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REVIEW

The post thrombotic syndrome: Ignore it and it will come back to bite you

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ABSTRACT

Post thrombotic syndrome (PTS) is a very common chronic complication of deep venous thrombosis (DVT), as three out of ten patients with lower extremity DVT will develop PTS. The possibility to identify patients at risk is limited. Diagnosis is challenging, because there is no gold standard diagnostic method. Progress in diagnostic options may therefore change future diagnostic strategies. The better understanding of pathophysiologic processes that underlie PTS may stimulate the development of treatment modalities and improve and diversify management options. The quest for adequate preventive strategies and treatment is important because PTS has a detrimental effect on patients' quality of life and is associated with increased healthcare as well as societal costs. [1,2]The problem of PTS prevention is therefore clearly relevant to patients, doctors as well as policy makers.

1. Introduction

Post thrombotic syndrome (PTS) is defined as a combination of patient reported symptoms and objective findings such as swelling and skin changes in patients following DVT of the lower or upper extremity. This review will be limited to PTS of the lower extremity.

The condition of PTS and its implications have been under-recognized, and therefore under-studied for a long period of time. One of the main reasons for its relative obscurity has been the lack of standardized diagnostic methods. Therapy in the acute phase of DVT typically has focused on suppression of coagulation to prevent thrombus progression and pulmonary embolism, rather than on preventing its long-term sequels. The mere fact that evaluation of post thrombotic signs and symptoms was not part of recent large clinical trials that evaluated new direct oral anticoagulant treatment for acute DVT, once more illustrates the persistent underestimation of this very relevant clinical problem.

2. Diagnosis

PTS is diagnosed based on a clinical score; there is no objective diagnostic method or gold standard. Moreover, many different clinical scores are in use and their correlation is poor. [3] Validation of any of the clinical scores is challenging because of the lack of a gold standard comparator. Some scoring systems are derived from populations of patients with DVT [4,5,6] others are derived from patients with chronic venous disease. [7,8,9].

The Villalta scale, derived from a population with DVT, is used most frequently, and has proven to be a very useful tool for diagnosing PTS. [10,11,12] Its recommendation by a subcommittee of the ISTH as the preferred diagnostic tool has already contributed to a better comparability between different clinical studies. [13] Theoretically, PTS based solely on subjective complaints has the potential to evoke over-diagnosis, as there is a waxing and waning of symptoms; symptoms can be reduced or cured by adequate compression therapy. Therefore the main question is whether objective signs should be required in order to establish the diagnosis of PTS.

Even before objective signs are visible, patients can experience complaints such as heaviness of the leg, itching and cramps and even venous claudication, and these complaints may have a significant impact on daily functioning of patients. Therefore disease specific scores such as the Veines-Qol score [14]and generic scores such as the EQ 5D scores [15] are important tools in the assessment of patients.

Even though the Villalta score has its merits, there is room for improvement. According to some researchers factors such as ankle mobility, venous claudication, and stage of ulceration are components that should be either included or better specified in the current score in order to improve it. Others suggest that the addition of a Quality of life questionnaire to the Villalta score may be superior to the use of the Villalta score alone. [16].

Clinical validation of the Villalta score has been performed using disease specific quality of life scores and generic quality of life scores [17].

Vein wall abnormalities are frequently observed in patients with PTS; these correlate poorly with the onset of the disease [18]. The same holds true for valvular reflux. [10,19] It may very well be, that

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these poor correlations will improve with the introduction of more sensitive methods of visualization such as Magnetic Resonance Venography (MRV) or Intravascular Ultrasound (IVUS). MRI techniques nowadays provide adequate differentiation between acute, sub acute and chronic processes. [20] Acute thrombosis can be recognized by venous dilatation due to luminal filling with thrombus material. The sub acute phase can be recognized on basis of the vein wall thickening and edema surrounding the thrombosed veins due to the inflammatory response evoked by the thrombus. [21] Even processes of angiogenesis and revascularization can be distinguished, by differences in signal intensity [22]. Finally, post-thrombotic remnants such as trabeculation can be recognized in patients after an episode of DVT. [23] However, MRI sequences and protocols need to be harmonized to make objective diagnosis of PTS possible and reproducible, so that eventually, with better diagnostic options PTS may become an objectively diagnosed disease.

3. Pathophysiology of PTS

Following acute DVT recanalization is enabled by a combination of fibrinolysis, thrombus organization, and neovascularization. Complete lysis of the thrombus is associated with fewer PTS manifestations. [18,24,25].

Current understanding of the origin of PTS is that if these processes are hampered, this will result in a combination of valvular reflux and venous outflow restriction or obstruction. This will cause ambulatory venous hypertension, which as a consequence results in complaints such as pain and end organ manifestations like post thrombotic skin changes and edema. [26].

More detailed understanding of the pathophysiology of PTS may help identify potential preventive or therapeutic targets, to prevent or alleviate symptoms and signs of chronic venous disease, and slow down progression of symptoms.

4. Animal models

In order to address the mechanisms underlying venous thrombosis, several animal models, predominantly mouse models, of venous thrombosis have been described. [27].

Frequently used models are the inferior vena cava (IVC) Ligation or Stasis Model, the IVC Stenosis Model, the ferric chloride model, and the Electrolytic IVC Model. [27]. Although there are substantial differences in the nature of the thrombosis models, several general patterns can be recognized; thrombosis is usually triggered by altering blood flow and/or by inducing vessel wall injury.

Obviously, one has to consider that these animal models do not mimic natural conditions, as these animals do not spontaneously develop thrombosis and may not have the hydrostatic component that contributes to PTS.

While animal experimental data do not easily translate to the human situation, thrombus resolution in humans may be expected to follow the same sequence of events. Therefore these models may guide us towards uncovering the underlying pathophysiological processes in humans. Indeed, recent human histological section analysis of chronic occlusive scar tissue resembles late stasis animal model histology, suggesting validity to these models. [28].

5. PTS development

The development of PTS can be roughly divided into three phases.

The acute, thrombotic phase, denoted by active coagulation and inflammatory responses; the sub acute phase, where resolution of the thrombus is associated with pronounced inflammatory reactions, driven by reduced flow and reduced oxygenation; and the chronic phase in which inadequate revascularization and impaired fibrinolysis result in ongoing venous outflow restriction or obstruction. It has been shown that both the thrombus and the vein wall play a role in the development of PTS. [29] See Fig. 1.

6. Acute phase

In acute DVT there is a milieu of activated coagulation and inflammation.

Endothelial dysfunction may be at the origin of the thrombotic process; damaged endothelium may express tissue factor, release von Willebrand factor, and P-selectin, and produce E-selectin, all inducing and amplifying coagulation. Obstruction of the vein by the thrombus results in impaired flow; reduced flow induces hypoxia and consequent processes of inflammation. The thrombus stretches the endothelium resulting in increased permeation of inflammatory cells. [30].

In the early phase of thrombus resolution there is an influx of polymorphonuclear neutrophils (PMNs) that induce fibrinolysis and collagenolysis [31,32]. The leukocyte content of the thrombus is responsible for thrombus resolution, but also for associated vein wall injury. [33] Neutropenia is associated with larger thrombi and more damage to the vein wall. [34] Leucocytes adhering to the endothelium will transmigrate and induce an inflammatory response in the perivasculature; a cascade of inflammatory events will eventually lead to the post thrombotic vein wall changes. The duration, composition, and mechanism of VT all impact the vein wall response. [35] The prevention of leukocyte adhesion to the endothelium may therefore be a plausible target for pharmacotherapeutic interventions. [36].

7. Sub-acute phase

Following the neutrophil influx in the acute phase, monocyte influx peaks in the sub-acute phase. [33] Chemotactic proteins IL-8 and MCP-1 are produced in the thrombus to recruit macrophages. [37] It has been shown in an animal experimental setting that thrombus resolution can be accelerated by administration of these chemokines [38,39]. Inhibition of monocyte influx on the other hand resulted in impaired thrombus resolution, although possibly less vein wall fibrosis. [38] [40], Neovascularization eventually leads to thrombus resolution and recanalization of the vein lumen [41].

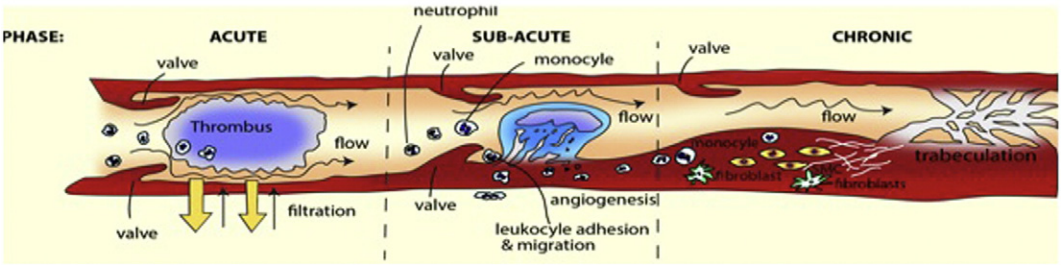

Fig. 1. This figure shows a simplified sequence of pathophysiological processes in the thrombosed vein involved in either resolution of the thrombosis (a mainly inflammatory process) in the acute phase and subacute phase with its associated veinwall remodeling and/or in case of hampered thrombus resolution the forming of trabeculations in the chronic phase, and the ultimate onset of PTS due to high venous pressure.