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Pathomechanism of chronic venous insufficiency and leg ulcer

T **Sándor**

2nd Department of Surgery, Semmelweis University, Budapest, Hungary

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Uniform view of chronic venous diseases has been formed in the last 3 decades. Chronic venous insufficiency (CVI) is a functional disorder of the venous system of the lower limb. The basis of the pathology is always the venous hypertension caused by valvular insufficiency and reflux with or without venous outflow obstruction. Epifascial, subfascial and transfascial forms of CVI can be distinguished. In the practice these forms are almost always combined. The consistent venous hypertension is the initiating factor in alterations in the microcirculation which leads to skin changes and venous ulceration. The precise mechanism of the development of venous leg ulcer is still uncertain. A recent hypothesis suggests that leukocytes are trapped in the capillaries and attaching to the endothel they become activated and release proteolytic enzymes, free radicals which have destructive effects on lipid membranes, proteins as well as on many connective tissue compounds. The endothelium plays active role in the complex mechanism. Increased expression of tissue metalloproteinases has been observed in the periulcer skin. The presence of perivascular leukocyte infiltration and fibrin cuff is a reflexion of an inflammatory process. The clinical stages of CVI are likely to be the results of a systemic inflammatory response to a period of venous hypertension.

Keywords: valvular insufficiency, venous outflow obstruction, white cell trapping, leukocyte-endothelium interactions, inflammation

The problem

Uniform view of chronic venous diseases affecting a quarter of the European population has been formed only in the last 30 years. Essentially, it was recognised that primary varicosity caused by valvular incompetence and reflux in the superficial veins and secondary varicosity caused by obstruction (practically thrombosis) in the deep veins

Correspondence should be addressed to
Dr. Tamás Sándor
2nd Department of Surgery
Semmelweis University
H-1125 Budapest, Kútvölgyi út 4, Hungary
Phone: 36-1-355-1122/206, Fax: 36-1- 375-4291
E-mail: dr.sandor.tamas@axelero.hu

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produce the same clinical syndrome on the lower limb: oedema, perimalleolar skin changes and finally a hardly curable venous ulcer.

The problem of the venous diseases is well known in all civilized countries. The incidence of deep venous thrombosis which is often responsible for the development of CVI is 1 per 1000 population per year. Approximately 1 in every 100 persons will have leg ulcer at some time in their life and recent epidemiologic studies have shown a 40% prevalence of varicosity in Hungary (1, 2).

It's easy to understand that venous diseases have serious socio-economic consequences. Direct health costs are very high in every countries and the indirect financial loss is also significant. The total cost of hospitalization, outpatient therapy, treatment at home and loss of work has been estimated close to £2 billion in the UK. Western European countries spend 1.5–2% of their total annual health budget for treating CVI (3).

The concept

Already Hippocrates thought that leg ulcers were associated with enlarged leg veins and dependency. He observed that leg ulcers had developed on Scythian warriors as a result of leg dependency owing to sitting in a saddle while horse riding. He recommended that these warriors should avoid standing or hanging their feet and abandon riding (4).

The association of varicose veins with incompetent valves was noted in the 17th century and the importance of deep vein valves leading to venous stasis has been emphasized repeatedly in the 20th century. It was also recognized that venous ulcer could develop even in the absence of varicose veins.

The Bostonian surgeon, Homans in 1916 noticed that incompetence of perforating veins of the ankle occurred in the post-thrombotic limb and introduced the term "post-phlebitic syndrome" to describe the effect of deep vein thrombosis (5). Later he described two types of ulcers: varicose ulcers associated with superficial varicose veins which were easily cured by the removal of the veins and venous ulcers found on the post-thrombotic limb which were often incurable by the removal of varicose veins alone. Both types of ulcers were found on the same position: the medial perimalleolar area (6).

The term "chronic venous insufficiency" was introduced by the Dutch van der Molen in 1957 (7). The new designation as a collecting term integrated the varicose symptom complex with the post-thrombotic syndrome and deep vein insufficiency. The definition refers to a heterogenous disease-group causing chronic venous circulatory disturbances (Fig. 1).

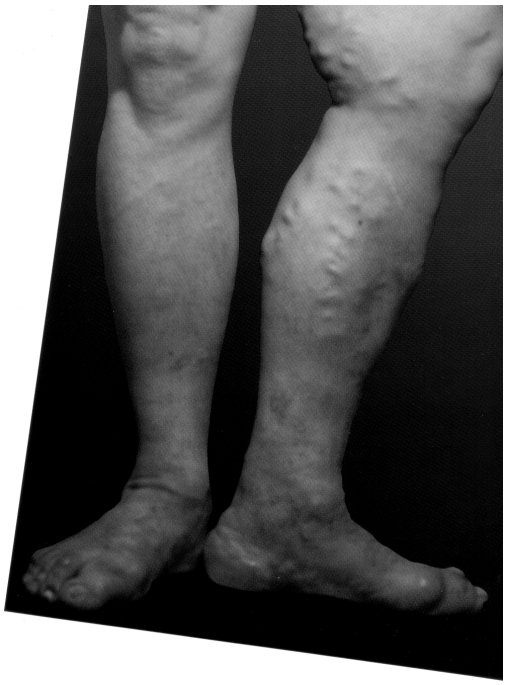


Fig. 1. Typical clinical picture of chronic venous insufficiency

CVI is defined as a functional disorder of the venous system of the lower limb. The basis of the pathology is always a venous hypertension caused by valvular insufficiency and reflux with or without venous outflow obstruction. An insufficient lymphatic drainage or a disfunction of calf muscle-pump can be associated with the disorder (8, 9, 10).

The forms of CVI

From pathological point of view 4 forms of CVI can be distinguished (Fig. 2):
- epifascial venous insufficiency,
- subfascial venous insufficiency,
- transfascial venous insufficiency,
- combined venous insufficiency.

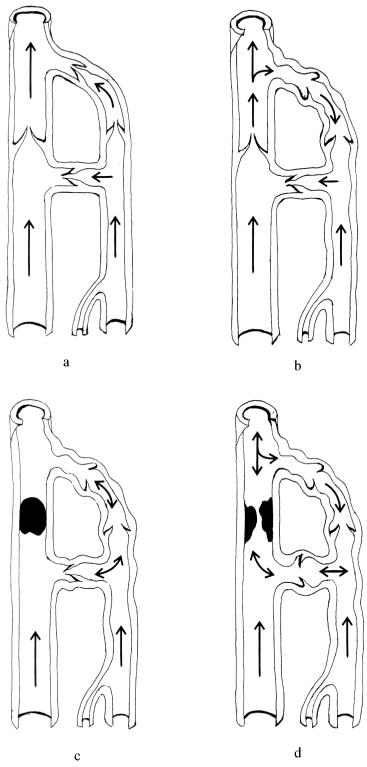


Fig. 2. The forms of chronic venous insufficiency: a) intact venous circulation; b) epifascial venous insufficiency; c) subfascial venous insufficiency; d) combined venous insufficiency

Epifascial venous insufficiency (primary varicosity)

In this form a valvular incompetence at the sapheno-femoral junction develops resulting a reflux. The surplus blood at the first perforate vein of the saphenous vein is conducting to the deep vein of the thigh. However, at the junction a part of the blood is flowing down again into the epifascial saphenous vein. Therefore a "private circulation" develops and the significant extra blood quantity ("blow down") dilates the wall of the saphenous vein. By walking, the muscle pump can counterbalance the hydrostatic plus pressure for a time, but by standing, the peripheral venous pressure increases, resulting a stagnation of significant surplus blood in the epifascial venous system. The valves of the saphenous vein become insufficient gradually, from above downwards and *primary* varicosity develops.

Subfascial venous insufficiency

In this form an outflow obstruction can be found in the deep vein. Below the obstruction a part of the blood is conducting through the perforate veins into the superficial veins and dilating them leads to *secondary* varicosity.

The cause of the obstruction is almost always a thrombus in the deep vein. After inadequate recanalisation and poor development of collateral circulation the valves are damaged, the wall of the vein becomes stiff, major quantity of the blood remains in the limb and venous hypertension is to occur. That's the cause of the *post-thrombotic syndrome* which is actually a form of subfascial CVI.

Less frequently the cause of deep vein obstruction is an extramural compression caused by a tumour.

Congenital anomalies such as partial or total absence of the deep veins can cause subfascial venous insufficiency, as well as arterio-venous fistules, micro-communications remaining from the intrauterine life.

Simply, the inactivation of the calf and foot muscle pump can lead to CVI. This is observed by the swelling and ulceration, seen in patients with calf muscle paralysis or ankylosis of the ankle joint. Many unexplained cases of severe CVI can be traced back to previous malleolar fractures with immobilization in plaster casts or long-term bed rest with chronic infections such as tuberculosis (11).

In recent years it has been demonstrated also, that routine descending phlebography performed in all patients with clinically "post-thrombotic" limb, one-third have dilated deep veins with reflux, but no evidence of any thrombosis in the past. The reflux was the result of floppy valve cusps with decreased venous tone and elasticity (12).

Transfascial (perforate) venous insufficiency

Insufficiency of the perforate veins can develop alone but usually it is caused secondarily. These transfascial veins are overloaded either by the surplus blood of primary varicosity, or by the retrograde blood flow caused by deep vein obstruction. A part of the venous blood flows through the insufficient valves of the perforate veins in opposite direction into the superficial veins, causing impaired function of the muscle pump.

Sometimes, a large quantity of blood flows under high pressure from the deep into the superficial vein past the incompetent valve of the perforate vein resulting a protruding bulb on the skin ("blow out"). Over these "blow outs" the microcirculation of the skin is impaired significantly.

Transfascial venous insufficiencies localised distally on the leg, in the perimalleolar "gaiter" area lead usually to serious skin changes and leg ulcer. More proximally localised incompetent perforate veins cause rather severe varicosity.

Combined (mixed) venous insufficiency

We rarely meet the different forms of CVI clearly as isolate forms. Practically, the epifascial, subfascial and transfascial forms are almost always mixed and combined.

The long-term venous pressure elevation which can be found in every type of CVI induces changes in the microcirculation and in the perivascular tissues.

Changes in the microcirculation

The consistent venous hypertension is the initiating factor in changes in the microcirculation, which lead to skin changes and venous ulceration.

As soon as in 1930 Landis showed that a rise in venous pressure produced an equivalent rise in the intraluminal pressure in the capillaries and he was thus the first to implicate involvement of the microcirculation in the venous diseases (13). A strong correlation was found between capillary bed abnormalities and incompetence of the calf pump mechanism. Experimental elevation of venous pressure in dogs produced similar changes in the microcirculation. Enlargement of the local dermal capillary bed was demonstrated experimentally and on histological sections of lipodermosclerotic skin (14).

Disease mechanisms in venous ulceration

The mechanisms whereby venous hypertension leads to leg ulcer are uncertain, therefore many theories are proposed. Research has concentrated on the microcirculation as the final determinant of the disease process.

Venous stasis hypothesis

Homans in 1917 suggested that stagnant blood pooling within dilated veins in the skin might cause anoxia and cell death leading ulceration. He found that the oxygen content of blood taken from varicose veins was lower than that taken from the cubital vein (15).

However, the theory was criticized on the basis that position of the limb had not been standardized during the study (16). Namely, it was shown that standing position caused a drop in the oxygen content of the blood taken from the varicose long saphenous vein, but in supine position this was higher than that in the case of antecubital vein.

Arteriovenous shunting hypothesis

The realisation that oxygen levels in varicose veins are actually higher than normal led to the concept, that abnormal arteriovenous communications may be present. Piulachs and Vidal Barraquer with arteriographic studies found a faster venous phase and faster circulation time and concluded that all types of varicosities are due to congenital arteriovenous communications (17). Nevertheless, modern studies using radioactive labelled macroaggregates failed to demonstrate these shunts in patients with varicose veins (18).

Fibrin cuff hypothesis

It was demonstrated in the late 70s that "interendothelial pores" stretched or enlarged if capillary intraluminal pressure is increased so affecting the capillary filtration. Through these enlarged pores fibrinogen could pass more freely into the interstitial space than albumin, where it was polymerized to fibrin. Fibrin which is relatively impermeable to oxygen, could not be removed because of poor fibrinolysis and exhaustion of fibrinoltic activators (19, 20).

Therefore Browse and Burnand proposed that a pericapillary fibrin cuff is seen in the skin of the patients with CVI that prevents diffusion of gases and results in tissue hypoxia, which causes ulceration (21).

The investigation of Clyne supported the oxygen diffusion block theory. Using transcutaneous tissue PO_2 measurements in the gaiter area, he found that patients with venous hypertension and lipodermatosclerosis had significantly lower PO_2 levels, than did healthy individuals (22). However, in his studies the transcutaneos PO_2 has been assessed with transducers heeled to unphysiologic temperatures (43 or 44°). When oxygen measurements were made at room temperature there is little evidence of tissue hypoxia (23). Studies with xenon – a molecule of similar size and diffusion characteristic to oxygen – suggest that this gas diffuses through lipodermatosclerotic skin as easily as it does in normal skin.

White cell trapping hypothesis

In recent years it was demonstrated that the cause of leg ulcer was a more complex process than simple failure to deliver oxygen to the tissues. In 1988 Coleridge Smith suggested a new hypothesis for the development of venous ulceration: "the white cell trapping" concept (24).

In the 80s the role of the white blood cells in the microcirculation was investigated intensively. Leukocytes have the ability to become activated. In this activated state they release enzyme-granules from their cytoplasm and produce oxygen free radicals which destruct the bacteria (25). Neutrophil activation occurs also during *acute* tissue ischaemia, when normal tissues are injured, e.g. in myocardial infarction (26). Despite their small numbers in the circulation white blood cells are 3 times larger and 1000 times more rigid than the red cells. The large and rigid leukocytes easily get struck and block many capillaries, become activated and this causes the damage of the endothelium.

It was suggested that the white blood cells played an important role also in *chronic* tissue injuries, i.e. in the development of CVI. The investigation of the behaviour of leukocytes during venous hypertension soon started.

Moyses studied the limbs of healthy volunteers in response to raised venous pressure and measured haematological parameters to assess the effect of venous hypertension. Their subjects sat on a bicycle saddle with the limbs dependent for 40 minutes, without moving. Then blood samples were taken from the long saphenous vein at the ankle. It was found that the haematocrit and red cell count increased in parallel,

but the white cell count remained unchanged, despite the increased haematocrit. White cells were being "lost" from the circulation, which after 40 minutes amounted to a 25% change (27). In a similar study these haematologic parameters were compared in the limbs of patients with CVI, as well as in the limbs of normal subjects (Fig. 3). After 60 minutes, 30% of white cells were "trapped" in patients with venous diseases, while on control subjects only 5% [$p < 0.01$] (28).

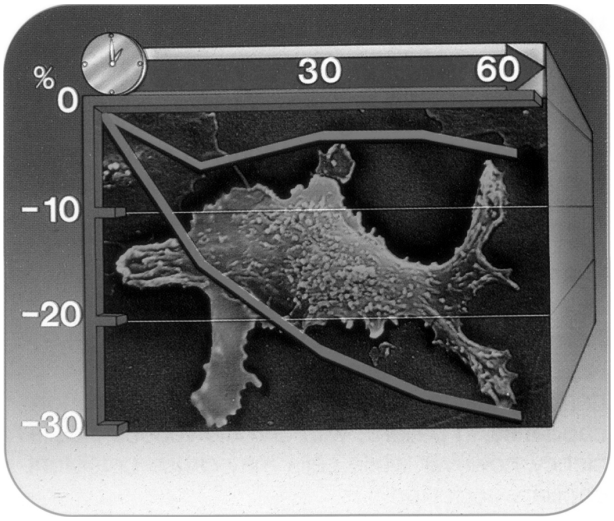


Fig. 3. White cell trapping. After 1 hour of dependency of the legs normal subjects had no change in the number of white cells leaving the foot, whereas in patients with CVI there was a reduction of 30%, indicating significant white cell trapping in the lower leg (28)

Another direction of research was to investigate the microcirculation with capillary microscopic technique. Bollinger using fluorescence video-microscopy showed that patients with CVI had areas of skin with no apparent flow of blood. He thought that some capillaries were not functioning because of thrombosis (29). Others also demonstrated with this method that the number of visible capillaries per square millimetre fell when the legs of the patients with CVI and lipodermatosclerosis were placed in a dependent position, but not in control subjects. Capillary loops are visible only when they contain red cells. In CVI a part of the capillaries contain only white cells (30). It was suggested that the increasing venous pressure reduced the capillary perfusion pressure and thereby the capillary flow rate. Low capillary flow rate alone is sufficient to cause trapping of white cells, plugging the capillaries and a potent initiation of leukocyte adherence to the endothelium (Fig. 4), (24).

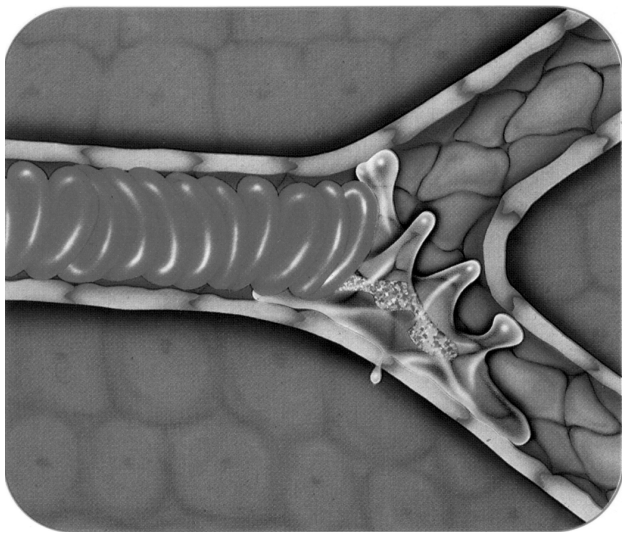


Fig. 4. White cell trapping. High venous pressure reduces the capillary perfusion pressure. The driving force in the capillary thus reduces, causing the rigid white cell to lodge in the narrow vessel. The trapped leukocytes attaching to the endothel with pseudopodia become activated

These findings were connected in the new hypothesis proposing that in CVI during venous hypertension the white blood cells are trapped in the capillaries and the activation of leukocytes leads to the damage of the vessel wall resulting in skin changes and eventually leg ulcer.

The role of the endothelium

Endothelium of the human saphenous vein plays an important role in maintaining smooth muscle contraction. In response to noradrenalin, contraction of the saphenous vein is more pronounced in normal, compared to a de-endothelialized vessel ring and endothelial cells seem to release a contracting factor: EDCF. In varicose veins the release of EDCF is diminished thus reducing wall tension (31).

According to the new theory polymorphonuclear leukocytes entrapped in the capillaries attaching to the endothelium become activated and release from their cytoplasmic granules proteolytic enzymes, free radicals and superoxid radicals which have destructive effects on lipid membranes, proteins and many connective tissue compounds (Fig. 5), (25). The chemotactic leukotrienes are also released attracting more polymorphonuclear cells into the capillaries. White cells cause occlusion of capillaries, but probably do not cause local hypoxia. Likely, the toxic products released by the white cells are the mediators of tissue injury.

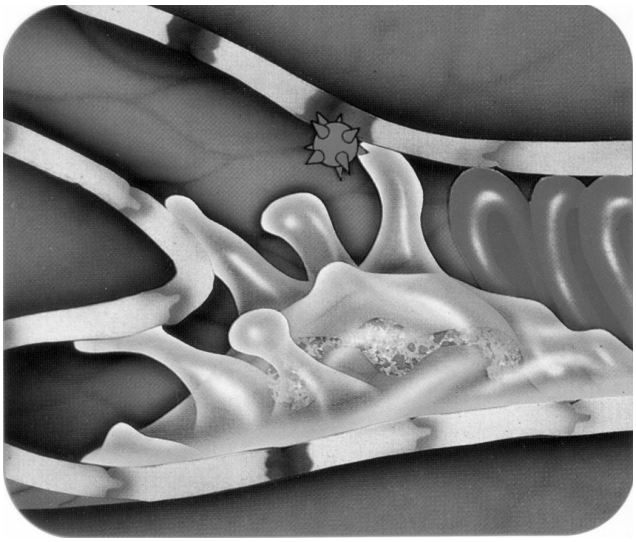


Fig. 5. White cell trapping. The activated white cells release free radicals, toxic superoxid radicals and lysosomal enzymes, which have destructive effects on lipid membranes, proteins as well as on many connective tissue compounds

The adhesion of neutrophil leukocytes and monocytes to the endothelium is a two-stage process. In the first stage these cells roll along the endothelium binding in a loose manner, using a ligand on the leukocytes known as CD62L or L-selectin. After the margination, in the second stage when the real binding occurs, a fragment of L-selectin is released into the plasma (soluble L-selectin) and can be detected by ELISA. It was shown that the concentration of L-selectin rose during venous hypertension (32).

The expression of a surface neutrophil ligands C11b/CD18 has been investigated as a marker of neutrophil activation. Increased levels of C11b were observed in patients with CVI and lipodermatosclerosis (33).

High levels of plasma lactoferrin and elastase which are also markers of leukocyte activation were found in patients with varicose veins (34, 35).

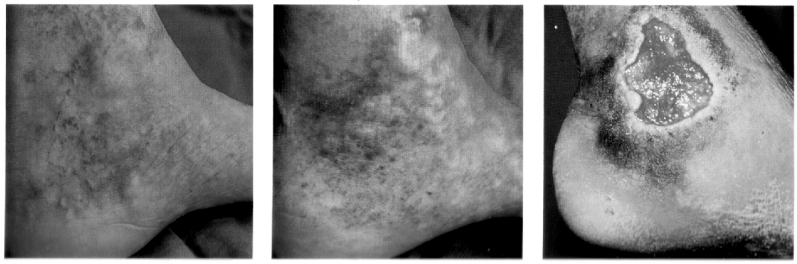
All classes of white cells become trapped and activated. Activated monocytes release cytokines interleukin 1 (IL-1) and a tumour necrosis factor alpha (TNF_{α}). These agents make the endothelial cells more permeable (36). IL-1 has some other effects. It causes decreased fibrinolysis and thrombotic processes in CVI by stimulating production of fibrinolytic inhibitor plasminogen activator inhibitor-1 (PAI-1) and decreases the production of tissue plasminogen activator (tPA) (37).

Measurement of plasma levels of soluble parts of vascular (VCAM), intercellular (ICAM) and endothelial (ELAM) leukocyte adhesion molecules show that these are elevated in patients with CVI, compared to controls. Following 30 min of venous

hypertension produced by standing, these levels are further increased. The perturbed endothelium expressing these adhesion molecules attracts the leukocytes and allows the passage of large molecules such as fibrinogen, through the capillary wall (38).

Skin changes, tissue proteases

Structural abnormalities in the lipodermosclerotic skin have also been investigated recently (Fig. 6). The plasma levels of vascular endothelial growth factor (VEGF) among patients with CVI were higher than those in control subjects (39). This may be one of the factors leading to vascular proliferation in the skin of patients with venous diseases. Fibrosis of the skin and subcutaneous tissues may be initiated by increased gene expression and production of transforming growth factor-β_1 (40).



a b c

Fig. 6. Skin changes in the ankle area. a) Corona phlebectatica paraplantaris: dilated cutaneous veins like rosary; b) Atrophie blanche (white atrophy): porcelain white skin with small red dots; c) Florid ulcer and scar

In another direction of research the metalloproteinases were studied. These enzymes are responsible for remodelling of connective tissues. Expression of matrix metalloproteinase (MMP) and tissue inhibitors of metalloproteinase (TIMP) was investigated in lipodermatosclerotic tissues surrounding leg ulcers. It was found that expression of MMP-9 was increased at the ulcer edge. Higher expression of MMP-9 was observed around leg ulcers which showed least tendency of healing, but this expression was reduced where ulcers showed evidence of healing (41).

In another study chronic nonhealing ulcers were found to contain increased levels of MMP-1 and MMP-8 and decreased amounts of TIMP-1 (42).

A further class of tissue proteinases, the plasminogen activators (PA) were investigated in the leg ulcer region and in normal skin, as well. The tissue plasminogen activator (tPA) was present in the normal skin, but was reduced in skin taken from the margin of ulcers and from the ulcers themselves. Urokinase-type plasminogen activator (uPA) activity was present in the ulcer margin skin, but was absent in normal skin (43).

It is suggested that increased expression of tissue proteases leads directly to breakdown of the skin in patients with venous diseases.

Inflammatory processes

Recent histological and immunohistochemical investigations of the skin of patients with CVI confirmed the presence of the pericapillary fibrin cuff (Fig. 7). However, it has shown that this pericapillary cuff contains far more compounds than fibrin. It also contains collagen IV, laminin, fibronectin and tenascin (44). A leukocyte infiltration has been also observed around the capillaries. These cells were monocytes, macrophages and T-lymphocytes.

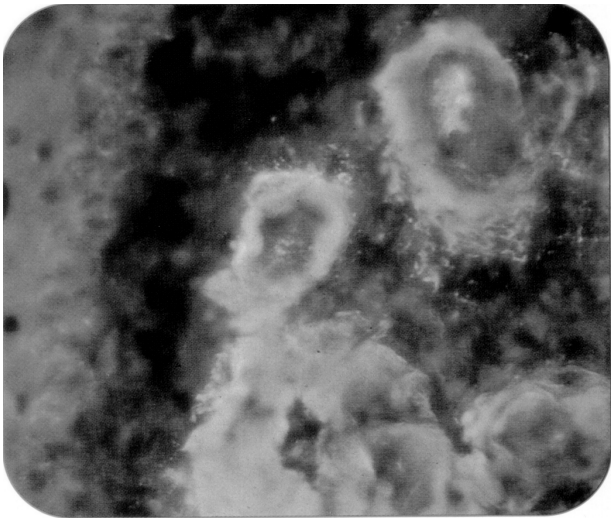


Fig. 7. Trapped white cells and pericapillary fibin cuff visualised by immunofluorescence technique

Comparing to the normal skin where a low number of leukocytes can be visible per 4 mm^2, there were 8 times as many in patients with lipodermosclerotic skin and 40 times as many in patients with healed ulcers (45).

The presence of perivascular cuff and leukocyte infiltration is a reflection of an inflammatory process and is seen in other chronic inflammatory processes as a tissue response to the inflammation. Monocytic infiltration has been also observed in the base of the damaged venous valve leaflets as a sign of chronic inflammation (46).

Pharmacologic treatment aimed at moderating of inflammatory process of CVI are under investigation (47). The efficacy of a micronised purified flavonoid fraction (MPFF: 90% diosmin, 10% hesperidin) was studied. Patients with CVI were treated with MPFF taken orally for 60 days. Plasma levels of soluble VCAM, ICAM and L-selectin decreased significantly at the end of the therapy. The reduction in the levels

of soluble adhesive molecules indicates, that MPFF reduced the leukocyte adhesion and the endothelial damage presumably by anti-inflammatory mechanism. The clinical response to the treatment was also satisfactory (38).

The clinical stages of CVI are likely the consequences of a systemic inflammatory response to a period of venous hypertension. This inflammatory response consists of a complex sequence of events, involving the leukocyte extravasation from the circulation into the tissues as well as the recruitment and proliferation of tissue and inflammatory cells. In the microcirculation the leukocyte-endothelial cell interactions in the capillaries and postcapillary venules represent an essential step in the process.

The progress from chronic inflammation to ulceration is difficult to investigate. It is suggested that the initiating stimulus, which may be thrombosis in the capillary loop, or a minor trauma to the region, causes massive activation of perivascular macrophages resulting in extensive tissue and blood vessel destruction.

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