Back to basics: understanding venous leg ulceration

KEY WORDS
- Chronic venous insufficiency (CVI)
- Venous leg ulcer
- Venous return

Venous leg ulceration is caused by chronic venous insufficiency (CVI) as a result of raised ambulatory venous hypertension. Persistent or chronic venous hypertension results in macro- and micro-vascular changes in the limb — leading to venous ulcers. The failure of venous return — the flow of blood back to the heart — is commonly due to valve and calf or foot muscle pump incompetence. Physical, biochemical and radiological examination will establish the underlying pathology and the severity of the CVI. The Comprehensive Classification System for Chronic Venous Disorders (CEAP) is a recognised system for recording the clinical manifestations of the disease and compression therapy remains the most commonly applied treatment for venous leg ulceration, as Trudie Young explains in this article.

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Chronic venous disease is a term used to describe both visual and functional manifestations of abnormalities in the peripheral venous system (Wittens et al, 2015). The number of people with leg ulceration in the UK is at least 730,000, which equals 1.5% of the adult population (Guest et al, 2017). The number of people diagnosed as suffering with venous leg ulceration is 278,000 (1 in 170 adults) (Guest et al, 2017). Unfortunately for individuals with venous leg ulceration, they are often subjected to a cycle of recurrent ulceration despite compliance with maintenance compression therapy (Ashby et al, 2014; World Union of Wound Healing Societies, 2009). The prevalence of venous leg ulcers is not a static phenomenon and it is increasing, coinciding with an ageing population (Franks et al, 2016). Venous leg ulceration has an adverse effect on an individual's quality of life (Franks et al, 2016). Venous leg ulceration is associated with prolonged disability and significant psychosocial morbidity (O'Donnell Jr et al, 2014). Furthermore, there is a wider social and economic impact on society in general (Franks et al, 2016).

HISTORICAL RECORDS

Hippocrates had recognized that an upright position was inappropriate for a leg with ulceration. However, it was around 2,000 years later that Vassaseus, a Spanish anatomist, could add details to what was already known of the venous system by describing the valves and their function (Caggiati and Bertocchi, 2001). Subsequently, at the beginning of the 17th Century, the Italian Marcello Malpighi recognised the finer details in the circulatory system by identifying the presence of the capillary network. In 1670, the function of the calf muscle pump on venous return was described by Richard Lower, and the secondary aspect of the pressure changes brought about by thoracoabdominal respiration was attributed to Valsava in 1710. The term 'venous ulceration' was coined by John Gay, a London surgeon, in 1868 (Negus et al, 2005). The classic Trendelenberg Test, which allows clinicians to assess superficial and deep reflux/retrograde flow within the venous system, was designed the German surgeon Friedrich Trendelenburg in 1891. In 1953, Richard Linton brought the pieces of information together by identifying the concept of ambulatory venous hypertension and its relevance to chronic venous disease.

PHYSIOLOGY OF THE VENOUS SYSTEM

The construction of the veins is similar to that

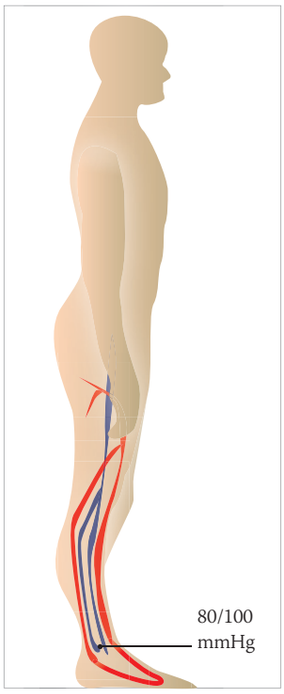

Figure 1a. When standing, the ambulatory hydrostatic pressure in the veins measures around 80/100 mmHg

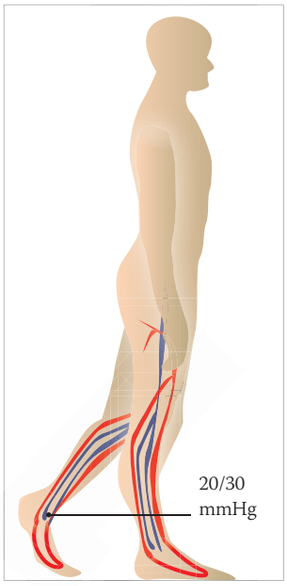

Figure 1b. When walking, the combined action of the valves in healthy veins, calf muscle and foot pump reduce hydrostatic pressure to 20/30 mmHg

of arteries. Veins have three layers; an inner layer of endothelium, a middle muscular layer and an outer fibrous adventitia layer. The deep veins have a less powerful muscle layer than the superficial veins as they act in a more passive role than the superficial veins, which require the more powerful muscle layer for contraction (Negus et al, 2005).

The valves within the venous system consist of collagen fibres covered by a thin layer of endothelium and are stronger than the vein wall (Negus et al, 2005). When the venous system is working normally, the blood is conducted from the superficial veins via the perforating veins into the deep veins. Thus, the flow of the blood is in one direction only, apart from the foot where bi-directional flow is found within the perforating veins of the foot (Wittens et al, 2015). The superficial system is located above and the deep veins are below the muscle fascia layer, whilst the perforating veins cross the fascial layer to connect the superficial and deep system (Eberhardt and Raffetto, 2014).

The superficial veins drain the skin and subcutaneous fat. The deep veins are responsible for venous return from muscle and other structures deep to the deep fascia. The volume of blood passing through the deep system far exceeds that through the superficial system.

FUNCTION OF THE VENOUS SYSTEM

The peripheral venous system is a low pressure, low velocity system that contains a high volume (60%) of the resting blood volume. The primary function of the venous system is to return circulating deoxygenated blood to the heart and the lungs for re-oxygenation and subsequent redistribution around the body. In a normal situation, venous return is equal to cardiac output, thus maintaining equilibrium within the circulatory system. The volume of blood within the venous system, most of which is found in the post-capillary venules of the lower leg, results in it having a secondary role in the regulation of body temperature (Wittens et al, 2015).

The venous system has a difficult task when an individual is in an upright position, as it must return the blood from the foot to the heart against the force of gravity. The shift of position from lying to standing can result in an increase of volume in the venous system by 10%. To compensate for this, the veins become flaccid (under the influence of the muscle layer in the vein wall), allowing them a greater capacity to accommodate the increase in volume and thus keep the pressure within the venous system at a low level (5–25 mmHg).

The changes in venous muscle tone are mediated by the sympathetic nervous system (Negus et al, 2005). The hydrostatic pressure is determined by the blood column between the heart (right atrium) and the foot (Wittens et al, 2015). In the supine position the hydrostatic pressure within the venous system is low and then rises to 80–100 mmHg when in the upright position (Attran and Ochoa Char, 2017).

To compensate for the force of gravity the superficial, deep and perforator veins contain one-way, bi-cuspid valves. There are more valves in the lower leg (calf veins) reducing in number in the more proximal veins, with only one or two in the femoral and popliteal veins. The valves prevent an increase in pressure in the calf veins, because of gravity, when upright (Eberhardt and Raffetto, 2014). The valves work in a four-phase cycle: opening, equilibrium, closing and closed (Eberhardt and Raffetto, 2014). The function of the valves is to divide the column of blood into segments and prevent reverse flow. In a limb with veins in good working order, they can resist reverse flow pressures of up to 300 mmHg; however, in limbs with damaged valves (valvular incompetence) they are unable to stem the reverse flow at much lower pressure. The foot and calf muscle pumps act in unison during walking to assist the venous return and thus lower the hydrostatic pressure present in the upright position. However, the foot pump works in a different way by elongating the plantar veins during walking which in turn pushes the blood in an antegrade direction. The calf muscle pump has been described by Negus et al (2005) as the peripheral heart. The movement of the foot during walking and weight bearing also stimulates the calf muscle pump. The resulting action of the venous pump (a combination of the valves, calf muscle and foot pump) is to reduce the ambulatory hydrostatic pressure from 80–100 mmHg to 20–30 mmHg (Wittens et al, 2015); (*Figure 1a and b*). Following

walking, the pressure is the venous system is low because the vessels have emptied; however, once the calf muscle pump relaxes, the deep venous system refills with blood.

Inspiration has a positive effect on venous return. It creates a negative pressure in the thoracic cavity that helps to pull the blood upwards. During inspiration, there is a decreased flow in the abdominal system, the opposite occurs during periods of expiration (Wittens et al, 2015).

CHRONIC VENOUS INSUFFICIENCY

CVI is a condition that affects the venous system of the lower limbs, resulting in pain, skin changes and ulceration (Eberhardt and Raffetto, 2014). Thus is in contrast to a venous leg ulcer, which can be defined as an open-skin lesion of the leg or foot that occurs in an area affected by venous hypertension (O'Donnell Jr et al, 2014).

In CVI, there are abnormalities and weaknesses in the walls of the superficial veins, consequently they are unable to empty and send the blood in a timely fashion back into the deep veins and on to the heart during episodes of walking (Chi and Raffetto, 2015). A contributing factor is valvular incompetence in which the valves will open to allow the blood to be pushed up into the next segment, unfortunately, they do not close properly and this allows some of the ejected blood to flow backwards (reflux) and eventually there is a backflow. When this occurs, the superficial veins become engorged with blood and their walls become dilated and permeable to the release of substances normally contained within the vessel.

The deep veins are more affected by acute obstruction (deep vein thrombosis) or chronic damage to the veins (stenosis, occlusion) caused by post-thrombotic changes, trauma or scarring resulting from injecting recreational drugs into the veins. The acute and chronic obstruction within the deep veins limits the outflow of blood resulting in an increased venous pressure with muscle contraction and secondary muscle pump dysfunction (Eberhardt and Raffetto, 2014; Wittens et al, 2015).

The reverse flow results in high pressures and pooling of blood in the superficial veins, the excessive local high pressure can result in secondary failure of the superficial valves (Eberhardt and Raffetto, 2014). It is unclear if the vein wall changes precede valve insufficiency or if the latter causes the abnormalities of the endothelium of the veins. An alteration in the collagen deposition in the veins may result in a weakness and decreased elasticity of the vessels (O'Donnell Jr et al, 2014).

In addition, valvular incompetence is hindered even further if there is a lack of optimal functioning of the calf and foot muscle pumps. This may be due to fixed ankle joints and factors affecting the person's ability to mobilise and exercise (World Union of Wound Healing Societies, 2008).

Because of the valvular incompetence, a lack of vessel patency and suboptimal muscle pump function, the ambulatory venous pressure (venous pressure higher than normal when an individual exercises) is higher than the system can tolerate (Harding et al, 2008).

The abnormalities caused by CVI can also be seen in the venous microcirculation. The capillaries become elongated and dilated, they have damage to their endothelium with widening of the endothlieal spaces and there is localised oedema and inflammation. Increased localised pressure and capillary permeability allows for macromolecules and extravasated red blood cells to leave the capillary vessel and go into the interstitial spaces. The exact mechanism for this localised damaged is unclear, however, the early theories were based on the following suggested mechanisms of action. An initial theory was the formation of fibrin cuffs (Browse and Burnand, 1982) in which fibrin deposits, (which can be seen via fluorescent microscopy), wrap themselves around the already enlarged capillary beds and act as a physical block to the diffusion of gases, noticeably a decrease in oxygen perfusion to the surrounding tissues that results in ulceration. The trapping of white blood cells in the capillaries was evident following histological examination of the sub-epidermal capillary bed in people with venous hypertension. The reduced capillary perfusion and the low capillary flow rate caused a physical trapping of white blood cells (leukocytes) within the vessels. The trapped cells subsequently release toxic oxygen metabolites and proteolytic enzymes, which increases the permeability of the capillary wall with loss of fibrinogen and other plasma proteins

Box 1. Clinical signs of lipodermatersclerosis

- Discolouration of the gaiter area (above the ankle and below the knee)
- Atrophie blanche
- Ankle flare (dilated veins visible around the medial and lateral malleolus)
- Fibrosis of the tissue in the gaiter area which makes the skin firm and hard on palpation
- Alteration of the leg shape into a 'champagne bottle' with a wide knee and a narrow ankle.

into the interstitial space (Smith et al 1988). A subsequent theory recognises the inflammatory process initiated by the trapped white blood cells and the subsequent tissue destruction. It also acknowledges the presence of cuffs that contain several molecules other than just fibrin (Herrick et al, 1992).

Therefore, persistent inflammation plays a critical role in the progression of CVI involving leukocyte/endothelial interactions triggered by abnormal venous flow (Harding et al, 2008). The activated leukocytes produce a complex of cytokines, chemokines, growth factors and proteinases that perpetuate the inflammatory process and may delay ulcer healing (Raffetto and Mannello, 2014).

Parker et al (2015) identify ulcer surface area, duration and venous (specifically deep vein) abnormalities and a history of previous ulceration as consistent predictors of delayed healing in venous leg ulceration.

GENETIC CONDITIONS LEADING TO VENOUS DYSFUNCTION

As with any clinical picture there can always be an alternative diagnosis and Klippel-Trenaunay syndrome (varicosities and venous malformations, capillary malformation, and limb hypertrophy), and Parkes-Weber syndrome (venous and lymphatic malformations, capillary malformations and arteriovenous fistulas) are genetic conditions that also result in venous dysfunction.

RISK FACTORS FOR CVI

The risk factors for CVI include age, obesity and family history along with pregnancy, phlebitis and previous leg injury or surgery. Additional factors that result in an individual standing or sitting for long periods will also contribute to CVI (Eberhardt and Raffetto, 2014; Wittens et al, 2015; Franks et al 2016).

Box 2. Comprehensive Classification System for Chronic Venous Disorders (Eklöf et al, 2004)

- **C0** = No signs of venous disease
- **C1** = Telangiectasia or reticular veins
- **C2** = Varicose veins
- **C3** = Presence of oedema
- **C4a** = Eczema or pigmentation
- **C4b** = Lipidermatosclerosis or atrophie blanche
- **C5** = Evidence of a healed venous leg ulcer
- **C6** = Active venous leg ulcer

The assessment of an individual with CVI includes looking for potential risk factors along with a more detailed investigation of the individuals past medical and surgical history. Biochemical and radiological investigations should be undertaken to establish the underlying aetiology. Specifically venous Duplex ultrasonography will provide a detailed account of the arterial and venous status of the individual (Moffatt, 2007). Franks et al (2016) recommend that the precursor to more detailed radiological investigation is a hand-held Doppler ultrasound examination, however, with the advancement in the technology a more sophisticated assessment can now be undertaken with these machines. The machines providing a visual record of the Doppler wave form are very helpful and the Doppler wave form analysis has excellent inter-rater reliability amongst clinicians (Formosa et al, 2013).

CLINICAL PRESENTATION OF CVI

A physical examination of the lower limbs will reveal the clinical characteristics of CVI. The presentation of CVI includes telangiectases, reticular veins, varicose veins and can develop to include hyperpigmentation, eczema, lipodermatosclerosis *(Box 1)* and ulceration (Eberhardt and Raffetto, 2014). The progressive nature of CVI is evident in the internationally recognised CEAP revised classification system (Eklöf et al, 2004). The CEAP classification is an international consensus method of assessing venous disease. It incorporates clinical, aetiological, anatomical and pathophysical evaluation. The scale consists of seven classifications from C0 to C6 that describe the severity of the patient's venous disease. Patients presenting with one or more active venous leg ulcers would be classified as C6, which describes the most severe venous disease. Patients with evidence of healed venous leg ulcers are categorised as C5 due to the high risk of recurrent ulceration *(Box 2)*.

TREATMENT OF CVI

To reverse the high pressures within the venous system experienced by individuals with CVI, the

application of external compression therapy is required. Prior to the application of compression therapy the individual's arterial status should be assessed to establish that the application of compression is safe for the individual. Therefore, an ankle brachial pressure index should be established before applying compression therapy.

The treatment choice will depend on additional factors, which include the mobility and dexterity of the individual, leg ulcer pain and psychological aspects such as wellbeing and quality of life (Franks et al, 2016).

There are various methods of applying the compression therapy and a description of the advantages and disadvantages can be found within the best practice statement on the holistic management of venous leg ulceration (Wounds UK, 2016).

CONCLUSION

The venous system functions by a combination of the heart muscle pump, the calf muscle pump and functioning valves within the veins.

In a healthy individual, blood is returned from the lower limb to the heart from the superficial veins into the deep veins via the communicating perforator veins. This return of blood is compromised in CVI due to weakness in the walls of the superficial veins along with valvular incompetence in the deep veins and a suboptimal functioning of the calf and foot muscle pumps. This results in abnormally high pressures within the venous system.

In addition, there are changes within the microvascular venous system. The elevated ambulatory venous pressure affects the endothelial cells of the veins, which in turn initiate an inflammatory response.

The result of CVI is venous leg ulceration accompanied by one or more of the clinical signs of lipodermatosclerosis *(Box 1)*. The application of external compression therapy is necessary to reduce the high pressures in the venous system. WUK

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