Can The Postthrombotic Syndrome Be Avoided?
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Deep vein thrombosis (DVT) is a serious health care problem despite available methods for prevention, improved diagnostic and treatment modalities. Based on the population study from Rochester, MN, Heit recently demonstrated over 900,000 cases of venous thromboembolism (VTE) yearly in the US and close to 300,000 deaths from pulmonary embolism (PE). Despite appropriate anticoagulant therapy 30-50% of patients with DVT will develop postthrombotic sequelae that may vary from minor signs to severe manifestations. The established postthrombotic syndrome (PTS) is a significant cause of chronic illness with considerable consequences for both the patient and the society.

According to Prandoni and Kahn the precise incidence of PTS following confirmed DVT is still controversial, as the rate of postthrombotic sequelae reported in published studies has varied between 20% and 100% (1). This rate has decreased in studies performed in the last 25 years which could be due to improved diagnostic and therapeutic approaches to patients with DVT. However, owing to large differences among studies in terms of study design, definition of PTS, sample size, length of follow up, and use of compression elastic stockings, the reported incidence of both overall and severe PTS still shows considerable variability.

Can the PTS be predicted?
Our understanding of the development of PTS after an acute episode of DVT is still incomplete but there are factors that are important in the prevention and management of this devastating syndrome. The location of the initial thrombus plays a role with higher risk for PTS after iliofemoral thrombosis compared to distal thrombosis. The importance of initial treatment with compression, effective anticoagulation and early thrombus removal is increasingly recognized. Prevention of recurrent thrombotic events is probably the most important issue to preserve valvular function and avoid deep venous reflux as well as proximal obstruction.

1. Iliofemoral DVT is associated with a higher frequency and more severe PTS than distal DVT. Patients with extensive iliofemoral DVT had significantly worse PTS Villalta scores than those with distal or popliteal DVT (2).

2. Insufficient anticoagulation treatment is associated with an increased risk of thrombus propagation, PE and recurrent DVT. However anticoagulation alone imperfectly protects against the occurrence of venous obstruction and valvular destruction, resulting in ambulatory venous hypertension and potentially PTS.

3. The effects of elastic compression stockings (ECS) following DVT have been well documented with reduction in venous hypertension, decreased edema, and improvements in tissue microcirculation. The effectiveness of ECS in the prevention of PTS has been demonstrated in prospective RCT's (3,4). When ECS is combined with early ambulation, rates of PTS are decreased (5).

4. In acute iliofemoral DVT early surgical thrombectomy has been shown to decrease vein wall injury, preserve valve function and ultimately decrease the occurrence of PTS (6). Catheter directed thrombolysis (CDT) has also been demonstrated to reduce PTS (7,8). The new pharmacomechanical thrombectomy/thrombolysis methods have the benefit of decreased treatment time, amount of thrombolytic used, cost and hospital and intensive care unit stay. Whether this benefit will translate into decreased
rates of PTS is unknown. Furthermore, the role of venous stenting of remaining iliac obstruction after lysis has not been established. We will hopefully get guidance from the ATTRACT trial, a NIH sponsored multicenter trial to test the hypothesis that active thrombus removal plus best medical therapy is superior to best medical therapy in preventing PTS at 2 years.

5. Recurrent ipsilateral DVT is a primary and probably the most important etiologic factor in the development of PTS. Reducing the rate of recurrent DVT will thereby decrease the incidence of PTS. This can only be accomplished by modifying approaches to the current management of primary DVT by: identification of subgroups of patients who are at risk for recurrence; optimizing the initiation, duration and type of anticoagulation and use of ECS; early thrombus removal in iliofemoral DVT; provision of anti-thrombosis prophylaxis to high risk medical and surgical patients; educating patients and front line physicians regarding appropriate DVT management and risks of recurrent DVT (9).

6. How do we stratify patients with acute DVT who are at risk for developing the severe PTS? Although it is not possible to foresee the development and course of PTS in the individual patient, clinical predictors of PTS are identifiable at the time of acute DVT. Clinical factors at initial presentation and at 30 days, can allow categorization of patients at risk for severe PTS. Proximal DVT involving the common femoral or iliac veins, elevated BMI, previous ipsilateral DVT, and older age are associated with the development of PTS. Patients who demonstrate symptoms of PTS at one month following acute DVT are predicted to develop severe PTS at 2 years in a dose response fashion based on the Villalta scores (2). New data suggest a role for cytokines or adhesion molecules as a surrogate biomarker for inflammation associated with the transition from acute DVT to chronic PTS.

7. The diagnosis of PTS has subjective elements. Recently the International Society on thrombosis and hemostasis put forth recommendations, suggesting the Villalta PTS scale be used primarily, complimented by the CEAP classification when appropriate. Although it appears that early PTS symptoms after DVT correlate with poor long term outcome, we have yet to elucidate the underlying pathology of this process. The mechanism driving the progression of PTS, and whether its course can be halted or even reversed is unknown. Certainly, the inflammatory response is involved, but its role in PTS and the relationship between inflammation and venous reflux and obstruction is unclear. The measures to be pursued include development and validation of a DVT clinical score to predict risk of PTS after DVT, much like the CEAP score. The American Venous Forum suggests SEAP as a DVT PTS risk prediction score where S = symptom severity (1=no overt symptoms, 2=mild symptoms, 3=moderate symptoms, 4=severe symptoms, 5=limb threatening symptoms); E=provoked versus unprovoked; A=anatomy (1=iliofemoral, 2=femoropopliteal, 3=calf veins); P=pathophysiology (1=primary, 2=recurrent) (9).

8. Chronic obstruction of the iliofemoral segment following acute DVT is common as only 20% to 30% of the iliac vein thrombi recanalize with anticoagulation alone. Proximal venous obstruction, independent of reflux, is the principle cause of PTS in approximately one third of cases. Percutaneous endovenous venoplasty and stenting is the method of choice for venous outflow obstruction with primary and secondary patency rates of 57% and 80% at 72 months for postthrombotic disease (10).
The following patient is at high risk to develop severe PTS:
1. Iliofemoral DVT;
2. Old age;
3. Elevated BMI;
4. Recurrent ipsilateral DVT;
5. Non-optimal anticoagulation;
6. Non-compliance with early ambulation and ECS;
7. No attempt of early thrombus removal;
8. Poor recanalization on duplex scanning after one month with elevated D-Dimer;
9. High Villalta score after one month;
10. Remaining iliac vein obstruction.

References: