CRITICAL ISSUES IN PREVENTING POST-THROMBOTIC RE-ULECERATION

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The lack of effective therapies and the recurrent nature of chronic venous insufficiency (CVI) place a heavy burden on the United States healthcare system. The population-based costs in the United States for treatment of CVI and venous ulcer care has been estimated at over one billion dollars a year. The high incidence and increasing cost of CVI care has renewed interest in this disease process and much has been learned in the past decade.

Primary valvar incompetence with or without obstruction causes ambulatory venous hypertension in the lower extremity. Increased pressure is transmitted to the dermal microcirculation resulting in extravasation or red blood cells (RBCs) and macromolecules. RBCs and macromolecules cause an injury to the dermal architecture resulting in microcirculatory activation of adhesion molecules and leukocyte recruitment. Activated leukocytes in conjunction with increased extra-cellular matrix tension may be the underlying cause of venous ulcer formation. Recently published data from our laboratory indicates that CVI disease progression is associated with increased fibroblast mediated contractile properties and a potential ability to accelerate venous ulcer healing. A consequence of this adaptive wound healing response is increased stored kinetic energy and tension in dermis of patients with CVI. In our experiments, we observed gel contraction in unstipulated gels indicating that fibroblasts surrounded by an extracellular matrix, exert a baseline degree of tension on their surrounding environment. This tension is increased when stimulated with transforming growth factor β1 and/or extracellular signal-regulated kinase inhibition. We believe that an injury to the CVI dermal architecture releases stored kinetic energy in the dermis and clinically manifests itself initially as wound separation. This clinical situation is analogous to a stretched rubber band. When external forces are used to stretch a rubber band, tension is exerted on the elastic fibers within the band. When the rubber band is released, the stored kinetic energy within the elastic fibers is released and the band contracts. It is clear that increased fibroblast contractility is beneficial in healing wounds. However, in patients with dermal fibrosis and increased matrix tension, an injury that causes architectural damage may be the underlying stimulus that releases kinetic energy and causes initial wound separation.

If the above hypothesis is true, then it is logical to assume that medical or surgical correction of venous hypertension should prevent RBC and macromolecule extravasation and stops the underlying inflammatory injury event. Given the fact that compression therapy is the mainstay of venous ulcer healing, there seems to be credence to this hypothesis. Therefore, one must assume that venous ulceration is partially if not completely related to the persistence of venous hypertension in primary CVI. In patients with PTS, the effectiveness of clot resolution and anticoagulation is another related factor.

PTS is the development of CVI after an episode of deep venous thrombosis. Patients with PTS can manifest any of the signs of the CVI from pain and edema to severe lipodermatosclerosis and venous ulceration. Every clinical venous study performed has indicated that PTS patients have worse symptoms and higher venous ulcer recurrence rates. Why the outcomes are poorer is currently unknown. In a recent review by Prandoni in the British Journal of Hematology a proximal venous thrombosis, previous ipsilateral DVT, insufficient oral anticoagulation, and poor vein recanalization after 6 months of anticoagulation were all strong predictors for the development of PTS. Based upon these facts, what are the current roadblocks to preventing re-ulceration in patients with PTS?

1. Pathophysiology of venous ulcer formation. Although great progress has been made over the past 2 decades, the pathophysiology of ulcer formation is still poorly understood. Effective medical and surgical therapies cannot be developed without a better understanding of how end organ damage is caused by venous hypertension.

2. Ineffective anticoagulation and poor venous recanalization strongly suggest that lytic therapy may play a significant role in decreasing the incidence of PTS. Presumably this effect is secondary to valve function preservation and/or the prevention of venous outflow obstruction. Randomized trials are currently being conducted to evaluate the role of venous lysis in the prevention of PTS.

3. We have no objective method or good imaging techniques for determining venous obstruction. Current data on surgical valve repairs or valve transplants have all depended heavily on the subjective assessment of vein patency based on venography. Examination of excised, recanalized veins have documented high-grade stenoses in damaged veins despite their patent appearance on venography. To overcome this roadblock, I suggest the following:
   (a) Re-assess valve repair in conjunction with stenting and/or endophlebectomy.
   (b) Consider re-evaluating angioscopy as a method to assess venous obstruction. Perhaps the angioscope can be modified with a side port that can cut endovenous scar tissue and widen lumen patency.
   (c) Consider a natural history study using an intravascular ultrasound scan to assess venous anatomy in patients with PTS.

4. Compression therapy is currently the gold standard for ulcer healing and recurrence. Despite this fact, ulcer recurrence is still seen in compression patients for reasons that are currently unknown. I propose the following to overcome this roadblock:
(a) We need a different type of stocking. I propose developing smart stockings that can provide clinicians with clinically relevant data. For example, can stocking fibers that change color when the degree of compression decreases be developed? Can we develop remote pressure sensors or holter type pressure sensors that can be interrogated to determine the effectiveness of compression much like holter monitors collect heart rhythm data over a 1-week to 2-week period.

(b) Can we develop a technology that measures skin tension? The greater the dermal fibrosis and scarring the higher the skin tension and, therefore, the greater the likelihood of a venous ulcer recurrence.

5. We need an objective way to assess end organ damage. Imaging that identifies high-risk dermal architecture may help clinicians determine which patients are at risk for developing ulcer recurrences and who are not.