Important Considerations in the Biology of Postthrombotic Syndrome

Biomarkers, research, and new horizons in the treatment of this serious disease.

BY PETER HENKE, MD

Postthrombotic syndrome (PTS) is the most common sequela to occur after acute deep vein thrombosis (DVT), affecting up to 50% of patients. Approximately 10% to 15% of patients develop severe PTS, and 5% have leg ulceration, which can be severely disabling.[1] From Kahn et al, it is clear that the severity of PTS is set relatively early in its course, generally by 6 weeks.[2] Factors associated with PTS include age, sex, obesity, and, in particular, recurrent ipsilateral DVT. Thus, therapies to decrease the risk of severe PTS need to be timely—specifically, during and around the time of the acute DVT episode. Beyond rapid and therapeutic anticoagulation, limb compression therapy has been called into question. The results from the SOX trial have highlighted the need for effective PTS therapies. Specifically, in this well-designed placebo-controlled trial with more than 2 years of follow-up, 30 to 40 mm Hg of compression did not prevent incidence of PTS.[3] Some concerns have been raised as to whether the placebo compression and therapeutic compression were tracked well for patient compliance. Nevertheless, it is clear that compression may not yield an obvious benefit at this point.

BIOMARKERS OF PTS

There are several biomarkers for incident PTS, relating to perithrombotic inflammation and thrombus resolution (Table 1). In a pilot study, Deatrick et al showed that correlation of acute DVT and resolution was inversely correlated with vein wall thickness and several correlative biomarkers, including toll-like receptor 9, an important factor in sterile inflammation resolution.[4] Rabinovich et al, analyzing data from the Bio-SOX trial, showed that interleukin-6 (IL-6) at 1 month and intercellular adhesion molecule-1 (ICAM-1) at 6 months and 2 years were the best biomarkers for incident PTS.[5] Others have also shown that ICAM-1 and IL-6 were associated with incident PTS.[6] The optimal time to assess biomarkers for predictive value is not clear, as most studies determined the timing empirically. However, a more important unanswered question is this: If severe PTS is predicted by a certain biomarker profile, what additional therapy can be offered?

CURRENT CLINICAL THERAPIES AND LIMITATIONS

Current clinical therapies believed to prevent PTS are primarily rapid and therapeutic anticoagulation and consideration for pharmacomechanical thrombolysis (PMT) for iliofemoral DVT in selected patients. The latter is costly and potentially risky, and the patients who might benefit most from this have not been well defined.[7] The results from a multi-institutional trial, called the

TABLE 1. BIOMARKERS OF VENOUS THROMBOEMBOLISM AND RELATION TO PTS		
Biomarkers	**Activity**	**PTS Prediction**
D-dimer	Fibrin breakdown	No
C-reactive protein	Inflammatory marker	+/-
Brain natriuretic peptide	Cell injury marker	No
ICAM-1	Cell adhesion molecule	+++
IL-6	Inflammatory mediator	++
IL-1	Inflammatory mediator	No
Symbol key: +/- = weak association; ++ = moderate association; +++ = strong association.		

TABLE 2. POTENTIAL NONTHROMBOLYTIC PTS THERAPIES			
Agent	**Mechanism**	**Human Translation**	**Clinically Used**
Low-molecular-weight heparin	Anti-CAM, anticytokine	Yes	Yes
Statin	Antithrombotic, pre-endothelial	Yes	No
P-selectin inhibitor	Anti-CAM, antifibrotic	Not yet	No
Antifactor Xa inhibitor	May decrease fibrosis mediated by IL-6	Unclear	Yes
Anti-MMP agents	Decrease fibrosis	Not yet	No
Abbreviation: Cellular adhesion molecule, CAM.			

ATTRACT trial, which will compare the efficacy of PMT with best medical therapy alone for iliofemoral DVT, will be forthcoming in approximately 2 years. This should provide definitive evidence for or against PMT and hopefully define the spectrum of patients who may benefit most from aggressive intervention.

EXPERIMENTAL STUDIES OF POSTTHROMBOTIC VEIN WALL INJURY

Basic studies of PTS have used rodent DVT models at time points to 21 days.[8] The inferior vena cava (IVC) is used for vein wall tissue and thrombus analysis. The murine models typically used are total stasis with IVC ligation or nonstasis that allows flow around the thrombus as it develops from either an IVC stenosis or an electrolytic injury.[8] Figure 1 shows the current hypothesized early and late vein wall injury after a DVT. The IVC is histologically similar to humans; postendophlebectomy specimens from humans have shown a histoarchitecture very similar to chronic murine IVC appearance, with macrophage and myofibroblast cellular content and predominance of type I collagen.[9-11] Studies have shown that the duration of vein wall thrombus contact, mechanism of thrombogenesis, and thrombus composition itself all contribute to the vein wall response.[9] Plasminogen activator inhibitor-1 and urokinase plasminogen activator are the primary factors involved with thrombus resolution and the size of the thrombus at any given time.[12] As shown by several different experimental studies, the thrombus size itself does not dictate the vein wall injury response.[13-15] Rather, the balances of matrix metalloproteinase activities play a major role, and the vein wall injury response is probably dependent on the plasmin axis.[16,17] For example, genetic deletion of matrix metalloproteinase (MMP)-2 or MMP-9 is associated with less vein wall fibrosis, and plasminogen activator inhibitor-1 overexpression, which inhibits plasmin and MMP-2/-9 activity, is associated with less vein wall fibrosis.[14,15] How these experimentally important factors are related to clinical translation is not yet entirely clear. However, it is clear from work in our lab that low-molecular-weight heparin confers antifibrotic and proendothelial effects.[15,18] Similarly, inhibition of P- or E-selectin (cell adhesion molecules) has also been shown to decrease vein wall fibrosis, probably through modulating leukocyte activities.[19]

ON THE HORIZON

Several key unanswered questions should drive research opportunities going forward (Table 2). First, experimental data suggest that statins may decrease DVT by promoting a profibrinolytic state and may also decrease vein wall fibrosis.[20] Trial data suggest statins may decrease incident DVT,[21] although many at-risk older patients may already be on the statin, and so the clinical affect is unclear. If tri-

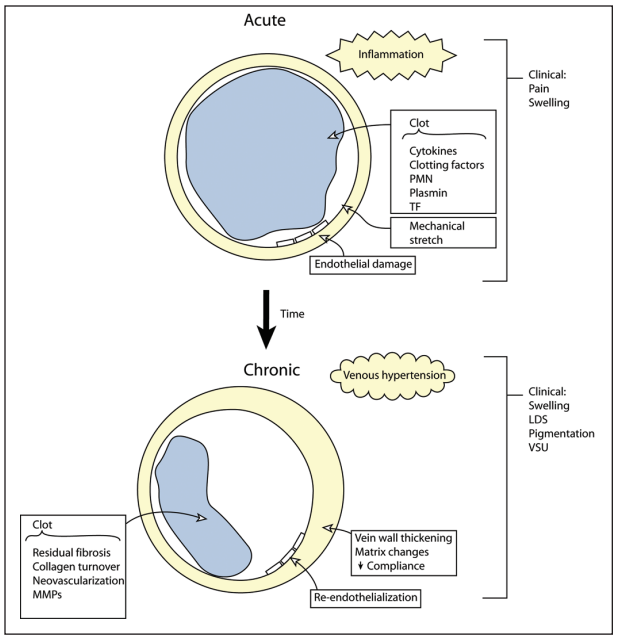

Figure 1. Schematic of early and late experimental vein wall injury. Early venous thrombosis is characterized by distending thrombus of red blood cells and platelets, with release of cytokines, clotting factors, and tissue factor, as well as the primary leukocyte, neutrophil. The later or chronic phase is characterized by dense and contracting thrombus and collagen neovascularization. Macrophages and myofibroblasts populate the residual thrombus and may contribute to release of matrix metalloproteinases. The vein wall is stiff and thickened. Clinically, leg swelling, lipodermatosclerosis (LDS), pigmentation, and possible venous leg ulcer (VLU) may result. PMN = polymorphonuclear neutrophil; TF = tissue factor. Reprinted from J Vasc Surg, 53, Henke PK and Comerota AJ, An update on etiology, prevention, and therapy of postthrombotic syndrome, p. 502, Copyright 2011, with permission from Elsevier.

als of these agents were to be performed in patients who have an acute DVT to determine if statins can decrease incident PTS, the results would likely be both interesting and enlightening. Clinical trial data suggest that low-molecular-weight heparin for a 3-month duration may decrease the risk of severe PTS as compared with warfarin.[22] This is particularly relevant, as not all patients will be thrombolysis candidates. An oral P-selectin inhibitor is currently in trial for sickle cell disease (NCT 01895361) and could be studied for the treatment of acute DVT without the anticoagulant side effects, as well as potentially modifying PTS. Previous work has shown that IL-6 may mediate vein wall fibrosis,[23] as well as being a biomarker, as mentioned; hence, this agent has potential for PTS. An anti-IL-6 receptor called tocilizumab has been used for autoimmune diseases, such as rheumatoid arthritis, with good success.[23]

Other unanswered questions include the timing of novel agent administration in relation to the acute DVT and how the thrombus character may change if fibrosis is impaired. For example, a paradoxic increase in pulmonary embolism might result due to less thrombus–vein wall attachment. Second, it is still unclear how the fibrin scaffold provides the matrix for collagen synthesis, which ultimately leads to vein wall scarring and thickening, as well as potential obstruction. Third, does the iron-rich DVT mediate inflammatory effects that translate to vein wall injury? Moving forward, basic and human research will continue to offer potential exciting therapies to treat this difficult disease. ■

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