ОГЛЯДИ

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Pathophysiological mechanisms of varicose veins in the lower extremities

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Varicose veins are a frequent, multifactorial disease. Despite its prevalence, the pathophysiological mechanism of varicose veins remains incompletely understood. According to various sources, the key mechanisms of the development of this disease are valvular insufficiency and changes in the venous wall. The fundamental question is whether valvular insufficiency precedes and affects the development of changes in the venous wall, or vice versa. The purpose of this study is to analyze the current state of the problem of studying the mechanisms of development of varicose veins of the lower extremities. This review presents the latest data on etiological, pathophysiological and pathogenetic factors involved in the development of varicose veins. Anatomical, ultrasound, and plethysmographic studies have proven that the presence of valvular insufficiency is often found in patients with varicose veins of the lower extremities. Examination of the venous wall reveals structural remodeling in all three layers, hyperplasia of intimal cells and smooth myocytes. The structures of the extracellular matrix play a special role in changes in the venous wall. Changes in the structure of the veins further deepen the valve insufficiency, starting a vicious circle. In addition, the review examines the role of heredity, increased intraabdominal pressure, hormonal and other etiological and provoking factors of varicose veins.

Key words: chronic venous insufficiency; varicose veins; venous valves; venous wall, extracellular matrix.

INTRODUCTION

The term chronic venous disease (CVD) includes the full spectrum of morphological and functional abnormalities of the venous system, from telangiectasias to venous ulcers. Functional disorders of the lower extremity veins causing edema, skin changes, or venous ulcers are clinically known as chronic venous insufficiency (CVI), a term reserved for advanced CVD [1].

The most common manifestation of CVD is varicose veins, or varicose disease of the lower extremities (VDLE). In Western countries, about one third of the adult population suffers from varicose veins. Morphological and functional disorders of the venous system last for a considerable time and are manifested by symptoms that indicate the need for examination and treatment. Patients with CVD may suffer from pain, itching, swelling, skin discoloration, bleeding, and venous ulceration [2]. In addition to visual manifestations and symptoms, CVD carries an increased risk of venous thrombosis and thromboembolism [3].

Despite its prevalence, the pathophysiological mechanism of varicose veins remains not fully understood. Valvular insufficiency and reflux are common features of primary varicose veins and have long been considered their cause. A fundamental question is whether venous hypertension and valvular insufficiency precede and influence the development of changes in the venous wall, or vice versa [4, 5].

The purpose of this study is to analyze the current state of the problem of studying the mechanisms of development of varicose veins of the lower extremities.

The venous system depends on the capacity

of the valves, the ability of the vein wall to stretch and contract, and the hemodynamics of the venous blood flow. These components are interdependent, and a violation of one affects the integrity of the others. Secondary changes in the structure of the veins further affect the initial factor, starting a vicious circle. By the time when varicose veins manifest themselves clinically, and the patient seeks an appointment with a doctor, all components of the venous blood flow are usually already disturbed, which makes it difficult to determine the sequence of pathological events [6-8]. In addition, etiological and provoking factors such as heredity, prolonged standing as a result of professional activity, pregnancy, etc., are distinguished. The multifactorial etiology of the disease makes it difficult to understand the pathogenesis of varicose veins [9].

The role of hemodynamic factors in CVD

The veins of the lower extremities consist of a deep venous system and a superficial one, interconnected by perforating veins that pass through the fascia. The most important driving force behind venous blood flow is the contraction of the skeletal muscles surrounding the veins, which act as pumps that squeeze and empty the veins, pushing blood toward the heart. Perforating veins play an important role in the hemodynamics of the lower extremities. Linton defined direct perforating veins as veins connecting superficial veins with deep ones, and communicating veins as veins connecting superficial veins with muscular ones [6, 7, 10]. Valves are present in both venous systems to allow blood to flow in one direction: from the superficial to the deep system, to the heart, and against gravity. Under normal physiological conditions, venous flow is transmitted from the superficial system to the deep system and proximal to the central veins in the cranial direction. All mechanisms that ensure the movement of venous blood to the heart can function only if the valve apparatus is preserved [11, 12].

Varicose veins can be a consequence of insufficiency of these valves, leading to the reverse transfer of the pressure gradient from the deep system to the superficial through the saphenofemoral junction and perforating veins [11]. Depending on the type of valvular insufficiency, a distinction is made between vertical blood reflux (in superficial or deep veins) and horizontal reflux (in perforating veins) [13].

Anatomical, ultrasound, and plethysmographic studies have proven that the presence of valvular insufficiency is often found in patients with VDLE. The most common location of pathological valves was found in the distal segment of the venous network [14, 15]. Engelhorn et al. [16] conducted an ultrasound examination of 590 limbs in patients with class 2 according to the CEAP (clinical-etiological-anatomical-pathophysiological) classification. The prevalence of reflux during ultrasound examination revealed reflux in the large saphenous vein in 77% of patients, segmental reflux was detected in 58%, and only in 12% of cases reflux was detected in the saphenofemoral junction.

In some studies, it was also found that an increase in venous pressure, in particular the pressure in the inferior vena cava, correlates with the severity of the disease [17]. This hypothesis is supported by data that obesity, multiple fertility, and professions that require prolonged standing are strong risk factors for the development of VDLE [18, 19]. This is explained by the fact that the increase in intra-abdominal pressure is transmitted distally to the veins of the limbs, causing them to stretch, and the stretching of the venous wall leads to secondary valvular insufficiency due to non-closure of their leaflets [19-21]. And this is additionally confirmed by the clinical improvement of symptoms in compression stockings in patients with CVD, because properly selected compression stockings normalize venous pressure and at the same time do not affect the structure of the veins and their valves [22, 23]. Today, there are ascending

and descending theories of the development of VDLE. The so-called descending theory was the first, described for the first time by the founder of phlebology - Friedrich Trendelenburg, who published his experience of interrupting the great saphenous vein in 1891 [24, 25]. This theory has been dominant in phlebology for many years. In this theory, the leading role in the expansion of the veins is attributed to the insufficiency of the saphenofemoral junction [25]. As a result of insufficiency of the ostial valve, there is an overflow of blood in the superficial venous network and a gradual expansion of the veins in the distal direction. Treatment methods with ligation of the saphenofemoral junction and subsequent ablation or stripping of the great saphenous vein are based on this theory [26, 27]. Today there is a competing ascending theory. The development of varicose veins in this theory is explained by a large number of failed perforators in the distal parts of the venous system, most often in the lower part of the leg. Perforators are points of re-entry of venous blood flow, that is, points of reflux, which leads to overflow of the superficial venous network with the creation of an ascending column of hydrostatic pressure. Based on this theory, the principles of CHIVA surgery were developed, which stands for Cure Hémodynamique de l' Isuffisance Veneuse en Ambulatoire and is translated as a method of ambulatory conservative treatment of hemodynamic venous disorders [28, 29]. With a conservative hemodynamic technique, venovenous shunts (areas of retrograde blood flow) and reflux entry points are interrupted, the column of hydrostatic pressure is also interrupted, which allows normalizing the correct direction of venous flow from the superficial to the deep venous system, while the superficial veins, even varicose veins, are not completely removed [30]. In addition to CHIVA surgery, the ASVAL method is also based on this pathogenetic concept (Ablation Sélective des Varices sous Anesthésie Locale), which translates as selective ablation of varicose veins under local anesthesia, and consists in removing the varicose veins, but purposefully preserving the incompetent saphenofemoral junction, as well as the incompetent great saphenous vein [31-34]. The ASVAL method is a de facto modification of the old Madelung method, which was a common surgical procedure prior to the Friedrich Trendelenburg school of phlebology in the 19th century. Madelung removed varicose veins, carefully preserving the main trunk of the great saphenous vein. At the time, it was thought that removing the great saphenous vein would increase the stasis of varicose veins [35, 36].

However, hemodynamic factors do not fully explain the pathogenesis of varicose veins, because often during a duplex scan of the veins of the lower extremities, it is not possible to detect valve enlargement and retrograde blood flow, although clinically we can see varicose veins. This is often observed in patients with initial classes of CVD according to CEAP.

Changes in the venous wall in VDLE

The hypothesis of venous wall weakness is that changes in the structure of the vein wall precede valvular insufficiency. This hypothesis is partially based on the observation that the areas of greatest histological abnormality of the venous wall are often located distal to the venous valve, while the valve may be functional [1, 37]. Expansion of the lumen of the vein distal to the valve over time leads to the formation of a distance when its leaflets close, which makes the valve insufficient [38, 39].

Duplex ultrasound findings regarding the nature and progression of venous dilatation and reflux support venous wall changes as the primary event, although isolated primary valvular dysfunction may still occasionally contribute. Factors associated with blood stasis and venous hypertension, including hypoxia, mechanical distension, and low shear stress, are thought to contribute to changes in the venous wall [40].

The walls of varicose veins show significant histopathological changes, namely structural remodeling of the vein wall, hyperplasia of

intimal cells and smooth myocytes. A varicose vein is invariably ectatic, unable to contract, and the diameter of the lumen can be several times larger than that of a normal vein. The expansion of the vein is often not uniform, there is an alternation of areas of a normal vein and segments of expansion, which are often observed in the form of nodes. Histological examination of the wall of varicose veins showed that in places there are areas of thickening and fibrosis, and in some areas, on the contrary, there is thinning with signs of destruction [38, 41].

Recent studies of the pathogenesis of varicose veins have focused on structural and biochemical changes in the venous wall [41-43]. The formation of varicose veins, which can be detected macroscopically and clinically, is secondary to defects in cells and components of the extracellular matrix (ECM). These defects lead to decreased venous tone. The triggers for these changes remain unclear, although several factors related to hemodynamic disturbances - hypoxia, mechanical stretching and reduced elasticity - have been identified [43-46].

Histological examination of varicose veins revealed changes in all layers of the vein wall, in the cells and ECM. Certain regularities in these changes were also revealed. Foci of intimal hyperplasia were combined with places of collagen accumulation; smooth muscle cell proliferation and ECM degeneration were observed in the middle layer of the vein [46]. Similarly, the adventitia of varicose veins shows areas of increased smooth muscle cells, fibroblasts, and connective tissue with areas of atrophy and depletion of vasa vasora [47].

The extracellular matrix provides a structural basis made of collagen, proteoglycans, elastin, glycoproteins, and fibronectin, in which various cellular components are embedded [45]. The ECM is a dynamic structure that maintains vein integrity and homeostasis through interactions with cellular components such as endothelium and smooth muscle cells. Its degradation contributes to the weakening and, subsequently, the expansion of veins. Disorders in elastic fibers, including their fragmentation and thickening of individual collagen fibers, are often observed in varicose veins. The total content of elastin in varicose veins decreases compared to that in non-varicose veins [45, 46]. The total collagen content in varicose veins compared to non-varicose veins remains unclear, some studies report an increase in collagen, some report that the amount of collagen in varicose veins does not change, and some insist that it decreases. However, collagen subtypes in varicose veins differ from those in non-varicose veins. Type III collagen, which promotes elasticity and extensibility, is reduced while type I collagen, which provides tensile strength, is unchanged in varicose veins. Loss of elastin and type III collagen negatively correlates with vein diameter measured by ultrasound at rest and during the Valsalva maneuver, respectively. Therefore, a change in the balance of the content of elastin and collagen probably contributes to the weakening of the venous wall and leads to its varicose expansion [38, 42, 48].

Sustainability of the ECM is regulated by a group of enzymes called matrix metalloproteinases (MMPs) and their endogenous tissue inhibitors (TIMPs). To date, at least 23 MMPs have been identified in humans and 14 of them are expressed in vascular tissues. Their activities and roles in ECM can differ significantly. In addition, MMP regulation is complex and occurs at multiple levels, including gene transcription, protein translation, pro-MMP activation, and endogenous inhibition by plasma proteins such as α2-macroglobulin and TIMPs [49-51].

The studies describe the MMP-TIMPs imbalance observed in varicose vein transformation. [51]. A significant increase in the concentration of pro-MMP-9 and leukocytes (L-selectin) was observed in blood samples from patients with varicose veins compared to samples from patients without varicose veins after 30 min of postural blood stasis (patients were in a standing or sitting position with the legs down) [52]. These observations suggest that venous hypertension due to blood stasis

can increase the production of MMP, which not only leads to PCM degradation, but also causes persistent venous relaxation.

Among the structural elements of the vein wall, endothelial cells play an active role in the regulation of inflammation, remodeling, and vascular tone [53]. Endothelial cells of varicose veins are observed under electron microscopy, which peel off and degenerate. Damaged cells are known to release various types of inflammatory mediators and growth factors. Release of growth factors, including basic fibroblast growth factor (bFGF) and platelet-derived growth factor, can induce smooth muscle cell proliferation and migration [1, 53-56]. The endothelium is also able to regulate the vascular tone itself through the release of various vasoactive substances, some of them narrow, and others contribute to the relaxation of the vein wall. An imbalance of these vasoactive substances can contribute to the general relaxation of veins in varicose veins [57]. Thus, a decrease in factors that contribute to vasoconstriction, such as the noradrenaline, endothelin-1 binding and endothelin-B receptor density, probably due to endothelial injury, has also been shown in varicose compared with non-varicose veins [58]. Factors that promote vasodilation, including nitric oxide, prostacyclin, and hyperpolarization of underlying smooth muscle cells by endothelium-derived hyperpolarizing factor, are upregulated in varicose veins compared to non-varicose veins [38, 54].

Areas of hypertrophy and proliferation of smooth muscle cells occur at the site of varicose veins, although areas of their atrophy are also observed. Restructuring and migration of smooth muscle cells into the intima are also observed. Smooth muscle cells in varicose veins are disorganized and dedifferentiated from contractile to synthetic and proliferative phenotype. They show features such as vacuolization and phagocytosis. Changes in smooth muscle cells can be influenced by hormonal factors, in particular changes in estrogen and progesterone levels. With varicose veins, not only the structure, but also the contractile function of smooth muscle cells is disturbed. For example, the provoked contraction of the vein under the action of phenylephrine is not registered with severe varicose veins. In moderate varicose veins, a decrease in endothelium-independent relaxation was also shown when nitroprusside was administered. In smooth muscle cells cultured from varicose veins, there was a decrease in the organization of the actin cytoskeleton and fibronectin compared to non-varicose veins [58, 59].

Dysregulation of apoptosis and cell cycle dysfunction also occur in varicose veins. The total number of apoptotic cells and their activity are reduced in varicose veins compared to non-varicose veins. Dedifferentiation of smooth muscle cells can be caused by dysregulation of apoptosis. Differential expression of cyclin D1, a proto-oncogene required for cell cycle progression through the G1 phase, further suggests cell cycle alteration in varicose veins. Cyclin D1 expression is significantly increased in the nuclei of cells, but decreased in the cytoplasm [59-61].

Genetic influence in VDLE

Throughout the history of the study of VDLE, the importance of hereditary anamnesis has always been pointed out. In the questionnaires of patients with varicose veins, it was found that close relatives of at least 25% of patients suffered or are suffering from one of the forms of this disease. This is probably due to the inheritance of a certain connective tissue defect, which is confirmed by the frequent combination of varicose veins and hemorrhoids, hernia of the anterior abdominal wall, and flat feet. Unfortunately, cases of hereditary predisposition to varicose veins are not always easy to detect, since not only a tendency to general weakness of connective tissue can be inherited, but also isolated weakness of vein walls or even some venous valves [62-64].

A study in France found that a history of varicose veins in a first-degree relative is the

most important risk factor for both men and women. Patients with varicose veins were 21.5 times more likely to report a positive family history [65]. A study conducted in Japan found that nearly half of patients with varicose veins had a family history, compared with only 14 percent of patients without the condition [66].

Although no single gene has been identified as specific for the development of varicose veins, several congenital genetic disorders involving varicose veins have been described. Patients with Klippel-Trenone syndrome have varicose veins, limb hypertrophy, and capillary hemangioma of the skin. These patients have various venous abnormalities, including atresia, agenesis, valvular insufficiency, and venous aneurysms. It was reported that 72 percent of patients with this syndrome had varicose veins. Another example of a genetic disease associated with varicose veins is Chuvash polycythemia; 74% of patients in one study had varicose veins compared to 39% of controls without polycythemia [67].

In the literature, there are data on other gene mutations associated with the formation of varicose veins. These are, for example, mutations of FOXC2, which are usually found in patients with lymphedema-distichiasis, and NOTCH3 in patients suffering from cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. In duplex ultrasound of patients with the FOXC2 mutation, all 18 had saphenous vein reflux compared with only one case of reflux in 12 patients without the mutation [68].

It is also possible to prove the role of heredity in the development of varicose veins using a clinical and genealogical examination method. To analyze family cases of VDLE, to determine the type of inheritance of the disease in examined patients, to determine the prognosis of inheritance for descendants. The genealogical method is a method of analyzing pedigrees, which is used when a hereditary pathology is suspected. Thanks to this method, the presence or absence of similar diseases in the family is revealed. In the study of genealogies of patients with CVD using the clinical genealogical method, the inheritance of this pathology according to the autosomal dominant type was revealed. Direct inheritance is observed across generations. The tendency to develop varicose veins is transmitted from generation to generation without gaps [69, 70].

It is also described that certain classes of varicose veins have a separate family pattern of inheritance. For example, patients with reticular varicose veins have direct relatives (most often mother and grandmother) who also suffer exclusively from reticular varicose veins, with age in these patients, reticular varicose veins did not transform and did not progress to other classes of VDLE according to the CEAP classification, the number of dilated reticular veins simply increased and telangiectasias, they became larger in diameter, more tortuous in shape. During the ultrasound examination of such patients, pathology of deep veins, vertical reflux, reflux in the ostial valve was not detected, but only small communicants were detected that fed the reticular veins from the superficial venous system, or in several places from the deep venous system [70].

The influence of risk factors of VDLE and their pathogenetic explanation

The prevalence of varicose veins increases with age, and the severity of CVI increases with age [71]. The Edinburgh Vein Study is a population-based cohort study that randomly selected individuals aged 18 to 64 years who underwent an examination that included a questionnaire, a standardized assessment and classification of leg vein disease, and a duplex scan for venous reflux in eight segments of each leg. These patients were under observation for 13 years. Almost half of the group of patients with chronic venous disease worsened over 13 years, and almost a third with varicose veins developed skin changes. Age, hereditary history, previous deep vein thrombosis, overweight and superficial reflux, especially in the small saphenous vein,

influenced the progression of CVD [71, 72].

The Edinburgh Vein Study also reported an increase in prevalence with age: 11.5% in the 18-24 age group and 55.7% in the 55-64 age group. The increased risk of developing varicose veins with age may be related to a combination of factors, including weakening of the calf muscles, decreased mobility, and a general decrease in venous matrix components. The Framingham study showed a prevalence of varicose veins of only 1% of men and 10% of women under 30 years of age, compared to 57% of men and 77% of women over 70 [71].

Most studies show that varicose veins are more common in women than men, although some report the opposite. According to various authors, varicose veins of the lower extremities occur in every fifth woman and 2-3 times more often than in men. It has also been suggested that women are more likely to pay attention to varicose veins due to the cosmetic aspect and therefore consult doctors more often than men [72, 73].

The hormonal theory of the origin of varicose veins occupies a special place. At the same time, literary sources that relate to the pathogenesis of the disease specifically in women are few and contradictory and refer to the study of varicose veins during pregnancy. It is known that in 60-90% of women, the first manifestations of varicose veins (reticular varicose veins, telangiectasias) occur during pregnancy. The authors explain the pathogenetic mechanisms of this phenomenon not only as a result of compression of the main veins of the pelvis by the pregnant uterus and an increase in intra-abdominal pressure, but also as a result of hormonal changes during pregnancy, which lead to a decrease in the tone of the venous wall and dilation of blood vessels [73]. It is also important to maintain venous hypertension and blood reflux for a long period of time for women in an upright position both during pregnancy and in the postpartum period. This constantly keeps the vein wall in tension, which prevents it from shrinking to its original size in the postpartum period, when there is hypoplasia of the muscular layer of vessels with noticeable thinning of smooth myocytes [72, 73].

Dyshormonal restructuring of an age-related nature also complicates or provokes the development of varicose veins. This is evidenced by observations of vein damage during puberty or, conversely, during the climacteric period. The role of hormones is also indicated by the fact that before menstruation, women with any manifestations of varicose veins complain of pain in the lower limbs and a feeling of heaviness, which significantly decrease after the end of menstruation [61, 73].

Unfavorable anatomical and physiological conditions in which the superficial veins of the lower extremities are located, in particular, a weak connective tissue framework, contribute to the manifestation of vascular dystonia [61, 64]. Morphological features of the structure of the subcutaneous tissue of the limb are of considerable importance in the defeat of the subcutaneous veins. It was found that in women with well-developed, loose, large-lobed subcutaneous tissue, subcutaneous veins are more often thin-walled and tortuous. During operations, with relatively minor mechanical impact, they break off easily. Uneven nodular expansion of fine veins occurs as a result of their compression by connective tissue membranes that divide the subcutaneous tissue into separate lobes. Dissection of blood vessels during surgery revealed that these membranes in the form of thin threads squeeze thin-walled veins of small diameter, complicate blood flow and contribute to their prestenotic varicose expansion. It was found that compression of the subcutaneous veins is observed along the entire length of the vessel, usually every 1.5-2 cm [40, 42, 47].

Obesity and limited mobility are controversial risk factors for varicose veins. Some studies support their effect, but others deny it. The role of obesity in the development of VDLE is primarily also associated with intra-abdominal hypertension. Obese patients often have metabolic syndrome, which in turn negatively affects

the entire body and causes changes in vascular tone as well [72].

The impact of prolonged standing, for example due to professional activity, on the development of VDLE is also described. This pathology is more often found in teachers, hairdressers, sellers, medical workers and people of other professions whose activities are associated with long hours of standing. During standing, the venous pressure in the ankle, created by the column of blood, can reach 100 mm Hg [74, 75].

The venous system of human legs, in the course of evolution, has acquired mechanisms, such as venous valves, that help it cope with these stresses. However, the ability of the venous system to withstand stress may vary between individuals depending on genetic and environmental factors; this is evidenced by the multifactorial etiology of varicose veins. Leg veins of people who have worse adaptive mechanisms are more likely to suffer from VDLE more often. Chronic repetitive injury and overstretching causes inflammation of the vein wall, remodeling, and alteration of venous tone, leading to valvular dysfunction, venous reflux, and varicose veins.

Other risk factors, such as cigarette smoking, estrogen therapy, hypertension, and diabetes, may accelerate but not initiate the development of CHD, although their role remains to be studied [72].

CONCLUSIONS

According to the currently available evidence, varicose disease is a complex process with a multifactorial pathogenesis; it is still impossible to definitively state which provoking factor is responsible for the development of varicose veins, and its development can be the result of an imbalance of any number of several factors.

Two main pathophysiological mechanisms of varicose vein development can be distinguished - valvular insufficiency and changes in the venous wall. There is still no clear data on which of these mechanisms is primary, and it is more expedient to consider them together as a "vicious circle". Valvular insufficiency can occur both vertically, when insufficiency of the saphenofemoral confluence is key in the development of varicose veins, and horizontally with pronounced failure of the valves of the perforating veins. With varicose veins, microstructural changes occur in all three layers of its wall, in cells and the extracellular matrix.

Among the risk factors that are a prerequisite or trigger pathophysiological mechanisms, the greatest role is assigned to a burdened hereditary anamnesis. Also, dyshormonal restructuring of the body, professional activity associated with a long vertical position, obesity, etc., play a role.

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ПАТОФІЗІОЛОГІЧНІ МЕХАНІЗМИ ВАРИКОЗНОГО РОЗШИРЕННЯ ВЕН НИЖНІХ КІНЦІВОК

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Варикозне розширення вен – часте, багатофакторне захворювання. Незважаючи на поширеність, патофізіологічний механізм варикозної хвороби залишається не до кінця вивченим. За даними різних джерел ключовими механізмами й розвитку є клапанна недостатність та зміни венозної стінки. Фундаментальне питання полягає в тому, чи клапанна недостатність передує і впливає на розвиток змін венозної стінки, чи все навпаки. Мета нашої роботи проаналізувати сучасний стан проблеми вивчення механізмів розвитку варикозного розширення вен нижніх кінцівок. Огляд присвячений останнім даним щодо етіологічних, патофізіологічних та патогенетичних факторів, залучених у розвиток варикозного розширення вен. Анатомічні, ультразвукові та плетизмографічні дослідження довели, що саме наявність клапанної

недостатності часто зустрічається у разі варикозної хвороби нижніх кінцівок. При дослідженні венозної стінки виявляють структурне ремоделювання в усіх трьох шарах, гіперплазію клітин інтими та гладких міоцитів. Особливу роль у змінах венозної стінки відіграють структури позаклітинного матриксу. Зміни структури вен ще більше поглиблюють клапанну недостатність, запускаючи замкнене коло. Окрім того в огляді розглядається роль спадковості, підвищення внутрішньочеревного тиску, гормональних та інших етіологічних та провокувальних факторів варикозного розширення вен.

Ключові слова: хронічна венозна недостатність; варикозне розширення вен; венозні клапани; венозна стінка, позаклітинний матрикс.

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