Review paper

FACTORS CONTRIBUTING TO THE CHRONIC VENOUS INSUFFICIENCY

B. Fakin

SUMMARY

Insufficiency - whether retrograde or anterograde - of the venous circulation in the lower extremities causes hemodynamic disturbances. These appear first in the large veins and thence spread to the venous capillaries. A high venous pressure that fails to decline or declines inadequately with muscular activity leads to anatomical and functional changes in the microcirculation: inflammation, edema, a low pO_2, stimulation of fibroblasts and collagen formation. Fibrinolytic activity is reduced, and elevated fibrinogen levels in blood result in the formation of fibrin cuffs. The concomitant involvement of the lymphatic system contributes to the development of lymphedema. All these changes are ultimately manifested in the clinical picture of chronic venous, or venous and lymphatic, insufficiency.

KEY WORDS

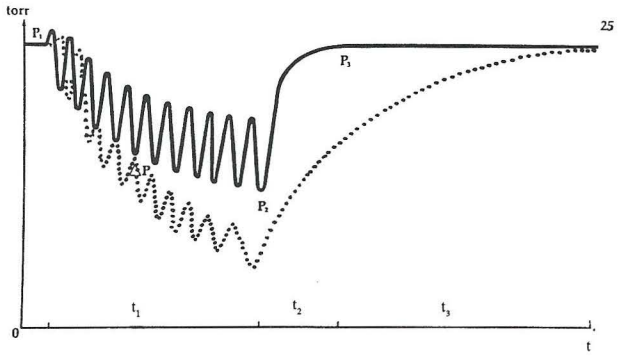
haemodynamics, "ambulatory" venous hypertension, changes of microcirculation.

A number of factors cooperate in the efficient pumping of blood from the periphery to the heart. In a recumbent person the post-capillary pressure is sufficient for a slow back-flow of venous blood to the heart (vis a tergo). Breathing which alters intrathoracic and intraabdominal pressure is also important (vis a fronte) The contraction of the heart is an additional factor; however, an effective muscle pump is the most important one. The following functions can be attributed to the venous system of human lower extremities:

1. back-flow of venous blood to the right part of the heart
2. functioning as a reservoir for a certain amount of blood
3. regulates the volume of blood reaching the heart
4. depending on climatic conditions contributes to the thermoregulation.

In the case of venous insufficiency the pressure in the veins is not reduced by the activity of the muscles to the same degree as in normal venous circulation; on the contrary, it remains high or even increases. Such a condition is labeled by varicologists as "dynamic venous hypertension" or "ambulatory venous hypertension". This happens if the deep venous system becomes insufficient. Due to the

reflux of blood in the distal direction, insufficiency of the large superficial (extrafascial) veins (secondary venous varicosities) may follow (Fig. 1).



Legend:

_____ pathological curve
..... normal curve

t_1 time of muscular activity
t_2 venous refill time at venous insufficiency
$t_2 + t_3$ venous refill time at normal venous circulation

Fig. 1. The pathological and normal curves of venous pressure at muscular activity

The insufficiency of the venous blood flow can be classified as a retrograde or antegrade. The retrograde venous insufficiency is characterized by the damage of the valves of the deep veins, which causes venous reflux. Such clinical situation is observed in the postthrombotic syndrome (PTS) where the vessels are completely recanalized, but the valves are destroyed anyway. A similar situation exists in cases of congenital displasy or agenesis of valves.

The antegrade venous insufficiency is due to the failure of the peripheral venous pump. The venous blood is not leaking into periphery, but is just not being pumped in the proximal direction. This is due to the ailment of muscles, nervous system, bones, joints, etc. (2).

Arteriovenous fistula is characterized by an elevated arterial pressure antagonizing the effect of the muscle pump. The fistula functions as a "blockade" to the vein. A similar situation occurs in case of occlusion of a deep vein and in case of extravasal compression. The extrafascial blood circuit develops which provides a way for the blood to drain away from the periphery (2).

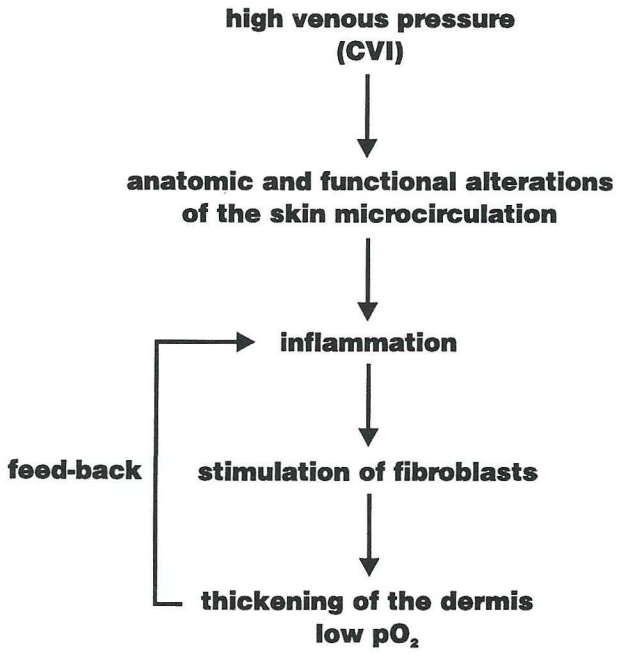


Fig. 2. Low $p0_2$ and CVI - as model

The decreased efficiency and/or failure of peripheral venous pump is followed by a chronic venous congestion.

The ankle joint plays an important role in the functioning of the peripheral venous pump. If immobile (which often happens due to pain caused by leg ulcer), it impairs the pump's functioning. Such a condition is also called the "arthrogenic stasis syndrome".

The antegrade insufficiency develops usually as a result of stasis in large veins, mostly in a femoral or popliteal vein. The venous pump is not able to drive the blood properly, and a dynamic venous hypertension with chronic stasis comes into being.

The disturbances in macrocirculation are followed by pathological events in the microcirculation influencing the changes in tissues (5). The increased venous pressure is translated into the venous sector of the capillary network: dilated capillaries, swollen endothelial cells, widening of spaces between the endothelial cells (4). Microangiopathy plays a decisive role in pathophysiology of chronic venous insufficiency (CVI). It seems to precurse the clinical signs of chronic venous congestion (3). The increased permeability of the capillary walls is responsible for the leakage of proteins, including fibrinogen, as well as

of erythrocytes, into the surrounding interstitial tissue. This is manifested clinically as purpura, yellow dermatitis, brown pigmentation and other symptoms. The so called dough-like oedema is an early sign of the impaired functioning of the venous system.

The already mentioned increased permeability has additionally provoked a hemoconcentration with increased viscosity which may be followed by thrombosis (6).

Histopathology reveals tortuous and extremely dilated capillaries, their number being reduced as observed with capillary microscopy. Using direct capillary microscopy, fewer capillary loops/mm were visible in patients sitting with their legs pending than in normal patients without CVI. Namely, capillary loops are visible only when they contain red cells. Capillary occlusion observed by Bollinger et al. is caused by white cells sticking in the capillaries of the skin (1).

When the capillary flow rate is reduced, this is sufficient to cause trapping of white cells which release toxic oxygen metabolites and proteolytic enzymes. Thereby, the capillaries are damaged and made more permeable to large molecules which enables the formation of fibrin cuffs (1,9).

The acute inflammation is diagnosed by European authors as hypodermitis and the chronic manifestations, appearing as indurated brownish plaques involving mainly the dermis, as lipodermatosclerosis. The thickened and homogenized collagen bundles, composed mainly of collagens I and III, are responsible for the decreased tension of oxygen (pO_2) which fact stimulates the activity of fibroblasts and thus an increased production of collagen (4) (Fig. 2).

Endothelial cells are normally covered by a thin film of fibrin which depends on the fibrinolytic activity of plasma. Endothelial lining of a normal vein is also endowed with an efficient fibrinolytic activity, while in chronic venous insufficiency this fibrinolytic activity is impaired. The decreased fibrinolytic activity and widened endothelial cell-gaps enable the diffusion of fibrinogen which is being deposited as fibrin cuffs around the capillaries. Due to the decreased supply of oxygen and nutrient metabolites as well as to the reduced clearing of toxic substances, the metabolism of tissue is impaired. The deposits of fibrin stimulate the production of collagen (fibrosation), which fact decreases additionally the oxygenation of tissue inducing even a necrosis (6).

Two hypotheses are currently valid, one of them being the "pericapillary fibrin cuff hypothesis" and the other "white cells trapping hypothesis" (7).

Only in certain regions of the leg where the microcirculation is most burdened by the venous pressure, sequestration of white cells sometimes takes place (8).

Lymphatic system may also be involved. In case of a prolonged capillary filtration time, the lymphatic system is overloaded and a dermal back-flow is observed causing a secondary lymphedema(5). Thus, a secondary lymphedema occurs when the CVI is long-lasting and is treated incorrectly. Further symptoms are Stemmer's sign, papillomatosis, pachydermia and a hard edema. The draining function of the lymphatic system is impaired (6). Long-lasting interstitial edema also stimulates the activity of fibroblasts as well as the process of fibrosation, and in such a way contributes to the decreased oxygenation of tissues (Fig. 3).

The cutaneous reflex-vasoconstriction in upright position is present in normal persons as well as in patients with CVI. It is manifested as a decreased pO_2 in the skin. Following the physical activity in healthy persons the oxygenation of the skin is increased due to vasodilatation. However this is not the case in CVI. In a patient this is possible to attain only while in the recumbent position. For this reason, such a position is recommended by some physicians in the treatment of leg ulcers (6) (Fig. 4).

Reasons for the decreased draining function of the lymphatic system

- sudden and excessive filling of lymphatic collectors
- lymphatic microangiopathy (insufficiency of valves, reflux in lymphatic system, increased permeability of endothelium)
- obliteration of perivenous collectors at DVT and PTS destruction of lymphatic walls due to fibrosis and infections
- appearance of pathological lymphovenous shunting (anastomoses)

Fig. 3. Reasons for the decreased draining function of the lymphatic system

In CVI the venous blood is saturated with oxygen because of a slow circulation, functional shunt mechanisms, sequestration of leukocytes and a decreased diffusion of oxygen into tissues due to

fibrin cuffs. It is possible to prove the above by transcutaneous measurement of oxygen. Transcutaneous oxygen measurements ($tcpO_2$) reveal that the oxygen pressure is substantially lowered (as compared to healthy skin) in the area surrounding the venous ulcer (esp. at its border) as well as in liposclerotic regions of the skin (3). On the other hand, however, ulcers do not necessarily occur at the sites of atrophie blanche where the $tcpO_2$ values are substantially lowered (between 0-3mm Hg).

Various other studies prove that the lack of oxygen due to fibrin cuffs is the decisive factor for the appearance of trophic changes of the tissue. However, the $tcpO_2$ is relatively high in lipodermatosclerosis with histologically proven fibrin cuffs. Therefore, different view arise regarding the question whether the decisive factor for the formation of venous ulcer really is the lack of oxygen. Comparative measurements of intracutaneous pO_2 ($icpO_2$) and transcutaneous pO_2 ($tcpO_2$) give different results. Therefore, new studies suggest that the skin damages in patients with CVI are not necessarily associated with dermal hypoxia (7).

Disturbances in fibrinolysis

- increased time of lysis of euglobulin
- increased concentration of fibrinogen in plasma
- increased adhesion of trombocytes to venous endothelium accompanied by thrombocytosis
- increased aggregation of thrombocytes
- diffusion of fibrinogen into the venous walls and the formation of fibrinous plaques

Fig. 4. Disturbances in fibrinolysis

To conclude, CVI is a syndrome which depends on numerous contributing factors. It seems that the ultimate consequences are better known that its pathogenesis. The primary cause (primum movens) often remains uncertain although a number of contributing factors have been extensively studied. It is, however, difficult to evaluate their sequence and importance.

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AUTHOR'S ADDRESS

Božo Fakin MD, dermatologist, Depatment of Dermatology
Medical Center, Zaloška 2, Ljubljana, Slovenia