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Review article

The inflammatory reaction during chronic venous disease of lower limbs

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Abstract: Chronic venous disease (CVD) is an insufficiency of distal veins caused by their partial or total obstruction, endothelial distension and functional disorders. Chronic venous disease of lower limbs is common problem and affects millions of people. In this article we suggest that inflammatory process is involved in the structural remodeling in venous valves and in the venous wall, leading to valvular incompetence and the development of varicose veins.

Key words: chronic venous disease, inflammatory process, leukocytes

Introduction

Chronic venous disease (CVD) is an insufficiency of peripheral veins caused by their partial or total obstruction, endothelial distension and functional disorders. Chronic venous disease is one of the most common diseases [1]. It is a significant social, medical and economic problem [2]. CVD of lower limbs is frequent among Western populations [3,4].

Manifestations of chronic venous disorders of lower limbs include: teleangiectases, varicose veins, edema, trophic changes and chronic leg ulceration. More advanced abnormalities of vasculature system such as: edema, skin changes and ulcerations are called chronic venous insufficiency (CVI) [5].

Implementation of the international classification system (CEAP) (the clinical class – C, the ethiology – E, the anatomical – A, the pathophysiology – P), created by American Venous Forum, describes occurrence and intensity of venous pathology, and it is a significant progress of chronic venous disorders characterization [5,6]. Thanks to the international CEAP classification the identification and treatment of CDV is easier.

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Despite numerous research about the pathophysiology of CVD the underlying etiology remains not well understood. The aim of this study is to present new views about the CVD pathophysiology. In this article we try to present the inflammatory process as the major cause of CVD.

Pathophysiology

The reason of the majority of chronic venous disease symptoms is prolonged exposure to venous hypertension caused by venous wall abnormalities and valvular incompetence [7].

The venous hypertension and outflow disorders may be caused by process which leads to pathological changes of the venous wall. Development of venous hypertension is caused by reflux through incompetent venous valves [8]. Reflux of blood can be present in deep veins of lower limbs, superficial veins of lower limbs and perforator veins of lower limbs. Venous reflux is one of the major mechanism responsible for development of venous hypertension [9]. A lot of research about the etiology of venous valves incompetence have been done. One of them assume, that the venous wall extension is the reason of valvu-

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lar incompetence [10]. Susceptibility of the venous wall for stretching mainly depends on the smooth muscles and connective tissue fibres content in tunica media. It's known that intracellular matrix alterations of the venous wall is the cause of the development of CVD [11-13]. The property qualitative and quantitative composition of the intracellular matrix is the condition of the correctly building and integrality of the venous wall. Collagen and elastin are venous wall proteins, that play the major role in maintenance of an appropriate resilience and endurance of the venous wall [14-16]. Glycosaminoglycans constitute structure of intracellular matrix and thanks to interaction with the other components they influence on the venous wall properties. There are reports that present connections between smooth muscles and elastin fibers. These connections are significant for venous endurance when venous pressure is elevated. In varicose veins alterations of elastic fibers structure are present and they are separated from smooth muscle fibers [17]. A deficiency of type III collagen was observed in CVD patients [18].

Recent studies suggest that proteinases released by inflammatory infiltration cells, may be responsible for the venous wall hypertrophy. Inflammatory infiltration cells cause matrix metalloproteinase (MMP) activation and collagen dissolution in extracellular matrix. Moreover, activated endothelial cells release transforming growth factor-β (TGF-β), which causes migration of muscularis cells and their proliferation in tunica intima [19]. The long-lasting secretion of TGF-β induces MMP and tissue inhibitor of metalloprotease (TIMP) releasing [20]. The balance disorder between MMP and TIMP also seem to be important in extracellular matrix damage [21,22]. The other evidence suggest that altered hemodynamics and abnormal blood flow are main causes of the valvular damage [23]. Next research suggest that reflux in vessel lumen is caused by the valvule extension, atrophy of valve cusp and hemodynamic alterations [24,25].

Recent studies has focused on the theory of the venous wall and valvular damage as the one of the major cause of the developmentof CVD, caused by chronic inflammatory process. Recent advances have shown that chronic inflammatory process and leukocytes – endothelial cells interactions are involved in vessel lumen dysfunctions, valvular incompetence, reflux, venous hypertension, varicose veins and ulcerations [26].

Molecular mechanisms involved in the inflammatory process

Recent advances in the understanding of CDV focused on interactions between leukocytes and vascular endothelial cells [27]. Attention has focused on the role of leukocytes in the pathophysiology of changes of the venous wall structure. The intense leukocytes infiltration, mainly macrophages and lymphocytes in CVD patients was observed [28]. The amounts of granulocytes, monocytes, macrophages and T lymphocytes increased in the venous wall of veins with the elevation of the blood pressure [29]. B lymphocytes also were present [30].

Chronic elevation of the blood flow through the venous pressure and shear stress alterations, may cause endothelial cell and leukocytes activation [31-33]. Investigation of the leukocytes shows that the most activated leukocytes are isolated from patients with venous hypertension [34]. Activation of endothelial cells may be caused by their mechanical extension and that is linked with pathological blood flow and shear stress alterations [35]. It is clear that and shear stress is the major factor which affects endothelial cell functions [36].

The molecular mechanism of leukocytes adhesion to endothelial cells involves two stages. The first stage is called "I type activation", and it appears quickly. The activation consequentions are: endothelial cells constriction, selectin expression and von Willebrand factor (vWf) releasing. The second stage is called "II type activation", and involves adhesion molecules, cytokines and tissue factor [37-39].

The process of leukocytes extravasation can be divided into four steps: rolling, activation, adhesion and transendothelial migration [40] (Fig. 1). Extravasation of lymphocytes involves interaction of cell-adhesion molecules, their activation and chemokines activity [41-43].

During rolling leukocytes attach loosely to the endothelium by a L-selectins and E-selectins, which tether leukocytes to the endothelial cells [44]. Leukocytes tumbles end-over-end along the endothelium. Subsequently leukocytes are activated by various chemoattractants *e.g.*: interleukin 8 (IL-8), complement split products, macrophage inflammatory protein (MP-1β) and N-formyl peptides. Moreover, hypertension is the cause of red blood cells (RBCs) extravasation, which degradation products are potent chemoattractants and presumably represent the initial signal for leukocytes. Also hypoxia leads to increased production of platelet activating factor (PAF), which activate leukocytes [44,45,46,47]. Binding of these chemoattractants with leukocytes surface receptors is an activating signal. In the next step, shedding of adhesion molecules from leukocytes surfaces occurs as a result of proteolytic enzymes action and they circulate as a soluble molecule in plasma [48]. Several studies have shown that plasma levels of soluble L-selectin increased in CVD patients [29]. Plasma levels of the adhesion molecules (ICAM-1), endothelial leukocytes adhesion molecule (ECAM-1), vascular cells adhesion molecule (VCAM-1) were higher in CVD patients than controls [49]. The acti-

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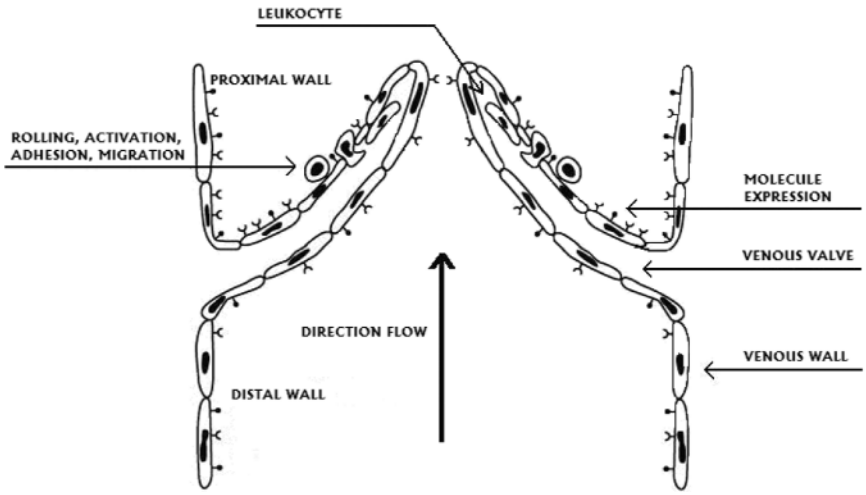

Fig. 1. Leukocyte- endothelial interactions on a venous valve [27].

vating signal induces a conformational changes in the integrin molecules. Increasing of the integrin molecule affinity for Ig-superfamily adhesion molecules on the endothelium occurs. The interaction between integrins and Ig-superfamily adhesion molecules provides firm adhesion of leukocytes to the endothelial cells. Leukocytes firm adhesion triggers their migration through the endothelium [50].

Numerous works have shown the leukocytes sequestration in valve cups and in the venous wall in CVD patients compared with controls [21]. Several studies confirm the "white cell trapping" hypothesis and massive leukocytes activation in the microcirculation followed by their migration to subcutaneous tissue [51]. This phenomenon is responsible for production and releasing of cytotoxic substances which lead to skin ulceration and also valve cups and the venous wall destruction [52-55]. Leukocytes produce, accumulate and release: histamine, tryptase, prostaglandins, leukotriens and cytokines. Histamine increases endothelial permeability and proliferation of smooth muscle cells. The evaluation of the amount and localization of infiltrative cells, shows that they are the most numerous in the proximal venous wall and in the valve cups [56].

Activated leukocytes migrate through proximal parts of endothelial cups and venous wall and cause the supporting elements destruction and valvular reconstruction, which may cause the valvular incompetence. Leukocytes through penetration to the skin and subcutaneous tissue may also trigger trophic changes and ulcerations [57].

Summary

Recent studies have shown that the inflammatory process plays a significant role in CVD pathophysiology. Reconstructions of the venous wall and venous valves, associated with their dilatation and relaxation, are the basic mechanism of the development of CVD and it is associated with the inflammatory process on their surface. Leukocytes activated during the inflammatory process release proteolytic enzymes, free radicals and cytokines which are responsible for the changes of the venous wall and venous valve, and also the development of tissue destruction and skin changes [58]. Moreover, inflammatory process in CVD patients secondarily leads to valvular incompetence, reflux and venous hypertension which further promote development of inflammatory reaction. Detailed understanding of these phenomenon may help with early CVD treatment, that aim is to inhibit inflammatory process. That may prevent complications of CVD development.

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