

# VENOUS ULCER – PHYSIOPATHOLOGIC ASPECTS

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**Keywords:** edema, inflammation, trophic changes, venous ulcer

**Abstract:** Although the etiology of the peripheral chronic venous insufficiency can be mono- or plurifactorial with the initiation of the pathological changes at supra or subfacial level, at a certain point in time, the physiopatological mechanisms will arrive at a common denominator: the inadequate arterial blood drainage with pressure increasing in the venous and lymphatic systems. Edema, inflammation, trophic changes are the physiopatological mechanisms of the venous ulcer.

**Cuvinte cheie:** edem, inflamație, tulburări trofice, ulcer venos

**Rezumat:** Deși etiologia insuficienței venoase cronice periferice poate fi mono- sau plurifactorială cu inițierea modificărilor patologice la nivel supra- sau subfascial, la un moment dat, mecanismele fiziopatologice ajung la un numitor comun: incapacitatea asigurării unui drenaj adecvat al sângelui arterial realizându-se hipertensiune în sistemele venos și limfatic. Mecanismele fiziopatologice ale ulcerului venos se concentrează pe trepidul: edem, inflamație, tulburări trofice, în care cele trei elemente sunt interconectate și se potențează reciproc.

## INTRODUCTION

Venous leg ulcer "is the consequence of the chronic venous insufficiency and its effects on microcirculatory system"(D. Forsea). Chronic venous insufficiency (van der Molen) is a clinical syndrome with different etiopathogeny, prognosis and therapy that is subsequent to chronic disturbances of venous circulation, especially in the lower limbs, resulting in significant changes of interstitial space, lymphatics and of skin.

Chronic venous insufficiency includes two subdivisions, clinically almost similar, but different in terms of etiopathogenesis, therapeutics and prognosis:

1. Superficially chronic venous insufficiency, representing the late stage of superficially veins insufficiency and varicose disease, sometimes called as the "varicose symptomatic complex" is the consequence of the inadequacies of the junctions of the large veins, internal and external saphenous vein, and/or perforating vein insufficiency.

All of these conditions can be treated successfully, thus superficially chronic venous insufficiency has a good prognosis. Varicose veins are not the actual cause of the superficial chronic vein insufficiency (L. Gherasim), but more likely they may have a common cause.

2. Chronic deep venous insufficiency is represented by the postphlebotic syndrome, the consequence of occlusions and deep vein functional disorders. The causes of these disorders cannot be suppressed except for certain exceptional cases, so that chronic deep venous insufficiency (postphlebotic syndrome) cannot be cured and often requires long term treatment

### Superficially chronic venous insufficiency

Endogenous factors: anthropological - biped position; anatomical and physiological factors; genetic factors; constitutional type; sex; age; endocrine factors; pregnancy; obesity; health; exogenous factors: physical factors (geographical, microclimate); social

### Deep chronic venous insufficiency

Deep chronic venous insufficiency is represented by

the postphlebotic syndrome– a consequence of certain occlusions and deep vein functional disorders. The postphlebotic syndrome is a set of vascular-tissue sequelae at the level of legs, installed as a result of deep thrombosis (O.V. Buțiu).

Virchow triad: venous stasis, wall lesion and venous blood hypercoagulability are the causes of vein thrombosis. Most of the times, two or all three factors are present at the same time.

Etiology of leg ulcers is not limited only to the suffering of the venous system, being very varied as it is emphasized by Dan Forsea et al.:

#### 1. Vascular diseases:

- a. Venous,
- b. Arterial (atherosclerosis, cholesterol embolism, Thromboangiitis obliterans, arteriovenous malformations),
- c. vasculitis (allergic vasculitis, Lupus erythematosus, Scleroderma, Behcet disease, White atrophy, Polyarteritis nodosa, Wegener granulomatosis),
- d. Lymphedema.

2. Neuropathies (diabetes mellitus, tabes dorsalis, syringomyelia);

3. Metabolic disorders (diabetes, gout);

4. Hematological:

- a. erythrocyte (thalassemia, polycythemia rubra vera),
- b. leukocyte (leukemia),
- c. Dysproteinemia (cryoglobulinemii, macroglobulinemia Waldenström).

5. Trauma (pressure, radiation, cold, burns);

6. Neoplasia (epiteliomas, sarcomas, lymphoproliferative disease, metastatic tumours);

7. Infections:

- a. Bacterial (ectima, septic embolism, infection Gram-negative or anaerobic, typical and atypical mycobacteriosis),
- b. fungi (deep fungal infections, granuloma Majocchi),
- c. protozoa (leishmania),

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- d. insect stings and bites,
- 8. Panniculitis (Weber-Christian disease, Lipoid necrobiosis);
- 9. Pyoderma gangrenosum.

Although, theoretically, the “starting point” of leg ulcers is extremely varied, more than 95% are the expression of chronic venous insufficiency. Ankle ulcer, “the most serious manifestation of venous decompensation” (Gerasim L., Pârnu V.) is mainly located in areas of mechanical stress, where disorders of the tissue favours ulcer appearance.

Pathogenetically, “venous ulcers are due to congenital or acquired valves dysfunction of the deep veins and/or of the communicant veins” (D. Forsea). According to the same author’s study, approximately 50% of the patients had a history of deep vein thrombosis mentioned as a cause of valves incompetence. DVT increases venous pressure, with effects on microcirculation. Isolated incompetence of the saphenous vein superficial system (varicose hydrostatic) rarely causes leg ulcers (20%). Congenital venous dysplasia is mentioned only in 3-4% of cases.

Although, the etiology of the chronic peripheral venous insufficiency can be mono-or multifactorial with the initiation of pathological changes at supra or subfascial level, at a given time, the pathophysiological mechanisms reach a common denominator: the inadequate arterial blood drainage with pressure increasing in the venous and lymphatic systems, with edema generation. The pathophysiological mechanisms of venous ulcers are focuses on the tripod: edema, inflammation, trophic disorders; the three elements are interconnected and reinforce each other. Edema is defined as the “presence of excess fluid in the body tissues” (AC Guyton). In many cases, edema may occur in the extracellular liquid compartment, but it may also involve the intracellular compartment.

Intracellular edema occurs in two situations:

The first one is the suppression of the metabolic system tissue or the inadequate nutrition of cells which can cause severe intracellular edema. It appears usually in any area of the body where blood flow is too low and the local supply of oxygen and other nutrition substances is too small to maintain normal tissue metabolism. This depresses the activity of ionic membrane’s pumps (Na-K pumps). Thus, when sodium enters the cell, Na-K pump’s inactivity produces sodium osmosis water in the cell. This can increase intracellular volume of tissue areas, e.g. even an ischemic leg in full, with twice and even more than normal. Usually this is a prelude to tissue necrosis.

A second situation is when the intracellular edema appears into inflamed tissue areas. Inflammation has usually a direct effect on cell membranes, increasing their permeability, so that sodium and other ions enter the cell at the same time with the consecutive osmosis of the water in the cell. Extracellular edema can occur by the extravasation of plasma that exceeds the drainage physiological mechanisms or by the insufficiency of the lymphatic system to drain the interstitial fluid, or it can be produced by the salt and water’s retention with renal cause on the other side.

Situations producing extracellular edema according to A.C. Guyton:

- I. Increased capillary pressure:
  - A. Excessive renal retention of water and salt;
  - B. Increased venous pressure: heart failure; venous stasis located; insufficiency of venous pump (muscle paralysis, parts of the body fixed, failure of venous valves).
- II. Decreased plasma protein: loss of protein in the urine (nephrosis); loss of proteins due to skin loss (burns, injuries); insufficient protein synthesis (liver disease; serious protein and caloric malnutrition).

III. Increased capillary permeability:

- A. Immune reactions that cause histamine release or other immune substances;
- B. Toxins;
- C. Bacterial.

IV. Lymphatic drainage blockage:

- A. Blockage of lymph nodes in cancer,
- B. Blockage of lymph nodes especially in infections (filariasis).

Characteristics of macro- and microcirculation underlying the extracellular edema:

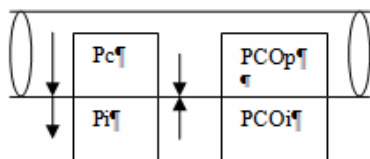
The hydrostatic pressure’s effect on veins pressure:

- A. In an individual in orthostatic position, the pressure in the right atrium remains around the value of 0 mm Hg, because any excess of blood that would accumulate at this level will be pumped into the arteries of the heart. If an adult is still in orthostatic position, the pressure in leg veins is about 90 mm Hg, due to the weight of the blood in the veins located between the heart and limbs. Venous pressure in the veins located between the heart and legs increases between 0 and 90 mm Hg at rest.
- B. Venous valves, “venous pump” and the venous pressure reduce considerably the pressure in the venous system; only the “venous pumps” reduces the hydrostatic pressure from 90 to 25 mmHg during muscle contraction.
- C. Venous valves insufficiency and varicose vein valves. Frequently, the venous system valves are “insufficient” and sometimes are destroyed. This situation occurs when the veins were over-stretched for weeks or months because of excessive venous pressure; it may be observed in pregnant women and in the persons providing an activity that requires long periods of prolonged standing. When valvular insufficiency develops, the pressure in the lower veins increases excessively, leading to insufficient venous pump which in turn, will increase the size of the veins, and finally will lead to the destruction of venous valves. Thus, that individual will develop “varicose vein” large spider veins of the superficial veins (under the skin) at the level of the lower limbs, mainly located in the calves. Venous and capillary pressure significantly increases, while the capillary fluid loss results in constantly leg edema, whenever individuals are standing more than a few minutes. In turn, edema prevents adequate diffusion of nutrients from capillaries to muscle and skin to the muscles so that they become painful and weak, while the teguments become gangrenous or ulcerated.
- D. Interstitial space and interstitial fluid. About one sixth of the body is represented by the space between cells, called the interstitial space in general. The fluid in this space is called the interstitial fluid. The interstitial space consists of two main types of solid structures: (1) collagen fibre bundles and (2) filaments of proteoglycans. Collagen bundles span large distances in the interstitial space. They are extremely strong and that gives most of the tensile strength of tissue. Proteoglycans filaments, on the other hand, are extremely thin; they are molecules containing 98% spiral hyaluronic acid and 2% proteins. These molecules are so thin that they cannot be seen with optical microscope and are difficult to spot even with the electron microscopy. They form a very fine network of reticular filaments. The interstitial “gel”. The interstitial fluid is the result of capillary filtration. It contains almost the same constituents as plasma does, except for the proteins occurring in low concentrations, because proteins are difficult filtered through the capillary. This fluid is “chained” especially in small spaces between the filaments

of proteoglycans. This combination between the filaments of proteoglycans and the liquid between them has the characteristics of a gel and therefore, it is commonly called gel tissue. Due to the large number of filaments of proteoglycans, the fluid flow through the gel tissue in a difficult manner. That is, it moves molecule by molecule from one place to another, being rather a process of kinetic motion than a process of movement as a whole. Fortunately, the diffusion through the gel occurs almost in the same way as the free fluid in proportion of 95-99%. Due to small distances between capillaries and tissue cells, this diffusion allows the direct transmission through the interstitial space not only of the water molecules but also of electrolytes, nutrients, products of cellular catabolism, O<sub>2</sub>, CO<sub>2</sub>.

**Free interstitial fluid.** Although almost all the liquid in the interstitial space is chained in the gel tissue, occasionally small "rivers" and free liquid vesicles are present, which means that the liquid can flow freely between the filaments of proteoglycans. When a dye is injected into the circulation, often in the interstitial space, small "rivers" may occur, which are often visible on the surface of the collagen fibers or cells. The quantities of the "free liquids" present in the normal tissues are very low, usually below 1%. On the other hand, when tissue edema develops, these "rivers" of free liquid will expand, reaching to represent half of the interstitial fluid.

**E.** The four main forces that determine the movement of liquids through the capillary membrane:



The above-figure shows the four forces that determine either the movement of the fluid from vessel into the interstitial space, or the opposite, they are called forces of Starling, in the honour of the first physiologist who demonstrated their importance. These are:

1. Capillary pressure which tends to move liquids through capillary membrane out of the vessel;
  2. Interstitial fluid pressure which tends to move the fluids through the membrane inside the vessel capillary when capillary pressure is positive and outside when the it is negative;
  3. Colloid osmotic pressure of plasma that tends to determine liquid osmosis in the vessel through membrane;
  4. Colloid-osmotic pressure of interstitial fluid tends to cause osmosis fluid outside the vessel, through capillary membrane.
- F.** Free interstitial fluid pressure. Experimentally, it has been shown that the real pressure of the interstitial fluid from the lax subcutaneous tissue is easily lower to the atmospheric pressure. A value of the pressure accepted by most professionals is of 3 Mm Hg.

### CONCLUSIONS

1. Chronic venous insufficiency (van der Molen) is a clinical syndrome with different etiopathogeny, prognosis and therapy that is subsequent to chronic disturbances of venous circulation, especially in the lower limbs, resulting in significant changes of interstitial space, lymphatics and skin.

2. Physiological considerations:

- veins are low pressure vessels with high compliance

(requires significant changes in volume to change blood pressure);

- cells are located at an optimal distance of maximum 25-50µm capillaries, which ensures homeostasis of nutrients and electrolytes exchanges;
  - capillary Starling equilibrium reveals the existence of a net force of 0.3 mmHg balanced filter which ensures the return movement of the fluid through the lymphatic system (1/10 of the rate of filtrated liquids at the arterial end);
  - "anti edema safety factor" (a slightly negative pressure of the interstitial fluid-3mmHg, lymph flow increase from 10 to 50 times, "washing" the proteins of the interstitial fluid through the lymphatic flow;
  - Hydrostatic pressure in the calves is 90 mmHg.
3. The etiology of leg ulcers varies from the vascular to the neuropathic, metabolic infectious, tumour, hematological, traumatic, panniculitis, pyoderma gangrenosum.
  4. Although the etiology of the peripheral chronic venous insufficiency can be mono- or plurifactorial with the initiation of the pathological changes at supra or subfacial level, at a certain point in time, the physiopatological mechanisms will arrive at a common denominator: the inadequate arterial blood drainage with pressure increasing in the venous and lymphatic systems.
  5. The pathophysiological mechanisms of venous ulcers are focuses on the tripod: edema, inflammation, trophic disorders, where all the three elements are interconnected and reinforce each other.

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