The development of postthrombotic syndrome in relationship to venous reflux and calf muscle pump dysfunction at 2 years after the onset of deep venous thrombosis

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Objective: **Postthrombotic syndrome (PTS) develops in 40% to 60% of patients with deep venous thrombosis. Factors that are important in the development of PTS include venous reflux, deep vein obstruction, and calf muscle pump dysfunction (CMD).**

Methods: **Reflux and CMD in relationship to the severity of PTS were evaluated in a 2-year follow-up study of patients with acute deep venous thrombosis. Duplex scanning was used to measure reflux. The supine venous pump function test (SVPT) measures CMD with strain-gauge plethysmography. The base-line examination was performed within 1 to 5 days after diagnosis. The next examinations were scheduled at 3, 6, 12, and 24 months.**

Results: **The study included 86 legs, and the 2-year follow-up period was completed for 70 legs. Significantly more reflux was found in previously thrombosed vein segments, with an odds ratio of 1.8 after 3 months, of 2.1 after 6 months, of 2.5 after 12 months, and of 3.2 after 24 months. Multiple regression results showed that the most important risk factor for early clinical signs of PTS was superficial reflux in months 3, 6, and 12 ($P \leq .02$). Deep reflux did not have a synergistic relationship with superficial reflux in correlation with the clinical signs of PTS. The SVPT was not able to predict the development of PTS.**

Conclusion: **More reflux develops in previously thrombosed vein segments. As early as after the third month, patients with superficial reflux have an increased risk of development of the first clinical signs of PTS. Within 2 years, the SVPT shows no relationship with clinical signs of PTS. (J Vasc Surg 2002;35:1184-9.)**

Acute deep venous thrombosis (DVT) may cause persistent venous abnormalities. In 40% to 60% of patients, DVT develops into postthrombotic syndrome (PTS).[1,2] This chronic syndrome varies from scarcely visible skin changes to pain and recurrent ulcerations, which in rare cases even can lead to amputation.[3] The social and economic burden of postthrombotic complications are considerable.[4]

The pathophysiology of PTS is not entirely understood. Factors that are probably important in the development of PTS are venous reflux,[5-11] deep vein obstruction,[12] and calf muscle pump dysfunction (CMD).[13-15] CMD can be evaluated with plethysmography.[13,14,16-19] The presence and location of venous reflux can be measured with duplex scanning.[8,9,20-23] Both tests are noninvasive, and therefore, serial examinations are possible. Plethysmography measures the global hemodynamics,[21] and duplex scanning can be used to localize the venous abnormalities.[22] Duplex scanning is reliable in the detection of reflux and even might be a better method for the detection of reflux than phlebography.[20] In a previous article, the development of PTS in relationship to the evolution of DVT and residual persistent outflow obstruction was described in the same patient database.[24] The purpose of this study was the evaluation of the development of PTS in relationship to venous reflux and CMD in a 2-year follow-up study of patients with acute DVT.

METHODS

Between 1995 and 1998, all patients with acute DVT who underwent diagnosis at the radiology department and gave informed consent were included in the study. The study was approved by the ethics committee of the hospital and all patients. At the vascular laboratory, the detailed baseline examination used in the follow-up study was performed within 1 to 5 days after diagnosis.

All patients were prospectively included in a follow-up program and underwent treatment with heparin (65 of 86 cases; 76%) or low molecular weight heparin (21 of 86 cases; 24%) administered for at least 5 days during the acute phase, which was continued until the simultaneous start of treatment with oral anticoagulation (OAC) therapy resulted in an international normalized ratio (INR) between

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Competition of interest: nil.

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Table I. Percentage vein segments (n = 12) with reflux over time (months) as derived from interperiod correlation matrix (*r*)

	Time (months)				
Vein segments	*3*	*6*	*12*	*24*	*r*
Superficial femoral proximal	41	42	47	36	0.40
Superficial femoral half	29	30	36	33	0.60
Superficial femoral distal	22	23	27	27	0.62
Popliteal	25	26	26	31	0.17
Posterior tibial 1	21	28	27	27	0.48
Posterior tibial 2	22	24	29	26	0.31
Anterior tibial 1	9	9	6	0	–0.07
Anterior tibial 2	9	8	7	7	0.13
Long saphenous proximal	25	24	30	37	0.49
Long saphenous half	22	11	17	13	0.45
Long saphenous distal	25	31	26	23	0.54
Short saphenous	21	12	16	13	0.45

2 and 3 during 2 consecutive days. Patients underwent treatment for 3 months, except the patients with pulmonary embolism or continuing risk factors (such as malignant disease) who underwent treatment for a longer period of time. The OAC therapy was continued for 3 months in 50% of the cases (43 of 86), for 6 months in 22% (19 of 86), for 1 year in 9% (8 of 86), and for 24 months in 9% (16 of 86). *Adequate anticoagulation therapy* with the coumarin derivative accenocoumarol was defined as an INR value of 2 or more within 4 days after the diagnosis.

Initially, compression therapy was applied for at least 5 days or longer until the leg showed no edema. At this time, all patients were instructed and motivated at each visit to wear graduated custom-made compression stockings for at least 1 year. A compete medical history was obtained. The evaluated thrombotic risk factors were immobilization, malignant disease, factor V mutation, surgery, and pregnancy or recent delivery.

A physician, blinded to the findings of the duplex scanning and plethysmography, quantified PTS in the patients at 1 and 2 years after DVT according to the seven-point CEAP clinical scale (Clinical, Etiologic, Anatomic, Pathophysiologic; range, 0 to 6) of the Ad Hoc Committee on Reporting Standards in Venous Disease, the update,[25] as shown in Table I. In the evaluation, the 2-year CEAP score preferably was used. If the patient did not complete the 2-year follow-up period, the 1-year CEAP score was used. Recurrent DVT was reported if the patients had new clinical signs of DVT and if this could independently be confirmed with a new thrombus with phlebography or compression ultrasound scanning at the radiology department.

Duplex ultrasound scan. Duplex scanning was performed as described previously[22] by two experienced vascular technicians with a Toshiba SSA 270A scanner (Tokyo, Japan) with a 3.75-MHz or 5-MHz probe in low-flow setting (minimal measurable velocity, 2 cm/s). All veins were examined with the patient in 45-degree sitting position, knees flexed and feet resting on a footstool. The results of this technique of reflux measurements are comparable with those of the cuff deflation technique.[23] The technical advantages (no cuff deflator), comfort for the patient, and its simplicity were arguments to use this technique.

The patients underwent scanning by a vascular technician blinded for the results of previous examinations. The following 12 vein segments were examined: the superficial femoral vein (proximal, middle, and distal), the popliteal vein, the long saphenous vein (proximal, middle, and distal), the short saphenous vein, and the posterior and anterior tibial veins. In the calf, two veins accompany each artery. The two veins were numbered, with number 1 being the most superficial and number 2 the deeper vein. In the longitudinal plane, the presence of reflux was measured. Proximally, reflux was measured after Valsalva's maneuver, and in the distal veins, reflux was measured with distal manual compression with sudden release. *Pathologic reflux* in the proximal veins was defined as a reversed flow duration of more than 1 second; in the distal veins, it was a reversed flow duration of more than 0.5 second. Reflux in the common femoral vein was not measured because, as shown in a previous study,[22] 60% of healthy individuals had a reflux duration exceeding 1 second with this method. With this definition and method of inducing reflux, the κ coefficient of the interobserver variability was 0.86.[22]

Supine venous pump function test. CMD was measured with the use of the supine venous pump function test (SVPT), which was performed with strain-gauge plethysmography as described previously.[13,19] Both feet of the supine patient rested against a foot support 10 to 15 cm above the bed, with the knees at an angle of about 120 degrees. Inflatable cuffs were placed around the thighs. The strain gauges were placed 1 to 2 cm below the origin of the Achilles tendon, avoiding the most muscular part of the calf to minimize motion artifacts. The cuffs were inflated, which resulted in a gradual increase of venous pressure and limb volume distal to the cuffs. After a maximum increase in volume was achieved, the patient was instructed to perform maximal dorsal flexion and plantar flexion of the feet. In total, 10 repetitions of each movement were performed during a 20-second period. Because of this muscle pump action, blood was squeezed past the cuff, which resulted in a decrease in the volume of the limb. This procedure was repeated at different cuff pressures of 50, 60, and 70 mm Hg (performed twice at each pressure).

In addition, a separate pressure-volume relationship was determined with measurement of the relative increase in volume at five different cuff pressures of 20, 30, 40, 50, and 60 mm Hg. With this relationship, the decrease in volume during exercise could be converted to a decrease in pressure. The decrease in pressure was expressed as a percentage of the initial pressure and was approximately the same at all cuff pressures. The average percentage pressure change at all the different cuff pressures in healthy individuals was 60% or more (coefficient of variation, 9%).[19]

The SVPT was measured because prior studies showed that patients with severe signs of PTS had abnormal SVPT

results (45%). This was assessed in patients 10 years after DVT.[13,19]

Statistical evaluation. Reflux was evaluated for the total score of all 12 vein segments and separately for each individual vein segment and for the four proximal deep vein segments (femoral and popliteal), the four superficial vein segments (long and short saphenous), and the four distal vein segments (posterior and anterior tibial). The Mantel-Haenszel test was used to evaluate the odds ratio and 95% CI for the development of reflux in initially thrombosed vein segments. For analysis of factors that contributed to the CEAP score, the following risk factors were tested with multiple regression: age, venous outflow resistance,[24] the presence of noncompressible vein segments, and the presence of reflux at each time interval. The relationship between the reflux over time, the SVPT, and the CEAP classification with age was studied with partial correlation coefficients.

The three patients with DVT in two different legs were considered statistically independent because the time interval between the DVT in both legs was more than 1 year. A *P* value .05 or less was considered statistically significant.

RESULTS

In the study, 86 legs of 83 patients with proven DVT were included. The mean age of the patients was 53 years (range, 17 to 88 years; standard deviation, 16 years), and 43 patients were male and 40 female. Of the 83 patients, 11 (13%) had prior DVT. In three patients (4%), the prior DVT was located in the same leg. Thrombosis was unilateral on the right side in 34 patients (41%), unilateral on the left side in 46 patients (55%), and bilateral in three patients (4%). The 2-year follow-up period was completed in 70 legs.

Individual risk factors for the initial DVT were immobilization in 17 patients, malignant disease in 13 patients, factor V mutation in 13 patients, surgery in four patients, and recent delivery in three patients. In 33 patients (40%), no risk factors were found.

The mean age of the 16 patients who did not complete the study was 63 years (range, 30 to 82 years; standard deviation, 16 years), and seven patients were male and nine female. Of these 16 patients, five died during the study and the other 11 were lost for various reasons. Seven of these patients (44%) had prior DVT. Thrombosis was unilateral on the right side in seven (44%) and on the left side in nine (56%). The most common risk factor was malignant disease in six of the patients (38%).

The distribution of DVT with the standardized examination of all vein segments at baseline was as follows. Sixty-eight legs with proximal DVT were found. In 26 (38%), not only proximal DVT, but also superficial thrombosis, was found. Of the remaining 18 legs, in eight (44%), thrombosis was found in the superficial veins as well.

The INR results were available in 73 patients, and in 59 (81%), dosage regiment was adequate and resulted in an INR of 2 or more within 4 days after the diagnosis. No major bleeding complications were encountered.

Table II. Number of patients with DVT with and without clinical signs of postthrombotic syndrome (CEAP score) at last follow-up examination

*CEAP score**	*Clinical signs*	*No. of patients*
0	No visible or palpable signs	18 (23%)
1	Telangiectases, reticular veins, malleolar flare	4 (5%)
2	Varicose veins	15 (19%)
3	Edema, without skin changes	26 (33%)
4	Hyperpigmentation and lipodermatosclerosis	16 (20%)

*No patients had CEAP score 5 or 6.

Of the patients in whom new clinical signs developed, such as a swollen leg or pain, recurrent DVT was diagnosed by the radiology department in eight patients, five in the leg initially involved and three in the contralateral leg. Of these eight patients, two underwent OAC therapy during the recurrence of DVT. In one patient, nonfatal pulmonary embolism developed 6 weeks after the 6 months of OAC treatment was ended.

Table II shows the number of patients and their CEAP scores at the last follow-up examination after 1 years (n = 9) or 2 years (n = 70). Significantly more reflux was found in previously thrombosed vein segments, with an odds ratio of 1.8 after 3 months (95% CI, 1.2 to 2.7), of 2.1 after 6 months (95% CI, 1.4 to 3.2), of 2.5 after 12 months (95% CI, 1.7 to 3.7), and of 3.2 after 24 months (95% CI, 2.1 to 4.9).

Multiple regression results showed that the most important risk factor for a high CEAP score was superficial reflux in months 3, 6, and 12 ($P \leq .02$). In each of the separate traceable vein segments, the mean of the CEAP classification was calculated for the vein segments with and without reflux. Only in the proximal and middle long saphenous vein was a significantly higher mean CEAP classification found in the vein segments with reflux in month 3 ($P \leq .03$), month 6 ($P \leq .01$), and month 24 ($P \leq .05$).

Table III shows the relationship between the number of vein segments with deep or superficial reflux over time and the CEAP classification. No correlation was found with deep reflux, but superficial reflux was found to be an increased risk factor for a higher CEAP classification. Deep reflux did not have a synergistic relationship with superficial reflux in correlation with the clinical signs of PTS. Each increasing single vein segment with superficial reflux upgraded the CEAP score by 0.4.

Table I shows the percentage of the 12 vein segments with reflux over time. The interperiod correlation matrix showed no significant increase or decrease in percentage of reflux over time. The correlations from time to time are quite variable (−0.07 to 0.60), meaning that the reflux situation is not stable within patients.

The Figure shows the relationship between the SVPT and the CEAP classification. The partial correlation coefficients for age (r) after 24 months was −0.01 ($P = 1$). This

Table III. Relationship between presence of deep or superficial reflux over time and final postthrombotic syndrome (CEAP) score

Time (months)	*Mean final CEAP score (SD)*			
	3	*6*	*12*	*24*
No. of vein segments with deep reflux				
0	2.0 (1.4)	1.8 (1.3)	1.9 (1.5)	1.4 (1.3)
1	2.3 (1.3)	2.0 (1.5)	2.3 (1.3)	2.2 (1.5)
2	2.1 (1.8)	3.0 (1.2)	1.8 (1.6)	3.4 (0.7)
3	2.5 (1.5)	2.0 (1.4)	3.1 (1.3)	2.6 (1.7)
4	2.9 (1.3)	2.7 (1.7)	3.0 (0.8)	2.4 (1.0)
5	2.0 (1)	2.5 (1.6)	2.5 (1.2)	2.3 (0.6)
6-8	2.0 (1.4)	3.0 (0.7)	3.0 (0.0)	3.0 (0.7)
Correlation*	–0.08	0.06	0.17	0.18
P value	0.5	0.6	0.2	0.2
No. of veins segments with superficial reflux				
0	1.6 (1.4)	1.7 (1.4)	1.9 (1.5)	1.8 (1.4)
1	2.4 (1.3)	2.5 (1.4)	2.2 (1.3)	2.2 (1.3)
2	2.5 (1.0)	2.8 (1.3)	3.4 (0.7)	2.6 (1.1)
3	4.0 (0.0)	3.7 (0.5)	3.7 (0.6)	4.0 (0.0)
4	4.0 (0.0)	†	4.0 (0.7)	†
Correlation*	0.37	0.36	0.32	0.33
P value	0.004	0.006	0.01	0.01

*Partial correlation coefficient corrected for age influence.
†No patients had reflux in this number of vein segments.
SD, Standard deviation.

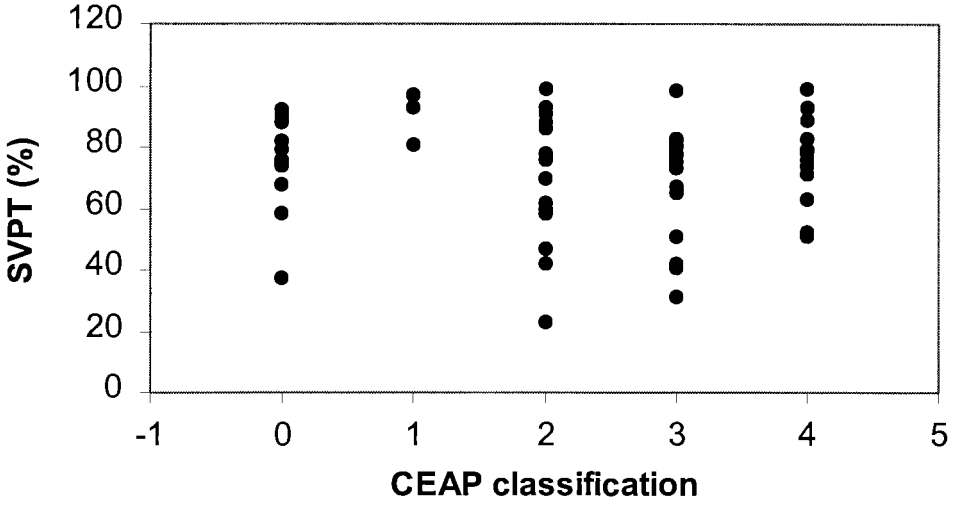

Fig 1. Relationship between 24-month SVPT and final postthrombotic (CEAP) classification.

means that the SVPT did not enable prediction of the CEAP classification. No relationship was found after 3 months ($r = .1$; $P = .7$), 6 months ($r = -.2$; $P = .2$), and 12 months ($r = -.04$; $P = .7$) either.

DISCUSSION

Superficial reflux. In recent years, superficial reflux was recognized as an important cause of chronic venous insufficiency.[26-31] Shami et al[30] reported that in just over half the patients with venous ulcerations, the insufficiency was confined to the superficial venous veins. It was also becoming clear that the presence of pathologic reflux was important in the development of PTS.[29,32] Although in the study of Labropoulos et al,[29] the importance of superficial reflux in the development of PTS was recognized, our study not only showed that the most important factor was reflux and in an increasing number of superficial vein segments but also that deep reflux plays no synergistic role with superficial reflux in relationship to the CEAP classification, within 2 years. Therefore, the presence of deep reflux seemed less important in the early development of PTS. This is in accordance with the van Ramshorst et al[23] study.

They found no relationship between the number of incompetent deep vein segments and the clinical symptoms after 34 months.

That superficial reflux was common in patients with DVT could be explained with the distribution of DVT. If not only the presence of DVT was measured but also the presence of superficial thrombosis, the superficial vein segments were shown to be involved in 40% of the patients. Because significantly more reflux developed in previously thrombosed veins, reflux also developed in previously thrombosed superficial vein segments, as also observed by other investigators.[33]

As shown in Table I, there is no linear increase during the follow-up period of the presence of reflux in each vein segment. This was because the presence of reflux not only continuously increases over time but may also disappear. In a preceding study,[22] we showed that the κ coefficient of the interobserver variability in the classification of reflux was good and therefore it was unlikely that this was entirely the result of a measurement error. In the same database[24] and as found by other investigators,[34] propagation was common. Reflux may disappear because of an occlusion of vein segments.

Calf muscle dysfunction. The presence of CMD within 2 years showed no significant relationship with the severity of the PTS, which is in contrast with a previous study 10 years after DVT[13] and with findings by other investigators[13,35] in patients with venous ulcers, probably because in this study none of the patients had CEAP scores of 5 or 6. Apparently, the damage to the calf muscle function takes more than 2 years. The study of Raju et al[36] suggested that in the mechanism leading to CMD, changes in properties of the vein wall were important. A vein must be able to collapse to push the blood cranially. It is likely that the decreasing ability of the vein to collapse is caused by a stiffening of the vein wall. A decreasing elasticity may be caused by a high venous pressure induced by an accelerated pressure recovery caused by reflux. This mechanism leading to the damage of the vein wall might take more than 2 years to develop. Another explanation may be that the patients with severe clinical signs of PTS have pain and therefore have the inclination to walk less and therefore over time an atrophic calf muscle develops. This process probably also takes more than 2 years.

A limitation of this study that must be recognized is that none of the patients had CEAP scores of 5 or 6. The use of graduated compression stockings probably delayed the development of the more severe signs of PTS. Therefore, a 2-year follow-up period is a short time in the development of severe PTS. In a previous study,[7] patients with more severe signs of PTS were measured 10 years after DVT and showed that reflux in the proximal deep veins contributed significantly to PTS. Perhaps reflux in the deep proximal veins becomes increasingly important in patients with more severe signs of PTS. Furthermore, this study provided no information about the perforating veins because other investigators[37] showed that duplex scan is unreliable in the evaluation of perforating veins. Perhaps development of perforator incompetence takes longer than 2 years. If perforator incompetence develops, possibly proximal deep reflux does play a synergistic role with superficial reflux in relationship to the severe signs of PTS.

CONCLUSION

Significantly more reflux developed in previously thrombosed vein segments. As early as after 3 months, patients with superficial reflux were at risk in development of the first clinical signs of PTS. Deep reflux did not have a synergistic relationship with superficial reflux in correlation with the first clinical signs of PTS. An increasing number of insufficient superficial vein segments led to an increasing severity of PTS. Within 2 years, the SVPT showed no relationship with clinical signs of PTS.

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Please see the related commentary by Dr Seshadri Raju on pages 1297-8.