	15	0	na	na	0	0	15	0
		AC + FRR	39	na	39	0	0	x	x	x	x	x	x	0	0	39	0	39	38	1	0	0	0	0	39	0	na	na	0	0	39	0	
Barnford ^[21]	33		33	na	16	17	0	6	11	0	0	17	0	33	0	0	33	0	33	0	0	0	0	0	33	0	8	25	0	0	33	0	
		AC + FRR	16	na	16	0	0	x	x	x	x	x	x	16	0	0	16	0	na	0	0	0	0	0	16	0	5	11	0	0	16	0	
		CDT + FRR	17	na	0	17	0	6	11	0	0	17	0	17	0	0	17	0	na	0	0	0	0	0	17	0	3	14	0	0	17	0	
Chang ^[22]	34	FRR	84	na	0	35	49	0	0	84	0	0	84	0	0	84	na	na	84	84	0	0	0	0	0	84	0	47	37	0	0	84	0
Bosma	35	CDT + FRR	17	na	0	17	0	0	0	17	0	17	0	17	0	0	17	0	17	0	0	0	0	0	17	0	0	0	17	0	0	17	0
Skallicka	36		42	na	8	34	0	0	0	34	0	0	34	30	12	0	0	42	42	0	0	0	0	0	42	0	0	42	0	0	42	0	42
		LMWH + FRR	8	na	8	0	0	x	x	x	x	x	x	8	0	0	8	8	0	0	0	0	0	0	8	0	8	0	0	8	0	8	0

Supplementary table S5. Continued

Author	ref	Management	p	Mean time to start treatment [range]	PRE-OPERATIVE TREATMENT					Recurrence Successful CDT / / Sympt. Recanalization with AC					SURGICAL MANAGEMENT										POSTOPERATIVE INTERVENTIONS													
					AC		CDT		? / O	Stent			FRR	TA	SC	IC	PC	T	R	? / O	Y	N	?	VR	PTA	Stent												
					?	0	Y	N		?	Y	N															?	Y	N	?	Y	N	?	Y	N	?	Y	N
Gelabert	45	CDT + FRR	24	na	0	24	0	0	24	0	0	24	16	8	0	0	24	12	0	0	0	0	12*	13	11	0	0	24	0	0	24							
				FRR	8	na	0	0	8	x	x	x	x	x	0	0	8	0	0	8	5	0	0	0	0	3*	3	5	0	0	8	0	8					
				47	14	na	0	30	0	0	30	0	0	30	28	2	0	0	0	30	30	0	0	0	0	0	0	0	30	0	11	19	0	30	0			
Pupka	50	CDT + FRR	23	na	0	23	0	0	23	0	0	23	0	0	23	0	0	23	0	0	0	0	0	0	0	0	0	23	0	0	23	0	23					
				Feugier	52	11	4.4d [0-9]	4	7	0	0	7	0	0	7	0	8	3	0	0	11	1	0	0	9	0	0	1*	4	7	0	0	11	0	11	0		
				53	23	9.4d [1-30]	0	23	0	1	22	0	1	22	0	23	0	0	1	22	0	0	0	0	0	0	0	7*	0	23	0	23	0	0	14	9	0	
Coletta	54	CDT + FRR	18	[0-304]d	0	18	0	0	18	0	0	18	0	0	18	0	0	18	0	0	0	0	0	0	0	0	0	18	0	8	10	0	6	12	0			
				Aburahma	55	8	na	0	8	0	0	8	0	0	8	0	0	8	0	1	7	0	0	0	0	0	1*	1	6	0	2	5	0	0	8	0		
				Green	56	11	na	0	7	0	0	7	0	7	0	7	0	7	0	7	0	7	0	0	0	0	0	0	7	0	0	0	1	6	0	2	5	0
Lee	57	AC + FRR	2	na	2	0	0	x	x	x	x	x	x	2	0	0	2	0	0	0	0	0	0	0	0	0	2	0	0	2	0	0	2	0	2	0		
				Yilmaz	58	19	na	0	19	0	0	19	0	0	19	0	0	19	0	0	19	0	0	0	0	0	0	0	19	0	2	17	0	0	19	0	19	0
				Héron	59	6	na	6	0	0	x	x	x	x	x	0	0	6	0	6	0	0	6	0	0	0	0	0	6	0	0	6	0	0	6	0	6	0
Azakie	60	CDT + FRR	21	<14d	2	19	0	7	12	0	1	18	0	21	0	0	21	0	0	21	0	0	21	0	0	0	1	0	20	4	17	0	0	21	0	21	0	

Supplementary table S5. Continued

Author	ref	Management	p	Mean time to start treatment [range]	PRE-OPERATIVE TREATMENT				Successful CDT / / Symp.				SURGICAL MANAGEMENT												POSTOPERATIVE INTERVENTIONS																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
									Recanalization with AC				Recurrence restenosis / no recanalization before surgery																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
					AC	CDT	? / O	PTA	Stent	Y	N	?	Y	N	?	Y	N	?	TA	SC	IC	PC	T	R	? / O	Y	N	?	Y	N	?	PTA	Stent																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
		AC+FRR	2	<14d	2	0	0	x	x	x	x	x	2	0	0	0	2	0	2	x	x	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na

Supplementary table S6. Surgical management 2

Author	Ref.	Management	p	FOLLOW UP (m)			Success of initial treatment			Recurrence of thrombosis or persistent occlusion			open at last FU			Symptom free at last FU		
				range			Y	N	?	Y	N	?	Y	N	?	Y	N	?
				mean	min	max												
Pesser	8		36	24	5	62	36	0	0	4	32	0	0	0	36	16	20	0
		AC + FRR (chronic)	30	na	na	na	30	0	0	na	na	na	0	0	30	12	18	0
		CDT + FRR (chronic)	4	na	na	na	4	0	0	na	na	na	0	0	4	2	2	0
		FRR (chronic)	2	na	na	na	2	0	0	na	na	na	0	0	2	2	0	0
Pesser	9	CDT+FRR	10	34.4	6	58	10	0	0	0	10	0	10	0	0	10	0	0
Hoexum	11		13	40.7	27	65	13	0	0	1	12	0	12	1	3	12	1	0
		AC + FRR	3	40.5	31	50	3	0	0	0	3	0	2	0	1	3	0	0
		CDT + FRR	10	40.7	27	65	10	0	0	1	9	0	7	1	2	9	1	0
Zehnder	12		19	na	na	na	0	0	19	1	18	0	18	1	0	15	2	0
		AC + FRR	4	na	na	na	0	0	4	na	na	na	na	na	na	3	0	0
		CDT + FRR	15	na	na	na	0	0	15	na	na	na	na	na	na	12	2	0
Bozzay	13		30	8.5	na	na	21	3	6	0	0	30	23	7	0	22	8	0
		AC + FRR	17	na	na	na	na	na	na	0	0	17	na	na	na	na	na	na
		CDT + FRR	13	na	na	na	na	na	na	0	0	13	na	na	na	na	na	na
Dua	14		109	59	na	na	102	7	0	7	102	0	103	6	0	109	0	0
		AC+FRR	29	na	na	na	na	na	0	na	na	0	na	na	0	29	0	0
		CDT+FRR	80	na	na	na	na	na	0	na	na	0	na	na	0	80	0	0
Thompson	15		21	9.6	1.4	48.5	0	13	0	2	19	0	19	2	0	19	2	0
		CDT + FRR (acute)	13	na	na	na	0	13	0	na	na	na	13	0	0	12	1	0
		AC + FRR (chronic)	5	na	na	na	0	0	5	na	na	na	6	2	0	7	1	0
		CDT + FRR (chronic)	3	na	na	na	0	0	3	na	na	na	na	na	na	na	na	na

Supplementary table S6. Continued

Author	Ref.	Management	p	FOLLOW UP (m)			Success of initial treatment			Recurrence of thrombosis or persistent occlusion			open at last FU			Symptom free at last FU		
				range														
				mean	min	max	Y	N	?	Y	N	?	Y	N	?	Y	N	?
Fairman	16		123	8	0,4	87,5	123	0	0	19	104	0	121	2	0	123	2	0
		AC + FRR	38	na	na	na	38	0	0	na	na	na	na	na	na	na	na	na
		PMT + FRR	27	na	na	na	27	0	0	na	na	na	na	na	na	na	na	na
		CDT + FRR	58	na	na	na	58	0	0	na	na	na	na	na	na	na	na	na
Madden	17	CDT + FRR	51	38	1	240	51	0	0	4	16	31	20	0	31	0	0	51
Kumar	18		22	3	0	7	20	2	0	2	20	0	2	20	0	5	14	3
		AC + FRR	12	na	na	na	11	1	0	1	11	0	1	11	0	na	na	na
		CDT + FRR	10	na	na	na	9	1	0	1	9	0	1	9	0	na	na	na
Gharagozlo	19	CDT + FRR	83	24	na	na	na	na	na	na	na	na	83	0	0	0	0	83
Ryan	20		48	na	na	na	na	na	na	2	46	0	47	1	0	35	13	0
		AC + FRR	22	na	na	na	na	na	na	na	na	na	na	na	na	15	7	0
		CDT + FRR	26	na	na	na	na	na	na	na	na	na	na	na	na	20	6	0
Mahmoud	21		60	13	11	60	55	5	0	5	55	0	55	3	2	41	17	2
		LMWH + FRR	17	na	na	na	na	na	0	na	na	0	na	na	na	na	na	na
		CDT + FRR	43	na	na	na	na	na	0	na	na	0	na	na	na	na	na	na
Kärkkäinen	23	CDT + FRR	18	24	1	60	18	0	0	3	15	0	14	3	1	17	1	0
Siracuse	24	CDT + FRR	33	3	0	16	33	0	0	2	31	0	32	0	1	32	0	1
Hawkins	25	CDT + FRR	30	24,2	na	na	30	0	0	1	29	0	30	0	0	30	0	0
Goss	27	AC + FRR	2	na	na	na	0	0	2	0	0	2	2	0	0	2	0	0
Trenor	28	CDT + FRR	21	12	na	na	21	0	0	1	18	2	19	0	2	19	0	2
Abularagge	29		159	13,8	na	na	114	44	1	9	148	1	152	6	1	0	159	0
		AC + FRR	78	na	na	na	na	na	na	na	na	na	na	na	na	0	0	78
		CDT + FRR	81	na	na	na	na	na	na	na	na	na	na	na	na	0	0	81

Supplementary table S6. Continued

Author	Ref.	Management	p	FOLLOW UP (m)			Success of initial treatment			Recurrence of thrombosis or persistent occlusion			open at last FU			Symptom free at last FU		
				mean	min	max	Y	N	?	Y	N	?	Y	N	?	Y	N	?
Chandra	30		14	34.5	13	144	0	0	14	0	0	14	0	0	14	13	1	0
		AC + FRR	1	na	na	na	0	0	1	0	0	0	1	0	0	1	na	na
		CDT + FRR	13	na	na	na	0	0	13	0	0	13	0	0	13	na	na	na
Elixène	31		33	240	1	316	28	5	0	5	28	0	23	10	0	23	9	1
		AC + FRR	20	na	na	na	15	5	0	5	15	0	12	8	0	10	9	1
		CDT / other * + FRR	13	na	na	na	13	0	0	0	13	0	11	2	0	13	0	0
Taylor	32		95	na	na	na	0	0	95	0	0	95	0	0	95	71	24	0
		CDT (<2w) + FRR	41	na	na	na	0	0	41	0	0	41	0	0	41	36	5	0
		CDT (>2w) + FRR	15	na	na	na	0	0	15	0	0	15	0	0	15	11	4	0
		AC + FRR	39	na	na	na	0	0	39	0	0	39	0	0	39	24	15	0
Barnford	33		33	44	3	85	33	0	0	8	25	0	0	3	30	28	3	2
		AC + FRR	16	na	na	na	16	0	0	na	na	na	na	na	na	na	na	na
		CDT + FRR	17	na	na	na	17	0	0	na	na	na	na	na	na	na	na	na
Chang	34	FRR	84	na	na	na	68	16	0	9	75	0	79	5	0	0	0	84
Bosma	35	CDT + FRR	17	56	na	na	16	1	0	4	13	0	0	0	17	10	7	0
Skallicka	36		42	na	na	na	42	0	0	0	40	2	35	5	2	14	26	2
		LMWH + FRR	8	na	na	na	8	0	0	na	na	na	na	na	na	na	na	na
		CDT + FRR	22	na	na	na	22	0	0	na	na	na	na	na	na	na	na	na
		CDT => TB + FRR	12	na	na	na	12	0	0	na	na	na	na	na	na	na	na	na
Guzzo	37		110	16	1	52	87	17	6	8	95	7	100	3	7	0	0	110
		AC + FRR	65	14.5	2	36	51	10	4	5	56	4	59	2	4	0	0	65
		CDT + FRR	45	20.1	2	63	36	7	2	3	39	3	41	1	3	0	0	45

Supplementary table S6. Continued

Author	Ref.	Management	p	FOLLOW UP (m)			Success of initial treatment			Recurrence of thrombosis or persistent occlusion			open at last FU			Symptom free at last FU		
				mean	min	max	Y	N	?	Y	N	?	Y	N	?	Y	N	?
Stone	38		36	65	na	na	22	0	14	0	0	36	24	2	0	25	4	7
		AC + FRR	6	na	na	na	na	na	na	0	0	6	0	0	6	na	na	na
		CDT + FRR	30	na	na	na	na	na	na	0	0	30	0	0	30	na	na	na
De Léon	39		56	na	na	na	42	12	2	7	49	0	53	2	1	54	0	2
		CDT + FRR	42	na	na	na	42	0	0	4	38	0	42	0	0	42	0	0
		FRR (chronic)	14	12	na	na	0	12	2	3	11	0	11	2	1	12	0	2
Molina	40	CDT + FRR	126	na	6	25Y	126	0	0	0	126	0	126	0	0	126	0	0
Urschel	41		573	na	na	na	0	0	573	0	0	573	0	0	573	535	38	0
		CDT + FRR (acute)	531	na	na	na	0	0	531	0	0	531	0	0	531	511	20	0
		CDT + FRR (chronic)	42	na	na	na	0	0	42	0	0	42	0	0	42	24	18	0
Melby	42		32	50.4	6	120	32	0	0	3	29	0	0	0	32	32	0	0
		AC + FRR	6	56.7	8	104	6	0	0	0	6	0	0	0	6	6	0	0
		CDT + FRR	26	48.3	6	120	26	0	0	3	23	0	0	0	26	26	0	0
Cordobes-Gual	43	CDT + FRR	14	na	na	na	14	0	0	0	14	0	14	0	0	12	2	0
Doyle	47		32	33	na	na	22	4	8	0	0	32	22	2	8	0	0	32
		CDT + FRR [†]	24	na	na	na	22	4	0	0	0	24	22	2	0	0	0	24
		FRR [†]	8	na	na	na	0	0	8	0	0	8	0	0	8	0	0	8
Gelabert	45	CDT + FRR	30	na	na	na	28	2	0	5	25	0	28	2	0	27	3	0
Shebel	46		14	na	na	na	0	0	14	2	12	0	12	2	0	13	1	0
		AC + FRR	6	na	na	na	0	0	6	na	na	na	na	na	na	na	na	na
		CDT + FRR	8	na	na	na	0	0	8	na	na	na	na	na	na	na	na	na

Supplementary table S6. Continued

Author	Ref.	Management	p	FOLLOW UP (m)			Success of initial treatment			Recurrence of thrombosis or persistent occlusion			open at last FU			Symptom free at last FU		
				mean	min	max	Y	N	?	Y	N	?	Y	N	?	Y	N	?
Pupka	50	CDT + FRR	23	na	na	na	23	0	0	0	0	23	0	0	23	20	3	0
Feugier	52		11	45	10	72	11	0	0	0	0	8	3	0	3	8	3	0
		AC + FRR	4	34.8	10	72	4	0	0	0	0	3	1	0	1	2	2	0
		CDT + FRR†	7	39.4	10	72	7	0	0	0	0	5	2	0	2	6	1	0
Kreienberg	53	CDT + decompression†	23	48	24	68	23	0	0	0	5	18	0	18	5	0	17	6
Coletta	54	CDT + FRR	18	na	na	na	18	0	0	0	0	18	0	18	0	0	17	1
Aburahma	55		8	na	na	na	8	0	0	1	1	7	0	7	1	0	7	1
		CDT + FRR	7	na	na	na	7	0	0	0	0	7	0	7	0	0	7	0
		CDT + VR	1	na	na	na	1	0	0	1	1	0	0	1	0	0	1	0
Green	56	CDT + claviculectomy	11	58	34	108	11	0	0	1	1	10	0	11	0	0	10	1
Lee	57		13	na	na	na	13	0	0	0	0	13	0	13	0	0	10	3
		AC + FRR	2	na	na	na	2	0	0	0	0	2	0	2	0	0	na	0
		CDT + FRR	11	na	na	na	11	0	0	0	0	11	0	11	0	0	na	0
Yilmaz	58	CDT + FRR	19	40	3	119	0	0	19	0	0	0	19	0	0	19	11	0
Héron	59	AC + FRR	6	na	na	na	0	0	6	0	0	0	6	0	0	6	2	4
Azakié	60		21	na	na	na	21	0	0	0	0	0	21	0	0	21	20	1
		AC + FRR	2	na	na	na	2	0	0	0	0	0	2	0	0	2	1	0
		CDT/TB + FRR	19	na	na	na	19	0	0	0	0	0	19	0	0	19	18	0
Lee	61		11	24	6	60	0	0	11	2	2	9	0	6	0	5	9	2
		CDT + FRR	9	na	na	na	na	na	na	na	na	na	na	na	na	na	8	1
		CDT + scalenectomy	2	na	na	na	na	na	na	na	na	na	na	na	na	na	1	0

Supplementary table S6. Continued

Author	Ref.	Management	p	FOLLOW UP (m)			Success of initial treatment			Recurrence of thrombosis or persistent occlusion			open at last FU			Symptom free at last FU		
				mean	min	max	Y	N	?	Y	N	?	Y	N	?	Y	N	?
Beygui	62	CDT + FRR	8	na	na	na	6	2	0	0	0	8	0	0	8	8	0	0
Adelman	63	CDT + FRR	10	na	na	na	10	0	0	0	0	10	0	0	0	10	0	0
Sheeran	64		5	16	1	29	4	0	1	0	0	5	0	0	0	5	4	1
		CDT + VR	1	29	na	na	0	0	1	0	1	0	0	0	1	1	0	0
		CDT + FRR	4	12.8	1	20	4	0	0	0	4	0	0	0	4	3	1	0
Meier	65	CDT + FRR	5	na	na	na	0	0	5	0	0	5	0	0	5	0	5	0
Machleder	66		36	36	7	84	0	0	36	0	0	36	0	0	23	13	0	25
		FRR [‡]	7	na	na	na	1	6	0	0	0	7	na	na	na	na	na	na
		AC + FRR [‡]	15	na	na	na	0	0	15	0	0	15	na	na	na	na	na	na
		CDT + FRR [‡]	14	na	na	na	0	0	14	0	0	14	na	na	na	na	na	na
Grassi	67	AC + FRR	1	60	60	60	1	0	0	1	0	0	0	1	0	1	0	0
Totals			2208	38.4	0	316	1159	86	824	100	1085	939	1183	80	938	1674	233	198
%							93.1	6.9	39.8	8.4	91.6	44.2	93.7	6.3	42.6	87.8	12.2	9.4

Table legend : AC = anticoagulation; blue = data presented as number of affected limbs, not included in totals because of overlapping data; CDT = catheter directed thrombolysis; FRR = first rib resection; FU = follow up; Green = data presented as number of affected limbs; LMWH = low molecular weight heparin; m = months; max = maximum; min = minimum; N = no; na = not available; p = patients; Red = not included in totals because of overlapping data; Ref = reference; TB = thrombectomy; VR = venous reconstruction; Y = yes; * = thrombectomy / (endovenectomy + patch); ? = unknown; [#] = or heparine followed by FRR; [‡] = 1 excision costoclavicular exostosis; [†] = 7 patients scalenectomy; [§] = 1 patient lost to follow up but unknown in which group, so 1 result subtracted in each group.

Supplementary table S7. complications of first rib resections

Author	ref	P	technique	C	Complications (management)
Pesser	8	36	TA	5	3 hematomas (re-operation), 1x transient Horner syndrome, 1x Permanent phrenic nerve injury
pesser	9	10	TA	2	2 hematomas (re-operation)
Hoexum	11	13	RA	3	1x pneumonia, 1x pleural effusion (drain), 1x bleeding (coiling)
Zehnder	12	19	RA	0	
bozzay	13	30	IC (n=15), SC (n=15)	4	2x hematomas (evacuation), 1x transient brachial plexus injury, 1x lymphatic leak (thoracic duct ligation)
Dua	14	109	IC (n=55), SC (n=54)	17	10x pneumothorax(?), 5x lymphocele(?), 1x hemothorax(?), 1x long thoracic nerve injury (permanent/transient ?)
Fairman	16	125	TA	25	17x pneumothorax (drain), 3x hemothorax (2x VATS), 2x pleural cap hematoma, 1x Pulmonary embolism, 1x transient scapula alata, 1x surgical site infection
Madden	17	51	IC (n=40), PC (n=11)	2	1x pneumothorax (drain), 1x hematoma (evacuation)
Kumar	18	22	TA	7	3x hematoma (?), 3x pneumothorax (?), 1x scapula alata
Mahmoud	21	60	T	19	6x transient port side neuralgia, 5x hemothorax (4x reoperation, 1x drain), 2 transient horner syndrome, 2 lower plexus injuries (1 transient), 1 pneumothorax (drain), 1x subcutaneous emphysema (drain), 1x chylothorax (drain), 1x intercostal nerve damage
stuck	22	4	Unknown	3	1x chylothorax + lymphfistula (reoperation), lymphocele (conservative)
Kärkkäinen	23	18	T (n=9), IC (n=7), TA (n=2)	2	1x hemothorax (drain) , 1x hemopneumothorax (drain)
Siracuse	24	33	IC	4	3x transient ulnar nerve paraesthesia (conservative), 1x hemothorax (reoperation)
Hawkins	25	30	PC	2	1x hemothorax (drain), 1x hemothorax (reoperation)
Trenor	28	21	PC	3	2x hemothorax (drain), 1x pneumothorax (drain)
Abularage	29	159	TA	45	35x pneumothorax (?), 6x hematomas (4 conservative, 2 reoperation), 3x transients scapula alata, 1x SSI
Chandra	30	14	SC/IC/PC	2	2x hemothorax (reoperation)
Eixene	31	33	TA (n=25), PC (n=8)	9	4x hematomas (conservative), 3x thoracic duct leak (drain), 2 pneumothorax (drain)
Taylor	32	95	TA (n=90), SC (n=8)	7	3x hemothorax (?), 2x pneumothorax (?), 1x pulmonary embolism, 1x superficial infection
Bosma	35	17	TA	2	1x hematoma (?), 1x Hemothorax (?)

Supplementary table S7. Continued

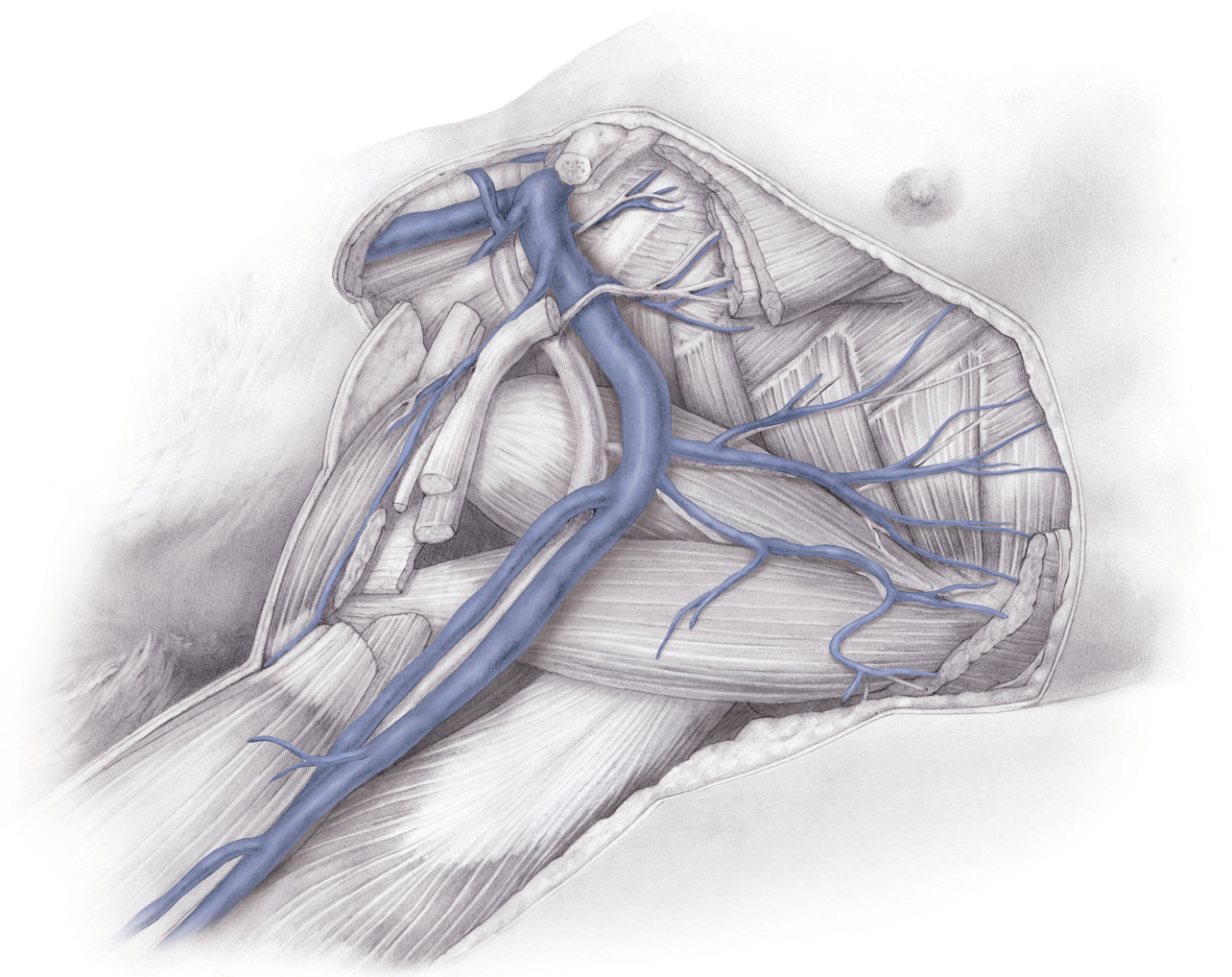
Author	ref	P	technique	C	Complications (management)
Melby	42	32	PC	4	2x hemothorax (reoperation), 2x wound hematoma/lymph leak (reoperation)
Doyle	44	17	TA	8	3x hematoma (?)*, 3x pneumothorax (?)*, 2x suspected pulmonary embolism
Gelabert	45	30	TA	2	1x mammary artery lesion (transfusion), 1x hematoma(?)
Shebel	46	14	SC	6	2x chyleous leak (?), 2x hematoma(?), 1x pneumothorax (?), 1x pleural effusion (?)
Feugier	52	11	PC (n=9), TA (n=1)	3	2x transient paresthesia C8-T1 root (conservative), 1x hematoma (reoperation)
Kreienberg	53	23	SC (n=16), scaleneotomy (n= 7)	6	3x wound hematomas (2x reoperation, 1x conservative), 2x transient brachial plexopathy (conservative), 1x hemothorax (reoperation)
Coletta	54	18	TA	2	1x SSI (conservative), 1x pneumothorax (drain)
Lee	57	13	SC	5	2x pneumothorax (1x drain, 1x conservative), 2x transient phrenic nerve palsy (conservative), 1x chylothorax (thoracoscentesis)
Azaki	60	34	combined TA and SC/IC/PC	4	2 transient nerve injuries (conservative), 1x bleeding (reoperation), 1x lymphatic leak (reoperation)
Beygui	62	8	TA (n= 5), SC (n=3)	2	1x hemothorax (drain), 1x bleeding (reoperation)
Adelman	63	10	TA	5	5x pneumothorax(drain)
Machleder	66	36	TA (n=35), transclavicular decompression (n=1)	2	1x pneumothorax + pleural effusion (drain), 1x peroperative arterial laceration (surgical repair + postoperative transfusion)
Totals		1145		208	

Table legend: P = number of procedures, C = number of complications, ref = reference SSI= surgical site infection, *= 1 reoperation needed in 8 complications, TA = transaxillary, RA = robot assisted transthoracic, IC = infraclavicular, SC = supraclavicular, PC = paracavicular, (?) = details of management unknown.

Supplementary table S8. Complications of catheter based therapies

1st author	ref	P	C	complications
Pesser	8	40	1	Venous injury during PTA (conservative)
Zehnder	12	18	1	Contrast related acute kidney injury
kärkäinen	23	22	1	intimal tear requiring surgical reconstruction and stent
Trenor	28	19	0	no complications of catheter based therapy
Bosma	35	31	1	pulmonary embolism**
doyle	44	26	1	stroke like episode
Gelabert	45	30	0	no complications of catheter based therapy
Coletta	54	6	1	flebitis after venography
Yilmaz	58	24	1	pulmonary embolism**
Machleder	66	28	4	2x allergic reaction to streptokinase, 1x flebitis, 1x hematoma
Totals		244	11	

Table legend: P= number of procedures, C= number of complications, **= possible overlapping data



CHAPTER 10

Robot assisted transthoracic first rib resection for venous thoracic outlet syndrome

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ABSTRACT

Background: Venous thoracic outlet syndrome (vTOS) is caused by extrinsic compression of the subclavian vein at the costoclavicular junction. It can be subdivided in McCleery Syndrome (MCS) and Paget-Schroetter Syndrome (PSS). To improve the venous outflow of the arm and to prevent recurrent thrombosis, first rib resection with venolysis of the subclavian vein can be performed. Open transaxillary, supraclavicular, infraclavicular or combined paraclavicular approaches are well known but more recent robot assisted techniques are introduced. We report our short- and long-term results of a minimal invasive transthoracic approach for resection of the anteromedial part of the first rib using the Da Vinci® surgical robot, performed through 3 trocars.

Methods: We analyzed all patients with vTOS who were scheduled to undergo robot assisted transthoracic first rib resection in the period July 2012 to May 2016. Outcomes were: technical success, operation time, blood loss, hospital stay, 30 day complications and patency. Functional outcomes were assessed using the “Disability of the Arm, Shoulder and Hand” (DASH) questionnaire.

Results: Fifteen patients (8 male, 7 female; mean age 32,9 years, range 20 - 54 years) underwent robot assisted transthoracic first rib resection. Conversion to transaxillary resection was necessary in 3 patients. Average operation time was 147.9 minutes (range 88 - 320 minutes) with a mean blood loss of 79.5cc (range 10-550cc). Mean hospital stay was 3.5 days (range 2 - 9). In three patients complications were reported (Clavien-Dindo grade 2-3a). Patency was 91% at 15,5 months follow up. DASH scores at 1 and 3 years showed excellent functional outcomes (7.1 (SD= 6.9, range 0 - 20.8) and 6.0 (SD= 6.4 , range 0 - 25)) and are comparable to the scores of the normative general population.

Conclusion: Robot assisted transthoracic first rib resection with only three trocars is a feasible minimal invasive approach for first rib resection in the management of vTOS. This technique enables the surgeon to perform venolysis under direct 3D vision with good patency and long term functional outcome. Studies with larger cohort size are needed to compare the outcomes of this robot assisted technique with other more established approaches.

INTRODUCTION

Venous thoracic outlet syndrome (vTOS) is caused by extrinsic compression of the subclavian vein at the costoclavicular junction. It can be subdivided in McCleery syndrome (MCS) and Paget-Schroetter syndrome (PSS).^[1] MCS is an intermittent, position dependent, swelling of the arm related to outflow obstruction of the subclavian vein without thrombosis.^[1] PSS is effort induced subclavian vein thrombosis.^[2] Although the true incidence of vTOS is unknown, it's estimated at 1 in 100,000.^[3] Conservative management of PSS results in postthrombotic syndrome in approximately 30% of patients^[4,5] and reoccurrence of thrombosis is reported in up to 23% of patients.^[6] Therefore, preferred treatment strategy of PSS is early catheter directed thrombolysis (CDT) followed by subsequent first rib resection (FRR).^[2,3,7,8] Open transaxillary, supraclavicular and infraclavicular approaches are associated with the risks of neurovascular complications and the occurrence of a postoperative pneumothorax.^[9,10] Furthermore, it can be difficult to perform a complete venolysis through a single supraclavicular approach. It's therefore often needed to combine a supra- and infraclavicular (paraclavicular) technique.^[7] An endoscopic procedure offers the advantage of better visibility of the subclavian vein and the anteromedial part of the first rib, thereby facilitating complete decompression and venolysis. To date, worldwide experience in robotic FRR is limited.^[11-16] The use of only 3 trocars is exceedingly rare and reported only by Kocher in one patient^[13]. We present the first series of patients with this 3-port technique with its patency, short term and long term functional outcomes.

MATERIAL AND METHODS

We retrospectively reviewed all patients who were scheduled to undergo robot assisted transthoracic FRR because of vTOS from July 2012 to May 2016 in the Amsterdam UMC, location VU Medical Center. Written informed consent of all patients for participation in this study was obtained and, after approval by our Medical Ethics Committee, their medical charts and electronical patient files were reviewed. Patients characteristics, initial management of PSS, interval between PSS and FRR, technical success, operating time, presence of a bone anomaly, blood loss, length of postoperative hospital stay, complications and follow up regarding patency were recorded.

Local management protocol vTOS: Patients suspected for PSS undergo duplex scanning of the affected arm. If duplex scanning is negative but clinical suspicion of PSS is present an additional venography is performed to confirm or rule out PSS. In case PSS is diagnosed immediate ultrasound accelerated CDT is instituted (EKOS Corporation, Bothell, Washington). Patients are admitted to the regular surgical ward and undergo serial venography to evaluate the progress of thrombolysis. If no residual thrombus

or no progressive lysis is seen, CDT is discontinued. In case of persistent narrowing of the vein, percutaneous transluminal angioplasty (PTA) is performed without the use of intravenous stents. Patients are prescribed oral anticoagulation (OAC) and are discharged with FRR scheduled as soon as possible, preferably within 2 months. McCleery syndrome is diagnosed with duplex scanning or venography with provocative tests. In case the complaints reported by the patient match the position dependent outflow obstruction objectified by duplex or venography surgical decompression is offered.

From July 2012 patients scheduled for decompression surgery for vTOS were offered the robot assisted technique as the standard procedure performed by a robot trained vascular surgeon. Alternatively patients could opt for the transaxillary approach. Patients were fully informed about both procedures and possible conversion from the robotic approach to the transaxillary approach was explicitly mentioned in the work up and recorded in the informed consent for surgery.

Surgical procedure of robot assisted transthoracic first rib resection: Robot assisted transthoracic FRR was first described by Gharagozloo et al.^[11] We adjusted this technique to customize it to our preferences as we will describe below. The operation is performed under general anaesthesia with single lung ventilation using a double lumen tube. The patient is positioned in a lateral decubitus position with the affected side up and slightly tilted backwards. The lung of the affected side is blocked and desufflated. We use three instead of four trocars during the procedure [figure1].

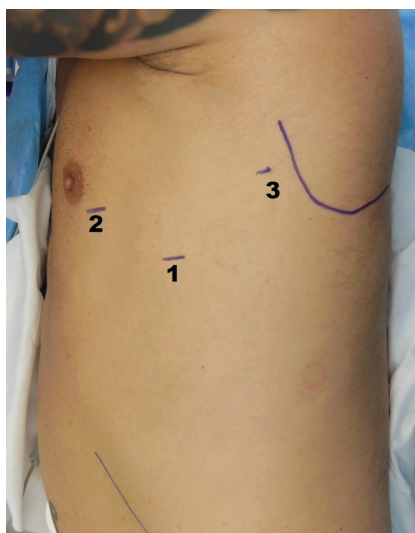


Figure 1.

The robot is brought in from the cranial side and is then positioned in 10-15 degrees clockwise to the longitudinal axis. The robotic endograsper and hook cautery through trocar are used for dissecting the first rib. The pleura is opened and the anterior scalenus muscle is identified, carefully isolated and transected. The anatomical plane between the first rib and the subclavian vein and artery is bluntly dissected, separating these vascular structures from the rib. In contrast to the trap door configuration of Gharagozloo we transect the cartilaginous costosternal junction at this stage with electrocoagulation, creating a floating rib. The robotic arms are then removed from the patient and through the posterior incision a bone cutter is introduced. The sulcus of the subclavian vein is located medial of the tubercle of the anterior scalene muscle, the sulcus of the subclavian artery lateral. In case of vTOS the smallest part of the first rib just lateral to the tuberculum of the anterior scalene muscle is transected under direct vision and hereby performing a partial first rib resection of the anteromedial region. After the transection the robot is installed again, as previously described, and all muscular insertions of the subclavius muscle and adhesions are removed from the rib. The rib is then retracted through the posterior incision using a grasper. After removal of the first rib, the subclavian vein and artery are easily identified. All compressive elements such as scar tissue, connective tissue and muscular fibres are removed from the subclavian vein. Upon completion of the procedure, the robot arms are removed from the patient and a 16 French chest tube is inserted through the most caudal trocar site. The incisions are closed with absorbable sutures.

On the recovery-room a chest X-ray is done to confirm the position of the chest tube and to assess the presence of any residual pneumothorax. Patients are admitted to a regular surgical ward with suction (20mmH₂O) applied to the chest tube. In the absence of leakage of air, the tube is placed on water seal. In case no substantial residual pneumothorax is present the next morning on a chest X-ray the chest tube is removed within 24 hours. Patients are encouraged to mobilize and discharge is deemed possible if the patient is comfortable with oral analgesics. Although no restrictions regarding physical activity were imposed, patients were advised not to overstrain their shoulder. A follow up appointment is made 6 weeks after the procedure in the outpatient clinic. A venography or duplex scan is performed to determine patency and in case of persistent narrowing a PTA is performed. The use of intravenous stents is discouraged and only performed in case serial PTA is unsuccessful in restoring adequate venous outflow of the affected arm with subsequent clinical symptoms. Oral anticoagulation is continued for 6 months. Further follow up in the outpatient clinic was performed at the discretion of the treating vascular surgeon. Functional outcome was assessed using the standardized

Disabilities of the Arm, Shoulder and Hand questionnaire (full DASH), scored from 0 to 100 (100 = worse) at 1 and 3 years postoperatively.

RESULTS

Between July 2012 and May 2016 in total 54 patients underwent 57 first rib resections in our institution (36 female, age 16-70 year). Indication for surgery were neurogenic TOS 26; vTOS 19; arterial TOS 2 and combined complaints in 10. All 19 patients scheduled for decompression surgery for vTOS were offered the robot assisted procedure, 4 declined the offer and elected decompression by the transaxillary approach. Detailed patient characteristics, the summary of management and outcomes of 15 patients treated by robot assisted transthoracic FRR are presented in table 1. The indication for performing robot assisted FRR in these eight male and seven female patients (mean age 32.9 years, range 20 - 54 years) was PSS in 13 and MCS in 2. None of the patients in this study were professional athletes. A possible provoking activity was reported in 6 patients. The affected side was right in nine, left in six. Active smoking was reported in 6 cases, 3 others had a history of previous tobacco use. Hormonal contraceptives were used by 71,4% (5/7) of female patients.

Eleven patients (PSS n= 10, MCS n= 1) were referred to our institution after initial treatment in other hospitals. In 9 out of the 10 referred patients diagnosed with PSS initial therapy was different to our institute's standard of care. Three patients (8,9,13) were treated with CDT after initial treatment with a low molecular weight heparin or a direct oral anticoagulant (DOAC). Three patients (6,11,12) were managed conservative with OAC only and were referred because of persistent complaints. Two patients (2,15) were treated with CDT and placement of an intravenous stent before surgical decompression. In one of these patient's occlusion of the stent occurred within one week after placement. During a readmission thrombolysis was successful in restoring patency and after institution of OAC he was referred to our institution for further treatment. In patient 5 a transaxillary first rib resection for the diagnosis MCS was aborted because the subclavian vein appeared to be occluded during surgery. Two weeks after surgery CDT was performed with successful recanalization. He was given OAC and was referred to our center for further treatment. Because of a deep surgical site infection with a Methicillin-Resistant Staphylococcus Aureus his surgery was delayed. He underwent a robot assisted transthoracic FRR 7 months after the subclavian vein thrombosis.

Table 1. patient characteristics, management, patency and functional outcome.

Pt	Sex, Age (y)	Diagnosis, provoked	Ref. Side (R/L)	Risk factors: TU / OHC	Initial management PSS before FRR	Time PSS - FRR (mo)	Procedure Conversion (Y/N)	Bone Anomaly (Y/N), Blood loss (cc)	Complication, Hospital Stay (d)	Patency	DASH SCORE							
											Short term			Long term				
											Δt (mo)	imaging	patent	G	W	S	G	W
1	F,31	MCS, -	Y, L	OHC	-	-	150, N	N, 40	None, 3	39	V	Y	0	0	0	2,5	0	-
2	M, 54	PSS, Unknown	Y, L	TU	CDT, PTA + stent, occlusion, re-CDT	1	320, N	N, 550	None, 3	Occlusion			20,8	0	0	2,5	0	12,5
3	F, 31	MCS, -	N, L	‡, OHC	-	-	134, N	N, 10*	None, 3	3	V	Y	16,7	0	43,8	13,3	12,5	43,8
4	M, 28	PSS, Playing guitar	N, R		CDT	1	182, N	N, NA	None, 3	1	V + PTA	Y	0,8	0	0	2,5	0	6,3
5	M, 43	PSS, Unknown	Y, R	TU	MCS, surgical decompression aborted because of PSS, CDT	6	244, N	N, 30	CT <48hr, 5	65	D	Y	6	12,5	-	10	12,5	-
6	M, 42	PSS, Unknown	Y, R	TU	OAC	1	123, N	N, 20	None, 4	NA			0	0	0	0	0	0
7	F, 23	PSS, Fitness	Y, R	OHC	CDT	10	120, N	N, NA	None, 3	3	V	Y	0,8	0	0	3,3	0	12,5
8	M, 22	PSS, dancing	Y, L	TU	LMWH, CDT	3	130, N	N, 40	None, 3	24	D	Y	13,3	43,8	50	1,7	0	0
9	M, 39	PSS, overhand work	Y, R		LMWH, CDT	5	166, Y	Y, 75	Pneumonia, 4	8	D	Y	10	6,3	-	7,5	18,8	25
10	M, 28	PSS, fitness	N, L		CDT	5	88, N	N, 10*	pleural effusion [†] , 2	2	V	Y	0	0	0	5,8	0	0
11	F, 23	PSS, Unknown	Y, R	TU, OHC	OAC	14	102, N	N, 10*	CT 7d, bleeding [‡] , 9	18	D	Y	NA			NA		
12	F, 20	PSS, Unknown	Y, R		OAC => rethrombosis, OAC	38	88, Y	Y, NA	None, 3	NA			2,5	0	18,8	0	0	0
13	F, 24	PSS, Unknown	Y, L	TU, OHC	DOAC, CDT	2	96, N	Y, NA	CT <72hr, 4	10	D	Y	8,3	0	-	2,5	0	-
14	M, 53	PSS, Unknown	N, R	‡	CDT, rethrombosis during analysis longnode, OAC	25	180, Y	Y, 10*	None, 3	2	V + PTA	Y	13,3	12,5	18,8	25	25	31,3
15	F, 33	PSS, Strenuous labor + crossfit	Y, R	‡	LMWH, CDT, PTA + stent	2	83, N	N, NA	None, 2	NA			NA			7,5	6,3	6,3
Mean (SD)	32,9					8,69 (10,7)	147,9 (62,2)				15,7 (17,0)		7,1 (6,9)	5,8 (11,9)	13,1 (18,0)	6,0 (6,4)	5,4 (8,1)	12,5 (14,1)

Table legend: cc = cubic centimeter; CDT = catheter directed thrombolysis; Δt = time of follow up; d = days; D = duplex; DASH = disabilities arm, shoulder and hand; DOAC = direct oral anticoagulant; F = female; FRR = first rib resection; G = general; hr = hours; LMWH = Low Molecular Weight Heparin; M = male; MCS = McCleery syndrome; mi = minutes; NA = not available; OAC = oral anticoagulants; OHC = oral hormonal contraceptives; pt = patient; PTA = percutaneous transluminal angioplasty; S = sports module; SD = standard deviation; TU = tobacco use; PSS = Paget-Schroetter syndrome; - = not reported (optional questions in DASH questionnaire); V = venography; W = work module; Y = yes; y = year; ‡ = history of tobacco use; † = necessitating readmission; § = selective coiling was performed, no need for transfusion; * = blood loss reported as negligible in operation report

No cervical ribs were present. No additional surgical procedures were performed in the same setting. An anatomic variation (bony tubercle) of the first rib was reported in 4 patients and was the cause of conversion in 2 out of three converted patients. In one patient conversion was required because single lung ventilation was not tolerated. Mean operation time was 147,9 minutes (SD= 62.2, range 88 - 320). Blood loss was recorded in 6 patients. In four other patients, blood loss was described in the operation report as “negligible” and was counted therefore as 10cc. Mean blood loss in all procedures was 79.5cc (SD 158.1, range 10-550cc). Mean hospital stay was 3.5 days (SD= 1.7, range 2 - 9). Subgroup analysis of the 12 successful robotic procedures revealed no significant difference in operation time, blood loss and hospital stay compared to the total cohort.

No mortality nor neurologic complications were reported. In 3 patients 3 complications were observed. One patient (9), in which the robotic procedure had to be converted to a transaxillary approach, was diagnosed with a pneumonia and was treated with oral antibiotics (Clavien-Dindo grade 2). One patient (10) was discharged after a rapid and uneventful recovery the next day but was readmitted because of pleural effusion which was managed with a chest tube (Clavien-Dindo grade 3a). One patient (11) was diagnosed with a haemothorax with a possible blush on a CT scan. Subsequent selective angiography showed a doubtful blush from a distal side branch of a bronchial artery. Out of precaution selective coiling was performed (two 3mm coils and embolization particles). No blood transfusion nor any other intervention was needed (Clavien-Dindo grade 3a). The chest tube could not be removed the following day in three patients because of a persistent residual pneumothorax (5,13,15) after successful robot assisted decompression. Short term functional outcomes at one year were available in 13 patients (10/12 robotic procedures), long term outcomes at 3 years in 14 (11/12 robotic procedures). Mean DASH scores at short term follow up were: General 7.1 (SD= 6.9, range 0-20.8); Work 5.8 (SD= 11.9, range 0 - 43.8) and Sport/Recreation 13.1 (SD= 18.0, range 0 - 50). Mean DASH scores at long term follow up were: General 6.0 (SD= 6.4, range 0 – 25); Work 5.4 (SD= 8.1, range 0 – 25) and Sport/Recreation 12.5 (SD= 14.1, range 0 – 43.8). Subgroup analysis of the 12 successful robot assisted procedures revealed no significant nor clinical relevant differences in functional outcomes. Objective follow up regarding patency was available in 12 patients. Eleven patients had a postoperative venography, only 2 of these patients had residual stenosis and were treated successfully with balloon angioplasty. Latest objective follow up is described in table 1.

At latest objective follow up (mean 15.7 months (SD= 16.9, range 2-65)) eleven patients had a patent subclavian vein on venography (n= 6) or duplex (n=5). One patient (2) had an occluded venous stent after 12 months. Because of a previous early occlusion after

placement (before referral for FRR) and limited complaints no further attempts were made for restoring patency, he was discharged from further follow up. No objective follow up was available in 3 patients. Only one patient (5) needed a stent after surgical decompression. During his 65 months follow up he experienced several episodes of increased complaints on the affected arm related to re-stenosis of the subclavian vein. He underwent three times successful PTA of these lesions at 11, 30 and 43 months. At 56 months he underwent his fourth PTA and we decided to place a stent. At 65 months a duplex showed good patency without stenosis.

Table 2. institutional review vTOS procedures 1997 to 2018

	Transaxillary	Supra/infra clavicular	Robot assisted	Totals
Patients	28	11	15	53*
Sex				
- male	12	7	8	27
- female	16	4	7	26
Age (range)	32.5 (17-64)	30.5 (21-46)	33.1 (20-55)	32.3 (17-64)
Side				
- right	18	7	9	34
- left	10	4	6	20
Operation time minutes (range)	78.5 (44-180)	205.7 (155-309)	147.9 (88 – 320)	125.2 (44-320)
Additional procedures (patients)	0	12 (11)	0	12 (11)
- removal cervical rib	0	1	0	1
- venous reconstruction	0	11	0	11
Postoperative hospital stay	3.3 (1-9)	7.2 (3-15)	2.5 (1-8)	3.9 (1-15)
Perioperative complications				
Removal 2 nd rib	1	0	0	1
Postoperative complications				
Patients	6 (21%)	7 (66%)	3 (20%)	18 (34%)
Complications ≤ 30 days	6	14	3	23
- bleeding / hematoma	2	4	1	7
- pneumothorax	1	1	0 [†]	2[†]
- pleural effusion	1	2	1	4
- hemothorax	0	3	0	3
- neurologic	2	1	0	3
- atelectasis / pneumonia	0	2	1	3
- venous stenosis / occlusion	1	1	0	2
- wound infection	0	1	0	1
Interventions (patients)	3(3)	6 (5)	2 (2)	11 (10)
- percutaneous / endovascular	2	2	2	6
- surgical	1	4	0	5

Legend table 2: institutional review vTOS procedures 1997 to 2018

* = in one patient a therapeutic first rib resection was succeeded by a preventative contralateral first rib resection

† = in 3 patients undergoing robot assisted transthoracic first rib resection the duration of the chest tube exceeded 24 hours, nevertheless the admission was not prolonged by the duration of chest drainage.

DISCUSSION

Our series demonstrated that the robot assisted transthoracic approach with three trocars for the resection of the anterior part of the first rib in the management of vTOS is feasible and may result in good patency with excellent long term functional outcomes. To date, no prospective randomized controlled trials are available to determine the best management strategy of PSS. Multiple case series have showed that conservative treatment with anticoagulation alone will result in residual complaints and a substantial risk of developing post-thrombotic-syndrome.^[4-6] More proactive management strategies with thrombolysis followed by surgical decompression of the thoracic outlet have favourable outcomes.^[2,6,18-20] Nevertheless there is still debate about the optimal treatment strategy for PSS and this is reflected in the divers management protocols followed in referred patients from other institutions. In our opinion immediate thrombolysis and subsequent early recanalization of the subclavian vein, could prevent the formation of collateral veins and thereby the flow through the native axillary and subclavian veins could be optimized. This could lead to a decreased risk of recurrent thrombosis even if residual venous wall irregularities persist. It is not recommended to use intravenous stents before surgical decompression because of the risk of stent related rethrombosis.^[21] A limitation of robot assisted transthoracic first rib resection is that the performance of an intraoperative venography, as advocated by some authors,^[17] is challenging. We believe that an intraoperative venography has limited additional value compared to a postoperative venography, provided that adequate initial management of acute PSS has been performed resulting in a complete recanalization of the subclavian vein. If residual stenosis persists after thrombolysis, we perform an adjunctive preoperative PTA. This may lead to a decrease in the number of patients who eventually require postoperative PTA. The findings in our small series are in line with this hypothesis, only 2/11 patients needed PTA at first postoperative venography. Nevertheless, intraoperative or postoperative evaluation of the subclavian vein is essential to identify and treat any residual stenosis particularly if initial management did not result in an adequate venous recanalization. For many years the transaxillary approach was our standard management of vTOS.^[22,23] A quick review of all patients who underwent FRR resections from September 1996 to May 2016 in our institution revealed a total of 197 FRR in 172 patients. Further details of the 54 FRR performed in 53 patients because of vTOS are summarized in table 2. In July 2012 we have started with robot assisted transthoracic first rib resection for the indication vTOS. This technique has several theoretical advantages compared to the transaxillary approach. The anatomical benefits of the transthoracic approach enable the surgeon

to perform a complete resection of the anteromedial (costosternal) region. This is the most important part of the first rib in the management of vTOS because the venous groove is located in this part of the first rib. The enhanced visualization of the Da Vinci® three-dimensional optical imaging system combined with the agility of the endowrist system promotes telemanipulation of tissues in an inaccessible working space. In addition to the osseous decompression by removing the first rib, a complete venolysis of the subclavian vein could be performed. All fibrotic tissue and compressive muscular fibres surrounding the subclavian vein can be transected or excised under direct vision to ensure an optimal release, possibly resulting in better outcomes. In two patients (9,14) an anatomical variation made it impossible to cut the rib with the bone cutter and conversion to a transaxillary approach was deemed necessary. In two other patients (12,13) a bony tubercle was seen. Bone anomalies are not an uncommon cause in TOS.^[24-26] Although the association of vTOS with bone anomalies is still debated in literature. Weber et al. reported 115 anomalies in 400 patients (29%), with cervical ribs accounting for 69% (80/115).^[24] Anatomical variation concerning the first rib was less often reported (10/400 = 2,5%, 9% of all anomalies).^[24] In the cohort of Weber et al. only 4% of all venous TOS cases were associated with a bone anomaly.^[24] In contrary Gharagozloo et al. compared 7 first ribs from human cadavers with 15 resected first ribs of patients with PSS and found in all 15 patients with PSS a bony tubercle that corresponded to the area of the subclavian vein groove.^[25] They proposed the pathogenesis of this bony tubercle as the cause of PSS.^[25] Furthermore a significantly increased width of the vertebral and sternal end of the first rib on posteroanterior chest and antero-posterior C-spine radiographs was reported by Chang et al. in 32 patients undergoing TOS related surgical decompression compared to 30 control patients.^[26] Our incidence of bone anomalies (4/15, 27%) is more consistent with Weber et al. compared to Gharagozloo et.al.. Because of our limited number of patients, we assume that bone anomalies of the first rib could be overrepresented in our cohort and they will be present in roughly 10% of patients. We don't advocate an additional work-up for specific identification of an anomalous first rib. Conversion in case of technical inability to cut the first rib endoscopically is an essential part of the preoperative informed consent as described above. The technique described by Burt et.al. looks promising in minimizing conversion because of an osseous anomaly. They use the Midas Rex drill (Medtronic corporation, Minneapolis, USA) to transect the first rib.^[16]

Downsides of this robotic procedure are the increased operation time, additional costs and the inability to perform a venous reconstruction through this approach in case of

chronic obstruction. As mentioned before, only patients with MCS and PSS in which successful recanalization has been achieved are eligible for this approach. Our mean operation time of the successful robotic procedures (148.7 minutes) was comparable with studies published by Gharagozloo et al. ($n=5$, mean 195 minutes^[12] / $n=83$, mean 127.6 minutes^[14] / $n=63$, mean 87.6 minutes^[15]). We had one outlier regarding operation time and blood loss. Patient 2 was morbid obese with a BMI of 41.4 resulting in a prolonged procedure with an above average blood loss. In our study a distinct learning curve was also noted. Our first 5 successful robotic procedures had a mean procedure time of 206 minutes (range 134-320), the last 5 successful robotic procedures had a mean procedure time of 102 minutes (range 96-130). The possible increase in cost was not analysed in this study but is an important topic in the discussion on affordable healthcare and should be included in further studies.

We reported 3 complications (3/15 patients). This complication rate of 20% is identical to the 21% in our transaxillary cohort. If we specifically take a look at the 12 successful robotic procedures, complication rate is 17% (2/12). With this incidence of complications robot assisted FRR is safe and has possible less complications compared to the transaxillary approach.

General limitations of this study lie in the limited number of patients and the availability of postoperative DASH scores. Patient compliance to return their questionnaires in time was limited, in the majority of patients several attempts were necessary to receive the questionnaires. Overall response was 90% (27/30 returned questionnaires). Unfortunately not from all patients long term objectively assessed patency could be retrieved. Largely because patients were referred from, and follow up was performed by, distant hospitals. Our study did not include objective data on patient satisfaction, postoperative pain scores or analgesia requirements. These important outcomes should be monitored in future and especially in studies comparing different surgical approaches. Overall long-term results correlate with the literature supportive of a surgical treatment of PSS. Mean postoperative DASH scores are comparable to the scores of the normative general population.^[27]

CONCLUSION

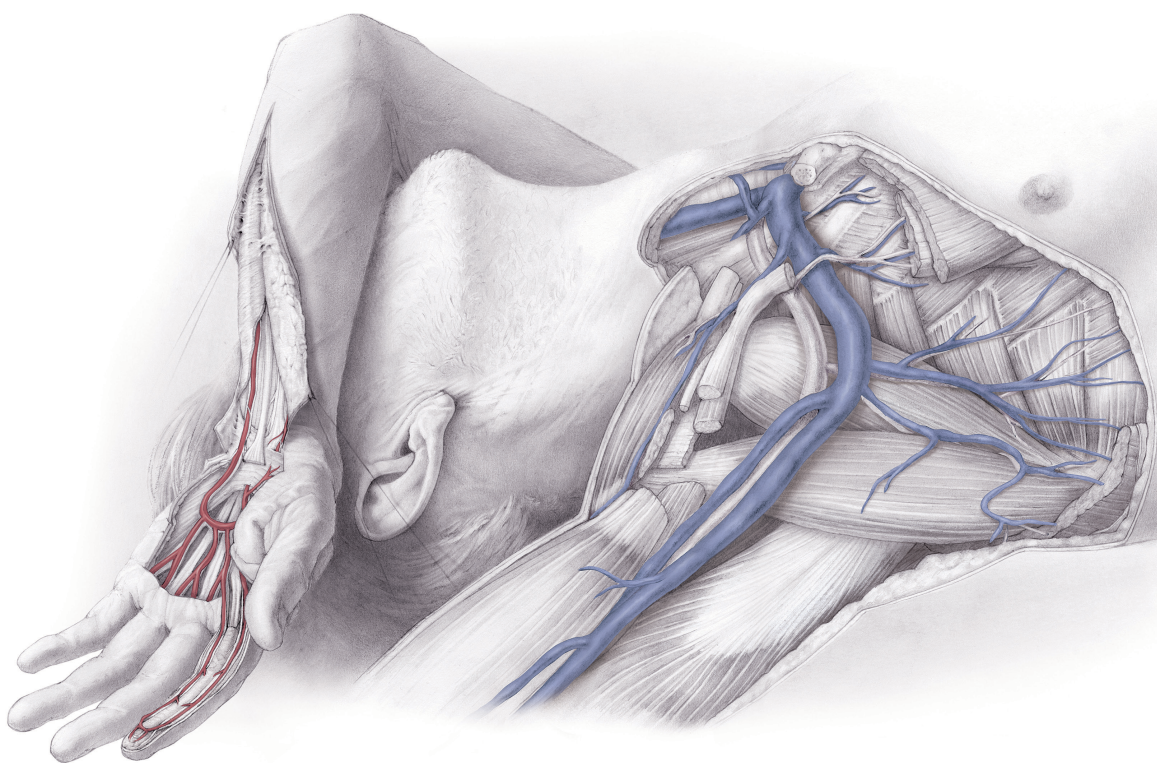
Robot assisted transthoracic partial first rib resection with only three trocars is a feasible minimal invasive approach in the management of venous thoracic outlet syndrome. This technique enables the surgeon to perform venolysis under direct 3D vision with

good patency and long term functional outcome. Although the number of patients in this study is not sufficient to draw firm conclusions, the results of our study are encouraging. Further research need to assess the potential advantages of this robot assisted procedure compared to other more established surgical approaches.

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CHAPTER 11

General discussion and future perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Thoracic sympathectomy

In the late 19th and beginning of the 20th century sympathetic surgery was used in the management of a variety of disorders (e.g. epilepsy, exophthalmic goitre, spastic paralysis, glaucoma, hypertension, angina pectoris, vasospastic disorders and peripheral arterial occlusive disease).^[1,2] With the advances in medicine the vast majority of indications is currently considered obsolete because less invasive therapies are available.

^[2] The use of thoracic sympathectomy in the management of upper extremity arterial disease remains up to this date controversial. Open procedures are associated with the comorbidities of thoracotomies. With the introduction of VATS less invasive procedures became available and risk of complications decreased.^[3,4] This thesis was aimed to evaluate the current evidence on thoracic sympathectomy in the management of upper limb ischemia and to investigate the role of an innovative robot assisted technique.

The (lack of) evidence on thoracic sympathectomy in literature for management of upper limb ischaemia and local experience

The available literature is scarce and at most of moderate quality. Regarding the 40 year time span we selected for our review (chapter 3), we could identify a mere 29 reports which met our inclusion criteria of which none were randomised studies on the outcomes of thoracic surgery. Only one study randomised patients between percutaneous chemical ablation or radiofrequency ablation of the thoracic sympathetic chain but this study lacked a control group. Only 6 out of 29 reports were prospective case series. This lack of high quality studies makes it impossible to draw firm conclusions.

furthermore patients suffering from upper limb ischemia represent a highly heterogeneous group because a variety of disorders can be underlying. This poses, combined with the lack of reporting standards on the outcome of thoracic sympathetic surgery, a significant risk of bias in the available literature. In example, patient selection of the included reports in our review was obscure, treatment varied across reports and outcomes were in the majority of cases subjective endpoints or vaguely described as “telephone based interviews”.

On the other hand some reports did mention the use of objective measures Doppler ultrasound, laser Doppler flowmetry, infrared thermography and rise of skin temperature in their studies. Although these outcomes are objective, arguments can also be raised against their use. In our opinion outcomes should be based on the perceived effects by patients. If patients experience no beneficial effect on their complaints, surgeons should

refrain from thoracic sympathectomy even if objective measurement could confirm technical success. We advocate the use of validated tools such as patient reported outcome measures (PROMS) in the evaluation of the effect of thoracic sympathectomy. Commonly used PROMS for the upper extremity are the Disabilities of the Arm, Shoulder and Hand (DASH), QuickDASH (qDASH), Michigan Hand Questionnaire (MHQ), Patient Evaluation Measure (PEM), Upper Extremity Functional Index (UEFI), and Duruoz Hand Index (DHI). Pain can be rated using the visual analogue scale (VAS). Ulcer healing can also be a useful endpoint because it can be assessed both by the individual and clinicians. In our review ulcer healing was reported in 12 reports (119 cases).

We encountered the same difficulties in performing our retrospective case series. Because we were interested if patients experienced a beneficial effect of their treatment we composed a questionnaire ourselves. The use of a validated questionnaire like the DASH would only provide a current assessment of complaints of the affected extremity and was therefore less useful. Although our questionnaire was not validated it provided a more objective patient reported outcome compared to the included studies in our review.

Our experience with thoracic sympathectomy and endoscopic thoracic sympathectomy were in line with the literature. We encountered a substantial loss to follow up. This was mainly due to mortality. Patients with severe ischemia of the upper extremity commonly are burdened by comorbidities. In example, prognosis of systemic sclerosis in a French cohort showed a 10 year mortality rate of 29%.^[5] Our extensive follow up ranged from 1,5 to 16 years and this could have attributed to this loss of follow up due to mortality. Beneficial effect on the long term were reported by 53% of patients which was slightly less compared to our review in which a beneficial effect was reported by 58% (22-100%) for patients with Primary Raynauds Disease and 79% (13-100%) for Secondary Raynauds Phenomenon. In our opinion the decrease in effect over time can be leading to this slight underperforming of our patients. The mean long term follow up of patients in our review was twice as long compared to the mean follow up in our review (98 vs 49 months). This decrease of effect over time is well known in literature and all authors of our review (**chapter 3**) mentioned a decrease of therapeutic effect over time. Several possible explanations are postulated as to why recurrence can occur. Surgical error, re-innervation of the sympathetic pathways, or hypersensitivity of the noradrenergic receptors regulating the pre-capillary sphincters reacting on very small amounts of circulating catecholamines have all been implicated as factors precipitating recurrence of symptoms.

Is surgery still the way to go?

Surgery inevitably inflicts trauma to the human tissues. Several less invasive strategies have become available. Percutaneous interventions, botulin injections and digital periarterial sympathectomy are alternatives to surgical thoracic sympathectomy. Innovative robot assisted procedures are also developed with the aim to minimize surgical trauma and side effects.

Percutaneous chemical or radiofrequency ablation were respectively introduced by Reid^[6] and Wilkinson.^[7] Only one article could be included in our review who used these techniques.^[8] Unfortunately no comparative reports are available for patients with upper extremity ischemia. Purtuloglu et al. reported on radiofrequency ablation in comparison with surgical sympathectomy for palmar hyperhidrosis. Radiofrequent ablation had a lower succesrate (75%) compared to ETS (95,6%) although patient satisfaction and incidence of compensatory sweating were not statistical significant different.^[9]

Several authors reported the effect of botulin toxin injections in the management of vasospastic disorders and ischemic finger damage after trauma of the hand.^[10-13] botulin injection alleviates pain and increases the blood flow to the affected digits and results in improved ulcer healing.^[10,11] In contrary the use in patients with scleroderma – associated Raynauds ` phenomenon is questioned by Bello et al.^[14]

Surgical digital periarterial sympathectomy is aimed at both mechanical denervation to decrease sympathetic tone and removal of the periarterial fibrosis through stripping of the adventitial sheath of the collateral digital arteries.^[15] Although it is a microsurgery technique the dissection of at the wrist and the palm of the hand are substantial. [figure 1] Several authors reported promising outcomes of this technique.^[15-17]

With the introduction of surgical robot systems new surgical approaches became available. Because of the advanced visualization and agility of the surgical instruments more selective transecting of the efferent sympathetic fibers (ramicotomy) could be performed with more ease. We have described the results of a feasibility study in a porcine model (**Chapter 5**). The skin temperature after ramicotomy increased significantly, subsequent transection resulted in an additional increase in skin temperature confirming and additional sympathetic denervation of the limbs. It is believed that the transection of these efferent fibers without transection of the sympathetic chain result in a decrease in side effects without leading to less clinical efficacy. The use of a ramicotomy in patients with upper extremity ischemia is not yet described in literature. Nonetheless several

authors have described the results of ramicotomy in the management of palmar, axillar and craniofacial hyperhidrosis and mention a substantial lower risk of adverse effects compared to conventional (endoscopic) thoracic sympathectomy.^[18-21]



Figure 1. Sympathectomy can be performed through three incisions—longitudinal incisions proximal to the distal wrist crease to expose the radial (white arrow) and ulnar (black arrow) arteries and an oblique incision over the palm to expose the superficial palmar arch (circle) and common digital arteries (asterisks)

Source: Satteson ES, Chung MP, Chung LS, Chang J. Microvascular Hand Surgery for Digital Ischemia in Scleroderma. *J Scleroderma Relat Disord*. 2020 Jun 1;5(2):130-136.

Although the above mentioned procedures are promising, unfortunately up to this date no comparative studies are available to identify which treatment is superior. Further research is warranted to provide more insight in efficacy, clinical benefits and adverse effects. Patient reported outcomes should be leading in determining the effect of treatments. As mentioned before, in our opinion surgery should be offered only as a last resort in patients persistent complaints and/or tissue loss after all less invasive therapies have failed to achieve a relief of symptoms.

Paget-Schroetter syndrome

Paget-Schroetter Syndrome (PSS) is a distinct entity within the venous thoracic outlet syndrome (vTOS) in which thrombosis of the subclavian vein is caused by external compression of the subclavian vein in the thoracic outlet at the costoclavicular junction.

^[22] Currently, there is no consensus on the optimal management of PSS. PSS can be treated non-operatively, surgical or by a combination of treatments. Non-operative treatment can be anticoagulation, catheter directed thrombolysis (CDT) or other comparable catheter based therapies. Surgical therapy is aimed to prevent recurrence of thrombosis and consist of decompression of the subclavian vein by resection of the first rib after patency is restored with AC or CDT. Published reports are predominantly retrospective in design and limited by short follow-up and/or not well documented functional outcomes.

Importance of patient reported outcome measures (PROMS)

The reports in this thesis all have been focused on the effects of the management perceived by the patients themselves. This is important because it is well known that there is a lack of association between venous hemodynamics, venous morphology and post thrombotic complaints.^[23,24] In line with this discrepancy several authors mention patients with a complete occlusion without any complaints.^[25-28] Objective measures and endpoint like patency are therefore less suited as primary outcomes in studies regarding PSS. Unfortunately only a minority of authors used PROMS to evaluate the efficacy of treatment in our review. We have used validated questionnaires (DASH, Villalta) to objectively score the efficacy of treatments in both our retrospective and prospective studies. A second argument to focus on the functional outcomes of patient is that PSS affects otherwise healthy individuals without severe comorbidities. Although non life-threatening, the functional impairment may be substantial. Multiple case series have shown a high percentage of persistent complaints or risk of recurrent thrombosis in non-operative treated patients.^[29-31] Our own case series demonstrated that 60% of non-operative managed patients had changed their lifestyle, daily activities or sports activities. We strongly advise the use of PROMS in future research and to focus on functional outcomes and implications on daily and sporting activities.

Need for long-term follow up

As mentioned before PSS is affecting young and otherwise healthy individuals. The long term effect of treatments are therefore important. Patients diagnosed with PSS will have to live with the consequences for the rest of their lives. In contrary, the current

literature on long term outcomes of patients treated for PSS is scarce. Mean follow up time of the 60 included reports in our review was 45 months. In our retrospective case series we have managed to retrieve the outcomes of patients with a mean follow up of more than 15 years (mean 184 months, range 43-459) after their first episode. Effort should be put in studies with adequate long term outcomes to provide more solid evidence for the best treatment of patients with PSS.

CDT could be considered in patient which meet the following criteria:

- *severe symptoms, with threatened arterial circulation due to venous congestion*
- *thrombus present in most of the subclavian and axillary veins*
- *symptom duration less than 14 days*
- *good functional status of the patient*
- *life expectancy of 1 year or more*
- *(relatively) low risk of bleeding complications.*

First rib resection could only be considered if a patient:

- *Has very serious complaints of so-called 'thoracic outlet' syndrome*
 - *Is young and has a massive arm vein thrombosis with a threat to the arm, secondary to the venous obstruction*
 - *Does manual labor or is a professional athlete.*
-

source: Dutch guideline Antitrombotisch beleid^[33]

Need for qualitative studies and collaboration

The quality of the current available literature is moderate. Several factors can be pointed out which can negatively influence the quality. Because the incidence of PSS is low, not many patients will be available to participate in studies. In our review only a mean of 4.6 patients were enrolled per year in the included studies. Overall numbers of patients in the studies (mean 48, median 27.5) was low. Cooperation in multicenter studies or even centralization could be necessary to provide the case load for high quality comparative studies. In the Netherlands the TROTS registry is set up as a prospective longitudinal observational registry for data collection on PSS patients.^[32] With this effort data can be collected and centralized. This may lead to future studies to determine the best treatment for patients. One advantage of the TROTS registry is that it is possible to include every patient with PSS regardless of the attending physician. Both vascular surgeons and in example vascular specialists of the internal medicine can refer patients for participation. Cooperation with vascular specialists from the internal medicine is essential because general practitioners will often not refer patients with suspected PSS to a vascular surgeon. This is probably due to the fact that PSS is treated equal to lower

extremity deep venous thrombosis in the Netherland by internal medicine physicians. Even the current Dutch guideline on thrombosis primarily states that catheter directed thrombolysis should not be initiated in patients with upper extremity deep venous thrombosis.^[33] In the considerations the guideline mentions the use of CDT and even first rib resection in selected cases:

Due to this guideline many internal medicine physician treat all patients with upper extremity deep venous thrombosis alike and do not appreciate the atypical patient with PSS. Although we fully agree with this guideline regarding the non PSS patient, we do not agree with the strong selection criteria for patients with PSS. Patients with PSS are an exception and should be treated accordingly. Our systematic review and meta-analysis presented in **chapter 7** pointed out that surgical management with CDT followed by first rib resection leads to residual complaints in 4% of patients compared to 46% of patients in which anticoagulation alone was used in as non-operative management. Although the overall quality was moderate and GRADE levels were “very low” the outcome could be used in the shared decision making with patients. Hopefully our review will be referred to in future guidelines and provide the opportunity to treat patients with PSS more in line with the current evidence.

Topics with conflicting evidence or discussion in the literature.

The incidence and clinical relevance hypercoagulopathy in patients with PSS is appreciated different by authors. Goss et al.^[30] reported hypercoagulopathy in all 13 patients in his report, on the other hand several authors did not encounter clotting disorders at all.^[34-39] The clinical relevance is in our opinion lacking. Although patients with hypercoagulability will presumably have an increased risk in developing PSS, the management will not differ. In our institution standard workup regarding coagulopathy is abandoned years ago because of the lack of clinical relevance. It may be of concern if it would lead to, for example a patient tailored postoperative anticoagulation strategy. This poses another subject of interest.

Postoperative anticoagulation

It is well known and generally accepted that as long as the external compression at the thoracic outlet persists, recurrence of PSS is lurking and this risk can be mitigated by anticoagulation. Less clear is the use of and duration of postoperative anticoagulant therapy. Although the majority of authors report the use of postoperative anticoagulation, Fairman noted no difference in the rate of early re-thrombosis or follow-up patency in

patients who received antiplatelet therapy instead of postoperative anticoagulation.^[40] Cessation of anticoagulation 2 weeks postoperatively is also proposed by Archie in 2017, although a venography without residual lesions was considered obligatory.^[41] Patients with residual stenosis may require prolonged anticoagulation up to 12 months.^[41] The discontinuation of anticoagulant therapy may be indicated postoperative because the provoking repetitive trauma to the subclavian vein is eliminated with the removal of the first rib. Further research is needed to confirm the non-inferiority of omitting postoperative anticoagulation.

Surgical approach to first rib resection

As mentioned in our review several surgical procedures are available for resection of the first rib. Open, thoracoscopic and robot assisted techniques are available. The transaxillary approach is reported the most in literature, in our review in 62%. In the majority of cases authors report data on one surgical technique, in only 10/60 reports in our review more than one surgical technique was used. Reports comparing different techniques are therefore scarce. Bozzay et al.^[42] and Dua et al.^[43] compared the infraclavicular to the supraclavicular approach and both reported a favorable outcome of the infraclavicular approach. Madden et al. concluded that the infraclavicular approach was superior to the paraclavicular approach.^[44] Faber et al. reported excellent results of both transaxillary and infraclavicular approaches to first rib resection in patients with subclavian vein thrombosis.^[45] No reports are available comparing the robot-assisted technique with other approaches. In our feasibility study on the robotic approach (**chapter 10**) we discussed this technique and compared the incidence of complications with our prior results of patients undergoing first rib resection by alternative approaches. To our knowledge this is the only comparative data on complication rate of robot assisted first rib resection. We do need to emphasize that the choice for a specific approach is predominantly affected by the characteristics of the vascular lesion in patients undergoing decompressive surgery for PSS. In patients with complete recanalization and a patent subclavian vein at time of surgery only decompression is indicated by resection of the first rib and if required venolysis. In patients with more extensive or severe residual lesions or even persistent occlusion, revascularization is sometimes necessary. This requires more exposure of the subclavian vein. Robot assisted or laparoscopic approaches are not suited for revascularization and even the transaxillary approach provide limited access. Infraclavicular, paraclavicular or a Molina approach are most suited for combined decompression and revascularization of the subclavian vein.

Future studies.

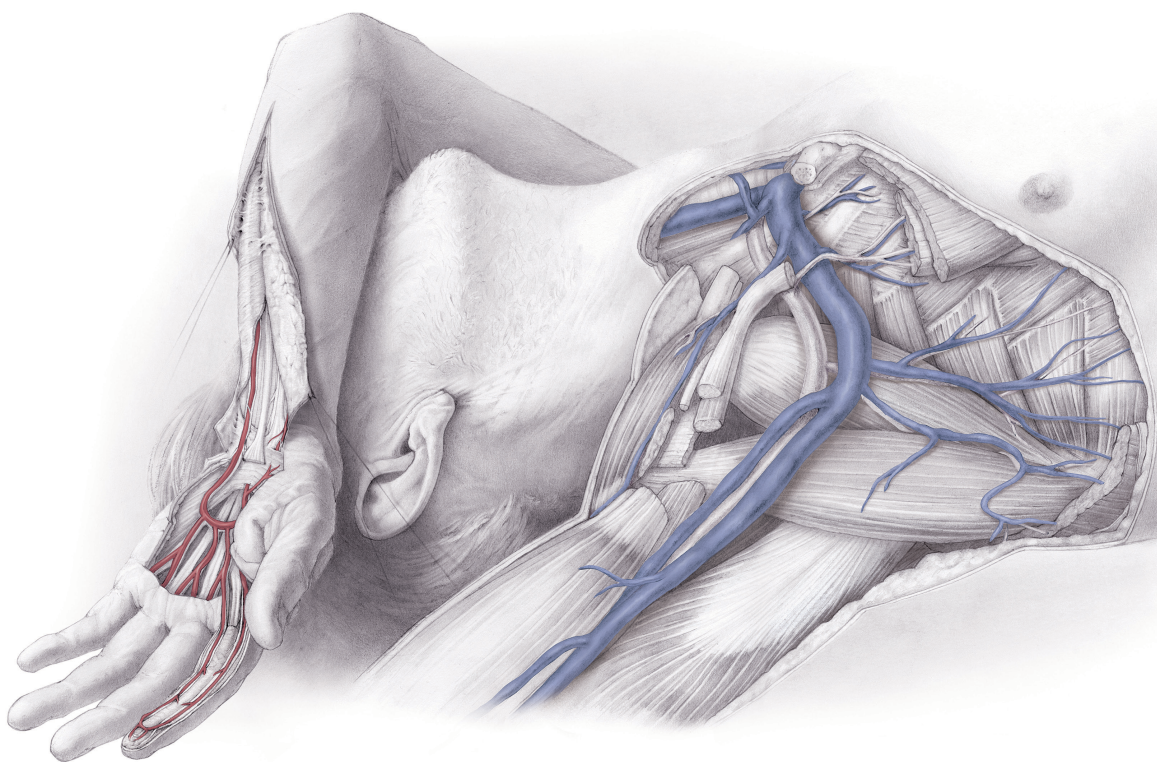
unfortunately up to this date no randomized trials are available. Collaboration should be the main focus of vascular surgeons and vascular specialist who are treating patients with PSS. Recognition by internal medicine physicians, that patient with PSS represent a highly selective subclass of patients completely incomparable to the normative population with provoked upper extremity deep venous thrombosis, is essential to provide the necessary case load of patients required for high quality studies. Preferable randomization of patients to both non-operative and surgical management strategies will determine the optimal treatment strategy. Focus on patient reported outcomes and implications on normal daily and sporting activities will be necessary to identify the adjustments patients make after diagnosis of PSS. Although less important, objective clinical endpoints like recurrence and/or patency can be used as secondary endpoints. Costs of both non-operative and surgical treatment should be analyzed to provide more insight of cost efficacy of the different treatments. If possible future studies should provide insight in factors contributing to the success or failure of non-operative management. This could be used to identify in the future those patients who will have satisfying result with non-operative management.

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Summary and main conclusions

SUMMARY

This thesis describes different aspects of both arterial and venous disease of the upper extremities. **PART 1** of the thesis encompasses studies on the treatment of ischemia of the hand and fingers by means of a thoracic sympathectomy. This is a surgical procedure in which the sympathetic nerves in the chest are transected, resulting in a vasodilation of the blood vessels in the arm. This vasodilation enhances blood circulation in the hand and fingers and thereby improving the complaints of patients. A novel robotic procedure is tested in a porcine model to assess its feasibility and efficacy.

PART 2 of this thesis is focused on the treatment of patients with venous thoracic outlet syndrome. In this specific group of patients, compression of the subclavian vein at the costoclavicular junction causes intermittent, position dependent outflow obstruction or thrombosis of the upper extremity. Effort induced upper extremity thrombosis is called Paget-Schroetter syndrome (PSS). Up to this date no consensus is reached regarding the optimal treatment. A new robotic technique for the resection of the anteromedial part of the first rib with the use of 3 trocars is evaluated.

PART 1 Upper extremity peripheral artery disease (UEPAD).

In **CHAPTER 2** we present the outcomes of a review on thoracic sympathectomy (TS) and endoscopic thoracic sympathectomy (ETS) in the management of upper limb ischemia. All articles published between 1980 and 2010 were eligible for inclusion. In total 18 reports were included. In **CHAPTER 3** we extended the search with 10 years (1975-2015) and added 11 reports to a total of 29. The endpoints in both reports were similar and focused on the efficacy of TS/ETS in the management of Primary Raynaud's Disease (PRD) and Secondary Raynaud's Phenomenon (SRP). Special attention was paid to ulcer healing and adverse effects of the surgical procedure. Short-term and long-term beneficial effects were reported for both PRD and SRP albeit with better results for SRP. Ulcer healing or improved healing was seen in almost all patients. The reported effect of improvement of symptoms decreased over time. Adverse effects of surgery were more frequent in the TS group (284 adverse effects in 525 procedures) compared to the ETS group (169 adverse effects in 584 procedures). Based on the available literature we concluded that ETS can have a role in the management of therapy resistant PRD or SRP because of its beneficial effects and low risk of adverse effects.

The results of 35 patients with upper extremity ischemia treated with ETS in our institution are reported in **CHAPTER 4**. Details on compensatory sweating (CS), a well-known side effect of ETS, were also carefully assessed. At follow up 22 patients were

still alive and we were able to include 19 patients in this study. During a telephone interview we graded the outcome of ETS on the complaints of the patients, the degree of CS and patient satisfaction. Mean follow up was 93 months (range 18-198 months). Postoperative beneficial effects were reported by 12 patients (63%). During the follow up period 11 patients (58%) reported a change of complaints over time. Two patients reported a further improvement of their complaints, nine patients reported a deterioration of their complaints. Of these nine patients four patients reported more severe symptoms compared to the pre-operative complaints. Three patients had less complaints compared to their preoperative situation and in two cases the complaints returned to their pre-operative level. Overall long-term beneficial effect of ETS was reported in 10 cases (53%). Patient satisfaction was consistent with 56%. CS was reported by 11 patients (58%). Although these results are worse than reported in the literature we concluded that ETS still has a role in the management of patients with refractory symptoms of PRD or SRP because adverse effects, other than CS, were infrequently reported.

As mentioned before, inducing CS is one of the most important drawbacks of ETS. It is postulated that reducing the surgical trauma on the sympathetic chain will reduce the incidence of CS. A more selective transection of the efferent rami communicantes of the sympathetic chain (ramicotomy) shows the lowest rate of CS. This procedure is sometimes challenging with the regular thoracoscopic approach. We tested a novel robot assisted technique with the use of the the Da Vinci® surgical robot to perform a T2-T5 ramicotomy in a porcine model. The results of this pilot study are mentioned in **CHAPTER 5**. The procedure was successfully completed in all 5 animals. In all cases, the sympathetic chain remained intact. After completion of the ramicotomy the skin surface temperature increased from 34.2 ° C (33.3–35.5) to 35.4 ° C (33.9–37.0) confirming an increase in skin perfusion. After total T2–T5 sympathectomy was performed the skin surface temperature rose to 35.8 ° C (33.8–37.1) confirming additional sympathetic denervation. We concluded that robot-assisted thoracoscopic T2–T5 ramicotomy was feasible and effective in a porcine model.

PART 2 Upper extremity deep venous thrombosis (UEDVT)

CHAPTER 6 serves as an introduction to the second part of this thesis. It sheds light on an illustrative case of a young, healthy, athletic male with upper extremity deep venous thrombosis. This case of PSS shows the reader in what type of patients this pathology may be seen. It is a real difference to the regular patient who need a consultation of a vascular surgeon.

The results of patients with Paget-Schroetter syndrome treated in our institution between 1990 and 2015 were retrospectively analysed in **CHAPTER 7**. Functional results were graded with questionnaires (DASH / Villalta / disease specific questions). In total 67 of 91 patients returned the questionnaires. Mean follow-up of was 184 months (range 43-459). All functional outcomes were better in the surgical group compared to the non-operative treated and surgical treated patients were more likely to be able to continue their original lifestyle and sports activities (84% vs 40%, $p = 0.005$). Patients with recurrence of thrombosis, or the need for surgical intervention after primary non-operative management reported worse functional outcomes. We concluded in this chapter that surgical management of PSS with immediate CDT followed by FRR leads to excellent functional outcomes with low risk of complications. The results of non-operative management were satisfactory for some patients, but resulted in worse functional outcomes overall and more patients needing to adjust their lifestyle compared to surgical treated patients.

All patients between June 2014 to July 2020 who were scheduled to undergo first rib resection in the management of PSS were eligible to participate in the prospective case series we present in **CHAPTER 8**. In total 24 patients could be included. Patients were divided into one of two groups based on their initial management strategy. All patients who were treated non-operatively and were scheduled voor FRR because of persistent or recurrent complaints were marked as the On-Demand FRR group (OD-FRR). Patients who were managed surgically with CDT or AC followed by scheduled FRR were marked as the primary FRR group (P-FRR). DASH scores at follow up did not differ significantly between P-FRR and OD-FRR patients: general DASH 12 months 6.5 versus 21.6 ($p = .166$). Complications ($n=20$) were reported in 12 patients (P-FRR $n= 5$, OD-FRR $n= 7$). The need for performing venous reconstruction or patch was associated with an increased risk of postoperative complications (87,5% vs. 31.3%, $p = .009$). Patency at mean follow up of 12.4 months was 80%. Recurrence of thrombosis was more frequent in the OD-FRR group (0/8 vs 4/12, $p = .068$) and was associated with worse postoperative DASH scores (9.4 vs 43.5, $p = .004$). We concluded that surgical management of PSS consisting of CDT followed by scheduled P-FRR leads to good results.

In **CHAPTER 9** we systematically reviewed the available literature from 1990 to 2021 on the management of PSS. It is an extensive effort to provide insight in the current evidence. Main focus of the review was the overall functional outcome with special attention to the initial therapy. Patients were catheterized by therapy in four main groups: anticoagulation (AC); catheter directed thrombolysis followed by anticoagulation (CDT+AC); anticoagulation

with subsequent first rib resection (AC+FRR) and catheter directed thrombolysis prior to first rib resection (CDT+FRR). Secondary outcomes were success of initial treatment, persistent occlusion or recurrence of thrombosis and patency at last follow up. Adverse effects of CDT or complications of FRR were also analyzed. In total 60 reports were included with a total of 2653 patients. The overall quality of the included reports was moderate and none of the studies had a randomized design. Single arm analyses of all included reports showed the highest chance of becoming symptom free (96%) in the CDT+FRR group. The non-operative groups (AC 54% and CDT + AC 71% symptom free) had less favourable outcomes. Pooled analysis of comparative reports confirmed the superiority of CDT + FRR compared to AC, CDT + AC and AC+FRR. The GRADE method was used to ascertain the level of certainty, because of the moderate quality of the included reports, the certainty was graded as “*very low*”. The secondary endpoints were all in favor of CDT + FRR. Side effects of CDT were scarcely reported. Complications of FRR were reported in approximately half (33/60) of the reports and were minor complications without the need for surgical intervention in the majority of cases. Overall, we concluded that based on the available literature patients treated with CDT+ FRR will probably have the best outcomes. Further high quality research is warranted to confirm the superiority of CDT + FRR compared to other treatments.

In **CHAPTER 10** we describe the initial results of a novel surgical approach for first rib resection using the Da Vinci® surgical robot. We performed this transthoracic technique with only three access ports (trocars). With this technique we were able to resect the anteromedial part of the first rib with decompression of the subclavian vein as result. The results of 15 procedures are presented. Conversion to transaxillary resection was necessary in 3 patients. In three patients complications were reported (Clavien-Dindo grade 2-3a). Patency was 91% at 15,5 months follow up. DASH scores at 1 and 3 years showed excellent functional outcomes (7.1 (SD= 6.9, range 0 - 20.8) and 6.0 (SD= 6.4 , range 0 - 25)) and are comparable to the scores of the normative general population. In this chapter we came to the conclusion that Robot assisted transthoracic first rib resection with only three trocars is a feasible minimal invasive approach for first rib resection in the management of vTOS with good patency and long term functional outcome.

MAIN CONCLUSIONS

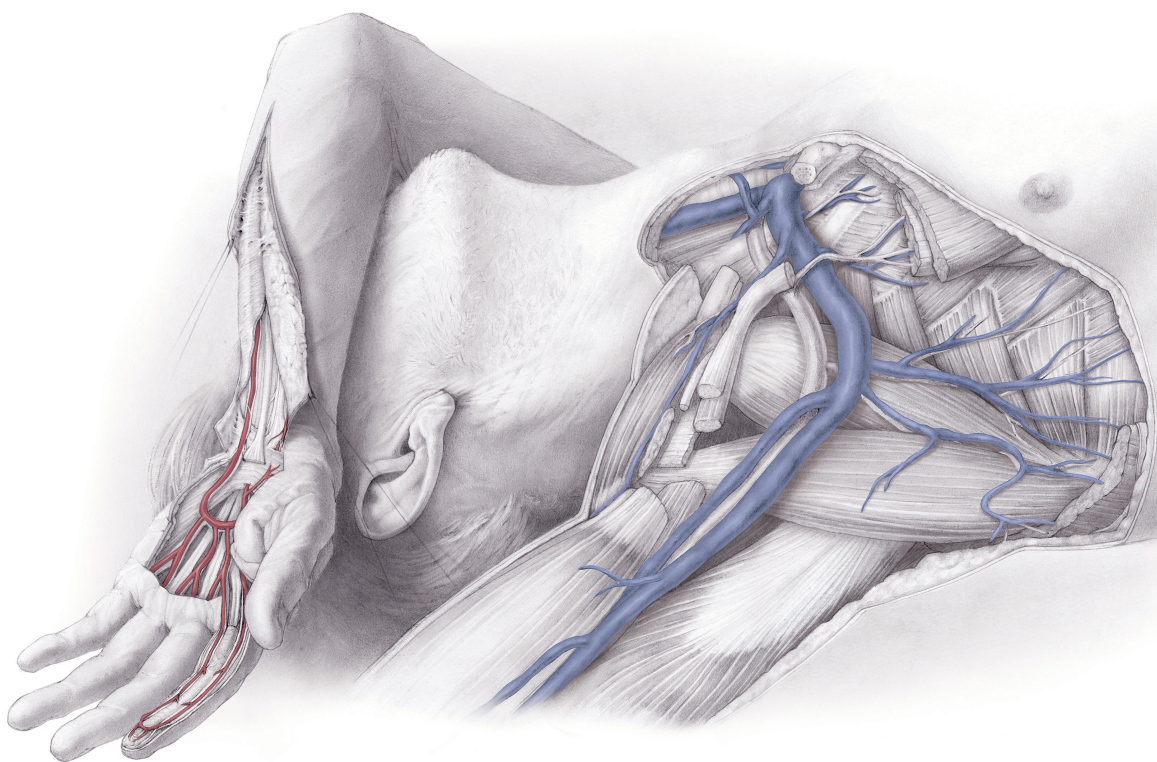
Sympathectomy in the management of upper limb ischemia:

We can state that there is evidence to support the option of performing an endoscopic thoracic sympathectomy in a selected group of patients with primary Raynaud's disease or secondary Raynaud's phenomenon, in which the results of supportive and non-operative therapies have been insufficient. The results of ETS described in the literature are promising, however we see less favorable results in daily practice. Due to the minimally invasive nature of ETS, the risk of side effects is small, except for compensatory sweating (CS). Performing a selective ramicotomy by means of the Da Vinci® surgical robot is possible and this technique could possibly lead to fewer complaints of CS.

Paget-Schroetter Syndrome:

Our literature review and retrospective study show better results in surgically treated PSS patients compared to the non-operative group. Nevertheless, a substantial part of non-operative treated patients will become symptom free with non-operative therapies. Patients themselves report fewer complaints after surgical treatment and can maintain their lifestyle and sporting activities more often than patients who have been treated non-operative. The results of a prospective study on the surgical treatment of Paget-Schroetter syndrome (PSS) show good functional outcomes. Removing part of the first rib with the Da Vinci® surgical robot is possible through 3 access ports and leads to good functional outcomes. Patients with persistent complaints or recurrence of thrombosis after non-operative treatment more frequently need elaborate surgery with increased risk of complications.

The information provided by this thesis can aid the shared decision making with patients diagnosed with upper extremity ischemia and PSS. It is clear that all patients have different perspectives on health and are willing to endure different risks in the pursuit of a cure for their complaints. Surgeons should be committed to take these personal considerations into account and counsel patients to their most suitable personalized therapy.



Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Dit proefschrift bestaat uit twee delen. In **DEEL 1** van het proefschrift worden studies beschreven over de behandeling van verminderde doorbloeding van de hand en vingers. Als de doorbloeding sterk afgenomen is kan dat leiden tot een zuurstoftekort. De medische term voor zuurstoftekort is “ischaemie”. Een bekende ziekte waarbij er ischaemie kan voorkomen is Raynaud. Als er geen onderliggende oorzaak is dan noemen we dat de primaire ziekte van Raynaud (PZR). Al er wel een onderliggende ziekte voor verantwoordelijk is dan noemen we dit het secundaire fenomeen van Raynaud (SFR).

De behandeling die we hebben onderzocht heet “*thoracale sympathectomie*”. Dit is een operatie waarbij bepaalde zenuwen in de borstkas worden doorgesneden. Deze zenuwen zorgen ervoor dat de bloedvaten in de hand samentrekken. Het doorsnijden van deze zenuwen zorgt er dus voor dat de bloedvaten in de hand uitzetten. Door het uitzetten van de bloedvaten kan er meer bloed naar de vingers stromen. Een ander effect is dat de aanmaak van zweet in de arm vermindert.

Als tijdens de operatie de borstkas geopend wordt is dit een open operatie en noemen we het een thoracale sympathectomie (TS). Als de operatie met een “kijk-operatie” gebeurt dan noemen we dat een “endoscopische thoracale sympathectomie”(ETS).

DEEL 2 van dit proefschrift gaat over de behandeling van patiënten waarbij een bloedprop in de ader van schouder/arm is gevormd. Het vormen van een bloedprop in een ader heet trombose. Trombose kan ontstaan door verschillende oorzaken. Als er sprake is van een trombose arm door een afknelling van een ader tussen het sleutelbeen en de bovenste rib dan noemen we dit het syndroom van Paget-Schroetter. In deel 2 hebben we onderzoek gedaan naar de beste behandeling van deze ziekte.

Hoofdstuk 1 is een inleiding. Het geeft uitleg over de twee verschillende ziekten die in dit proefschrift zijn onderzocht.

DEEL 1: Thoracale sympathectomie in de behandeling van ischaemie van de arm en hand

Hoofdstuk 2 is een literatuur onderzoek. Alle wetenschappelijke artikelen die tussen 1980 en 2015 zijn verschenen werden hiervoor gebruikt. Het effect van een TS/ETS op de klachten van patiënten met de primaire ziekte van Raynaud (PZR) en patiënten met het secundaire fenomeen van Raynaud (SFR) werden bekeken. We vergeleken ook het aantal complicaties van zowel TS als van ETS. In **hoofdstuk 3** hebben we deze studie opnieuw gedaan met extra artikelen die in de 5 jaar voor en 5 jaar na studie uit

hoofdstuk 2 zijn verschenen (dus 1975-2015). Er lijkt een duidelijk positief effect te zijn van het verrichten van een TS/ETS. Dit gunstige effect is minder groot bij patiënten met PZR in vergelijking met patiënten met SFR. Het effect neemt af na verloop van tijd. Complicaties treden bij TS geregeld op, bij ETS komen er veel minder vaak complicaties voor. Bij de meeste patiënten die wonden hebben door de verminderde doorbloeding genezen deze wonden of ziet men een verbetering van de genezing. Onze conclusie is dat patiënten, waarbij alle niet-operatieve behandelingen onvoldoende werken, het uitvoeren van een TS/ETS zinvol zou kunnen zijn om het verlies van lichaamsweefsel tot een minimum te beperken.

In **hoofdstuk 4** beoordelen we de lange termijn resultaten van ETS in de behandeling van patiënten met ischaemie van de arm, hand en vingers. Van de 35 patiënten die we tussen 1994 en 2009 hebben geopereerd waren er nog maar 22 in leven. Drie patiënten konden niet meedoen met de studie. Vragenlijsten werden bij 19 patiënten afgenomen tijdens een telefoongesprek. Gunstige effecten op korte termijn werden gemeld door 12 van de 19 patiënten (63%). Op middellange of lange termijn (gemiddeld 98 maanden na de operatie (spreiding 18-198)) werden gunstige effecten gemeld door 10 patiënten (53%). Van de patiënten was 58% tevreden met de behandeling die ze hadden ondergaan. Compensatoir zweten werd ervaren door 11 patiënten (58%). We concludeerden dat ETS vanwege zijn minimaal invasieve karakter een waardevolle optie kan zijn bij de behandeling van ischaemie van de bovenste ledematen, ondanks dat de werkzaamheid van ETS op de lange termijn in onze studie met 53% slechts matig was.

In **hoofdstuk 5** beschrijven we de eerste resultaten van een nieuwe operatietechniek waarbij de Da Vinci® operatie robot wordt gebruikt. Het betreft een diermodel. Doel van de operatie was om alleen de uittredende zenuwvezels uit de sympathische grensstreng door te nemen, de grensstreng zelf wilden we hierbij intact laten. De operatie is verricht in 5 varkens en was in alle 5 de gevallen een succes. De sympathische grensstreng bleef bij alle dieren intact. Er traden geen grote bloedingen op. Na het selectief doornemen van de uittredende zenuwvezels steeg de temperatuur van de voorpoten, het teken dat er toegenomen bloedtoevoer bewerkstelligd was. We concluderen dan ook dat deze techniek haalbaar is en effectief is om de sympathische innervatie van de arm en handen uit te schakelen.

DEEL 2: diep veneuze trombose van de bovenste extremiteit.

Hoofdstuk 6 is een inleidend artikel dat als overgang dient naar deel 2 van het proefschrift. Het hoofdstuk beschrijft een illustratief voorbeeld van een jonge man met

een trombose-arm, ook wel het Paget-Schroetter syndroom genoemd. Het heeft verder als doel om de lezer een beter beeld te geven van de patiëntengroep waar het tweede deel van mijn proefschrift over gaat.

De resultaten van onze eigen patiënten met een trombose-arm die we tussen 1990 en 2015 in het VUMC hebben behandeld presenteren we in **hoofdstuk 7**. In totaal bestaat deze groep uit meer dan 90 patiënten. Vragenlijsten worden door 67 patiënten ingevuld. Hoewel de scores voor chirurgisch behandelde patiënten op alle vlakken beter zijn kunnen we niet overal de statistische significantie bereiken. Ook is het maar de vraag of er een duidelijk klinische relevant verschil te vinden is. Wel duidelijk is het feit dat er veel meer patiënten hun levensstijl en intensiviteit van hun sportactiviteiten aan hebben moeten passen in de niet-operatieve groep in vergelijking met de patiënten die chirurgisch behandeld zijn. Het beeld dat er geschetst wordt past binnen de lijn van de huidige literatuur dat een chirurgische behandeling betere resultaten heeft dan een niet-operatieve behandeling.

In **hoofdstuk 8** beschrijven we prospectief de chirurgische behandeling van 24 patiënten die een eerste rib resectie ondergaan voor de behandeling van Paget-Schroetter Syndroom. De functionele uitkomsten in de vorm van de DASH scores verbeterden over het beloop van een jaar. Er traden met name complicaties op bij patiënten die ook een 2^e procedure ondergingen tijdens de operatie. Veelal was dit omdat er sprake was van schade aan het bloedvat wat verholpen moest worden met een veneuze reconstructie. Deze patiënten zijn veelal in eerste instantie niet met trombolyse en 1^e ribresectie behandeld. Door progressieve schade aan de vena subclavia door beknelling tussen het sleutelbeen en de eerste rib zijn ernstige restafwijkingen ontstaan. Hierdoor was het dus noodzakelijk om de ader te reconstrueren. Onze stelling blijft dan ook dat een snelle behandeling met katheter geleide trombolyse gevolgd door een 1^e ribresectie de beste resultaten geeft met een lagere kans op bijwerkingen en complicaties.

Hoofdstuk 9 is een zeer uitgebreide literatuurstudie van alle artikelen die er geschreven zijn tussen 1990 en 2021 over de uitkomsten van de behandeling van patiënten met het Paget-Schroetter Syndroom. We hebben in totaal 60 artikelen kunnen includeren. De kwaliteit van deze artikelen was middelmatig. Bijna alle studies zijn retrospectief in opzet en niet gerandomiseerd. Als we kijken naar de verschillende behandelingen dan zijn we komen we in dit hoofdstuk tot de conclusie dat, gebaseerd op de beschikbare literatuur, een chirurgische behandeling met trombolyse gevolgd door een 1^e rib resectie de beste behandeling lijkt te zijn voor patiënten met het Paget-Schroetter. Wel moeten we stellen dat door de lage kwaliteit van de geïncludeerde studies er nog

geen onomstotelijk bewijs is geleverd. Meer onderzoek van betere kwaliteit is nodig om definitief uit te maken welke behandeling het beste is voor patiënten.

In **hoofdstuk 10** gebruiken we de Da Vinci® robot voor het uitvoeren van de operatie waarbij de 1^e rib verwijderd wordt. We kijken naar de uitkomsten en complicaties van deze techniek. Het is de eerste klinische serie waarbij slechts 3 “werkpoorten” gebruikt worden om een deel van de 1^e rib te verwijderen.

BELANGRIJKSTE CONCLUSIES

Sympathectomie bij de behandeling van ischemie van de bovenste ledematen:

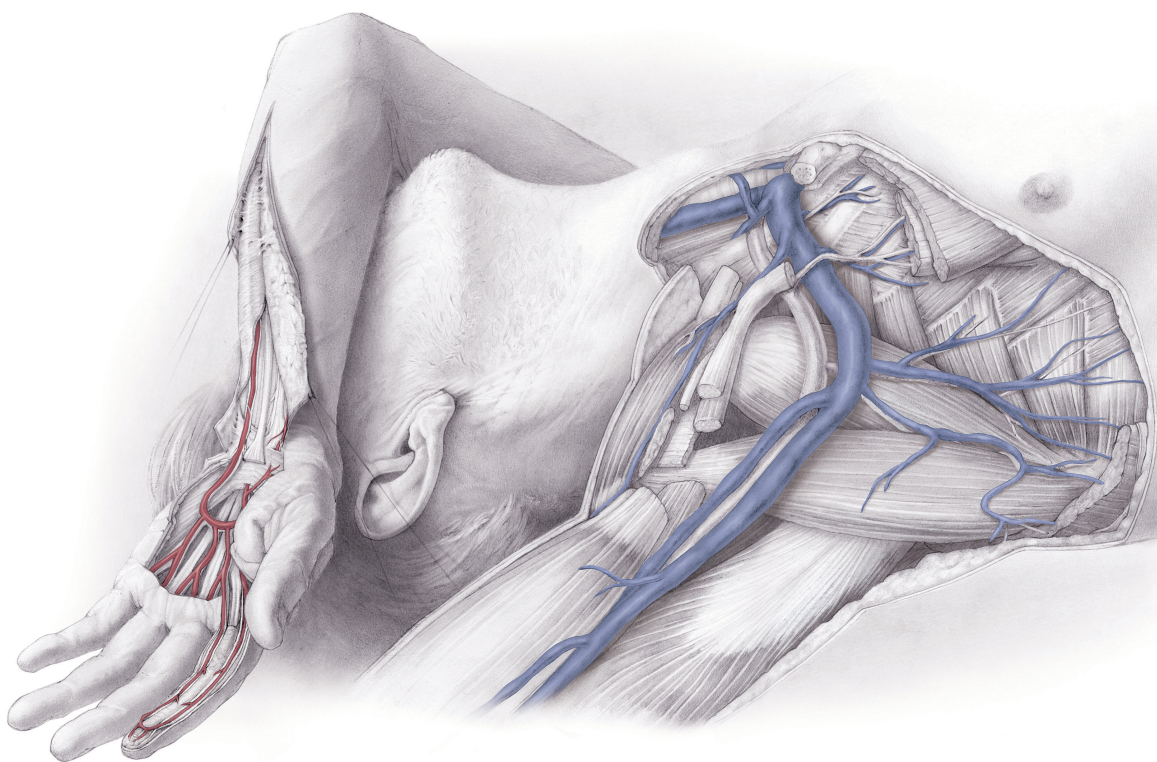
Er is bewijs dat het uitvoeren van een endoscopische thoracale sympathectomie een optie is bij een geselecteerde groep patiënten met de primaire ziekte van Raynaud of het secundaire fenomeen van Raynaud. Met name bij patiënten waarbij alle niet-operatieve behandelingen niet tot het gewenste effect hebben geleid. De resultaten die in de literatuur zijn beschreven zijn veelbelovend, maar in de dagelijkse praktijk hebben wij minder gunstige resultaten gezien. Het verrichten van een ETS kan minimaal invasief. Behoudens het optreden van compensatoir zweten is de kans op bijwerking en complicaties na ETS klein. Het uitvoeren van een selectieve ramicotomie met behulp van de Da Vinci® operatierobot is mogelijk en deze techniek zou mogelijk tot minder klachten van compensatoir zweten kunnen leiden.

Paget-Schroetter syndroom:

Ons literatuuroverzicht en retrospectieve onderzoek laten betere resultaten zien bij chirurgisch behandelde patiënten vergeleken met de niet-operatieve groep. Niettemin zal een substantieel deel van de niet-operatief behandelde patiënten symptoomvrij worden met niet-operatieve therapieën. Patiënten zelf melden na een chirurgische behandeling minder klachten en kunnen vaker hun leefstijl en sportactiviteiten volhouden dan patiënten die niet-operatief zijn behandeld. De resultaten van een prospectief onderzoek naar de chirurgische behandeling van het Paget-Schroetter syndroom laat goede functionele resultaten zien. Het verwijderen van een deel van de eerste rib met de Da Vinci® operatierobot is mogelijk via 3 toegangspoorten en leidt tot goede functionele resultaten. Patiënten met aanhoudende klachten of het opnieuw optreden van trombose na een niet-operatieve behandeling hebben vaker een uitgebreide operatie nodig met een verhoogd risico op complicaties.

De informatie uit dit proefschrift kan behulpzaam zijn bij het gezamenlijk nemen van beslissingen met patiënten met de diagnose ischemie van de bovenste ledematen

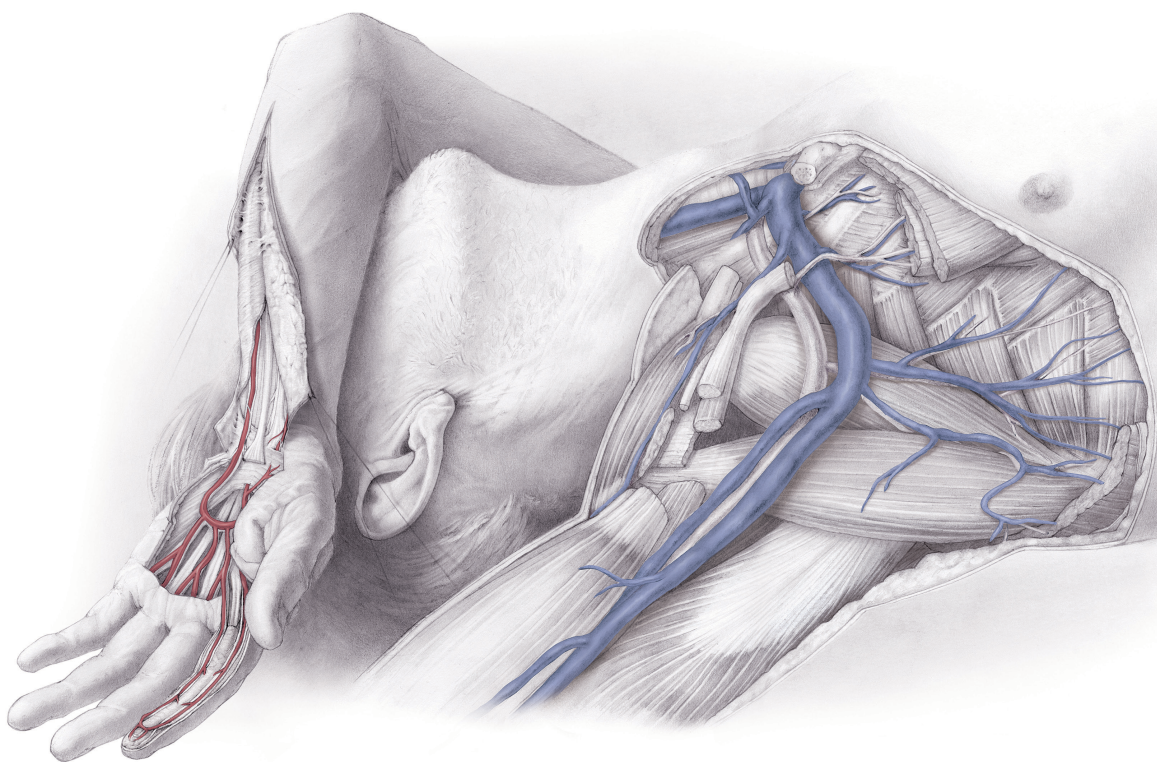
en het Paget-Schroetter syndroom. Het is duidelijk dat alle patiënten verschillende perspectieven op de gezondheid hebben en verschillende risico's bereid zijn te lopen bij het zoeken naar genezing van hun klachten. Chirurgen moeten zich verplicht voelen om rekening te houden met deze persoonlijke overwegingen en patiënten te adviseren over de meest geschikte gepersonaliseerde behandeling.



List of publications

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Dankwoord

DANKWOORD

Het zit erop! Mijn proefschrift is klaar!

De basis voor dit proefschrift werd meer dan 15 jaar geleden gelegd tijdens mijn wetenschappelijke stage. Het zal eenieder niet verbazen dat het dus een grote opluchting voor mij is om het af te ronden. In de afgelopen jaren beschreef ik mijn promotietraject aan belangstellenden steevast als een “kabbelend beekje, soms stroomt het hard, soms wat trager”. In werkelijkheid hebben er een paar flinke stuwdammen in gestaan, maar die zijn nu allemaal geslecht.

Hoewel mijn promotie grotendeels solistisch doorploeteren achter een PC is geweest, was het afronden nooit gelukt zonder hulp en af en toe een stevige vermaning om het nu eens eindelijk af te ronden. Een aantal personen wil ik in het bijzonder bedanken.

Geachte **Prof. Dr. Willem Wisselink**. Bedankt dat ik door u in 2010 met open armen ben ontvangen om te praten over het doorlopen van mijn wetenschappelijke stage bij de vaatchirurgie. Ik was op mijn verzoek vanuit het UMCG door **dr. Jan van den Dungen** naar u in het VU medisch centrum “verwezen”. U regelde voor mij een wetenschappelijke stage en samen hebben we dit promotietraject opgezet. U was mijn stok achter de deur. Niet frequent maar wel op de juiste momenten heeft u me op het hart gedrukt om deze queeste af te ronden. Na elk gesprek kreeg ik weer een nieuwe energie om mijn schouders er weer onder te zetten. Ik verzekerde u elke keer dat ik het echt zou afronden.....zie hier (eindelijk) het resultaat. Dank voor alle steun tijdens dit traject!

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Zonder jouw hulp kabbelde het beekje nu nog steeds **Vincent Jongkind**. Jij hebt me enorm weten te enthousiasmeren om het tweede deel van dit proefschrift vorm te geven en af te ronden. Je kwam op het juiste moment naar voren toen Hans uit het VU

medisch centrum vertrok. Je nam de begeleiding over en gaf me nieuwe energie om door te gaan. Ik waardeer je oprechte interesse, kritische wetenschappelijke blik, en no-nonsens opvattingen en visie op wetenschappelijk onderzoek. Dit resulteerde vaak in volledig herschreven manuscripten waarbij ik regelmatig eerst even moest slikken voor het werk dat het zou betekenen om alles om te gooien. Toch betekende het elke keer weer een grote verbetering van het eindresultaat.

Ik wil ook **alle leden van de promotie en leescommissie, prof.dr. J.D. Blankensteijn, prof.dr. F.W. Bloemers, dr. E.S. Van Hattum, prof.dr. E.S.G. Stroes, prof.dr. J.A.W. Teijink, prof.dr. C.J.A.M. Zeebregts** hartelijk danken voor het beoordelen van dit proefschrift. Voor u allen een gangbaar onderdeel van uw werkzaamheden, voor mij één van de belangrijkste dagen in mijn wetenschappelijke carrière.

Max Hoebink, Je hebt me gewoon in weten te halen! Van harte gefeliciteerd met je eigen promotie vorige maand! Jij was de motivator voor het afronden van de review over PSS. Het lag al een tijdje op de plank maar door jouw hulp is het echt gaan vliegen en vele malen beter geworden. Je bent inmiddels ook in opleiding tot chirurg, zeer verdiend en ik wens je al het goeds bij je verdere carrière.

Beste **Harry en Aleid**, door het beschikbaar stellen van de extra kamer in jullie huis heb ik vele avonden aan mijn proefschrift kunnen werken omdat ik niet terug naar Haarlem hoefde te reizen. Dit heeft zeker in de aanloop naar de laatste fase veel bijgedragen. Mijn dank is groot.

In 2013 was ik jouw paranimf en nu ben je eindelijk die van mij **Michael Sutton**. Wat was ik trots op jou toen jij promoveerde en ik hoor je nog zeggen dat “mijn tijd ook zou komen”. Ik had eerlijk gezegd toen niet verwacht dat het pas 13 jaar later zou worden, maar goed.....hier is ie dan eindelijk en wat ben ik blij dat we ook deze dag samen kunnen vieren.

Isabella Vos. Wat ongelooflijk fijn dat jij vandaag samen met mij deze mooie dag mag vieren als paranimf. Recent ben ik mezelf flink tegengekomen toen ik thuis kwam te zitten met een hernia. Ik voelde me veilig genoeg om mijn twijfels en zorgen ook te delen met jou. Jij was vereerd dat ik je vroeg als paranimf.....lieve Bel die eer is volledig wederzijds.

Beste **Collega Chirurgen van het Jeroen Bosch Ziekenhuis**, als jonge klare ben ik in jullie Bossche pareltje neergestreken en ik heb me daar direct welkom gevoeld. De klik was wederzijds en dat heeft er toe geleid dat ik nu al ruim anderhalf jaar als staflid samen met jullie mag optrekken. Ik heb zin in de komende jaren om met jullie aan de slag te blijven gaan!

Alle leden van het MHD Cambrinus. Mijn studententijd is nauw verweven met dit dispuut. Over smaak valt zeker niet te twisten. Bedankt voor alle avonden, weekenden en lustra samen. Dat mijn 3^e onderzoekslustrum samenvalt met het 7^e lustrum van ons mooie Dispuut kan geen toeval zijn!

Alle A(N)IOS met wie ik in de afgelopen jaren heb samengewerkt. Werken als jonge dokter op de afdeling chirurgie is met niets te vergelijken....en al helemaal niet met de series op tv. Je maakt de meest gekke dingen met elkaar mee, positief en negatief. Mij heeft de gezelligheid, het gevoel van kameraadschap en droge humor met zo nu en dan een rauw randje een geweldige assistententijd geleverd, bedankt allen daarvoor!

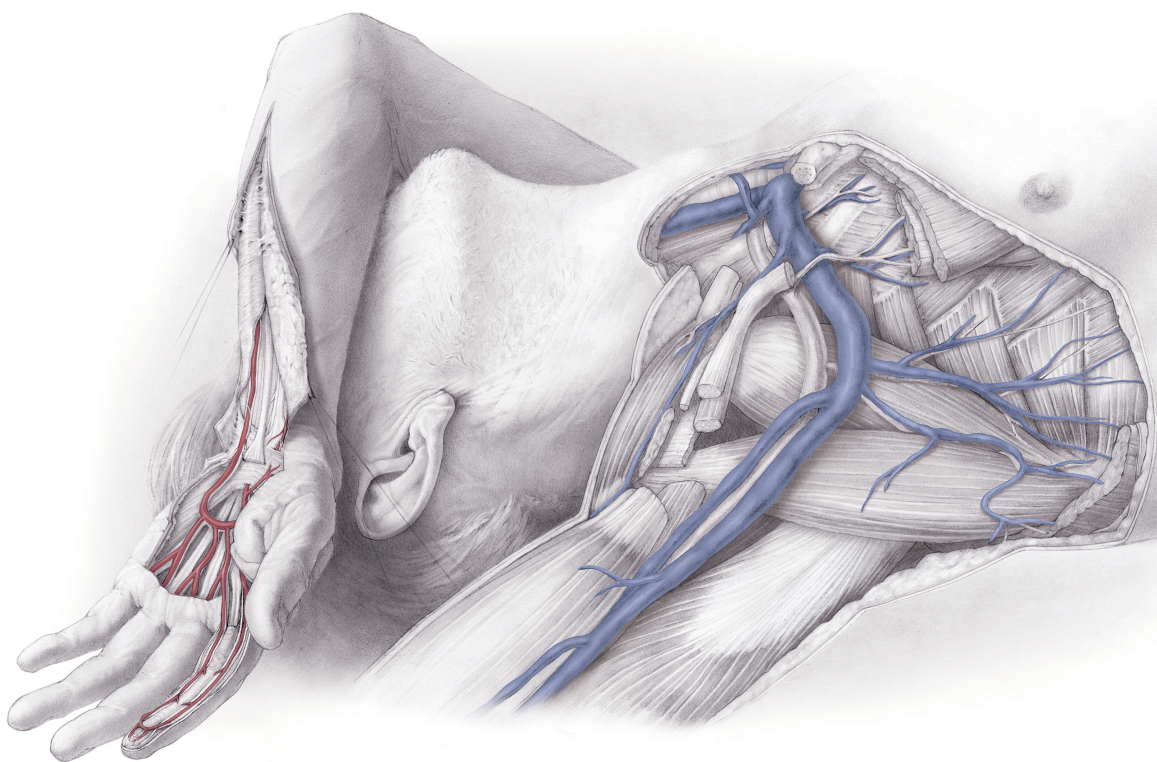
Ik wil **alle patiënten** bedanken die hun medewerking hebben willen verlenen voor mijn wetenschappelijke ambities. Ik ben er zeker van dat het meer inzicht heeft gebracht en uiteindelijk anderen kan helpen om betere keuzes te maken in hun behandeling.

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Simon, Max en Isa: jullie zullen pas later beseffen hoe belangrijk jullie voor mij zijn. Ik hou van jullie lieve schatjes.

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About the author

ABOUT THE AUTHOR

Frank Hoexum was born on October 13, 1985 in Groningen. He grew up with his parents Joop Hoexum and Lies Hoexum-Warmenhoven and 3 older brothers; Rob, Peter en Michiel. After obtaining his diploma at the Willem Lodewijk Gymnasium, he started medical school at the University of Groningen. During his years in medical school, his interest in surgery became clear and in his last year he decided to do his scientific internship and elective internship at the department of vascular surgery of the VU University Medical Center in Amsterdam. It was during this period that the foundations were laid for this thesis. After obtaining his doctorate degree, he worked for 4 years as house officer at the surgery departments of the Kennemer Gasthuis in Haarlem and the VU medical center in Amsterdam. On 1st. of July 2015 he started his surgical training at the Westfriesgasthuis Hoorn and VU Medical Center. After completing his training as a trauma surgeon he started a fellowship in trauma surgery in the Jeroen Bosch ziekenhuis in hospital in Den Bosch. In September 2024 he became a staff member of the department of surgery at the Jeroen Bosch Hospital.



Far more important; during his holiday job on Vlieland in 2005, he met Véza Vos. In 2007 she finally responded to his advances. After several years in a long-distance relation they moved in together and lived in the Pijp in Amsterdam. Simon was born on September 26, 2018. In the summer of 2019 Frank married Véza. The family moved to Haarlem in 2020 where Max was born on October 14, 2020. The family became complete with the birth of daughter Isa on the 16th August of 2023. In September 2024 the family continued their adventure and moved to Vught.