Eur J Vasc Endovasc Surg (2009) **38**, 229–233

Asymptomatic Deep Venous Thrombosis is Associated with a Low Risk of Post-thrombotic Syndrome

L.M. Persson [a,*], L.J. Lapidus [b], G. Lärfars [c], S. Rosfors [a]

[a] *Section of Clinical Physiology, Department of Clinical Science and Education, Karolinska Institutet, Södersjukhuset, Sweden*
[b] *Section of Orthopedics, Department of Clinical Science and Education, Karolinska Institutet, Södersjukhuset, Sweden*
[c] *Section of Internal Medicine, Department of Clinical Science and Education, Karolinska Institutet, Södersjukhuset, Sweden*

Submitted 7 January 2009; accepted 29 March 2009
Available online 30 May 2009

KEYWORDS
Asymptomatic deep venous thrombosis;
Colour duplex ultrasonography;
Post-thrombotic syndrome;
Venous function;
Venous plethysmography

Abstract Post-thrombotic syndrome (PTS) is a well-recognized condition that develops after symptomatic deep venous thrombosis, but the clinical significance and late complications of asymptomatic deep venous thrombosis (ADVT) are unclear.
Objective: To determine whether ADVT following minor surgery affects venous function and contributes to the later development of PTS.
Patients/methods: The study included 83 patients operated on for Achilles tendon rupture; 38 patients with postoperative ADVT and 45 patients without (control group). The follow-up examinations five years after the operation comprised computerised strain-gauge plethysmography, colour duplex ultrasonography, clinical scoring of venous disease, and quality of life (QOL).
Results: Villalta scores, CEAP classification and QOL did not differ between groups. PTS ($=$Villalta score ≥ 5) was found in three ADVT patients (8%) and in two controls (4%). Ultrasonography revealed post-thrombotic changes in 55% of ADVT patients and in none of the controls. Deep venous reflux occurred in 22 ADVT patients and in three controls ($P < 0.001$). There was no difference between groups in plethysmographic variables, demonstrating that the ultrasonographic abnormalities were of negligible haemodynamic significance.
Conclusions: PTS is not a common sequel to ADVT after minor surgery. Although more than 50% of patients with ADVT developed post-thrombotic changes according to ultrasound, these changes did not result in haemodynamically significant venous dysfunction.

Introduction

Symptomatic deep venous thrombosis (DVT) is a well-known important factor in the aetiology of long-term venous dysfunction and post-thrombotic syndrome (PTS).[1,2] The

* Corresponding author. Lena M Persson, Department of Clinical Physiology, Södersjukhuset, SE-118 83 Stockholm, Sweden. Tel.: +46 8 616 35 29; fax: +46 8 616 35 12.
E-mail address: lena.m.persson@sodersjukhuset.se (L.M. Persson).

1078-5884/$36
doi:10.1016/j.ejvs.2008.03.021

clinical course of asymptomatic deep venous thrombosis (ADVT) has not been well established and the extent to which ADVT causes venous dysfunction and long-term sequelae are unclear. The results of previous studies on the incidence of PTS subsequent to ADVT are inconsistent and concern mostly patients undergoing major surgery.[3–5]

The objective of this study was to determine whether ADVT following minor surgery affects venous function and whether it contributes to the development of PTS. We used colour duplex ultrasound (CDU) and computerised strain-gauge plethysmography (CSGP) to compare residual morphological and functional venous abnormalities five years after surgery for Achilles tendon rupture in patients who developed postoperative ADVT, with those who did not. Clinical symptoms and signs were scored, and quality of life was assessed. The Villalta score is based on ratings of both clinical signs and symptoms and a total score of $\geq$5 indicates the presence of PTS.[6]

Materials and Methods

Study population and design

Ninety-four patients enrolled in a prospective study of postoperative DVT after surgical treatment for Achilles tendon rupture were available for this study.[7] The initial study protocol involved DVT screening using colour duplex scanning three and six weeks after surgery and phlebography in instances of abnormal duplex results. Patients were classed into two groups based on the results of post-operative diagnostic tests: 38 patients with definite DVTs and 45 patients with no DVTs, and 11 patients were excluded (Fig. 1). All 45 patients classified as having no DVT had normal results three and six weeks postoperatively according to colour duplex scanning, a procedure shown to have very high sensitivity.[8] The follow-up consisted of a single visit at the hospital at a mean time of five years postoperatively (range, 43–74 months), including clinical examination and scoring, venous function studies and blood samples. The investigators performing these assessments were unaware of whether the patient had had a DVT or not.

Most patients in the ADVT group were treated with warfarin for three months. One patient was treated for six months and two patients received only low-molecular-weight heparin for less than three months. There were three proximal DVTs involving the popliteal vein and 35 distal DVTs (30 isolated peroneal DVT). All patients with a diagnosis of DVT were recommended to wear below-knee graduated compression stockings during the day for at least one year. During the first month a stocking with compression class I (i.e.18–20 mmHg) was prescribed followed by compression class II (i.e. 23–32 mmHg) when the limb swelling had decreased. The class II stocking was selected to fit the patient limb size and was worn for the remaining period.

The study was approved by the local ethics committee and conducted according to the declaration of Helsinki. All patients gave their written informed consent prior to their inclusion in the follow-up study.

Clinical examination

The circumference of each calf was measured in the standing position. Blood samples were taken to detect mutations in the prothrombin (20210 G-A) and factor V Leiden (1691 G-A) genes. Symptoms and clinical findings were rated according to the Villalta score: a total score of

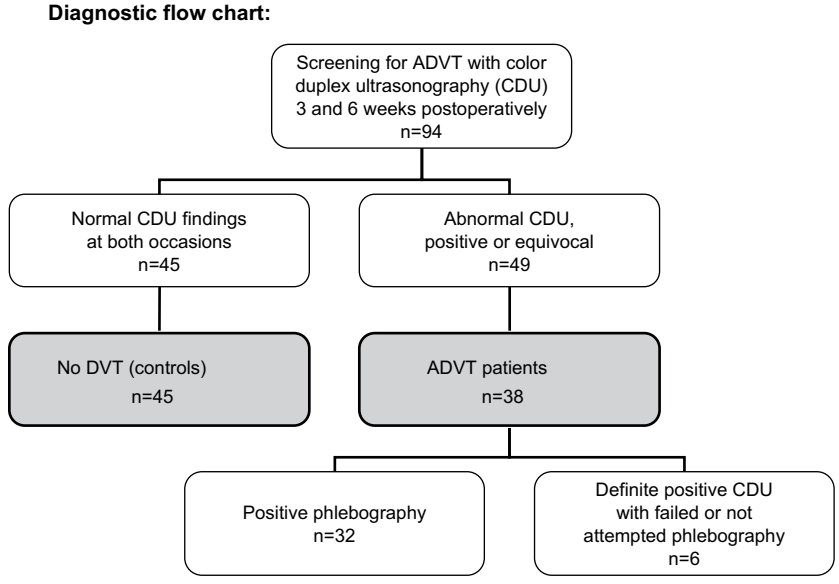

Figure 1 101 consecutive patients were enrolled in a prospective study of postoperative asymptomatic deep venous thrombosis (ADVT) after surgical treatment for Achilles tendon rupture (see Ref. [7]). Ninety-four of these were available for five-year follow-up; 5 patients declined to participate and 2 patients died, two and three years postoperatively. Eleven patients were excluded due to inconclusive diagnostic tests and no definite diagnosis. Definite positive CDU indicates proximal DVT or distal DVT involving more than one main stem. Phlebography images were evaluated by two independent radiologists and in case of discrepancy a final decision was made by a third experienced reader. This procedure diagnosed additionally one DVT compared with the results presented in the previous study (Ref. [7]).

0–4 was classified as absent or minimal PTS, a score of 5–14 as mild-to-moderate PTS and a score of ≥15 as severe PTS.[6] We used a total score of ≥5 to indicate presence of PTS. Clinical classification was accomplished using the C-classes of the CEAP score and quality of life by the disease-specific VEINES-QOL/Sym questionnaire.[9,10]

Colour duplex ultrasound

Duplex scanning was performed using a colour-flow duplex imager (Siemens Acuson Sequoia™ 512 Ultrasound System, Mountain View, CA, USA) by a sonographer unaware of the results of the previous duplex analysis. The following venous segments were evaluated for each patient: common femoral, femoral (mid-thigh), popliteal, posterior tibial, peroneal, gastrocnemius, soleus and great saphenous (thigh and calf). Vessel wall abnormality (irregularities, wall thickening, reduced or occluded lumens) and compressibility were used to assess post-thrombotic changes. Retrograde flow duration longer than 0.5 s following distal manual compression indicated significant reflux in deep or superficial veins.[11]

Computerised strain-gauge plethysmography

The procedure comprised static measurement of venous volume and outflow capacity and dynamic measurement of volume changes after muscular exercise, using a computerised mercury strain-gauge plethysmograph (S.I. Veintest 2, Sels Instruments N.V., Vorselaar, Belgium). Using strain-gauge wires around each calf, venous volume (V, ml per 100 ml) was measured as the maximal volume change during venous occlusion imposed by thigh cuffs inflated to a pressure of 60 mmHg and venous emptying (VE, ml per 100 ml × min) was expressed as the outflow rate during the first second after release of venous occlusion.[12,13] Outflow relative to venous volume was expressed as EV_4/V (volume of blood expelled during the initial 4 s after cuff release divided by V).[14] For dynamic measurements, strain-gauge wires were applied just proximal to the malleolus and volume changes were measured during and after 15 knee bends. Refilling volume (RV, ml per 100 ml) and half-refilling time (T½, s) were measured. A short T½ indicates venous reflux and a low RV indicates a deterioration in muscle pump function.[15] The mean of two measurements was used for all plethysmographic variables.

Data analysis and statistical methods

Normally distributed data are presented as the mean (SD) and differences between means were tested for significance using paired and unpaired two-sided Student's *t*-tests. Difference in Villalta PTS score between the groups was tested using the Mann–Whitney *U*-test. Differences between proportions were analysed using chi-square tests. Regression analyses or Spearman rank order correlations were used to characterise relationships between variables. Statistical significance was assumed at $P < 0.05$. The statistical analyses were performed using Statistica 8.0 (StatSoft Inc., Tulsa, OK, USA).

The size of the groups was predefined from the previous study.[7] Power analysis showed that 40 patients per group is sufficient to detect a 15% reduction in all plethysmographic variables and a 20% difference in PTS frequency between the groups with a power of 80% at a significance level of 5%. Thus, the number of patients can adequately detect a clinically important reduction in plethysmographic variables which is shown to be more than 25%.[14–16]

Results

The ADVT and control groups had similar baseline characteristics (Table 1). Two patients in the ADVT group had a new episode of DVT in the contralateral limb during the follow-up. Calf circumference was reduced in the operated

Table 1 Demographic and clinical data at the five-year follow-up.

	Patients with ADVT ($n = 38$)	Controls ($n = 45$)
Male sex, *n* (%)	30 (79)	37 (82)
Age, years, mean (SD)	44 (8)	44 (8)
Body mass index, kg per m^2, mean (SD)	26 (3)	26 (3)
Op side, *n* (right/left)	15/23	27/18
Heredity for VTE, *n* (%)	5 (13)	1 (2)
Factor V Leiden mutation, *n* (%)[a]	2 (5)	4 (9)
Prothrombin gene mutation, *n* (%)[b]	2 (5)	0
Difference in calf circumference, contralateral leg − op leg, cm, mean (SD)	1.6 (1.1)*	1.5 (1.0)**
Median Villalta PTS score (range)	1 (0–9)	0 (0–11)
VEINES-QOL/Sym (SD)[c]	49/49 (7/6)	51/51 (6/7)
CEAP clinical classification (C)		
Class 1, *n* (%)	8 (21)	4 (9)
Class 2, *n* (%)	5 (13)	5 (11)
Class 3, *n* (%)	1 (3)	0
Classes 4–6, *n* (%)	0	0

VTE = venous thromboembolism; *$P = 0.04$; ** $P = 0.005$.

[a] Measured in all ADVT patients and in 44 patients in the control group (all heterozygote).

[b] Measured in 37 ADVT patients and in 40 patients in the control group (all heterozygote).

[c] Scores are based on a mean of 50 and an SD of 10 (a low score indicates a bad QOL).

limb compared with the contralateral limb in both groups. However, there was no difference between groups in the circumference of the calf that was subjected to surgery.

The total Villalta PTS score ranged from 0 to 11 and did not differ between groups (Table 1). Three patients in the ADVT group and two patients in the control group were classified as having PTS (a score $\geq$5). No patient scored as severe PTS ($\geq$15). One patient in the ADVT group was classified as CEAP/C3 because of slight oedema. There were no missing data for the VEINES-QOL/Sym questionnaire items, which did not differ between groups.

Colour duplex ultrasound

There was a significant difference between groups in CDU findings: both post-thrombotic changes, deep and superficial venous reflux were more common in the ADVT group than in controls (Table 2). The majority of post-thrombotic changes occurred in the peroneal vein; 12 isolated peroneal veins, two isolated posterior tibial veins, six in both peroneal and posterior tibial veins and one peroneal, posterior tibial and popliteal veins. There were still occluded vein segments in 9 limbs in the ADVT group, all of these in peroneal veins. Three patients in the control group had isolated deep venous reflux in the calf, but there were no post-thrombotic signs. We found no significant correlation between the CDU findings (post-thrombotic changes and deep venous reflux) and Villalta PTS score ($r = 0.13$ and $r = 0.18$, respectively).

Computerised strain-gauge plethysmography

There was no significant difference between the two groups in any of the plethysmographic variables (Table 2). None of the patients had venous outflow obstruction (an VE of $<$50 ml per 100 ml $\times$ min or an EV_4/V of $<$0.6). There was plethysmographic evidence of significant venous reflux (T½ $<$ 7 s) in one patient of each group. One of these patients had superficial reflux according to CDU. Two patients in the ADVT group had reduced muscle pump function (RV $<$ 0.7 ml per 100 ml).

No relationship was noted between post-thrombotic changes and static plethysmographic indices of venous outflow function (VE or EV_4/V). However, the dynamic plethysmographic variable, T½, but not RV, was significantly related to the presence of deep venous reflux ($P = 0.02$). This relationship was significant even after adjustment for the presence of reflux in superficial veins.

Discussion

At a mean follow-up time of five years, symptoms and clinical signs associated with previous ADVT following minor surgery were absent or mild in the majority of patients. In addition, there was no difference in plethysmographically assessed venous function, symptoms or signs in comparison with the control group without ADVT. Fifty-five percent of patients in the ADVT group had segments with post-thrombotic changes and 58% had deep venous reflux.

The low frequency of PTS in our group of patients (3/38, 8%) differs from that reported by previous authors involving mainly patients who underwent major surgical procedures. A systematic review found an incidence of PTS after post-operative ADVT of 21%[5] and a more recent prospective study made the same observation.[4] In these studies, there were considerable differences in the definition of PTS. The effect of anticoagulation therapy on the development of PTS is difficult to assess. In earlier reports, the treatment regimen varied from no secondary prophylaxis to treatment of only proximal DVT to warfarin treatment of all DVTs for three to six months. Use of compression stockings and the fact that almost all our ADVT patients received early anticoagulation therapy for three months may have contributed to the beneficial clinical outcome. One might even speculate whether isolated peroneal DVT is a particularly benign condition.

There is no gold standard test for diagnosing PTS and several recent studies have illustrated that all diagnostic systems have merits and disadvantages.[17] In our study, we used validated clinical scales that are commonly used in clinical practice and a Villalta total score of $\geq$5 was used to indicate presence of PTS.[6,9,10] The most common symptoms reported were cramps, paraesthesia, heaviness and pain and their frequencies did not differ between groups. It is possible that the symptoms reported were in many cases related to the surgical procedure rather than being signs of venous disease. The high frequency of calf muscle atrophy in the limbs that were subjected to surgery supports this assumption. The reported symptoms did not markedly influence the quality of life, since both groups had a mean score close to the standardised response mean of 50.

Table 2 Results from colour duplex ultrasound and plethysmography at the five-year follow-up.

	Limbs with ADVT ($n = 38$)	Control limbs ($n = 45$)	P value
Patients with post-thrombotic changes, n (%)	21 (55)	0	$<$ 0.001
Patients with occluded segments, n (%)	9 (24)	0	$<$ 0.001
Patients with deep venous reflux, n (%)	22 (58)	3 (7)	$<$ 0.001
Patients with superficial venous reflux, n (%)	17 (45)	10 (22)	0.03
VE, ml per 100 ml $\times$ min, mean (SD)	103 (26)	105 (29)	N.S.
V, ml per 100 ml, mean (SD)	6.1 (1.4)	6.3 (1.3)	N.S.
EV_4/V, mean (SD)	0.71 (0.06)	0.70 (0.06)	N.S.
RV, ml per 100 ml, mean (SD)	1.7 (0.7)	1.7 (0.7)	N.S.
T½, s, mean (SD)	18 (9)	18 (9)	N.S.

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

In this study, we combined clinical scoring with detailed functional and morphological diagnostic tests. The validity of our findings is supported by experienced personnel performing all tests and a design with blinded evaluation of each test modality. With CDU we detected residual post-thrombotic changes in 55% of the ADVT patients. Moreover, of the 21 patients with post-thrombotic changes, nine still had isolated, occluded vein segments in the calf. These morphological abnormalities did not affect venous emptying of the limb and therefore have no or minor clinical and hemodynamic importance.

However, valvular function in deep veins did affect the plethysmographic results because T½ was inversely related to the presence of reflux in deep veins, but T½ did not differ between ADVT patients and controls. The presence of deep reflux in some controls explains this finding. We found segmental deep venous reflux in limbs without morphological signs of previous DVT in two ADVT patients and in three controls. This might reflect the normal variation, as has been shown in a cross-sectional survey showing a prevalence of reflux in deep vein segments that was greater in men than in women despite no clinically apparent disease.[18]

Reflux in superficial veins was more common in patients with ADVT than in those without ADVT. As varicose veins is a known risk factor for DVT it is possible that our observation of reflux in non-varicose superficial veins represents a pre-existing condition that contributes to the development of ADVT.[19] However, the possibility that this is a chance finding or a DVT-induced change in the balance between blood flow in deep and superficial veins cannot be excluded.

Conclusions

Eight percent of ADVT patients and 4% of control group patients developed PTS according to Villalta scoring. Therefore, PTS is not a common sequel to ADVT after minor surgery. Although more than 50% of patients with ADVT had post-thrombotic changes according to ultrasound examination, we did not observe any haemodynamically important venous dysfunction five years after ADVT. Our results suggest that the symptoms reported at the follow-up are related to the surgical procedure and postoperative muscle weakness rather than to venous disease. Frequent use of compression stockings and early initiation of anti-coagulation treatment in the majority of patients might contribute to the beneficial clinical outcome.

Conflict of Interest

None.

Acknowledgements

This project was supported by ALF project funding from the Stockholm County Council, Karolinska Institutet and the Foundation for Coagulation Research. We are grateful to research nurse Catharina Levander and sonographer Marie Herlitz-Lindberg for skilful contributions. We also thank Dr Anders Elvin and Dr Niklas Nyman for phlebographic evaluations.

References

1 Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996;**125**:1—7.
2 Ziegler S, Schillinger M, Maca TH, Minar E. Post-thrombotic syndrome after primary event of deep venous thrombosis 10 to 20 years ago. *Thromb Res* 2001;**101**:23—33.
3 Andersen M, Wille-Jorgensen P. Late complications of asymptomatic deep venous thrombosis. *Eur J Surg* 1991;**157**:527—30.
4 Schindler OS, Dalziel R. Post-thrombotic syndrome after total hip or knee arthroplasty: incidence in patients with asymptomatic deep venous thrombosis. *J Orthop Surg (Hong Kong)* 2005;**13**:113—9.
5 Wille-Jorgensen P, Jorgensen LN, Crawford M. Asymptomatic postoperative deep vein thrombosis and the development of post-thrombotic syndrome. A systematic review and meta-analysis. *Thromb Haemost* 2005;**93**:236—41.
6 Kahn SR, Shrier I, Julian JA, Ducruet T, Arsenault L, Miron MJ, et al. Determinants and time course of the post-thrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med* 2008;**149**:698—707.
7 Lapidus LJ, Rosfors S, Ponzer S, Levander C, Elvin A, Larfars G, et al. Prolonged thromboprophylaxis with dalteparin after surgical treatment of achilles tendon rupture: a randomized, placebo-controlled study. *J Orthop Trauma* 2007;**21**:52—7.
8 Lapidus L, de Bri E, Ponzer S, Elvin A, Norén A, Rosfors S. High sensitivity with color duplex sonography in thrombosis screening after ankle fracture surgery. *J Thromb Haemost* 2006;**4**:807—12.
9 Eklof B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg* 2004;**40**: 1248—52.
10 Kahn SR, Lamping DL, Ducruet T, Arsenault L, Miron MJ, Roussin A, et al. VEINES-QOL/Sym questionnaire was a reliable and valid disease-specific quality of life measure for deep venous thrombosis. *J Clin Epidemiol* 2006;**59**:1049—56.
11 Labropoulos N, Tiongson J, Pryor L, Tassiopoulos AK, Kang SS, Ashraf Mansour M, et al. Definition of venous reflux in lower-extremity veins. *J Vasc Surg* 2003;**38**:793—8.
12 Shi Z, Boccalon H, Elias A, Garcia-Serrano A. Detection of deep vein thrombosis with a computerized strain gauge plethysmograph. *Int Angiol* 1992;**11**:160—4.
13 Shi Z, Boccalon H, Elias A, Garcia-Serrano A. Plethysmographic findings in normal subjects using a capacitance mode. *Int Angiol* 1992;**11**:127—31.
14 Rosfors S, Ahlstrom H, Boccalon H, Nilsson S, Partsch H, Rooke TW, et al. Computerized strain-gauge plethysmography using a capacitance mode in the diagnosis of deep venous thrombosis. *Scope on Phlebology and Lymphology* 1996;**3**:8—12.
15 Rooke TW, Heser JL, Osmundson PJ. Exercise strain-gauge venous plethysmography: evaluation of a ''new'' device for assessing lower limb venous incompetence. *Angiology* 1992;**43**:219—28.
16 Rosfors S, Noren A, Hjertberg R, Persson L, Lillthors K, Torngren S. A 16-year haemodynamic follow-up of women with pregnancy-related medically treated iliofemoral deep venous thrombosis. *Eur J Vasc Endovasc Surg* 2001;**22**:448—55.
17 Kolbach DN, Neumann HA, Prins MH. Definition of the post-thrombotic syndrome, differences between existing classifications. *Eur J Vasc Endovasc Surg* 2005;**30**:404—14.
18 Evans CJ, Allan PL, Lee AJ, Bradbury AW, Ruckley CV, Fowkes FG. Prevalence of venous reflux in the general population on duplex scanning: the Edinburgh vein study. *J Vasc Surg* 1998;**28**:767—76.
19 Oger E, Leroyer C, Le Moigne E, Pomey MP, Bressollette L, Clavier J, et al. The value of a risk factor analysis in clinically suspected deep venous thrombosis. *Respiration* 1997;**64**:326—30.