

James Laredo and Byong Boong Lee

Clinical Pearls

1. Chronic venous disease is caused by venous reflux, obstruction, or a combination of both.
2. Primary varicose veins result from superficial venous dilatation or valvular incompetence without previous DVT.
3. DVT is the most common cause of deep valvular insufficiency and/or obstruction and causes secondary varicose veins.

Venous System

The function of the venous system is to deliver deoxygenated blood from the organ systems and tissues to the right heart. The blood in the right ventricle then enters the pulmonary circulation and lungs where it is oxygenated. From the lungs,

the oxygenated blood is then delivered to the left heart where the left ventricle pumps the blood into the arterial system delivering oxygenated blood to the rest of the body.

Lower extremity veins are essentially tubes with valves that function as passive conduits for blood flow. These structures also have a reservoir function with variable capacity accommodating up to 60–70% of the body's total blood volume [1]. Blood flow through the venous system is under neuromuscular control and is affected by gravity and muscular contractions. Venous flow is intermittent and ranges from high velocity to no flow, and its flow patterns are more complex than those observed in arteries [1].

The hydrostatic pressure at any point in the venous system results from the weight of the column of blood from the level of the heart to that point. This pressure is dependent on body position and varies with the height of the column of blood where the pressure at the ankle changes from a negative value with the legs elevated in a person supine, to around 10 mmHg with the legs lying flat. In an upright, standing person, the hydrostatic pressure at the ankle is around 90 mmHg. Muscular activity such as moving, walking, or running reduces the hydrostatic pressure from 90 to 30 mmHg in a person with normal venous function due to competent venous valves that fractionate the pressure column during lower extremity muscular contraction (systole) and relaxation (diastole) [1, 2].

J. Laredo, MD, PhD (✉)
Department of Surgery, Division of Vascular Surgery,
George Washington University Medical Faculty
Associates, 1860 Town Center Drive, Suite 420,
Reston, VA 20190, USA
e-mail: jlaredo@gwu.edu

B.B. Lee, MD, PhD
Department of Surgery, Division of Vascular Surgery,
George Washington University Medical Center,
1860 Town Center Drive, Suite 420, Reston,
VA 20190, USA
e-mail: bblee38@comcast.net

In patients with venous disease, venous insufficiency predominantly occurs below the knee as excessive hydrostatic pressure cannot be reduced in the upright position because of valvular incompetence or outflow obstruction. The normal function of venous valves is called dynamic fractioning of the hydrostatic pressure [1, 2].

The behavior of a vein depends on the structure of the three layers that comprise the vein wall. In diseased veins such as varicose veins, the venous wall structure is altered, while an abnormal intraluminal thrombus adherent to the intima can add an additional internal layer. Both of these situations produce complex mechanical responses.

Volume and pressure in veins can change under different conditions. The venous volume depends on the transmural pressure, active tone of the muscular media layer, and passive compliance of the adventitial layer [1]. Large-diameter veins have a high passive compliance and variable venous tone and can store blood with a low variation of transmural pressure. These high capacitance vessels can store 60–70% of the blood volume [1]. This phenomenon is known as the “reservoir effect” of the venous system. By increasing the tone of the venous wall, this blood can be mobilized when needed.

Venous Valves and Valvular Function

Venous valves are present in nearly all of the veins of the lower extremities. Valves are found in the deep and superficial veins and inside most perforating veins. In the venous system, the further away from the central circulation, the more frequent a venous valve is present [1]. Venous valves are often absent in the iliac veins and inferior vena cava. The valves are usually bicuspid where the orientation of the leaflets results in centrally directed venous blood flow [3].

In the majority of perforating veins, the valve leaflets are oriented toward the deep system, while in some veins, the valves are absent [4]. The valves in each perforating vein are usually located below the fascia, and their number may vary from one to three.

Normal valve function consists of a water-tight closure against a retrograde pressure gradient opposite to the direction of the leaflets. The valve leaflets remain passively open when the pressure gradient is antegrade in the same direction as the leaflets [5]. This function ensures unidirectional flow and emptying of venous compartments and physiologic drainage and flow of blood from superficial to deep, regardless of posture or changes in intra-abdominal or intrathoracic pressures [6]. Normal valve closure also produces dynamic fracturing of the gravitational hydrostatic pressure and is essential for proper function of the peripheral muscle pumps [1, 2].

Venous Muscle Pump Systems

During normal walking, the three vein-pumping systems (the foot, calf, and thigh) compress in sequence to promote venous return. Even moderate muscular movements of the feet and legs in the seated position are able to activate the pumping mechanism and reduce the distal vein pressure [1, 7].

The calf muscle pump is activated at the beginning of a step and starts with dorsiflexion of the foot as the foot is lifted [1]. The anterior compartment muscles contract and empty their veins. Dorsiflexion then passively stretches the Achilles tendon and thus empties blood from the lower portions of the peroneal and posterior tibial veins. As the foot strikes the ground, weight bearing and contraction of the foot muscles activate the foot pump, a second phase where the plantar venous plexus is able to overcome the hydrostatic pressure within the deep venous system of the calf [1, 8, 9]. The weight of the body and contraction of the plantar muscles result in compression of the lateral plantar veins where the middle portion is dilated and acts like a reservoir [1, 10]. Each step squeezes a small volume of blood, approximately 20–30 mL [11]. Plantar flexion initiates a third phase as the foot comes up on its toes. During this phase, the muscles of the posterior compartments, mainly the gastrocnemius and soleus muscles, contract to empty the calf venous sinuses.

The Calf Pump

The calf muscle pump is the most active pump in the lower extremity where the soleus and gastrocnemius muscles are rich in venous sinuses. During walking, contraction of the soleus and gastrocnemius muscles compresses the venous sinuses propelling blood out of the calf. During each step, calf muscle pressures exceed 200 mmHg, and calf blood volume decreases by 80% [12].

Calf muscle contraction (systole) produces a significant pressure gradient between the deep veins in the calf and the popliteal vein resulting in rapid efflux of blood from the calf into the thigh. The venous pressure exceeds the intramuscular pressures in the calf compartments, and competent venous valves prevent retrograde blood flow [10]. During calf muscle relaxation (diastole), venous pressure falls below the pressure at rest. In the deep veins, the fall in pressure is greater than that observed in the superficial veins. Perforating veins allow blood to flow from the superficial veins into the deep veins. There is no significant change in the popliteal vein pressure during calf muscle relaxation. Competent venous valves prevent backflow from the popliteal vein into the calf veins [10].

Effect of Exercise on Venous Function

When a person moves from the horizontal to the standing position, the hydrostatic pressure increases equally in both the arteries and veins of the foot by 80–90 mmHg and is dependent on the distance of the foot from the right atrium. Because the arterio-venous pressure gradient remains unaffected, arterial blood flow in a normal limb is unchanged. However, blood flow in the veins is temporarily reduced until they become fully distended with increased venous volume. When the pressure in the veins is increased by 40 mmHg or more, a veno-arteriolar reflex is elicited producing arteriolar vasoconstriction which together with the decreased blood flow results in a protective mechanism to minimize edema formation [13–15].

Exercise (walking, running, or tiptoeing) is very effective in emptying veins resulting in a significant reduction in hydrostatic pressure. Intramuscular pressures in the gastrocnemius and soleus muscles increase from 9–15 mmHg when they are relaxed to 215–250 mmHg during muscle contraction [1, 8]. In normal individuals, tiptoeing causes the pressure in the foot to reduce from 80–90 mmHg to 25 mmHg. As a result, the pressure gradient from arterioles to venules is increased allowing the high blood flow required by the leg muscles and increased blood supply to the right atrium required to maintain an increased cardiac output [1, 8].

Early experiments demonstrated that during walking the mean venous pressure is decreased in a normal limb by approximately 60 mmHg after 3–12 steps reaching a steady state which is approximately 22 mmHg at 1.7 miles per hour (40 steps per minute) [16]. There is very little further decrease in pressure at higher speeds. However, below this speed the decrease in pressure (steady state) is proportional to the walking speed [17, 18]. At the end of exercise, the pressure returns to the resting level within 30 s. Figure 2.1 shows a typical recording of venous pressure measured in a dorsal vein of the foot during standard tiptoe movements in a patient with varicose veins, saphenofemoral incompetence, and competent valves in the deep venous system [19]. The exercise was repeated after inflating a 10-cm-wide pneumatic cuff just below the knee to occlude the superficial veins [1, 28]. By eliminating the venous reflux with the pneumatic cuff, the pressure recording became completely normal [19].

Deep Vein Thrombosis

The hemodynamic changes that occur in patients with acute deep vein thrombosis (DVT) are dependent on the level of thrombosis, its extent, and whether thrombus progression is slow or rapid. The severity of the hemodynamic disturbance caused by the venous obstruction will determine the development and magnitude of the presenting symptoms and signs experienced by the individual.

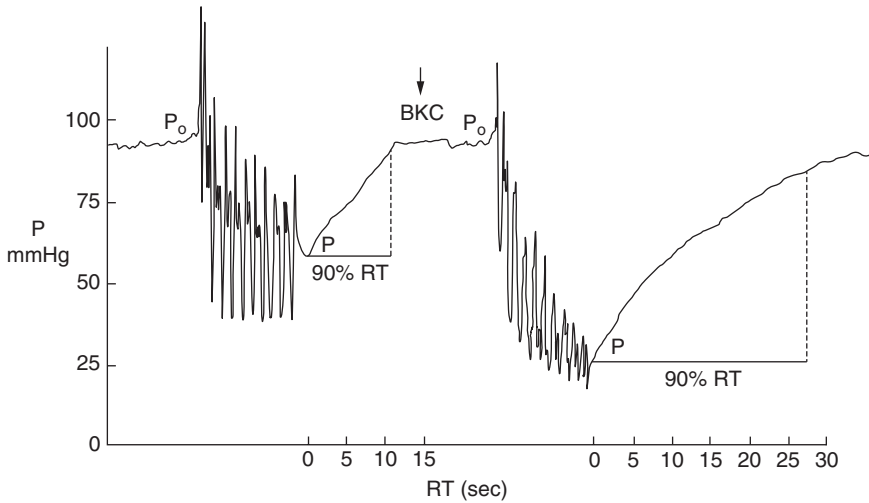


Fig. 2.1 Recording of ambulatory venous pressure at rest and during ten tiptoe movements in a patient with varicose veins and saphenofemoral incompetence. The first recording was without a below-knee cuff and the second recording

was with a below-knee cuff (*BKC*) which occluded the great and small saphenous veins normalizing the ambulatory venous pressure (*P*) and the refilling time (90% *RT*) (modified from Ref [19])

Localized DVT in one or two veins in the calf as shown by venography is often asymptomatic producing mild ankle edema and calf tenderness in only 50% of patients [20]. In contrast, extensive calf DVT involving the popliteal vein is often symptomatic. Significant lower extremity edema will not occur as long as the thrombus is confined to the femoral vein distal to the junction with the deep femoral or the great saphenous veins which act as collateral drainage channels. When thrombosis involves these junctions or occurs proximal to them, massive limb edema is likely to occur [21]. Furthermore, rapid progression of thrombus proximally may not allow development of a collateral circulation and may result in venous gangrene.

Plethysmographic studies of patients with lower extremity DVT have demonstrated reduced venous volume and increased outflow resistance [22–24]. The reduced venous volume is thought to be due to the reduced capacity of the lower extremity veins when they are filled with thrombus in patients with proximal obstruction. In addition, increased extravascular tissue pressure due to edema decreases the distensibility of the veins further decreasing venous volume [22–27].

Lower extremity venous pressure is increased in patients with acute DVT [28]. In patients with DVT, venous pressure was measured in the foot in patients in the horizontal position. Venous pressure was 8.5–18.4 mmHg when thrombosis was confined to the calf and/or popliteal vein, 20–51 mmHg when thrombosis involved the femoral vein, and 32–83 mmHg in patients with iliofemoral DVT [21]. Limb edema was rarely present in patients with venous pressures less than 20 mmHg and always present in patients with venous pressures greater than 50 mmHg.

Venous flow and velocity are phasic with respiration in normal limbs in the horizontal position. During inspiration, intra-abdominal pressure increases with contraction of the diaphragm. The increase in intra-abdominal pressure is transmitted to the inferior vena cava and iliac veins resulting in a decrease in the pressure gradient between the lower extremity vein and the inferior vena cava. The end result is a decrease in blood flow from the lower extremities.

During expiration, the reverse occurs as the diaphragm relaxes and intra-abdominal pressure decreases. The decrease in intra-abdominal pressure results in an increase in the venous pres-

sure gradient between the inferior vena cava and lower extremity veins. This results in an increase in venous flow and velocity from the lower extremity veins.

In patients with acute iliofemoral DVT, the outflow resistance increases much more than the respiratory fluctuations so that this becomes the limiting factor, and flow in the deep veins distal to the obstruction loses phasicity and velocity decreases [1]. In contrast, flow and velocity in the collateral circulation increase, and higher velocities are observed. These findings explain why an ultrasonographer should look for a more proximal obstruction when performing a DVT scan in a patient with the dual finding of the absence of respiratory phasicity in the deep veins and increased velocity in the collateral veins of the lower extremity [1].

Chronic Venous Disease

Chronic venous disease (CVD) is a term that includes all long-term morphological and functional abnormalities of the venous system, manifested either by symptoms or signs indicating a need for investigation and treatment. In patients with CVD, hemodynamic disturbances occur which result in the inability of valves, pumps, and conduits in the venous system to maintain a normal venous pressure and normal flow toward the heart. Hemodynamic disturbances are primarily caused by venous reflux, obstruction, or a combination of both [1].

Varicose Veins

Varicose veins are a common manifestation of CVD and are believed to result from the abnormal distension of connective tissue in the vein wall. Veins from patients with varicosities have different elastic properties than those from individuals without varicose veins [29, 30]. There is hypertrophy of the vein wall with increased collagen content [31], fragmentation of elastin fibers [32] with degradation, and accumulation of extracellular matrix [33].

Primary varicose veins result from venous dilatation and/or valve damage without previous DVT. Secondary varicose veins develop as a result of a prior DVT, congenital venous malformation, or arteriovenous malformation [34].

Varicose veins may also be associated with pelvic vein reflux in the absence of incompetence at the saphenofemoral junction (SFJ), thigh, or calf perforating veins. Retrograde reflux in ovarian, pelvic, vulvar, pudendal, or gluteal veins may be also associated with clinical symptoms and signs of pelvic congestion [35–38].

Elevated venous pressure is considered to be the main precipitating factor in the development of varicose veins. Varicose veins would not occur without hydrostatic pressure from a gravitational force [1]. The effect of dilatation is easily understood from the unrelenting radial forces against the wall of the varicose vein. What is not understood is why the dilatation of varicose veins predominantly occurs in the thigh portion of the great saphenous vein (GSV) in many patients and not in the ankle portion where the hydrostatic pressure is highest (descending theory) [1]. In addition, it is also unknown as to why superficial veins dilate and become tortuous forming varicose veins; in contrast, the GSV usually dilates and rarely becomes tortuous within the saphenous fascia.

Varicose veins have increased wall thickness and increased diameter and length [39]. This is likely due to the different elastic properties observed in varicose veins compared to normal veins [29, 30]. The ratio between collagen I and collagen III is altered as are dermal fibroblasts from the same patients suggesting a systemic disorder with a genetic basis [40]. Leukocyte activation, adhesion, and migration through the endothelium as a result of altered shear stress [41–43] contribute to the inflammation and subsequent remodeling of the venous wall and valves [44–47].

Cell culture studies have shown that smooth muscle cells have undergone phenotypic modulation from a contractile state to a proliferative and secretory state [48]. Reduction in shear stress stimulates production of transforming growth factor- β 1 (TGF- β 1) by activated endo-

thelial cells and smooth muscle cells (SMCs) inducing SMC migration into the intima and subsequent proliferation as well as phenotype change. Fibroblasts proliferate and synthesize matrix metalloproteinases (MMPs) overcoming the effect of tissue inhibitors of metalloproteinases (TIMPs). The MMP/TIMP imbalance results in degradation of elastin and collagen [42, 49, 50]. These effects may contribute to the development of hypertrophic and atrophic venous segments and valve destruction that is observed in varicose veins. Remodeling of the venous wall and abnormal venous distension prevents valve leaflets from closing properly resulting in valve failure and reflux.

Genetic factors may also play a role in the development and subsequent progression of primary varicose veins to advanced CVD. A relationship between the C282Y polymorphism in hemochromatosis (HFE gene) and venous ulceration has been described [51].

Deep Venous Insufficiency

Imaging studies in patients with deep venous insufficiency have shown that approximately 30% of these patients have primary valvular incompetence rather than findings consistent with post-thrombotic injury [52, 53]. Valve agenesis or aplasia is a less likely cause of deep venous reflux [54].

Following the development of a DVT, spontaneous lysis often occurs over days or weeks, and recanalization that occurs over months or years can be found in 50–80% of patients [55–57]. Rapid thrombus resolution after DVT is associated with a higher incidence of valve competency [55, 58]. The duration of DVT recanalization and resolution depends on thrombus extent, location, local inflammation, potency of local fibrinolytic agents and proinflammatory mediators [59, 60]. Recanalization may give rise to relative obstruction and reflux in deep, superficial, and perforating veins [57]. Incomplete recanalization following DVT can lead to outflow obstruction. Less frequently,

obstruction results from extramural venous compression (most commonly left common iliac vein compression by the right common iliac artery) [61, 62], from intraluminal changes [63–65], or rarely from congenital agenesis or hypoplasia [66].

Most post-thrombotic symptoms result from venous hypertension due to valvular incompetence, outflow obstruction, or a combination of both. Venous hypertension increases transmural pressure in postcapillary vessels leading to skin capillary damage with increased microvascular permeability, [67] followed by lipodermatosclerosis and, ultimately, ulceration [68]. Edema will develop when the increased lymphatic transport fails to adequately compensate for increased fluid filtration into the tissue, and thus long-standing venous hypertension is invariably associated with damaged lymphatic drainage in the skin and subfascial space in cases of post-thrombotic syndrome [69, 70]. The reported prevalence of post-thrombotic syndrome following DVT has been variable (35–69% at 3 years and 49–100% at 5–10 years) and depends on the extent and location of thrombosis and treatment [71–81].

Patients with both chronic obstruction and reflux have the highest incidence of clinical C of CEAP 4–6 disease [71]. The risk of ipsilateral post-thrombotic syndrome is highest in patients with recurrent thrombosis and is often associated with congenital or acquired thrombophilia [82–85]. More recent studies suggest that skin changes and/or ulceration are less frequent (4–8% in 5 years) in patients with thrombosis proximal to the knee if they have been treated with adequate anticoagulation, early mobilization, and long-term compression therapy [86, 87]. Mechanical dysfunction of the calf muscle pump may enhance development of leg ulceration suggesting the importance of the range of ankle motion [88] and patient activity [89] in relation to progression of disease. Obesity is another risk factor for severe venous disease and may be related to its association with decreased fibrinolytic activity in blood and tissues [90].

Perforating Veins

Incompetent perforating veins (IPVs) can be defined as those that penetrate the deep fascia and allow blood flow from the deep to the superficial system. The flow in IPVs in the calf is usually bidirectional, outward during muscular contraction and inward during relaxation. In normal legs and in the majority of patients with primary uncomplicated varicose veins, the net flow is inward from superficial to deep (reentry perforating veins) [91, 92]. The net flow is also inward in patients with femoral vein reflux, provided the popliteal valves are competent. However, flow is predominantly outward in the presence of popliteal valve incompetence (axial reflux) and especially when there is associated deep venous obstruction [92, 93]. The IPVs are associated with superficial and/or deep venous reflux but are rarely found in the absence of reflux [94–96]. In the majority of IPVs, their diameter, volume flow, and velocity increase with clinical severity of CVD whether or not there is coexisting deep venous incompetence [92, 97–102]. Up to 10% of patients, often women, presenting with clinical C of CEAP 1–3 disease, have non-saphenous superficial reflux in association with unusually located IPVs [103].

Superficial Venous Insufficiency

The valves and walls of superficial veins are more prone to structural failure than deep veins because they are surrounded by connective tissue and subcutaneous fat. In contrast, deep veins are surrounded by rigid structures such as muscle and fascia. Therefore, the walls and valves of the superficial veins are more vulnerable to the changes in shear stress and hydrostatic pressure [104–106].

The concept of retrograde flow in the GSV and the presence of a “private recirculation” were first demonstrated by Trendelenburg in 1891 [91] by placing a tourniquet at mid-thigh and asking the patient to tiptoe repeatedly when it was observed that veins emptied with refilling from above when the tourniquet was released. We now

know that the circuit consists usually of a reflux source feeding a saphenous trunk, conduction of reflux, down toward the foot, and reentry points back into deep veins via perforating veins. The presence of this phenomenon has been demonstrated using two simultaneous duplex probes, above and below the knee [107]. In this study, reflux was demonstrated to start and stop simultaneously, even when the probes were swapped around. In another study, volume displacements in patients were quantified within saphenous trunks using duplex ultrasound in response to calf compression [108]. The findings of bidirectional flow in the GSV and perforating veins by Bjordal [109, 110] were confirmed in the same year by Folse [111] who used the CW Doppler which had just become available and by duplex ultrasound scanning in later years. The conclusion was that in the presence of competent deep veins, despite inward and outward flow in perforating veins during walking, the net effect is inward. However, when deep venous valves were incompetent and valves in the GSV were competent, Bjordal found that calf contraction caused upward flow in the saphenous vein and that in limbs with both deep and superficial venous reflux, walking produced bidirectional flow in IPVs with the net effect being outwards [109, 110]. It is now recognized that in the majority of patients, the origin of the downward flow in the superficial system of veins is through the SFJ, thigh IPVs, the SPJ, or a combination of two or even all three and that calf IPVs are reentry points. This is the basic rationale for the CHIVA technique [1]. However, two RCTs have shown that following ablation of superficial incompetence, only 35–40% of IPVs function normally and that new IPVs appear over time [112, 113]. Furthermore, some 6–8% of ulcer patients show only isolated IPVs as a possible cause for their ulcers [114].

Manifestations of Venous Hypertension

Changes in the hemodynamics of veins that result in venous hypertension are transmitted into the microcirculation resulting in an increase in the

hydrostatic pressure in capillaries. This results in transcapillary filtration that exceeds lymphatic drainage and contributes to interstitial edema formation. Venous hypertension slows blood flow in the capillaries allowing leukocyte adhesion to capillary endothelium and initiating an inflammatory reaction [115]. One theory contends that inflammation opens gaps between endothelial cells through a mechanism involving vascular endothelial growth factor (VEGF), nitric oxide synthase (NOS), and contraction of actin and myosin filaments present in endothelial cells [116]. If the gaps continue to enlarge, this results in increased capillary permeability to fluid and macromolecules, allowing extravasation of red and white blood cells into the interstitial space with edema formation. Swollen endothelial cells with enlarged intercellular spaces make the capillary lumen irregular. The subsequent increase in macromolecular permeability causing plasma, fibrinogen, and red blood cell leakage impairs nutrient exchange [117, 118].

The skin is the final target of chronic venous hypertension and the hemodynamic changes in veins. Clinical manifestations caused by alteration in skin capillaries are hyperpigmentation, venous eczema, lipodermatosclerosis, atrophie blanche, and eventually venous ulceration (Fig. 2.2). Several mechanisms for the development of venous ulcers have been postulated of which the theory of “leukocyte trapping” is the most likely [119]. It is hypothesized that the primary injury to the skin is extravasation of macromolecules such as fibrinogen and alpha-2-macroglobulin as well as red blood cells causing pigmentation into the dermal interstitium [120, 121]. Red blood cell degradation products and extravasation of interstitial proteins are potent chemoattractants and presumably generate an initial inflammatory signal that results in leukocyte recruitment and migration into the dermis [115]. Pathologic events occur during leukocyte migration into the dermis, and the end product is dermal fibrosis. An increase in transforming growth factor beta-1 (TGF- β 1), released by macrophages and mast cells or auto-induced by dermal fibroblasts, causes an imbalance in tissue remodeling which results in increased colla-

gen synthesis and affects matrix metalloproteases (MMPs) as well as their tissue inhibitors (TIMPs). It is hypothesized that an imbalance in MMPs and their regulation may cause or contribute to venous ulcer formation. A cascade of inflammatory events results in cutaneous changes which include skin hyperpigmentation caused by hemosiderin deposition and eczematous dermatitis. Fibrosis may develop in the dermis and subcutaneous tissue lipodermatosclerosis. There is an increased risk of cellulitis and leg ulceration [118, 120, 121].

Lymphedema

The function of the lymphatic vessels is very important. They are involved in the recirculation of lymphocytes and proteins, transport of microorganisms by lymph, and drainage of interstitial fluid to blood. The average human body weighing 65 kg contains 3 L of blood plasma and 12 L of interstitial fluid. Up to 8–12 L of afferent lymph are produced each day of which 4–8 L of ultrafiltrate are reabsorbed into the bloodstream. The concentration of proteins in plasma, interstitial fluid, afferent lymph, and efferent lymph is 70 g/L, 20–30 g/L, 20–30 g/L, and 60 g/L, respectively. The fluid turnover reaches up to two thirds of the total volume of interstitial fluid daily [122]. The skin on the lower extremities contains a denser and more extensive network of lymphatic capillaries than the skin of the upper extremities [123]. Due to orthostatism, lower extremities have higher filtration pressure and influx of fluids, and it is thought that the capacity for lymph transport in the lower extremities is greater in order to compensate for the higher influx of interstitial fluid caused by the effects of orthostatism and gravity. Spontaneous contractility of lymphatic vessels contributes to lymph transport. Regular contractions of lymph vessels at a frequency of 2–4 per minute were observed in vitro, and spontaneous contractions of prenodal lymphatic vessels that drive lymph have been observed in human legs [124]. Internal extensions of lymphatic endothelial cells act as valves and guarantee a one-way lymph flow



Fig. 2.2 Skin changes associated with chronic venous insufficiency. (a) Hemosiderin pigmentation. (b) Stasis dermatitis. (c) Lipodermatosclerosis. (d) Ulceration

[122]. In a steady state, extravasation of fluids and proteins from blood vessels is balanced by lymphatic drainage and return into the bloodstream. If microvascular filtration in blood capillaries and venules as occurs in advanced CVD exceeds the capacity for lymphatic drainage for

sufficiently long periods, edema develops in afflicted areas by accumulation of tissue fluid in the interstitium. In addition, lymphatic dysfunction and structural damages to the lymphatic network are associated with varicose veins, and subsequent lymph stasis and reduced lymph

transportation lead to inflammation [125]. This is associated with lipid accumulation in the media of the diseased veins. Such accumulation of inflammatory lipids in the vein wall might further damage adventitial lymphatic vessels.

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Current Management of Venous Diseases

Chaar, C.I.O. (Ed.)

2018, XVII, 582 p. 245 illus., 174 illus. in color.,

Hardcover

ISBN: 978-3-319-65225-2