Reconstructive deep venous surgery and endovascular venous intervention in the treatment of chronic venous insufficiency

PhD thesis

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Reconstructive deep venous surgery and endovascular venous intervention in the treatment of chronic venous insufficiency
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This journey started right after I came to the department of vascular surgery at Aker hospital. I want to express my deepest gratitude to Proff. Andries Kroese a visionary, wise and knowledgeable man, who in his dream of forming the Oslo vascular centre, he saw reconstructive deep venous surgery as one of its main areas. And in 1991 he put his confidence in me to develop this area further. We have now become the Norwegian National Unit for Reconstructive Deep Venous Surgery (NOVI). His teachings in decision making and technical surgical principals made an everlasting impact in me.

Proff. Jørgen J. Jørgensen took over as principal supervisor in 2005. He added disciplined and well-structured guidance to this thesis. I am grateful for his tutoring and friendly support. His wise and supportive words in dark periods kept me going. It is great to be able to share common interests in meticulous surgical technique, boats and foot-ball.

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And last but not least my eternal gratitude and love to my wife and best friend Rocio, for her unconditional support and unequivocal belief in my ability to accomplish anything and everything. To my sons Tomas, Pablo and Pedro, who always believed in me and at times showed genuine curiosity and interest towards my work and research.

Special thanks to all my coauthors for having a common interest.
List of papers

Paper I: External Venous Valve Plasty (EVVP) in Patients with Primary Chronic Venous Insufficiency (PCVI)

Rosales A, Slagsvold CE, Kroese AJ, Stranden E, Risum Ø, Jørgensen JJ.


Paper II: Venous Valve Reconstruction in Patients with Secondary Chronic Venous Insufficiency (SCVI)

Rosales A, Jørgensen JJ, Slagsvold CE, Strand E, Risum Ø, Kroese AJ.


Paper III: Stenting for Chronic Post-Thrombotic Vena Cava and Iliofemoral Venous Occlusions: Mid-term Patency and Clinical Outcome

Rosales A, Sandbæk G, Jørgensen JJ

## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>A-V</td>
<td>Arterio-venous</td>
</tr>
<tr>
<td>AV</td>
<td>Ascending venography</td>
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<tr>
<td>AVP</td>
<td>Ambulatory venous pressure</td>
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<tr>
<td>CBT</td>
<td>Catheter based thrombolysis</td>
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<tr>
<td>CDU</td>
<td>Colour duplex ultrasound</td>
</tr>
<tr>
<td>CEAP</td>
<td>Clinical, etiology, anatomy, pathophysiology</td>
</tr>
<tr>
<td>CTV</td>
<td>Computer tomography venography</td>
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<tr>
<td>CVI</td>
<td>Chronic venous insufficiency</td>
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<tr>
<td>DVT</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>EVI</td>
<td>Endovascular venous intervention</td>
</tr>
<tr>
<td>EVVP</td>
<td>External venous valve plasty</td>
</tr>
<tr>
<td>FVL</td>
<td>Factor V Leiden</td>
</tr>
<tr>
<td>IVC</td>
<td>Inferior vena cava</td>
</tr>
<tr>
<td>IVVP</td>
<td>Internal venous valve plasty</td>
</tr>
<tr>
<td>MRV</td>
<td>Magnetic resonance venography</td>
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<tr>
<td>PCVI</td>
<td>Primary chronic venous insufficiency</td>
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<tr>
<td>PTS</td>
<td>Post-thrombotic syndrome</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized clinical trial</td>
</tr>
<tr>
<td>RDVS</td>
<td>Reconstructive deep venous surgery</td>
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<tr>
<td>SCVI</td>
<td>Secondary chronic venous insufficiency</td>
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VCSS  Venous clinical severity score
VOP  Venous occlusion plethysmography
VPG  Venous pressure gradient
VVR  Venous valve reconstruction
Summary

Background

Chronic venous disorders in the lower extremity give rise to a range of signs and symptoms such as pain, varicosities, swelling, skin changes, throbbing and ulcer in the leg. The term chronic venous insufficiency (CVI) applies to the most severe cases. The two main pathophysiological factors to be assessed in patients with CVI are venous reflux and venous obstruction. Etiologically, patients can suffer from primary chronic venous insufficiency (PCVI) of unknown origin although familial disposition plays a role. It is not yet clear whether the defect is primarily in the endothelial layer of the venous wall or the valves themselves. Some new reports advocate that PCVI is a pressure-driven inflammatory process. Regardless, the defective deep venous valves in this group of patients often are amenable for repair.

In secondary chronic venous insufficiency (SCVI) the valve leaflets have been damaged after an episode of deep venous thrombosis (DVT), making surgical repair of the valves impossible and warranting the need of a replacement.

The main focus of this thesis was to answer the following question: Do surgical and/or endovascular intervention have role in the treatment of patients with chronic venous insufficiency?

The history of reconstructive deep venous surgery (RDVS) extends back to 1968 when Robert L. Kistner performed the first internal valve plasty to treat deep venous axial reflux. Surgery was also performed to treat deep venous obstruction but the development of percutaneous recanalization and stenting turned endovascular intervention (EVI) into the modality of choice.
Material and methods

Oslo Vascular Centre, Oslo University Hospital (OUH) established a vein clinic in the beginning of the 1990’s to select patients with CVI that could benefit from RDVS and EVI. From referrals to this clinic 49 patients were selected for RDVS and 34 for EVI. For this purpose, it was necessary for a vascular surgeon to have access and support from a vascular laboratory, the innovative collaboration from an interventional radiologist and the advice from a haematologist in order to create a systematic workup scheme.

This workup scheme adhered to the framework that the CEAP (Clinical, Etiology, Anatomy, Pathophysiology) classification provides to categorise the patients with chronic venous insufficiency.

The work-up of patients to be considered for RDVS and EVI included a combination of hemodynamic and imaging techniques.

- Colour duplex ultrasound (CDU)
- Ambulatory venous pressure measurement (AVP)
- Venous occlusion plethysmography
- Trans-femoral venography (ascending and descending)

Haematological assessment is also mandatory since about 55% of patients with SCVI have a hereditary thrombophilia.

The Venous clinical severity score (VCSS), first validated in 2003 was used in the third paper only.

All patients with superficial and/or perforator incompetence were surgically treated and then submitted to a supervised period of six months of compression treatment with class 2 stockings, with a compression pressure of approximately 30 mm Hg at the ankle. Those who
did not benefit from this regimen were then considered for deep venous surgical and/or endovascular intervention.

The results were reported in terms of clinical and hemodynamic outcomes. The terms used are ulcer-healing and ulcer free period. CDU is used to assess competency (normal valve closure time with retrograde flow ≤0.5 seconds) of the reconstruction and AVP to quantify the hemodynamic improvement. Patency is determined by the time a stent remains opened verified by CDU.

Durability is defined by the time a reconstruction remains competent assessed with CDU.

Results

The ulcer-healing rates were 57% for the PCVI group and 68% for the SCVI after RDVS, while the ulcer-free period was 55 and 36 months, respectively.

Competency and clinical improvement were directly related in the follow-up period. In the PCVI group multiple valve plasties seem to give a longer durability than single plasty. (Paper I, page 575).

In the SCVI group the durability was longer in patients with haemodynamtic improvement after valve reconstruction (24 months against 18 months). Popliteal vein reconstruction alone or combined gave hemodynamic improvement and therefore enhancing durability with statistical significance (24 months versus 6 months, P= 0.014) (Paper II, page 471).

Endovascular venous intervention (EVI) for venous obstruction yielded a two-year primary patency rate of 14/21 (67%), primary-assisted patency of 16/21 (76%) and secondary patency of 19/21 (90%) with significant clinical improvement according to VCSS (Paper III, page 238).
Conclusions

The role of RDVS in the treatment of CVI has become clear but is not yet widely spread. This is probably due to the need for advanced vascular laboratory, extensive knowledge of the pathophysiology involved to be able to interpret the examinations and the necessary surgical skills.

EVI has demonstrated good long-term clinical outcomes and secondary patency making it our first-choice of treatment for venous obstruction.
Reconstructive deep venous surgery and endovascular intervention in the treatment of chronic venous insufficiency

Introduction

The main objective of this PhD thesis is to define the role of reconstructive deep venous surgery (RDVS) and endovascular venous intervention (EVI) in the treatment of patients with chronic venous insufficiency (CVI).

Background

Chronic venous disorders in the lower extremity give rise to a range of signs and symptoms such as pain, varicosities, swelling, skin changes, throbbing and ulcer in the leg. The CEAP (Clinical, Etiology, Anatomy, Pathophysiology) consensus classification (Table 1-2) provides the framework to categorise the disease. The C2 group (varicosities) constitutes about 62%. The term chronic venous insufficiency (CVI) applies to the most severe cases (C3-C6) where functional abnormalities of the venous system cause oedema, skin changes and venous ulcers (1,2). The Venous Clinical Severity Score is another assessment tool that attempts to correlate the progressive disability to the specific CEAP class (Table 3).
Table 1 and 2. Classification of chronic lower extremity venous disease

<table>
<thead>
<tr>
<th>Mark</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>C</td>
<td>Clinical signs supplemented by (s) for symptomatic and (a) for asymptomatic</td>
</tr>
<tr>
<td>E</td>
<td>Etiologic Classification (Congenital, Primary, Secondary)</td>
</tr>
<tr>
<td>A</td>
<td>Anatomic Distribution (Superficial, Deep, or Perforator, alone or in combination)</td>
</tr>
<tr>
<td>P</td>
<td>Pathophysiologic Dysfunction (Reflux or Obstruction, alone or in combination)</td>
</tr>
</tbody>
</table>

Table 2.

<table>
<thead>
<tr>
<th>Class</th>
<th>Clinical signs</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>No visible or palpable signs of venous disease</td>
</tr>
<tr>
<td>1</td>
<td>Telangiectasia, reticular veins, malleolar flare</td>
</tr>
<tr>
<td>2</td>
<td>Varicose veins</td>
</tr>
<tr>
<td>3</td>
<td>Oedema without skin changes</td>
</tr>
<tr>
<td>4</td>
<td>Skin changes (pigmentation, venous eczema, lipodermatosclerosis)</td>
</tr>
<tr>
<td>5</td>
<td>Skin changes in conjunction with healed ulceration</td>
</tr>
<tr>
<td>6</td>
<td>Skin changes in conjunction with active ulceration</td>
</tr>
</tbody>
</table>
Table 3. Venous Clinical Severity Score (VCSS)

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Absent = 0</th>
<th>Mild = 1</th>
<th>Moderate = 2</th>
<th>Severe = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>None</td>
<td>Occasional</td>
<td>Daily</td>
<td>Limit activities</td>
</tr>
<tr>
<td>Venous oedema</td>
<td>None</td>
<td>Evening, ankle</td>
<td>Afternoon, leg</td>
<td>Morning, leg</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>None</td>
<td>Limited area</td>
<td>Wide (lower 1/3)</td>
<td>Wider (above 1/3)</td>
</tr>
<tr>
<td>Inflammation</td>
<td>None</td>
<td>Cellulitis</td>
<td>Cellulitis</td>
<td>Cellulitis</td>
</tr>
<tr>
<td>Induration</td>
<td>None</td>
<td>Focal (&lt; 5 cm)</td>
<td>&lt; Lower 1/3</td>
<td>Entire lower 1/3</td>
</tr>
<tr>
<td>Number of active ulcers</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Duration of AC</td>
<td>None</td>
<td>&lt; 3 months</td>
<td>3 months – 1 year</td>
<td>&gt; 1 year</td>
</tr>
<tr>
<td>Size of AC</td>
<td>None</td>
<td>&lt; 2 cm diameter</td>
<td>2-6 cm diameter</td>
<td>&gt; 6 cm diameter</td>
</tr>
<tr>
<td>Compression therapy</td>
<td>Not used</td>
<td>Intermittent use</td>
<td>Most days</td>
<td>Continually</td>
</tr>
</tbody>
</table>

LSV, long saphenous vein; SSV, short saphenous vein; AC, active ulceration; lower 1/3, lower 1/3 of the leg.

Etiologically, patients can suffer from primary chronic venous insufficiency (PCVI) of unknown origin although familial disposition plays a role. It is not yet clear whether the defect is primarily in the endothelial layer of the venous wall or in the valves themselves. Some new reports advocate that PCVI is a pressure-driven inflammatory process (3).
Regardless, the defective deep venous valves in this group of patients often are amenable for repair.

In secondary chronic venous insufficiency (SCVI) the valve leaflets have been damaged after an episode of deep venous thrombosis (DVT), usually making surgical repair of the valves impossible and thus warranting the need of a replacement.

In 55% of patients with previous DVT an underlying coagulation defect (thrombophilia) such as factor V Leiden (FVL), prothrombin mutation, protein S and C is found.

Venous valve destruction and insufficient recanalization occur during both the acute inflammatory phase of thrombosis and during the re-absorption of the thrombus; which in turn may lead to venous reflux and/or outflow venous obstruction.

The pattern of spontaneous recanalization after DVT varies according to the affected anatomical segment as shown by colour duplex ultrasound (CDU) studies. While recanalization occurs in up to 90% of the femoro-popliteal veins after one year, this is rarely the case (<5%) after ilio-femoral thrombosis (4).

Anticoagulation as the conventional treatment for DVT only prevents progression of the thrombus and reduces the risk of pulmonary embolism. But the fact that removal of thrombus is not accomplished with anticoagulation, may have a severe impact in the long-term disability caused by DVT (5,6).

Post-thrombotic syndrome (PTS) develops in 40% of DVT cases following anticoagulation and is characterized by reflux and/or obstruction (7–12). Venous claudication (throbbing pain when walking), and/or leg ulceration are serious clinical consequences experienced by at least 15% of patients developing PTS. Persistent venous outflow obstruction in the femoral, iliac and/or cava veins leads to the development of venous claudication in about 43% of patients (13).
Patients with chronic venous insufficiency (CVI) and leg ulceration (C5-C6) constitute a serious medical socio-economic problem. The prevalence of venous leg ulcers is estimated to be approximately 1% (14). The total direct annual cost of treatment of venous leg ulcers in Sweden has been estimated at 73 million euro (15). In the UK the cost is between 400-600 million pounds per year and in the USA 3 billion dollar per year. Approximately 2% of the national budget in western countries is spent in the care of leg ulcer patients (16,17).

Correlation between quality of life and CVI by using both generic and disease-specific questionnaires (Short-Form Health Survey, 36 items (SF-36) and the VEINES-QOL, respectively) have been established. C5-C6 patients have similar quality of life impairment as those with heart failure or cancer and, worse than patients with arthritis or diabetes mellitus (18).

The main purpose in the treatment of CVI is to reduce venous hypertension by eliminating axial reflux (uninterrupted retrograde venous flow from the groin to the calf) and to re-establish sufficient venous drainage from the lower limbs. The prevention of post thrombotic syndrome following a DVT episode relates directly to the ability of clot removal and valve preservation of the treatment form.

**Rationale**

The conventional treatment of CVI with compression stockings combined with superficial surgery improve venous hemodynamics but achieves only 65% ulcer-healing rate after 24 weeks and recurrence rate of 12% per year (19).

RDVS and EVI have played a limited role in the treatment. This is partly due to the need of an accurate pre-operative hemodynamic evaluation, clear indications for operation and demanding operative technique. In addition, CVI is a lasting disease, under-prioritized in
most surgical units and the reported results do not seem to have generated the necessary impact in the vascular surgical community (20, 21).

**Aims of the thesis**

The main purpose of this study was to evaluate the efficacy and durability of deep venous surgical and endovascular intervention in treating CVI with the use of clinical and hemodynamic outcome measures. Emphasis was put specially in avoiding mixing treatment modalities, therefore all patients to be considered for RDVS or EVI, were first submitted to the conventional treatment with compression during six months and superficial/perforating surgery if needed. The clinical and hemodynamic outcomes in papers I, II and III are after only RDVS and EVI interventions.

Specific aims of each paper:

1. Paper I. To evaluate the effect of external venous valve plasty (EVVP) on patient symptoms, ulcer-healing rate, ulcer free period and period of competence following repair in patients with severe PCVI.

2. Paper II. To evaluate the durability of venous valve reconstruction (VVR) and its benefits in terms of symptom improvement, ulcer-healing or ulcer recurrence among patients with SCVI in whom conventional treatment had failed.

3. Paper III. To assess the mid-term patency and clinical outcome after recanalization and stenting of post-thrombotic chronically occluded vena cava and ilio-femoral venous segments.
Material and methods

Design

This is an interventional study.

Statistical analysis

Data was collected in a prospective database by using FileMaker Pro version 10 software. The statistical analysis was performed with Graph Pad Prism (a commercially available statistic program). The medians with range have been used as descriptors since the data distribution is considered to be non-parametrically. A Mann-Whitney U-test was used to determine significance in clinical outcome. Survival analysis with the Kaplan-Meier and log rank test was to extract actuarial survival curves to be able to compare primary, primary assisted and secondary patency rates, as well as durability and competency (page 37).

Investigations and interventions

Ambulatory venous pressure (AVP)

AVP measurement is still considered the reference standard in the assessment of global reflux, function of the vein-muscular pump and the severity of venous hypertension (22,23). A 21-gauge ‘‘butterfly’’ needle was inserted into a vein in the leg and connected to a pressure transducer, a pressure monitor and a recorder. Cannulation of dorsal foot veins should be avoided due to the possibility of falsely normal values caused by functioning valves at the ankle level (24). The patients then performed a standardized ‘‘walking on the spot’’ exercise. The mean venous pressure recorded when the curve flattens at the end of this exercise indicates the ambulatory venous pressure (AVP) (Fig. 1).
Fig. 1. The value of AVP is the one reached at the end of the step exercise (see arrows).

AVP normally drops below 30 mmHg in healthy subjects, indicating muscle-pump function of the limb. The recovery time, which is the time taken from cessation of the step test until the resting pressure level is reached indicates venous refilling and exceeds 20 s in healthy subjects (Fig. 2). The measurement is repeated after selective occlusion of the superficial veins. A 30 cm wide pneumatic tourniquet is placed around the thigh and inflated to 60 mmHg to occlude the long saphenous and other superficial thigh veins. The short saphenous vein may be occluded using a rubber tourniquet. By selectively occluding the superficial segments it is possible to identify the incompetent venous system (i.e. either the great or small superficial saphenous veins or the deep venous system) (Fig. 2).
Fig. 2. A: Vein pressure recording setup. B: Typical superficial vein pressure curves at rest and during walking in subjects with no venous insufficiency (Normal <30mm Hg), superficial- and deep venous insufficiency, and venous outflow obstruction. Note that dorsal foot vein is not cannulated. Pt: Pressure transducer, PM: Pressure monitor, AVP: Ambulatory venous pressure; RT: recovery time.

**Colour duplex ultrasound (CDU)**

CDU is used to evaluate axial reflux in the different anatomical segments of each venous system. The examination is performed with the patient standing, weight bearing primarily on the contralateral limb. A 12 cm wide pneumatic cuff is placed distally to the segment to be examined, and connected to a venous compression unit, which enables very fast (<0.2 s) inflation and deflation (VenoPulse, E. Stranden). The inflation pressure is adjustable, and set at 150 mm Hg. The venous compression unit ensures a standardized repeatable venous reflux procedure (inflation of the cuff, sustained for 3 s and then deflated). Five and 10 MHz ultrasound probes were used to detect venous reflux. A valve closure time >0.5 s was defined as pathological. Although there are recent reports in the literature suggesting that the peak
reflux velocity correlates better with the severity of venous insufficiency, valve closure time is more widely used (25). In addition to reflux assessment, the B-mode imaging was used to identify the valve segment and to describe morphological changes such as thickening of the venous wall and intraluminal trabeculae.

**Trans femoral venography**

Trans femoral venography is a dynamic imaging technique of the venous valve leaflets. It allows the classification of the severity of axial reflux and excludes an obstruction in the ilio-caval segment. Contrast medium is injected through a 4 French catheter introduced in the common femoral vein. In supine position, the patient is tilted 60 degrees (feet down) and contrast medium injected during a Valsalva manoeuvre. The dye column is followed with fluoroscopy distally until it stops or the Valsalva manoeuvre is completed. Reflux is graded into four categories described by Kistner: Grade I. proximally in the thigh, grade II. above the knee, grade III. below the knee, and grade IV. to the ankle (26). (Fig. 3).
Fig. 3. In this sequence of six pictures from the video descending venography when dye is injected when the patient performs a Valsalva manoeuvre. Insufficient valves allow the passage of dye to the knee level.

**Venous occlusion plethysmography (VOP)**

To evaluate the hemodynamic significance of post-thrombotic vein obstruction, VOP was performed to exclude persistent venous outflow obstruction by using an air plethysmograph (MacroLab, E. Strand) (Fig. 4). In recumbent position venous occlusion and recording cuffs were applied proximally to the patella and at the calf, respectively. An occlusive thigh cuff pressure of 50 mm Hg was maintained for one minute. This permits uninhibited arterial flow into the limb, while the venous outflow is compromised, resulting in an increased leg volume. On decompression of the thigh cuff, the leg volume decreases rapidly when the venous outflow is normal. In the presence of a functional venous obstruction, the leg volume will decrease more slowly. Normally, on decompression the outflow velocity is ≥25 mm/second.
Venous occlusion cuff applied around the thigh at a pressure of 50 mm Hg pools blood in the extremity and a cuff in the leg registers the velocity of the venous outflow after occlusion is released. Normal velocity is $\geq 25$ mm/second. If obstruction is present, the velocity will decrease.

**Surgical and endovascular interventions**

Prior to inclusion all patients eligible for RDVS had been treated conservatively with compression stockings and superficial venous surgery.

Both RDVS and EVI are procedures that require a hybrid suite and are performed under general anaesthesia with full anticoagulation.

RDVS is precision surgery requiring magnifying loupes and proper lightning. It is essential to treat obstruction before an antireflux procedure is performed. The following algorithm illustrates patient handling. (Fig. 5).
Fig. 5. The algorithm depicts the pathway from referral, conservative treatment and workout to the selected treatment according to the pathophysiological feature to correct.

**Surgical Procedures and technique**

*External and internal venous valve plasties*

The Internal venous valve plasty (IVVP) was first introduced by Kistner in 1968. Some years later he also developed the External venous valve plasty (EVVP). Especially in patients with PCVI it is possible to find valves amenable to repair. The feasibility of valve repair is determined by preoperative CDU and descending video venography.

A conventional approach is applied in the groin through a longitudinal incision and a posterior approach in the popliteal fossa by using an S-shape incision. The valve site and the commissural sites of the leaflets are identified by careful adventitial dissection.
IVVP requires a venotomy, either longitudinal or T-shaped. Special attention is needed to avoid injury to the leaflets. Single sutures of 7-0 polypropylene are placed to tighten the cusps laterally. The result of this plasty can only be tested after the venotomy has been closed. (Fig. 6).

Source: Paper I

Fig. 6. Internal venous valve plasty (IVVP) requires a venotomy. Sutures are placed to tighten the “floppy” valves.

EVVP avoids a venotomy but requires the clear visualization of the cusps and commissures through the vein wall. Angioscopy can be helpful in identifying the valve commissures and testing valve function. A continuous suture line of 5-7 stitches with polypropylene 7-0 is started at the cranial end of the valve to tighten the leaflets. This procedure is performed at both commissures. (Fig. 7).
Fig. 7. The surgical technique of external venous valve plasty (EVVP) assisted by angioscopy: a view of incompetent valve cusps and the first external suture placed in a commissure (a), external sutures in both commissures (b) and the finished valve repair (c).

The repaired valve, either by IVVP or EVVP, is then tested by the “strip-test” (Fig. 8) or angioscopy.

Fig. 8. The strip-test presses blood against a valve to test competency after a procedure.
Single plasty can be performed at the femoral or popliteal level. Multilevel plasties can be performed at both levels in the same extremity. The term multistation plasties refers to repairing more than one valve at the femoral level (common, superficial and deep femoral vein).

**Transposition**

Infrequently, a transposition may be considered, involving anastomosing an incompetent venous segment end-to-side, distally to a competent valve, for example the femoral vein anastomosed distally to a competent valve in the great saphenous or deep femoral vein. (Fig. 9).

![Fig. 9](image_url)

Source: Paper I

Fig. 9. Transposition involves taking an incompetent post-thrombotic vein segment and anastomosing it end-to-side, distally to a competent valve.

**Autotransplantation**

This technique can be used in those patients with SCVI in whom destroyed valves after DVT need to be replaced. The procedure requires that a competent valve is identified preoperatively with CDU in the axillary or the saphenous veins. A donor vein diameter <5 mm and signs of fibrosis/trabecula diagnosed by CDU and/or venography represent exclusion
criteria. A 6-8 cm. long vein segment containing a functioning valve is harvested. The donor venous valve function is tested peroperatively by injecting saline solution. The venous segment containing a competent valve is implanted as an interposition by using in-lay suturing technique (Fig. 10). This involves two end-to-end anastomoses with 6-0 polypropylene. We use a running suture, interlocking every other suture, to avoid a “purse-string” effect. The cranial anastomosis is performed first. The “strip test” confirms the competence of the transplant. The native vessel is “wrapped” around as reinforcement. Diameter discrepancy, thickening and fibrosis of the native vessel pose the major technical challenges in this procedure.

Source: Paper II

Fig. 10. Autotransplantation

The venous segment containing a competent valve (saphenous or axillary) is transplanted as an interposition by using in-lay technique.
**Endovascular venous intervention (EVI)**

The development of percutaneous endovascular techniques has made recanalization and stenting of chronic venous occlusions possible.

**Procedure**

Endovascular procedures should be performed in a hybrid suite. The availability of a wide range of vascular interventional guide wires, catheters, snares, balloons and stents is of upmost importance. General anaesthesia is recommended since the procedure may be time-consuming and predilatation of fibrotic and thickened veins can be painful. Therapeutic anticoagulation pre-, per- and postoperatively with low molecular weight heparin must be administered (dalteparin 100 IE/kg/ twice daily) followed by warfarin for three to six months. The access route is determined by the inflow and outflow conditions outlined by the imaging investigations. Ultrasound-guided puncture through the popliteal, femoral and jugular vein are favoured. (Fig. 11).

![Image of puncture of the popliteal vein](image)

Source: Paper III

Fig. 11. Puncture of the popliteal vein is performed with ultrasound guidance.
In some instances, it is necessary to combine access using crossover or through-and-through (jugular/femoral) technique to accomplish recanalization. By using a variety of guide-wires (hydrophilic and non-hydrophilic), rotation and support from a catheter, recanalization is usually accomplished. Collaterals are a sign of high pressure rather than compensation. Predilatation to the intended diameter and disruption of fibrotic trabeculae with high pressure balloons is an important part of the procedure. Resilient stenosis/occlusions required the use of up to 30 atmospheres in pressure to give in. (Fig. 12a & b).

![Fig. 12 a & b.](image)

Source: Paper III

a. Baseline venography shows occlusion of the left iliac and femoral veins, with pelvic, paravertebral and suprapubic collaterals.  
b. A resilient stenosis/occlusion needing high-pressures to disrupt fibrotic obliteration (see arrows).
The use of large diameter (14-20 mm) self-expanding stents is recommended with at least 2 cm overlap. Inflow must be secured even if it implicates stenting across the inguinal ligament. (Fig. 13 a, b & c) (27). The stent is deployed at least 1-2 cm into the vena cava to secure outflow and to prevent stenosis in the confluence. Lesions including the proximal part of the common iliac veins and the inferior vena cava necessitates stenting of all three.

Fig. 13 a, b & c

a. Large diameter, self-expanding stents are chosen, tapering from 18 to 12 mm. The stents are deployed well into the vena cava (1-2 cm) to avoid re-stenosis. b. It is essential to secure inflow even if it means crossing the inguinal ligament with a stent (see arrows).
**Indications**

The main indications for endovascular recanalization and stenting in deep venous obstruction are venous claudication and venous leg ulcer (C3-C6). The involvement of inferior vena cava and/or superficial femoral vein does not represent a contraindication. On the other hand, post-thrombotic changes that extend to the popliteal vein will result in compromised inflow jeopardizing a durable procedure.

**Source of material for each paper**

The material for papers I and II was collected from 1800 referrals with chronic venous insufficiency during a ten-year period (1993-2004). For paper III another 10 year period (2000-2009) and 2400 referrals were required. Patients were categorised according to CEAP following a standard work-up constituting a combination of hemodynamic measurements and imaging techniques.

Altogether 17 patients with primary deep reflux (paper I), 32 with secondary deep reflux (paper II) and 34 with deep venous obstruction (paper III) were included.

**Material and methods for each paper**

Paper I: External Venous Valve Plasty (EVVP) in Patients with Primary Chronic Venous Insufficiency (PCVI)

Patients with Primary Chronic Venous Insufficiency (PCVI) were investigated with ascending venography and descending video venography and 17 were selected for EVVP. Six patients
were C4, four C5 and seven C6. All had deep reflux and high levels of AVP (above 60 mm Hg).

Paper II: Venous Valve Reconstruction in Patients with Secondary Chronic Venous Insufficiency

Secondary chronic venous insufficiency (SCVI) was diagnosed on the basis of the clinical history, CDU and AVP findings. A group of 121 patients with poor response to conventional treatment were selected and further investigated with ascending venography, descending video venography and air plethysmography. Thirty-two patients with venous reflux who did not have venous outflow obstruction were identified as amenable for reconstructive deep venous surgery (RDVS) and constitute the patient group included in the present study. Forty-three procedures were performed in 32 patients. Twenty-one patients received a single procedure and 11 patients multiple procedures (all multilevel). Several different techniques were used, but in the majority of cases a venous valve autotransplantation was performed (32/43). External venous valve plasty and venous transposition were combined with transplant and/or used alone (table 3, side 479, paper II).

Paper III: Stenting for Chronic Post-Thrombotic Vena Cava and Iliofemoral Venous Occlusions: Mid-term Patency and Clinical Outcome

During the period 2000-2009, 2400 patients with severe CVI were initially evaluated with colour duplex ultrasound (CDU) and ambulatory venous pressure measurement (AVP). Fifty-nine patients with severe symptoms including venous claudication, oedema, pain and leg ulcer suggestive of venous outflow impairment were further investigated with ascending venography (AV), venous occlusion plethysmography (VOP) and CT venography or transfemoral/popliteal venography. The severity of these symptoms rendered these patients
incapable of functioning at work and/or in other physical activities, representing indication for endovascular treatment. Twenty-five patients were found unavailable for endovascular treatment due to the extension of the post-thrombotic occlusion to the popliteal level that precluded adequate restoration of venous blood inflow. The remaining 34 patients had chronic venous occlusions after DVT with open popliteal and distal femoral veins, and were chosen for treatment and included in the study. The severity of the symptoms was assessed using the venous clinical severity score (VCSS) (Table 3).

**Clinical and hemodynamic outcomes**

CDU is used to assess competency (normal valve closure time with retrograde flow ≤0.5 seconds) of the reconstruction and venous pressure measurements to quantify the hemodynamic improvement. Patency is determined by the time a stent remains opened verified by CDU. Durability is defined as the time a reconstruction remains competent assessed with CDU.

**Clinical outcome measures for papers I, II and III**

- Symptom relief
- Ulcer-healing
- Ulcer-free period
- Venous clinical severity score (VCSS) before and after a procedure
- Endpoint was defined as recurrence of symptoms/ulcer

**Hemodynamic outcome measures**

- Competency assessed by CDU and AVP measurement
- Patency assessed by CDU and VOP
- Durability (time to endpoint)
**Endovascular outcome**

- Primary success defined as achieved recanalization, deployment of stents and venographic signs of good inflow and run-off with absence of collaterals
- Patency (venography)

**Results for each paper**

Paper I: External Venous Valve Plasty (EVVP) in Patients with Primary Chronic Venous Insufficiency (PCVI)

In PCVI patients in whom EVVP was performed an ulcer-healing rate of 4/7 (57%) was accomplished within three months. The rate of competency at three and five years was 64% and 52%, respectively. Multiple valve plasties at the same level (multi-station plasties) seemed to yield the longest durability, but the number of patients included are too small to conclude.

The ulcer-free period was a median of 55 months (12-72).

Paper II: Venous Valve Reconstruction in Patients with Secondary Chronic Venous Insufficiency (SCVI)

There was a need to combine different techniques in one third of SCVI patients. Clinical success (defined as symptom relief and/or ulcer-healing) was accomplished in 78% (25/32). In 68% (13/19) the ulcer healed after the procedure with an ulcer-free period of median 36 months (6-108). Reconstructing the popliteal level appears to be a key factor (p=0.014). Popliteal reconstruction and hemodynamic improvement together provided the best durability and the longer recurrence-free period. Multiple repairs seemed to give longer durability, although this finding did not reach statistical significance.
Successful primary recanalization and stenting was accomplished in 94% (32/34). Venous claudication and pain resolved in those successfully recanalized. Four ulcers healed after three months. The clinical improvement recorded by using the VCSS score was statistically significant for both C3 and C4 groups (p=0.0001 and p=0.002, respectively).

Symptom recurrence occurred in 13 patients after a median of 12 months (range 0.5-19.0) and was investigated with both CDU and trans-popliteal venography. In two cases, a significant stenosis compromising the inflow was demonstrated. New stenting was performed in both, supplemented by an A-V fistula in one of the subjects. In six patients with occlusion, catheter-based thrombolysis (CBT) and additional stenting were performed with construction of an A-V fistula in three of the subjects. In the remaining five patients with occlusion, re-intervention was considered contraindicated due to poor inflow conditions.

The 2-year primary patency rate was 67% (14/21), primary-assisted patency was 76% (16/21) and secondary patency was 90% (19/21).

By survival curve analysis (Kaplan-Meier), we attempted to identify factors that could influence patency. Stents deployed above the inguinal ligament showed a better primary patency than those crossing the inguinal ligament, but secondary patency was not different. Thrombophilia did not seem to influence patency.
Review of the results reported in the literature after RDVS and EVI

The historical landmark for the start of RDVS is the description of the internal venous valveloplasty in 1968 by Robert L. Kistner (28) to treat deep venous reflux. The same author described venous transposition in 1979 and the external or transcommisural technique in 1990, all three for primary deep venous insufficiency (29). Eriksson demonstrated the influence of the deep femoral vein in venous hemodynamic in 1988 (30).

Initially valveloplasty was performed at the femoral level, but the importance of the popliteal vein was soon recognized and verified in our department (31). Secondary chronic venous insufficiency poses a different surgical challenge. Taheri and Raju reported the first series of autologous venous valve transplant from the brachial and axillary vein to correct post-thrombotic reflux (32,33). However, auto-transplantation is associated with problems related to size discrepancy and lack of donor sites (38).

Raju introduced multilevel approach, with reconstruction in both the femoral and popliteal level improving results in the SCVI group.

In 2006, Maleti incorporated the construction of a neovalve by dissecting the thickened intima from the adventitia to create two leaflets, potentially representing a major breakthrough in surgical technique for SCVI patients. Some of the technical problems related to auto-transplantation are avoided through the neovalve procedure (34). Currently, lacking reproducibility of long-term results represents a challenge.

A Cochrane review by Hardy et al. from 2004 and revised in 2009, found no evidence to recommend RDVS in the treatment of CVI due to the lack of randomized clinical trials (RCT).
Clinical improvement and ulcer-healing are reported to be better in the PCVI group than SCVI group (33,35,36).

Maleti et al. reviewed the results after RDVS in 655 patients from 10 different materials (41). The indication was patients classified as C4, C5 or C6, not responding to the conventional treatment. The clinical improvement was approximately 80% and ulcer-healing rates approached 70%. Ulcer/symptom recurrence occurred in nearly 25% after 3 years follow-up (31,35,37–44).

Currently, the most important challenge is to improve the durability of RDVS, especially considering the relative young age of these patients (average 48 yrs.).

Åkesson et al. published in 1997 one of the first papers describing EVI with venous stents in chronic iliac vein occlusions. Raju and Neglen followed with several papers, addressing issues like crossing the inguinal ligament, extending into the inferior vena cava to gain outflow and recanalizing occluded inferior vena cava (IVC). The results were so favourable that the question was raised whether treatment of reflux was required to accomplish ulcer-healing (45–48).

Several publications have contributed to the consolidation of endovascular treatment in managing venous obstructions (49).

In the obstruction group re-establishment of venous outflow has resulted in ulcer-healing and improvement of severe symptoms such as venous claudication, oedema and pain (50,51). The good midterm patency and clinical outcome has led a group of relative young patients back to work and a productive life.
Discussion

The level of scientific evidence regarding deep venous surgical and endovascular intervention in the treatment of CVI has been limited due to papers reporting single centre experience, small materials and heterogeneous groups of patients having undergone several simultaneous procedures in the different vein systems.

In order to avoid mixed materials and facilitate the interpretation of our results, only non-responders to conventional treatment were submitted to RDVS. Thus, the reported ulcer-healing rates of 57% for the PCVI group and 68% for the patients with SCVI are related to RDVS alone.

The indication for RDVS in other reports was mainly C5 and C6 patients. We have extended the indication to C4 patients with severe symptoms and a high AVP (>60 mmHg), since intervention at this stage may reduce disease progression.

Our results with EVVP for PCVI compare favourably with the literature (42,52). Raju et al. reported a cumulative competence period and ulcer-free interval of 63% after 30 months with a similar technique. Tripathi et al. showed an ulcer-healing rate of 50% and competence of 31% after 2 years. Our 3 and 5-year competency after EVVP was 64% and 52%, respectively.

As to the SCVI group, our long term results are similar to those reported in the literature by Masuda et al. (36), but are inferior to those of Raju (40). We were unable to prove that competency of the saphenous vein as a donor is better than the axillary, but have demonstrated that saphenous veins can actually be used effectively. The saphenous vein was donor in 26 of 32 cases in this study.

Reconstructing the popliteal level appears to be a key factor (p=0.014) in accomplishing hemodynamic improvement. Popliteal reconstruction resulting in hemodynamic improvement provided the best durability and the longer recurrence-free period. Regardless the clinical stage it would appear that the durability of the reconstruction stabilizes at around 24 months.
Internal valve plasty is regarded as more durable, but has some disadvantages (40).

A venotomy is required with the risk of cusp damage and assessment cannot be done until the venotomy is closed. External trans-commissural valve plasty may be as effective as the internal technique but it requires adventitial dissection. Comparative studies have not been carried out.

The available donor sites for autotransplantation are axillary veins and great or small saphenous veins. Sometimes the axillary vein valve is incompetent after harvesting and a bench plasty is required. Due to their anatomical location, saphenous valves are exposed to a higher pressure than the axillary valves. Thus, the saphenous vein is probably best suited as valve donor.

The relatively short durability of RDVS raises concern since the average age of a patient requiring RDVS is approximately 48 years.

For EVI in venous obstruction, our 2-year primary patency was 67%, the primary-assisted patency was 76% and secondary patency was 90%. This is better than a comparable previous report with a primary patency of 49%, primary assisted patency of 62% and secondary patency of 76% (51). Other articles published address both stenosis (non-occlusive lesions) and occlusions; furthermore, aetiology is mixed. The mid-term patency rate reported by Hartung et al. compares with our results, but this series included only 10 post-thrombotic cases of a total of 44 patients (53). In a material published by Neglen et al. (54) in 2007, 45% of 982 lesions were post-thrombotic, but only 6% were occlusions. Their patency is comparable with ours at 24 months. Kolbel et al. (55) published in 2009 results of a series of 66 limbs where 66% lesions was post-thrombotic with primary patency of 67%, assisted primary patency 75% and secondary patency 79% at 2 years.
The size of our series may represent a lack of power, but considering the number of equivalent cases (total occlusions after DVT) in other publications, converted to cases per year, the figure varies from one to six per year. We report 3.7 per year.

Due to post-thrombotic changes also in the common femoral vein, crossing the inguinal ligament with stents is often necessary (in 21 of 32 subjects). Even though it may negatively influence primary patency, placing stents distally improves inflow and thus better secondary patency. Neglen published in 2008 a paper assessing the risk of placing stents across the inguinal ligament, concluding with that the risk of stent fracture was low (0/77 after 54 months (48).

In our study, all patients with chronic venous obstruction and leg ulcer, also had reflux. In 4 of 7 subjects the ulcer healed within 3 months after treating the obstruction. The other 3 patients needed an anti-reflux procedure to accomplish ulcer-healing. This illustrates the need to use different techniques in the same patient to accomplish good clinical results. In accordance with others, our experience is that the hemodynamic tests for venous obstruction currently available lack accuracy and sensitivity, correlating poorly with clinical symptoms. Consequently, imaging techniques and clinical symptoms constitute the main factors both for the evaluation of indications and for outcome following treatment. Development of hemodynamic tests for venous obstructions is an area that deserves further research.

The experience gained through many EVI procedures performed in the last ten years has opened the possibility to expand and treat patients who have a chronic occluded inferior vena cava. Primarily these are young patients with a variety of symptoms sometimes traceable back to infancy and sometimes with bilateral iliac DVT as the first manifestation. MRV or CTV often indicate atresia or agenesis of the IVC. However, the diagnosis is challenged in a series of 20 cases of recanalization and stenting since 2011 (unpublished data). Our approach with multiple access sites (jugular and femoral) and recanalization supports that in some cases the
radiological absence of the IVC may be due to previous thrombosis. Mid-term results are promising with a primary patency of 67% and secondary patency of 83% after 2 years.

Despite the fact that non-invasive imaging techniques such as CT- and MR venography have remarkably improved providing detailed information of the vein system, it is still limited to morphological descriptions. The investigations are performed supine reducing the possibility for hemodynamic assessment.

The patients included in the material for the first papers were all non-responders to conventional treatment. Therefore, the ulcer free period accomplished by RDVS could represent an actual socio-economical gain to be determined. This particular topic was not within the scope of the present study.

**Lessons learned and limitations**

The role and place of RDVS and EVI in the treatment of CVI has become clearer but is currently not yet widely implemented. The need for advanced vascular laboratory, targeted imaging techniques, pathophysiological knowledge and necessary surgical skills may be possible explanations. All of these are attainable if vascular units prioritize this field and engage in a multidisciplinary approach.

**CONCLUSIONS**

Detailed knowledge of the underlying venous pathophysiology is mandatory in planning effective treatment in patients with CVI.

The CEAP classification provides the framework for a systematic work-up. A vascular laboratory is necessary to investigate CVI patients.
EVVP represents an alternative surgical treatment for selected patients with PCVI. The durability of this technique seems to be related to clinical severity and the multiplicity of repairs.

Knowledge of the various VVR techniques and combinations achieve the best hemodynamic results.

Endovascular intervention is not only feasible, but also safe in the treatment of venous obstruction. The use of the VCSS score showed significant clinical improvement after successful recanalization and stenting.

Reconstructive deep venous surgery including valve plasty, transplant and neovalve construction has limitations with the rare availability of valves to be repaired, lack of donor sites and inadequate conditions to create new valves.

**Future developments**

The possibility of performing CTV/MRV with the patient standing may add hemodynamic information to the detailed imaging obtained at present time. The quantification of inflow and runoff necessary to secure stent patency and assessment of the combination reflux/obstruction in partially recanalized post thrombotic segments are two potential areas where this modality could help. There is need of more research to develop reliable techniques for the hemodynamic assessment of obstruction.

Endovascular solutions have rapidly evolved in the last decades. Several attempts to create a stent-mounted, percutaneous implantable valve are reported in the literature, hereunder some examples:

- Z-stent-based venous valves
- Bovine jugular vein valve mounted inside an expandable stent
• Square stent-based bio-prosthetic venous valve
• Percutaneous glutaraldehyde-preserved venous valve
• Percutaneous venous valve construction

All of these devices are still at the experimental stage. The challenge is to create a device that does not migrate over time, and which both, is non-immunogenic and non-thrombogenic (56,57).

At present time open surgery continues to be the most viable alternative when deep venous reconstruction is necessary to solve the most severe cases of CVI (57). The neovalve construction is a technique that makes use of the vein wall thickening caused by the inflammation in a DVT process (34). It solves the problems of availability of adequate donor sites and has become an alternative for SCVI patients in addition to autotransplantation.

Reconstructive deep venous surgery represents a technical challenge since it requires precision and the use of magnification 2.5 to 3.5 times.

The use of natural, human scaffolds to produce tissue engineered venous segments containing functioning valves may revolutionize the surgical correction of deep venous reflux in patients with chronic venous insufficiency and leg ulcer (58,59). This tissue engineering procedure produces the functioning unit “valve-conduit” and surgery will only be used to implant it.

We collaborated in an in vitro study that demonstrated the successful preservation of valve function of tissue-engineered human valve-bearing vein segments (60). Further histological structure, imaging and cell characterization studies need to be performed before clinical use.

Another futuristic concept is 3D bioprinting, creating implantable blood-vessels, skin tissue or complete solid organs lays in the future. Recently, a method for scaling up tissue engineering through the 3D printing of thick vascularized tissue constructs, complete with stem cells, extracellular matrix and circulatory channels, was reported by Harvard’s school for
engineering and applied sciences (SEAS) and the Wyss institute for biologically inspired engineering.
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