Clinical and haemodynamic sequelae of deep venous thrombosis: retrospective evaluation after 7–13 years

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1. In contrast to the extensive documentation on diagnosis and treatment of deep venous thrombosis (DVT), information about long-term complications, like the post-thrombotic syndrome (PTS), is scarce. Most studies report on clinical examination only, whereas adequate haemodynamic investigation is lacking. Therefore 81 patients with venographically confirmed lower extremity DVT were clinically and haemodynamically reexamined 7–13 years after DVT (mean 10 years) to assess PTS. Interest was focused on the relation between clinical and haemodynamic PTS and the relation between location of the initial DVT and incidence of PTS.

2. Clinical signs and symptoms of PTS were classified according to the latest consensus of the international consensus committee on chronic venous disease. Non-invasive venous vascular laboratory tests were performed to assess the venous outflow resistance and calf muscle pump function (CMP). CMP was determined by the supine venous pump function test (SVPT).

3. Clinically only 20 of 81 patients (25%) were asymptomatic, 34 (42%) had mild PTS (class 1–3), 25 (31%) moderate PTS (class 4) and 2 (2%) severe PTS (class 5–6); 57% had an abnormal CMP. Both the severity of clinical symptoms and the haemodynamic abnormalities were related to the location of the initial thrombus. Of the patients with distal DVT 11% developed moderate clinical PTS and 39% developed an abnormal CMP. CMP and difference in CMP between post-thrombotic and non-thrombotic leg were significantly related to the different classes of PTS.

4. This study indicates that 7–13 years after DVT 31% of the patients had moderate and 2% had severe clinical PTS, while 57% of the patients had abnormal haemodynamic findings (both related to the initial site of the thrombosis). Secondly, it reveals that the risk of PTS after distal DVT is not negligible, which causes concern about not diagnosing and treating patients with distal DVT. Thirdly, we have demonstrated that a functional test, such as the SVPT, is a sensitive test to assess post-thrombotic damage. Therefore its use as a screening tool after a period of DVT should be investigated to select patients at risk of PTS.

INTRODUCTION

Patients who experience an episode of deep venous thrombosis (DVT) are at risk of developing several sequelae, like the post-thrombotic syndrome (PTS). The incidence of PTS after a first period of DVT varies in the literature between 10 and 100%. There are conflicting reports concerning the relationship between the location of the initial DVT, the prevalence of late symptoms and objectively measured deep venous insufficiency at follow-up. Studies are difficult to compare because of different periods of follow-up, initial therapy and definition of PTS (clinical compared with haemodynamic). Most studies have performed clinical examination only, and adequate functional examination, especially a longer period after DVT, is lacking.

The incidence of PTS after distal DVT varies in the literature between 0 and 60% [1–5]. Except for Franzcek et al. [2] and Eichlisberger et al. [5] the other follow-up studies evaluated a short period (mean 0.5–7 years) [1, 3, 4, 6–17]. As it possibly takes a longer time to develop PTS after distal DVT, we investigated patients 7–13 (mean 10) years after a first period of DVT.

Two mechanisms may account for the development of PTS: persistent outflow obstruction due to residual outflow obstruction, and valvular insufficiency, which allows reflux of blood and prevents efficient functioning of the calf muscle pump, resulting in venous hypertension. Through a mechanism which has not been fully elucidated, a longstanding transmural venous pressure exceeding 20–30 mmHg gives rise to changes in the microcirculation. Subse-

Key words: calf muscle pump function, deep venous thrombosis, post-thrombotic syndrome, strain-gauge plethysmography, supine venous pump function test.

Abbreviations: CMP, calf muscle pump function; DVT, deep venous thrombosis; IVPMs, invasive venous pressure measurements; PTS, post-thrombotic syndrome; P–V, pressure-volume relation; SVPT, supine venous pump function test; VER, venous emptying rate; VOR, venous outflow resistance.

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sequently these changes may lead to the various clinical symptoms of PTS, such as oedema, trophic skin changes and ulceration. A major difficulty has been to assess objectively the severity of the clinical problems and to relate this severity to the site and magnitude of the haemodynamic changes in the venous system. It has been demonstrated that with invasive venous pressure measurements (IVPMs) an elevated lower extremity ambulatory pressure can be measured that is characteristic for PTS [18, 19]. A correlation of $r = 0.79$ has been found between IVPMs and severity of PTS [19]. However, the specificity and discriminating power of IVPMs for the presence or absence of PTS is questionable. Because IVPMs are invasive, impractical for routine screening and difficult to standardize, the supine venous pump function test (SVPT) was recently developed in our hospital. We have demonstrated that this non-invasive method may replace IVPMs in the assessment of calf muscle pump function (CMP) and that its reproducibility is good [20].

In the present study we have used the combination of clinical examination and non-invasive functional investigation to determine the clinical and haemodynamic status of patients 7–13 years after venographically confirmed lower extremity DVT, and related the findings to the initial DVT. Special interest was focused on differences in long-term sequelae when thrombosis occurred in the deep veins of the calf compared with more proximal veins. We also assessed the SVPT to detect damage of the venous system after a period of DVT and related this to the severity of clinical PTS.

**PATIENTS AND METHODS**

In the period 1983–1989 256 patients were diagnosed by venography as having a first acute DVT of the leg. At follow-up (1996), 92 of these patients had died, 33 were aged over 80 or too ill for reinvestigation, 28 patients could not be traced and 22 refused reinvestigation. Consequently, 81 patients were studied 7–13 years (mean 10 years) after venographically confirmed lower extremity DVT. At the time of admission all patients had been promptly treated with heparin intravenously and oral anticoagulants 1–3 days later. The duration of heparin therapy was 5–10 days and oral anticoagulants were given for at least 3 months. All patients had been instructed to wear graduated compression stockings.

The study was approved by the ethics committee of the hospital and written informed consent was obtained from each subject. Each patient was asked about subjective criteria of PTS: heaviness, restless legs, pain, oedema, itching, cramps and tingling. The acute symptoms, risk factors, complications, treatment and concomitant diseases were also noted with emphasis on the use of elastic stockings and duration of therapy. Secondly the patients were examined for the objective clinical criteria of PTS (varicosis, oedema, corona phlebectatica, pigmentation, atrophy blanche, ulceration) and classified according to the updated consensus [21]. PTS was classified as absent in the case of class 0, mild in the case of class 1–3, moderate in the case of class 4 and severe in the case of class 5–6. Because of the small number of patients in class 5–6, patients of class 4–6 are analysed together.

The investigators classifying the patients in the study were blinded for the initial venographic findings. The extent of the initial DVT was determined by independent review of the original venograms by standard techniques [22]. The criteria for DVT were intraluminal filling defects in the deep veins in at least two projections. The lower limb veins were divided into three segments: the distal veins, proximal veins (including popliteal and femoral veins) and iliac veins.

**Vascular testing**

*Venous outflow resistance (VOR).* Detailed information about the measurement of VOR has been published [23, 24]. The subject lies in a relaxed supine position. Strain-gauges are fitted around both calves and connected to the plethysmograph. Pneumatic cuffs are placed around the thighs. After inflation of the cuffs the venous volume increases gradually. Maximum volume is achieved when the venous pressure equals the effective congestion pressure. At this moment the cuff-pressure is released, resulting in a volume decrease that is measured by the plethysmograph. At the point 0.5 s after pressure release the tangent to the volume record is drawn and the slope is converted into a flow rate, which is the venous emptying rate (VER). This procedure is performed at cuff pressures of 50, 40, 30, 25, 20 and 15 mmHg. Subsequently, the corresponding VER values are plotted against the effective cuff pressures. The slope of the line straight through the points gives the proportionality between outflow rate and pressure. This line intersects the pressure axis at an angle $\beta$. By analogy with Ohm’s law the VOR is calculated as $1/\tan(\beta)$. The VOR value is expressed in resistance units: $(\text{mmHg} \times \text{min})/\%$. In a previous study normal values were determined at $<0.80$ resistance units [25].

The non-thrombotic leg was used as the control leg. The measurement is controlled and analysis is performed by a personal computer, which makes it an objective technique.

**SVPT.** The supine patient has the knees slightly bent at an angle of $120^\circ$ while the feet rest against a foot support 10–15 cm above the bed. Strain gauges are strapped around the lower leg. Inflatable cuffs are placed around the thighs. Measurements start with inflation of the cuffs to 50 mmHg. This results in a gradual venous volume and pressure increase distal to the site of the cuff compression due to the venous occlusion. Maximum volume is achieved
when the venous pressure equals the effective congestion pressure. Subsequently the patient is instructed to perform maximum dorsiflexion of the feet followed by maximum plantar flexion. In total, ten such movements are made in 20 s. This muscle pump action causes blood to be squeezed beyond the cuff, resulting in volume decrease of the limb. This procedure is repeated five times at different congestion pressures. Additionally, a pressure-volume (P-V) relation is determined by measuring the ensuing relative volume increase at five different cuff pressures. By plotting the volume changes against congestion pressure, the P-V relation is found which is characteristic for the limb at that strain gauge location. Using this P-V relation, the volume reduction during exercise can be converted into a pressure decrease. Pressure decrease \( (P_1 - P_2) \) is expressed as a percentage of the initial pressure \( P_1 \) before the exercise was started and is a measure of CMP: \( \text{CMP} = \left( \frac{P_1 - P_2}{P_1} \right) \times 100\% = \%_{\text{pf}} \). The procedure is fully controlled by a personal computer.

This SVPT was recently validated by comparison with IVPMs [20]. Reproducibility of the test is good (coefficient of variation = 9%, coefficient of repeatability = 13%) and normal values of the SVPT have been determined to be > 60%pf.

Using the SVPT both legs were examined. The non-thrombotic leg was used as the control leg.

### Statistical evaluation

Statistical analysis was performed using one-way analysis of variance (Scheffe's F-test). Independent t-testing was applied when appropriate. Differences were considered to be significant at \( P < 0.05 \).

### RESULTS

Eighty-one patients participated in the study, 54 male and 27 female patients (ages ranging from 21 to 80 years, mean 52 years). Nine (11%) patients developed recurrent DVT, diagnosed with venography. Risk factors for DVT among the patients were recent surgical procedure (25), leg trauma (11), familial history of DVT (17), oral contraceptives (12), prolonged bedrest (11), Crohn's disease/colitis ulcerosa (5), malignancy (3) and pregnancy (4). No risk factor for DVT was detected in 23 patients.

Location of initial thrombosis, current age distribution and haemodynamic status of the patients are listed in Table 1. VOR, indicating obstruction, was elevated in only nine patients (11%). CMP was not significantly different. Remarkably, 53% of the study patients were still wearing compression stockings: 61% of them had clinical class 4–6 PTS and 74% had an abnormal CMP.

Figure 1 shows the relation between the initial site of DVT and clinical symptoms of PTS. Overall, 75% of the patients had clinical signs of PTS (42% class 1–3, 31% class 4 and 27% class 5–6) and 57% had an abnormal CMP. The occurrence of moderate to severe clinical symptoms (class 4–6) ranged from 11% in patients with distal DVT to 47% in patients with iliac DVT.

Table 2 and Fig. 2 show that the haemodynamic abnormalities were generally related to the proximal extent of the thrombus and to the degree of clinical PTS. The occurrence of a low CMP (<60%pf) ranged from 39% in patients with distal DVT to 65% in patients with iliac DVT. CMP was significantly different between different classes of clinical PTS, as indicated in Table 2. The severity of the symptoms was generally related to the magnitude of the measured haemodynamic changes. Almost all

<table>
<thead>
<tr>
<th>Initial DVT</th>
<th>n</th>
<th>Age (years) (range)</th>
<th>Mean CMP (%pf) (SD)</th>
<th>CMP &lt; 60%pf (%)</th>
<th>ΔCMP (%PF) (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal</td>
<td>18</td>
<td>53 (33–73)</td>
<td>64 (21)</td>
<td>39</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Proximal</td>
<td>35</td>
<td>52 (28–76)</td>
<td>54 (23)</td>
<td>63</td>
<td>10 (14)</td>
</tr>
<tr>
<td>Iliac</td>
<td>19</td>
<td>53 (21–80)</td>
<td>47 (23)</td>
<td>65</td>
<td>18 (15)</td>
</tr>
<tr>
<td>Total</td>
<td>81</td>
<td>52 (21–80)</td>
<td>56 (23)</td>
<td>57</td>
<td>10 (15)</td>
</tr>
</tbody>
</table>
Table 2. Haemodynamics related to site of initial DVT and to the different classes of clinical PTS. ΔCMP = difference in CMP between thrombotic and non-thrombotic leg. *P < 0.003; **P < 0.007.

<table>
<thead>
<tr>
<th>Initial DVT</th>
<th>Class PTS</th>
<th>n (%)</th>
<th>Mean CMP (%pl) (SD)</th>
<th>ΔCMP (%pl) (SD)</th>
<th>Mean CMP of control leg (%pl) (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal</td>
<td>0</td>
<td>7 (39)</td>
<td>74 (17)</td>
<td>0 (8)</td>
<td>68 (18)</td>
</tr>
<tr>
<td></td>
<td>1–3</td>
<td>9 (50)</td>
<td>61 (23)</td>
<td>5 (10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4–6</td>
<td>2 (11)</td>
<td>45 (9)</td>
<td>14 (23)</td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>0</td>
<td>10 (29)</td>
<td>57 (24)</td>
<td>12 (18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–3</td>
<td>12 (34)</td>
<td>65 (17)</td>
<td>3 (12)</td>
<td>64 (22)</td>
</tr>
<tr>
<td></td>
<td>4–6</td>
<td>13 (37)</td>
<td>45 (22)</td>
<td>14 (12)</td>
<td></td>
</tr>
<tr>
<td>Iliac</td>
<td>0</td>
<td>2 (11)</td>
<td>64 (36)</td>
<td>2 (11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–3</td>
<td>8 (42)</td>
<td>55 (21)</td>
<td>13 (9)</td>
<td>65 (19)</td>
</tr>
<tr>
<td></td>
<td>4–6</td>
<td>9 (47)</td>
<td>38 (17)</td>
<td>24 (15)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>20 (25)</td>
<td>62 (25)</td>
<td>6 (16)</td>
<td>68 (24)</td>
</tr>
<tr>
<td></td>
<td>1–3</td>
<td>34 (42)</td>
<td>61 (23)</td>
<td>7 (12)</td>
<td>67 (18)</td>
</tr>
<tr>
<td></td>
<td>4–6</td>
<td>27 (33)</td>
<td>45 (20)**</td>
<td>17 (16)**</td>
<td>62 (19)</td>
</tr>
</tbody>
</table>

patients with clinical class 4–6 PTS scored below 60% pf.

The haemodynamic status of the leg with the positive venogram was compared with that of the contralateral limb (no symptoms, no venogram). Table 2 and Fig. 2 show the differences in pump function between the thrombotic and non-thrombotic leg for different classes of clinical PTS. It shows that the mean CMP of the non-thrombotic leg was equal in all categories of patients. The difference in CMP between the thrombotic and non-thrombotic leg was significantly different for patients with proximal and iliac DVT and for patients with class 4–6 PTS.

**DISCUSSION**

The current study supports previous observations that many patients with DVT have long-term sequelae typical of PTS. Seven to 13 years after DVT 31% of the patients had moderate PTS (class 4), although only two patients (2%) developed an ulcer; 89% of the limbs returned to normal VOR, which means that there was no proximal obstruction. CMP was abnormal in 57%. Comparison of our haemodynamic abnormalities with the literature is difficult because in most studies no, or other types, of haemodynamic investigations have been performed.

The relationship between the site of thrombosis and the frequency or severity of PTS has received only limited attention in the literature. Some investigators have shown that the incidence of clinical PTS correlated with the site of the original thrombus [1, 3–5, 7, 26], in contrast to others [8, 15, 17, 27]. We demonstrated a relation between the initial site of DVT and both clinical and haemodynamic signs of PTS.

Remarkably, 53% of the patients were still wearing compression stockings on a regular basis, some of them because it was advised to wear compression stockings lifelong, but most of them because of complaints. This study was not designed to prove the efficacy of compression therapy in the prevention of PTS in a randomized fashion. However, in the group with class 4–6 PTS only two patients developed a venous ulcer. This might indicate that in patients with moderate signs of PTS compression stockings are able to prevent ulcers. It has yet to be determined whether any therapeutic intervention is effective in preserving venous valve function after DVT.

Of greatest interest in the present study is the percentage of post-thrombotic changes in patients with DVT limited to the calf; 11% of these patients showed class 4 PTS and 39% showed an abnormal CMP. This is an important issue concerning the present techniques to diagnose DVT. Compression ultrasound has currently almost replaced veno-
graphy as the gold standard for the detection of DVT. It has been suggested that only distal DVT extending to proximal should be detected and that DVT limited to the calf should not be treated, because the risk of pulmonary embolism is negligible [28–30]. From the current study it is clear that the risk of PTS after distal DVT is considerably less than after more proximal DVT, but should not be neglected, which causes concern about not diagnosing and not treating patients with distal DVT. One might consider providing patients with distal DVT at least with adequate compression stockings. In the future randomized follow-up studies concerning distal DVT should be performed, comparing treated with non-treated patients.

No single test has yet been accepted as the ideal non-invasive measure of venous function [31]. Different kinds of techniques have been used in assessing PTS, such as Doppler [2], duplex [11, 32–36], photoplethysmography [37–39] and air plethysmography [40]. All of these techniques measure obstruction or reflux, but not venous pressure. It is supposed that the haemodynamic factor that causes long-term damage is venous hypertension, caused by a decreased CMP. The period after which clinical signs arise is different in every individual and is dependent on other mechanisms of compensation. So, in an early phase after DVT, there might be venous hypertension, but no clinical signs yet. Measurement of a decreased CMP might predict which patients are at risk of developing clinical PTS. For measuring CMP, IVPMs are still the gold standard.

We recently developed a non-invasive plethysmographic test (the SVPT) which was able to replace the IVPMs in measuring CMP [20]. CMP is measured as the pressure decrease caused by tip-toe movements as a percentage of the initial pressure. A unique element is the translation of volume changes into pressure changes by using a P–V relation. We used this objective test to assess functional abnormalities (decreased CMP) in this study.

The SVPT values were generally related to the presence of clinical post-thrombotic changes. CMP and difference in CMP between thrombotic and non-thrombotic leg were significantly different in several classes of PTS (Table 2, Fig. 2). Thus the SVPT might be of value to detect damage of the deep venous system, for example as a screening test after a period of DVT. Patients with a low CMP might be at risk of developing PTS, one should be alerted in particular if there is a large difference between the thrombotic and non-thrombotic leg after a period of DVT. This test might also be a useful tool to test the efficacy of different kinds or durations of therapy, such as oral anticoagulants and compression stockings.

Figure 2 shows that there is an overlap in values of the SVPT in the different classes of PTS. An explanation for the normal CMP in patients with clinical PTS might be that it is due to a purely superficial venous insufficiency, since the SVPT predominantly measures the deep venous system. An explanation for abnormal CMP in patients without or with a mild clinical PTS might be the consequent use of compression stockings, which may prevent development of clinical PTS. Another reason might be that venous hypertension exists in these patients, but clinical signs have not arisen yet.

There are some weaknesses in our study. First, the study is retrospective. Instead of consecutive patients in a prospective follow-up study, retrospective long-term studies frequently include both a limited number and a selection of patients. Because of this selection the results might be biased, because the patients lost to follow-up could be different from those actually followed up. Selection, although present, is minimized in our study because almost 80% of the patients that we invited took part, so not just successfully or unsuccessfully treated patients have been included. Also we included patients of different ages (mean 53.7, range 25–80 years) and with a sufficient distribution in initial sites of DVT. A second weakness is the fact that the discriminating power of the SVPT is not known. Not every leg with a low CMP or signs of chronic venous insufficiency is a post-thrombotic leg [6]. For this reason we compared the clinical and haemodynamic investigation of the thrombotic with the non-thrombotic leg (no symptoms, no venogram). The PTS signs considered in this paper therefore have a high probability of thrombotic origin, although we are not completely sure that no silent DVT had occurred in the other leg. A third weakness of our study is that the duration of both anticoagulant therapy and the wearing of compression stockings was not standardized.

In conclusion, the problem of DVT is not solved when the patient is treated and released from the hospital. During long-term follow-up 31% of our study population developed moderate and 2% developed severe signs of PTS. These are related to the site of the initial DVT, but even after distal DVT the incidence of moderate PTS was 11%. The SVPT provides a good tool to detect a decreased CMP, especially when the non-thrombotic leg is considered as a control leg. This test might be valuable in follow-up studies to detect patients at risk of developing PTS and to compare different kinds of treatment.

REFERENCES
