

Involvement of Varicose Veins in Superficial Venous Thrombosis

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Abstract

Varicose veins are usually a sign of a benign disease, however with progression of the disease and advanced age, they can lead to serious clinical problem. Beside chronic venous insufficiency, superficial venous thrombosis (SVT) represents one of the most frequent complications which can complicate with deep venous thrombosis (DVT) and pulmonary embolism. Classical risk factors for SVT are similar as for DVT. However, varicose veins represent one of the most important risk factors for the development of SVT. In varicose veins blood flow is usually turbulent, with increased shear stress which causes vascular damage, resulting in endothelial dysfunction and structural deterioration of vessel wall accompanied by inflammatory response. Because of changes in hemodynamic conditions, in varicose veins the constitution of blood is changed. In varicose veins haematocrit level is increased and consequently blood viscosity. Further, in the blood of varicose veins circulating inflammatory markers are increased, as well as circulating markers of endothelial damage. There is also imbalance between the pro-and anticoagulant factors and between pro-and antifibrinolytic agents favouring hypercoagulable microenvironment. Therefore, varicose veins represent the highest risk for development of SVT.

Keywords: Varicose veins; Superficial venous thrombosis; Deep venous thrombosis; Hemodynamic conditions

Introduction

Varicose veins are one of the most frequent vascular diseases, with the highest prevalence and incidence in advanced age (prevalence 40 to 60% in females and 15 to 30% in males) [1]. In most of the cases the disease takes a benign course. However, advanced stages are frequently associated with complications, such as chronic venous insufficiency with or without ulceration and thrombotic complications, especially superficial venous thrombosis (SVT) and deep venous thrombosis (DVT).

Therefore, early detection and management of varicose veins is very important to prevent progression of the disease and thromboembolic complications.

SVT represents one of the most frequent and serious complications of varicose veins which can cause DVT with related complications, like pulmonary embolism. Therefore, SVT is accepted as part of a venous thromboembolic syndrome, which should be very carefully managed.

Pathogenesis of Superficial Venous Thrombosis

Already in the middle of 19th century, Virchow proposed a triad of causes for venous thrombosis postulated that blood stasis, damage of vessel wall and changes in the blood constituents could lead to thrombus formation. All these pathogenetic mechanisms are involved in thrombus formation in the deep and in the superficial veins [2]. Risk factors for SVT are similar as for DVT and include cancer, oestrogen pill for birth control, hormone replacement treatment, obesity, genetic predisposition, intravenous catheters and varicose veins. Risk factors can provoke development of SVT through one of the mechanisms described by Virchow. Varicose veins represent one of the most important risk factors for SVT and varicose veins are present in up to

90% of patients with SVT [3,4] and 10-20% of patients with varicose veins develop SVT [5]. Varicose veins represent increased risk for SVT because of the involvement of all three basic pathogenetic mechanisms described by Virchow. In tortuous and dilated varicose veins, particularly in convolutes blood flow is turbulent, allowing blood to pull in the dilated vessel instead of streaming straight through in one direction. It causes damage of vessel wall endothelium and is responsible for changes of blood composition. Turbulence flow causes vibration of vessel wall and these vibrations produces accelerated degenerative changes in vascular tissue and contribute in the degeneration of elastic fibres of vessel wall [6]. Sustained laminar flow with high shear stress upregulates expression of endothelial cell genes and proteins that are protective against vessel wall damage, whereas disturbed flow with low shear stress upregulates the endothelial genes that promote deterioration of vessel wall [7]. The abnormal pattern of blood flow leads to thrombosis also because of prolonged platelet contact with endothelium and reduced blood flow, due to weakness of vein wall and disruption of function of vessel valves [8]. Stasis of blood and turbulent flow influence the constitution of blood in the direction of increased coagulability. Valvular stasis, particularly in valvular sinuses is associated with hypoxia, which cause endothelial dysfunction and increased haematocrit [9], constituting potentially hypercoagulable microenvironment. Slow and turbulent blood flow, because of hypoxia and mechanical damage down regulate expression of anticoagulant proteins (activated protein C and thrombomodulin), contributing to the initiation of thrombosis [10] and can lead to upregulation of procoagulant activity including tissue factor on endothelium [11]. In addition hypoxia and damage of endothelial cells may also upregulate the expression of P-selectin on endothelium leading to the recruitment of leukocytes and microparticles containing tissue factor. Therefore, also microparticles, wearing tissue factor appear to play a role in thrombus formation [12,13].

Varicose veins, inflammation and increased thrombotic potential

Evidence has accumulated to support the role of venous hypertension and changes in shear stress because of turbulent flow in the development of inflammation of venous wall. Low shear stress and blood stasis promote the production of inflammation and thrombotic mediators [14]. Studies have also shown that plasma markers of leukocyte activation and vascular cell adhesion molecules are increased after subjecting patients with varicose veins to 30 minutes standing in order to induce venous hypertension [15]. In recent studies we compared the blood constituents of local blood taken from varicose veins and systemic blood [16]. It was shown that some circulating inflammatory markers as high sensitive CRP (hs-CRP) and interleukin 6 (IL-6), were significantly increased in blood samples taken from varicose veins.

The data indicates that inflammation and haemostasis are coupled with common activation pathways and feedback regulation system. During inflammation, the haemostatic balance may be disturbed resulting in increased production of procoagulant factors and down regulation of anticoagulant mechanisms [17]. Inflammation also inhibits fibrinolytic activity, as confirmed by negative relationship between some inflammatory markers and tissue plasminogen activator (t-PA) activity. However, the crosslink between inflammation and haemostasis is complex and involves different reactions, endothelial damage and the production of cell derived microparticles [18]. Therefore, local inflammation of venous wall because of turbulent flow maybe involved in the progression of the disease and appearance of SVT. This presumption is confirmed by clinical findings which showed that thrombosis of the superficial veins appears in 90% case of varicose veins [19]. Only a few studies have investigated systemic inflammatory response in patients with varicose veins. One of the studies found a marked expression of monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein, interferon gamma inducible protein10 (IP-10), and interleukin-8 in varicose veins. These chemokines may play an important role in the pathophysiology of varicose veins by recruiting the leukocytes to the vein wall, contributing to inflammation and thrombotic occlusion [20].

Endothelial Dysfunction and Superficial Vein Thrombosis

Trauma of endothelium and damages arising from shear stress of venous hypertension and turbulent flow are expected in varicose veins. We also showed that endothelial dysfunction is present in patients with idiopathic venous thrombosis and is probably the starting point of venous wall cell damage in patients with varicose veins followed by thrombotic occlusions of affected vascular segments [21]. The studies also reported that von Willebrand factor (vWF) an indicator of endothelial damage is significantly increased in varicose veins compared to the levels in systemic blood taken from the cubital vein [16]. Vascular endothelium is important regulatory organ in maintaining cardiovascular homeostasis. Its function includes control over thrombosis and thrombolysis, platelet and leukocyte interaction with the vessel wall, regulation of vascular tone and smooth muscle cells proliferation. Endothelial damage contributes to the inflammation of vessel wall, vasoconstriction, excessive thrombus formation and adhesion of leukocytes to the vessel wall [22]. Endothelial dysfunction additionally influences the venous flow and causes imbalance between the pro-and anticoagulant activity with increased release of

procoagulant factors and reduced release of profibrinolytic substances. Therefore, also because of endothelial dysfunction, in varicose veins there is an imbalance between pro-and anticoagulant as well as pro-and antifibrinolytic factors with promoting prothrombotic state which can result in SVT. Increased thrombotic potential in varicose veins is also confirmed by increased levels of D-dimer [16]. These findings suggest increased local formation of thrombin and not fibrin which is probably a consequence of damage of the vessel wall and increased tissue factor release, which can induce thrombus formation and development of SVT.

In conclusion: varicose veins in most cases represent benign disease. However, with progression of the disease hemodynamic conditions change so far that convolutes of affected veins are forming and blood flow is disturbed. Because of turbulent and stagnant blood flow, venous pressure increases. Consequently, vessel wall is damaged because of changes in shear stress and blood constituents in varicose veins in comparison to systemic blood are changed, constituting a potentially hypercoagulable microenvironment. Damage of vessel wall is followed by inflammatory response, which affects the endothelial function and promotes procoagulant processes in affected varicose veins. In varicose veins procoagulant factors are increased and anticoagulant and profibrinolytic mediators are decreased. Therefore, varicose veins are associated with a high risk for development of superficial venous thrombosis.

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