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

**Seshadri Raju, MD,** *Jackson, Miss*

Haenen and colleagues present a prospective study of the early evolution of postthrombotic syndrome (PTS) in this issue of the *Journal of Vascular Surgery*. The authors found that significant signs of PTS (CEAP classification 3 or higher) were evident in 53% of limbs as early as 2 years after the onset of acute deep venous thrombosis (DVT); reflux had developed concurrently (23% to 36% incidence rate) in a number of superficial and deep venous segments monitored. PTS severity correlated with superficial but not deep reflux. Pain, an important component of PTS, was not considered in the clinical evaluation of PTS. The CEAP classification does not include the pain component in assigning clinical class. Recently developed quality-of-life criteria for use in chronic venous insufficiency do include pain and may provide a more complete picture of PTS severity. The pathologic findings detailed in this study provide a time-specific (2 years) snapshot of a process that evolves over many more years, often with transient intermediate findings. Variance in some details from other publications may be attributable to this and to technologic limitations (see subsequent).

The current and related recent publications by Haenen et al and similar studies by other investigators[1-4] confirm in general the original seminal work of Strandness and colleagues on PTS evolution. In a remarkable series of papers (many appearing in this journal), the University of Washington researchers used serial duplex scan examinations in patients with DVT to illuminate most of the salient features currently known regarding the evolution of thrombus and PTS. It is now known that thrombus evolution is a dynamic and often unstable process with simultaneous regression and progression occurring in different venous segments. Progression was more likely to occur in the proximal venous segments. Increasing age and slow rate of thrombus resolution were negative factors in ultimate resolution. About 15% to 20% of superficial femoral veins remain occluded[2,4] but with excellent collateral development from the deep femoral vein. The process of PTS evolution was continuous, spanning years, not months.[3] The distribution and number of occluded and refluxive venous segments at 8 to 12 years[1,4] are far different from those encountered in shorter term linear studies, such as the one presented by Haenen and colleagues. Partial or total lysis/recanalization occurs in most venous segments by 6 months.[2,3] By 8 to 12 years, more than 75% of previously occluded venous segments have partially or fully recanalized.[3,5] However, complete resolution occurs in only about a third of the limbs,[5] with residual segmental lesions persisting in the great majority. Test results of venous function remain abnormal in 70% to 83% of postthrombotic limbs. Reflux invariably occurs in venous segments with partial recanalization.[4] Reflux was more likely to occur in previously thrombosed segments, but there is a significant incidence rate of reflux development in previously nonthrombosed segments[6] as well. The latter category of nonthrombotic reflux mostly occurs in venous segments distal to the thrombus but curiously, in about 12% of limbs, develops in proximal segments. Reflux, especially the nonthrombotic variety, can be transient, with surprisingly high (40%) incidence rates in some locations.[6] The nonthrombotic reflux was not the result of segment dilatation,[7] and the causative mechanism remains unknown. With time, both superficial and deep reflux develop in about two thirds of postthrombotic limbs, but the rate of development of superficial reflux is similar to that of the contralateral nonthrombotic extremity.[8] Unlike Haenen and colleagues, the University of Washington group found no correlation between PTS and the development of superficial reflux. Complete lysis of thrombus, especially when it occurs rapidly (<90 days), restores luminal size, compliance, and valve integrity to normal values in the involved venous segment.[2,9] However, in some instances, venous segments that took as much as 6 months to clear the thrombus were competent! Many of the prior findings were previously unsuspected and have important therapeutic implications. On the basis of prior histologic studies of thrombosed venous segments, it had been assumed that fibrous organization of the thrombus was the inevitable outcome and the delicate valve structures were destroyed in the process. The University of Washington group also established that combined obstruction/reflux was the dominant lesion encountered in the postthrombotic extremity.[5] However, hemodynamic confirmation of

From the University of Mississippi Medical Center.
Competition of interest: nil.
Reprint requests: Seshadri Raju, MD, 1020 River Oaks Dr, #420, Jackson, MS 39208 (e-mail: rajumd@earthlink.net).
J Vasc Surg 2002;35:1297-8.

0741-5214/2002/$35.00 + 0 **24/9/122887**
doi:10.1067/mva.2002.122887

the obstructive component with functional tests remains difficult.[1] This may be related to the rapid development of collaterals but is more likely a reflection of the relative insensitivity of currently available techniques for assessment of obstruction. Indirect evidence that residual iliac venous obstruction plays a major role in PTS comes from recent favorable clinical experience with iliac venous stent placement.[10] Interestingly, stasis ulcers—generally attributed to reflux, not obstruction—healed in 62% of limbs after stent placement, although the refluxive component remained uncorrected. It is clear that the complex interplay between reflux and obstruction in the PTS limb is poorly understood. The iliac venous segment has been generally ignored in most serial studies dealing with PTS because the duplex scan technology is not well suited for this purpose.

There is wide disagreement regarding the relative importance of superficial versus deep reflux and proximal versus distal reflux in the genesis of PTS.[2,3,8,11] Most groups, including Haenen and colleagues, use valve closure time (VCT) of more than 1 second (<0.5 second in some instances) as a definition of reflux. This is at best a qualitative measure. Several previous attempts to use VCT and related indices in this manner to correlate with symptoms of chronic venous insufficiency have failed. In our own laboratory, we have observed that the rate of volumetric reflux (calculated from absolute VCT duration, time averaged reflux velocity, and valve station area) can vary widely among refluxive (VCT > 1 second) valve stations from as little as a few mL/min to one or more magnitudes higher (<10 mL to >1000 mL)! All "reflux" is not the same. The controversies regarding the relative importance of various regional reflux patterns and PTS are unlikely to be resolved until a more precise measure of reflux is developed and applied.

Prospective studies have now clearly established the very high incidence and morbidity rates of PTS after current heparin/warfarin anticoagulation protocols for the treatment of DVT. Recurrent DVT (about 30% incidence rate at 10 years) and inadequate strength or duration of warfarin anticoagulation therapy further increase the incidence rate of PTS.[5,12] Use of low–molecular-weight heparins has not reduced the incidence rate of PTS.[12] Stockings have been shown to be of little use as a preventive measure.[13] Better monitoring and longer term warfarin therapy may reduce the incidence rate of PTS somewhat, but a meaningful reduction seems unlikely without a major shift in therapeutic stratagem. The study by Haenen et al and other similar studies suggest that a successful new strategy must focus on the early and complete lysis of the thrombus load after the onset of DVT.

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Submitted Dec 4, 2001; accepted Dec 6, 2001.

Please see the related article by Dr José H. Haenen et al on pages 1184-9.