Pathophysiology and Principles of Management of Varicose Veins.

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Abstract: The management of superficial and deep venous reflux and obstruction that leads to the development of varicose veins (VV)[1] and the post-thrombotic syndrome (PTS)[2] forms a large part of the workload for most vascular and endovascular specialists and is likely to increase as the population ages.[3] However, the epidemiology,4,5 genetics6 and pathophysiology of these conditions remains incompletely defined[7,8,9,10,11] and many clinicians lack a clear understanding of the underlying anatomy and vascular biology.[12 ]As a result, treatment outcomes are not infrequently sub-optimal.

1. Introduction

Varicose veins (VV) are dilated, tortuous subcutaneous veins that permit reverse flow. They are most commonly found in the lower limb and may be primary, or secondary to deep venous pathology.

1.1 Anatomy

Venous blood from the lower limbs returns to the right heart against gravity through the superficial and deep venous systems. The superficial venous system comprises the great saphenous veins (GSV) and small saphenous veins (SSV) and their tributaries [13]. The GSV originates from the medial end of the dorsal venous arch, passes anterior to the medial malleolus, and continues up the medial aspect of the calf and then the thigh to enter the common femoral vein in the groin at the saphenofemoral junction (SFJ).

The SSV originates from the lateral end of the dorsal venous arch, passes posterior to the lateral malleolus and then continues up the back of the calf between the heads of gastrocnemius to enter the popliteal fossa. It is joined variably by gastrocnemius veins and then usually enters the popliteal vein at the sapheno-popliteal junction (SPJ). These systems interconnect at many other (highly variable) points through an extensive network of tributaries. In the deep system, veins, which are often paired, accompany each named artery. The superficial and deep systems connect at numerous points at various non-junctional perforators in addition to the SFJ and SPJ. These systems and interconnections are interdependent, both anatomically and functionally in health and disease. In health, the deep venous system transmits 90% of the venous return from the leg. The superficial system drains only the skin and subcutaneous tissues, with most of that blood draining immediately into the deep system via perforators in the foot, calf and thigh. It also plays a role in thermoregulation.

1.2 Histology

The vein wall comprises three layers but these are less well defined than in the arterial system. The intima is thin and surrounds a fine elastic lamina. The media is made up of elastin and layers of muscular bundles that are arranged in different orientations. The relative amounts of muscle and elastin varies with the calibre and working pressure of the vein. Beyond this, the adventitia merges with the perivenous connective tissue, which contains nerve fibres and vasa vasorum and provides for vessel distension which is an important part of normal venous function. With increasing age, and particularly with the development of disease, abnormalities have been described in all three layers[14] and the structure of the vein wall becomes progressively more disorganised[15]. Typically, there is thickening of the intima with disorientation of the elastic fibres. The outer muscle layer of the media becomes hypertrophied with dystrophic elastic fibres and the adventitia is increasingly fibrous.

1.3 Physiology

Venous return against gravity is primarily dependent on muscle pumps located in the foot and the calf. Pressure on the sole of the foot, and muscular contraction (systole) in the fascial compartments of the calf compresses the sinusoidal intramuscular veins directing blood into the deep system and thence up the leg. Superficial veins collect blood from the superficial tissues, and during muscle relaxation (diastole) this blood enters the deep system through the perforating veins down a pressure gradient, filling the sinuses. Reverse flow (reflux) during muscle relaxation is prevented by the closure of
valves. These are delicate but strong bicuspid leaflets at the base of a localized dilated sinus in the vein. In both superficial and deep systems the density of valves is greatest in the calf and reduces gradually up the lower limb, with the iliac and inferior vena cava (IVC) frequently lacking valves altogether. Valves are present in venules down to about 0.15mm diameter.

During systole, blood is prevented from re-entering the superficial system through the closure of junctional (SFJ, SPJ) and non-junctional perforators (NJP). This was originally thought to occur solely through the closure of valves but several studies have failed to demonstrate such valves in NJP. Instead, external pressure from the fascia and muscle through which the perforators pass is thought to be responsible for limiting outward blood flow; somewhat akin to the ‘pinch-cock’ mechanism that prevents reflux at the gastro-oesophageal junction. Importantly, this also protects the superficial veins, subcutaneous tissues and skin from the extremely high deep venous pressures (up to 250mmHg) generated by the calf muscle pump in systole. When standing motionless, with venous valves in the neutral position, the pressure in the foot veins gradually increases as blood continues to enter the veins from the arterial side. As soon as the pressure in one venous segment exceeds that in the segment just above, the valve opens. Eventually the hydrostatic pressure in the veins of the foot is that developed by an unbroken column from the foot to the right atrium – perhaps 90mmHg in a person of average height. With active movement, deep veins and sinuses are compressed raising venous pressure and moving blood cranially and, initially, caudally. However, valve closure normally prevents retrograde flow within 0.5-1.0 seconds. At this point, these closed valves divide the high-pressure, single column of venous blood described above into a large number of low-pressure, shorter columns. As a result, the pressure in the foot veins falls in health to less than 25mmHg on walking; the normal ambulatory venous pressure (AVP).

This reduces venous pooling and lowers capillary hydrostatic pressure, reducing the tendency for accumulation of interstitial fluid (oedema) in the feet. Patients with muscle pump and/or venous valve failure and/or venous outflow obstruction, demonstrate raised AVP. It is this raised AVP that underlies all the symptoms and signs of chronic venous insufficiency (CVI).

2. Etiology

The GSV system is most frequently affected with the SSV being involved in about 20% of cases. The aetiology of VV at a microscopic level is still disputed but the essential defect macroscopically is generally agreed to be the failure of venous valve closure resulting in the superficial veins becoming dilated, elongated and tortuous[17,18]. The main factor contributing to the development and progression of varicose veins is sustained venous hypertension that increases the diameter of the superficial veins resulting in further valve incompetence.

2.1 Valvular abnormalities

Failure of valve closure leading to valve incompetence and reflux may affect the deep and/or superficial venous systems and may be primary or secondary. Primary valvular incompetence (PVI) is believed to be due to loss of mural elastin and collagen, which leads to dilatation and separation of the valve leaflets. The commonest clinical consequence of this process is the development of VV. As an investing fascia often supports the main GSV trunk, it is often the tributaries that become varicose. PVI may also affect the deep venous system although because other tissues support the deep veins, the clinical consequences of PVI are less obvious and certain. Secondary valvular incompetence may be due to a developmental weakness in the vein wall leading to secondary widening of the valve commissures, resulting in valvar incompetence and clinically, primary VV. It also follows thrombosis, most commonly in the deep venous system; deep venous thrombosis (DVT). Blood flowing within the lumen of the vein provides the vascular endothelium with its oxygen and nutrition. DVT prevents this, therefore leading to endothelial destruction and inflammation within and around the affected veins. Although most venous segments occluded by DVT recanalise over the subsequent 6–12 months the vein is often scarred and narrowed and, because the valves have been destroyed, incompetent. If recanalisation does not occur, blood is forced to find an alternative drainage route. For example, blood may be forced out of the deep venous system via the SFJ, SPJ and NJP leading to dilatation of the superficial veins (secondary VV). Obstruction of the iliac veins may lead to the development of groin and pelvic collaterals. Venous reflux and obstruction secondary to DVT leads to PTS which represents the most severe form of chronic venous insufficiency (CVI). The superficial venous system may also be affected by thrombosis, either in isolation or in combination with DVT, leading to superficial thrombophlebitis (SVT). Rarely, VV and CVI may be due to congenital valve hypoplasia or agenesis, or due to arterio-venous malformations. In Klippel Trenaunay syndrome, for example, there is deep venous hypoplasia and a laterally placed venous complex that acts as the main venous outflow of the limb. All the symptoms and
signs of chronic venous insufficiency are due to ambulatory venous hypertension resulting from these various pathological processes acting upon the microvasculature of the skin and subcutaneous tissues.

### 2.2 Muscle pump Failure

Any cause of chronic debility or immobility is associated with calf muscle pump dysfunction; for example, old age, stroke, neuromuscular conditions, arthritis and trauma. Injuries that limit or prevent ankle movement have a particularly adverse effect upon the calf muscle pump.

### Venous recirculation

In patients with VV there is often a recirculation of venous blood within the leg. During calf relaxation abnormally large volumes of blood enter the muscle pump from the superficial varices (increased preload). During exercise the muscle pump expels blood from the leg only for it to re-enter the lower leg by refluxing down GSV and/or SSV VV (akin to an increase in afterload due to aortic regurgitation). This blood then re-enters the muscle pump through the perforating veins in the lower calf and so on. The effect is that the same blood can re-circulate up and down the leg several times before eventually finding its way up the iliac veins to the heart. Patients with mild superficial reflux and/or an efficient calf pump are able to compensate for this by increasing their calf muscle pump ‘stroke volume’ and output. This allows them to still reduce their AVP to (near) normal levels on walking. However severe reflux and/or a weak muscle pump may overwhelm the deep system and lead to the development of sustained venous hypertension and skin changes of CVI.

This accounts for two important clinical observations:

- CVI & ulceration can develop without primary deep venous pathology
- In a proportion of patients with VV and deep venous reflux the latter disappears following eradication of superficial disease.

### 3. Recurrent varicose veins

Recurrent VV after conventional surgical or endovenous intervention may be classified into three groups: new, persistent and true recurrent.

#### 3.1 New varicose veins

This is the development of new VV, often in a second saphenous system, since the original operation. This may be due to: Inadequate assessment at the time of the initial treatment; however, now that most patients undergo full duplex ultrasound mapping prior to intervention for their VV this should be less common. Reflux developing at a site that was previously demonstrated to be competent; in other words, true disease progression.

#### 3.2 Persistent varicose veins

This is due to inadequate treatment of VV at the time of the original intervention. Again, with proper use of duplex ultrasound and modern techniques this should be a relatively uncommon scenario in current phlebological practice. The risk is perhaps greater with catheter based techniques such as radiofrequency ablation (RFA) and Laser ablation (EVLA) which, while being highly successful in eradicating truncal reflux, do not deal with the varices themselves. A proportion of patients undergoing RFA and EVLA will, therefore, need further treatment, either with foam sclerotherapy or local anaesthetic phlebectomies.

#### 3.3 True recurrent varicose veins

This is where further VV develop in the same, previously treated saphenous system. When surgery was the main treatment modality most were the result of failure to properly perform a ‘flush’ SFJ (SPJ) ligation and/or to ‘strip’ the GSV or SSV. Neovascularisation (NV), defined as the ‘development of new vessels connecting previously ligated superficial veins to the deep venous system’, and the role it might play in the development of recurrent VV after surgery has received a lot of attention over the years. There is no doubt that in a proportion of patients with recurrent GSV (SSV) VV, duplex ultrasound clearly shows the presence of small venous channels within scar tissue apparently connecting the ‘stump’ of the GSV in the groin (SSV in the popliteal fossa) to recurrent VV in the thigh (calf).

However, it seems unlikely that such small, therefore high resistance, veins will be capable of transmitting significant reflux and thus of constituting a significant cause of recurrence on their own. In an era where the vast majority of patients can have nonsurgical treatment for their VV, the whole issue of NV becomes much less important.

Going forward, most true recurrent VV are likely to be due to recanalisation of the trunk veins and/or their major tributaries that have previously been occluded by means of foam sclerotherapy, RFA or EVLA [20, 21]. However, unlike redo surgery which is technically demanding and often associated with disappointing outcomes, such recanalisation can be successfully treated as an out-patient and so poses no real clinical difficulty [19].
Cellular and molecular biology of varicose veins

The molecular biology of varicose veins has recently been reviewed. The aetiology of varicose veins is undoubtedly multifactorial. In recent years there has been much research to define the structural and molecular events that accompany the formation of varicose veins, with an overall underlying hypothesis that varicose vein formation is most likely due to a structural, cellular or molecular abnormality within the vein wall. On a gross level, varicose veins exhibit intimal hyperplastic areas and underlying plaques with infiltration of leukocytes and mast cells. There is fragmentation of elastin fibres and the total content of elastin and Type III collagen is reduced. These extracellular matrix abnormalities may be regulated by disordered MMP and TIMP production. Cell types within the varicose vein may show disordered function with endothelial activation leading to vasodilatation and a possible loss of venous tone. Many of the smooth muscle cells in the varicose vessels wall exhibit a synthetic rather than a contractile phenotype, and appear to have reduced rates of apoptosis. These cells may have a reduced capacity for contraction, which may exacerbate the vasodilatory tendency. The stimuli for the disordered function demonstrated by these intrinsic cells remains ill defined, but hypoxic stress and low shear stress may play a role.

Conclusion

Despite the very large numbers of patients affected by CVI and VV, research into venous disease is generally given low priority and so there are still significant gaps in our knowledge. Further work is needed if we are to improve our understanding of the aetiology of the disease and improve the results of treatment.

References


