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Stasis microangiopathy: from pathogenesis to treatment

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Abstract

Stasis microangiopathy includes all the pathological changes in the microcirculation and interstitium due to venous hypertension. Venous valve incompetence occurring in the superficial or deep venous system or in both is the most common cause of venous hypertension, a pathological condition that plays a key role in most or all clinical signs of chronic venous disease, including edema and venous ulcers. The aim of the first and main part of this review is to focus on the various pathogenetic mechanisms of stasis microangiopathy triggered by venous hypertension, including hemodynamic and hemorheological alterations, inflammation, and functional alterations. The rationale underlying the current available treatment options of stasis microangiopathy is mentioned briefly in the second part of the review.

Keywords: Stasis microangiopathy, microcirculation, venous hypertension, chronic venous disease, venous ulcer

INTRODUCTION

The term stasis microangiopathy was coined by J.F. Merlen in 1984[1] to define all the pathological changes in the microcirculation and interstitium. The entire microcirculation is affected, at the arteriolar, venular, capillary, and lymphatic level. Venous hypertension represents the starting point of the cascade of pathogenetic events [Figure 1]. In most cases, it is caused by reflux through incompetent valves occurring in

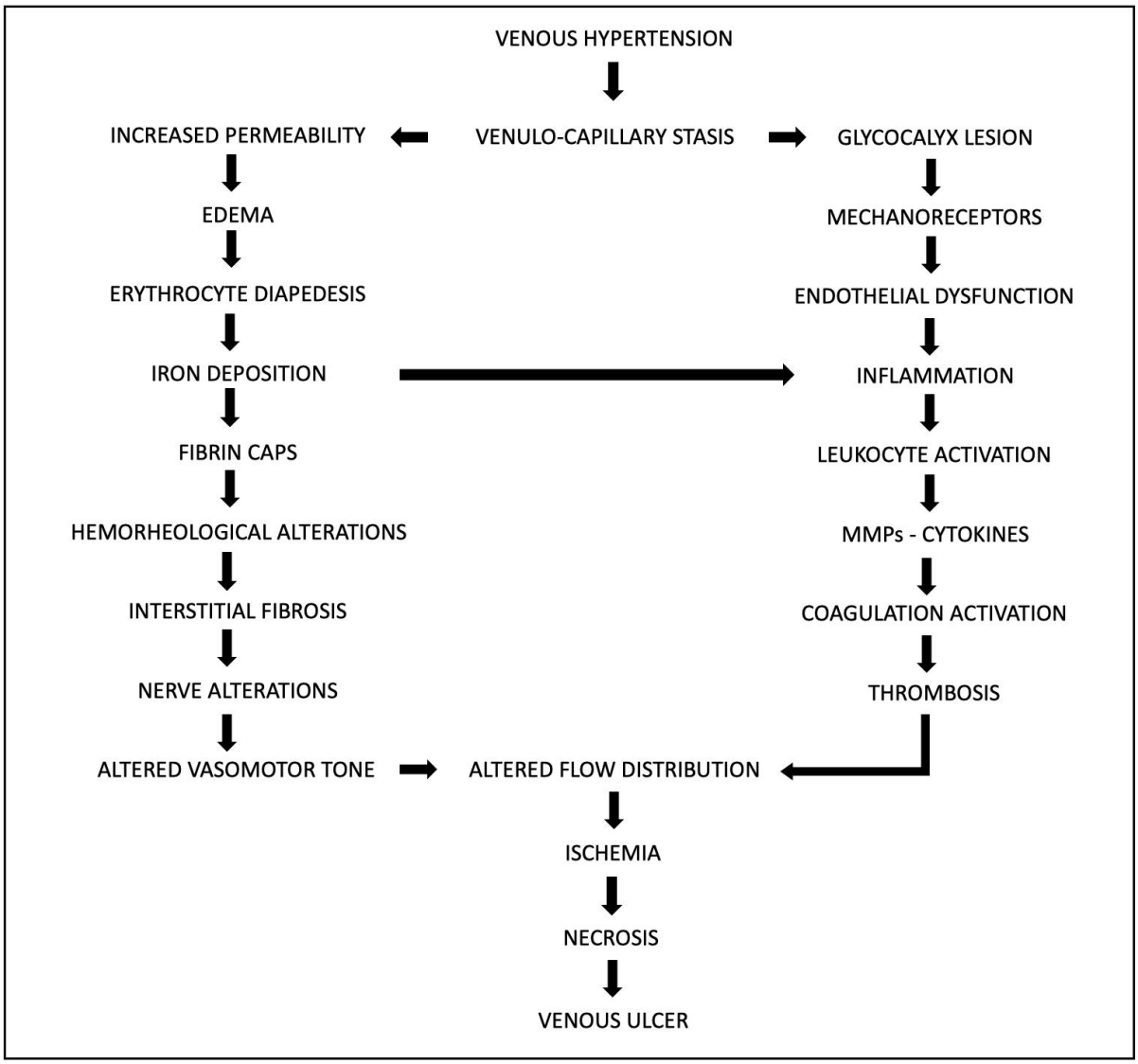

Figure 1. Pathogenesis of stasis microangiopathy. MMPs, matrix metalloproteinases.

the superficial or deep venous system or in both. However, other causes of venous hypertension include venous outflow obstruction, as in post-thrombotic syndrome[1], and severe calf-muscle pump failure owing to paralysis, obesity, or prolonged standing. The increase in venous hydrostatic pressure has peripheral repercussions on the post-capillary venules and capillaries, causing severe hemodynamic changes that affect the arterioles[2]. This review focuses on the various pathogenetic mechanisms of stasis microangiopathy triggered by venous hypertension and the currently available treatment options.

STASIS MICROANGIOPATHY: PATHOGENESIS

Hemodynamic aspects

Building upon their previous research, in 1990, Curri *et al.*[3] showed the presence of microvalves in post-capillary venules and collecting venules and described valvular sclerosis and hyalinosis with consequent loss of function in patients with severe chronic venous insufficiency. In 2006, Caggiati *et al.*[4] confirmed the existence of these microvalves and hypothesized their role as venular anti-reflux devices in the

microcirculation. The microvalves are located in venules, and they reach their maximum number in the vessels with a caliber less than 100 microns[2]. In 2011, Vincent *et al.*[5] showed the incompetence of these valves in patients with severe chronic venous insufficiency using retrograde resin venography. Therefore, venous hypertension is transmitted from the macrocirculation to the microcirculation by the post-capillary venular system. Lesions of microvalves secondary to venous pressure overload lead to the phenomenon of venulo-capillary stasis. The stasis causes a reflex constriction in the pre-capillary arterioles with a blood flow reduction[1]. Venulo-capillary stasis causes an increase in endothelial permeability, with opening of the intercellular spaces, slipping of the basement membrane, extravasation of liquids from the capillaries, and interstitial flooding[6]. The increased shear stress secondary to venous hypertension causes damage to the glycocalyx that covers the endothelium and consequent activation of inflammatory events, which we discuss in a dedicated section[7].

The role of the lymphatic system

The drainage of interstitial fluids is an almost absolute prerogative of the lymphatic circulation, which acts as a "safety valve" against inflammation, removing proinflammatory molecules from interstitium, and edema[8]. In fact, edema develops only when the production of interstitial fluid exceeds the drainage capacity of the lymphatic vessels. The increased intra-capillary pressure is initially counteracted by the increase in interstitial pressure, secondary to the accumulation of interstitial fluid, and by the decrease in colloid osmotic pressure, which determines a pressure gradient that favors the entry of liquid into the capillaries. The balance is altered when a condition characterized by a progressive increase in intra-capillary pressure occurs, such as in case of inflammation (e.g., stasis dermatitis and lipodermatosclerosis). At this point, the lymphatic system reacts to avoid edema by increasing its drainage capacity[9]. It is interesting to understand why edema still occurs despite this compensation mechanism. Studies with fluorescence microlymphography have shown an obstruction of the superficial lymphatic vessels, a reflux from the deep to the superficial lymphatic system, and an increased capillary permeability[10]. Studies with CapiFlow have shown an absence of flow motion and an activation of deep lymphatics due to interstitial hypertension[11]. At the histological level, lesions of the anchoring filaments opening the lymphatic vessels and collapses of the lymphatic vessels of the dermis have been reported[6]. Other histological studies at the bed of venous ulcer and its edges revealed a severe loss of lymphatic vessels that resulted totally absent in the bed of the ulcer[12]. This severe alteration of the lymphatic circulation also causes a localized immune deficit, secondary to loss of immune surveillance, and susceptibility to infections. This finding would provide an explanation for the susceptibility to skin infections observed in patients with chronic venous disease (CVD) at Clinical Etiological Anatomical Pathophysiological (CEAP) classification C6 stage[6].

Hemorheological aspects

When stasis occurs, there is a marked increase in the aggregation of erythrocytes with consequent obstruction of the capillaries, altered distribution, and slowing of tissue blood flow until it stops. In addition, the erythrocytes lose their discoid shape, transform into spherocytes and echinocytes, and become rigid, with further reduction in tissue blood flow. This phenomenon was described in 1975 by Schmidt and Schombein as "collateral blood viscidation"[13]. In this setting, there is an increased erythrocyte diapedesis with deposition of erythrocytes in the interstitium, deposition of hemosiderin, and release of iron, which causes both direct tissue lesions secondary to toxicity and production of free radicals that activate inflammation[14].

The fibrin caps

In 1982, Burnand *et al.*[15] showed the presence of fibrin deposits in the pericapillary space secondary to the increased capillary permeability and hypothesized that these "fibrin caps" reduced exchanges between blood and tissues, contributing to the formation of the venous ulcer. However, this hypothesis was rejected by

other studies which showed that fibrin caps were also present in healed ulcers and that application of Xenon-133 to the skin of patients with fibrin caps had the same clearance as healthy subjects[13,16]. Falanga *et al.*[17] hypothesized that fibrin trapped growth factors, making them unavailable for ulcer healing, thereby delaying reparative processes.

Inflammation

The lesions of the glycocalyx secondary to the venulo-capillary stasis and the consequent increase in shear stress cause the activation of endothelial mechanoreceptors and the endothelial production of E-selectins that interact with the L-selectins produced by leukocytes, leading to rolling of these cells along the endothelial surface. When leukocytes are activated, they express integrins, which bind to intercellular adhesion molecule 1 (ICAM-1) expressed by endothelial cells, and this event represents the starting point for their migration into the interstitium and for their subsequent degranulation[18-19]. The activation of matrix metalloproteinases (MMPs), especially MMP-2[20-22], is a subsequent event. On the other hand, the tissue inhibitor of MMP-2 (TIMP-2) is reduced[20-22]. The reduction of TIMP-2 activates inflammation and causes damage to the intercellular matrix by MMPs. The deposition of iron in the tissues further activates the MMPs, which, together with free radicals, accentuate the tissue damage. On the other hand, the production of transforming growth factor β1 (TGF-β1) in the context of inflammation stimulates collagen production leading to fibrosis[14].

Functional alterations

Inflammation does not spare the peripheral nerves, and for this reason a neuropathy secondary to venous stasis also develops leading to vasomotor changes[23], consisting of abolition of the veno-arteriolar reflex[24], reduction of reactive hyperemia, heating hyperemia, and neuro-mediated vasodilation[25-27]. At the level of the venous ulcer, laser Doppler imaging has allowed detecting a high blood flow in the areas with granulation tissue, a low blood flow in the areas without granulation tissue, and a high blood flow both at the edges of the ulcer and at the adjacent areas of lipodermatosclerosis[28]. On the other hand, transcutaneous carbon dioxide tension was very low both at the bed of the ulcer and at the edges[29]. These two apparently conflicting observations led Partsch to define this condition as "hyperemic hypoxia"[30]. At the capillaroscopic level, different conditions have been described in the areas of lipodermatosclerosis depending on the clinical stage of the ulcer. The initial stages are characterized by a pericapillary halo secondary to increased permeability, a moderate capillary dilation, and capillary tortuosity. In the intermediate stages, the pericapillary halo and capillary dilation are accentuated. The advanced stages are instead characterized by a reduction in the number of capillaries. In the zones of atrophie blanche (white scar tissue), there are avascular areas and few huge and convoluted capillaries. In the ulcerated areas without granulation tissue, there are no capillaries, while, in the areas with granulation tissue, there are few giant capillaries and edema[31-32]. The histological examination revealed micro-vessels occlusions, dilation of endothelial junctions, alteration of lymphatic vessels and anchoring filaments, and fibrosis of the interstitial matrix[23].

STASIS MICROANGIOPATHY: TREATMENT

Compression therapy

It has been reported that compression therapy can significantly improve symptoms and reduce lower limb volume in patients with CVD by improving the function of cutaneous microcirculation[33]. Grenier *et al.*[34] investigated the relationship between skin microcirculatory activities and external compression provided by elastic compression stockings by measuring skin thermal conductivity in a group of 30 female subjects having minor symptoms of CVD (CEAP C0S and C1S) and observed an improvement of microcirculatory activities in 83% of them.

Compression therapy performed with both bandages and elastic stockings has multiple actions on the microcirculation, such as a reduction in venulo-capillary permeability, an increase in skin capillary perfusion with increased nitric oxide and activation of fibrinolysis, and an increase in cutaneous vasodilation through the activation of capsaicin receptors[33-36]. Histological studies have shown that compression reduces edema and venulo-capillary ectasia[37]. Studies with CapiFlow[38] have shown a reduced endolymphatic pressure. A reduction in leukocyte adhesion and oxidative stress has also been demonstrated.

Pharmacological therapy

Two classes of drugs have been shown to significantly interfere with stasis microangiopathy: the purified micronized flavonoic fraction (FFPM) and glycosaminoglycans (GAGs).

FFPM increases sympathetic-mediated venular contractility, reduces leukocyte adhesion by reducing the production of adhesion molecules, and reduces the production of pro-inflammatory molecules. Furthermore, FFPM increases the production of antioxidant factors; reduces the concentration of ICAM-1, vascular cell adhesion molecule 1 (VCAM-1), and vascular endothelial growth factor (VEGF); and reduces the permeability of capillaries.

GAGs (sulodexide and mesoglycan) restore the glycocalyx, activate fibrinolysis by acting on plasminogen activator inhibitor and tissue plasminogen activator, have antithrombotic action by acting on antithrombin and heparin cofactor II, and reduce thrombin-induced platelet aggregation. GAGs also have anti-inflammatory action by acting on cytokines, tumor necrosis factor α (TNF-α), TGF-β1, VEGF, and interferon gamma (IFN-γ); blocking chemokines; modulating macrophages; and blocking MMPs (sulodexide)[2,39,40].

Maresca *et al.*[41] studied the effect of mesoglycan on cutaneous blood flow measured by laser Doppler fluometry (LDF) in a group of 75 female patients (aged 45.5 ± 9.6 years) in different stages of CVD, according to the CEAP classification. The active group (N = 37) received mesoglycan 50 mg twice daily in adjunct to standard care. After 90 days of treatment, mesoglycan obtained a significative increase in peak flow at LDF in the entire group of treated women[41]. In a systematic review and meta-analysis, Bignamini *et al.*[42] assessed the efficacy and safety of sulodexide for treatment of signs and symptoms of lower extremity CVD. Sulodexide was found to have a beneficial venoactive effect on the major signs and symptoms of CVD such as pain, cramps, heaviness, and oedema, with the exception of discoloration, which appeared unaffected by the treatment. Furthermore, sulodexide was found to be effective in decreasing the release of inflammatory markers present in CVD, such as interleukin-6, monocyte chemoattractant protein-1, soluble intercellular adhesion molecule-1, and free radicals.

Interestingly, it has been shown that vasoactive and anti-inflammatory properties of aminaphtone may be useful in treatment of chronic venous and lymphatic stasis[43]. Aminaphtone reduces the expression of endothelial-leukocyte adhesion molecule 1 (ELAM-1), VCAM-1, and ICAM-1, as well as the production of cytokines and vasoconstrictor agent endothelin-1, playing a potential role in treatment of other vascular diseases such as Raynaud's phenomenon[44].

The combination of Ruscus, hesperidin methylchalcone (HMC), and vitamin C has recently been awarded a Grade 1A recommendation by the international guidelines[45]. A review of clinical studies and a meta-analysis have confirmed its clinical efficacy across a wide spectrum of CVD clinical classes: C0S, C1S, C2, C3 and C4[46]. The combination of Ruscus, HMC, and vitamin C acts by increasing venous and lymphatic

tone, protecting microcirculation, and reducing inflammation. In the microcirculation, Ruscus showed a protective effect against histamine-and ischemia/reperfusion-induced leakage in the hamster cheek pouch model, and these effects appeared to involve α1-adrenoreceptors and muscarinic receptors[46-48].

CONCLUSIONS

Stasis microangiopathy is a pathology with a very complex pathogenesis characterized by the interaction of multiple factors. There are still many areas of uncertainty that need further studies to be fully understood. Treatment of stasis microangiopathy is based on compression therapy and drugs. Compression therapy removes the "upstream" pathological trigger by reducing venous hypertension, which is the "primum movens" of the disease. Drugs, on the other hand, act "downstream" on various hemodynamic, hemorheological, and biochemical factors, which interact and cause the tissue damage that characterizes stasis microangiopathy.

DECLARATIONS

Authors' contributions

Literature review, manuscript preparation, review of the manuscript: Bilancini S
Literature review, review of the manuscript: Lucchi M
Literature review, review and editing of the manuscript: Ciacciarelli M

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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