Vascular system 3: diseases affecting the venous system

Venous disease is common and represents a heavy burden for patients and health services. It covers a wide array of conditions, some of which can cause significant mortality. Peripheral venous disease (PVD) refers to diseases affecting the veins of the lower limbs, which usually impair the return of deoxygenated blood to the heart. This leads to venous stasis, increased venous pressure, valvular incompetence, thrombus, potential embolisation and tissue damage.

Chronic venous disease in the lower limbs is the most common vascular disorder. Varicose veins arise as a result of incompetence of the valves in the superficial, deep and/or perforating veins. A deep vein thrombus can move into the lungs and create a pulmonary embolism, which is potentially life-threatening.

Cerebral vein and dural sinus thrombosis is more common in women than in men.

Chronic venous disease
The most common vascular disorder, CVD in the lower limbs may manifest in a variety of ways. Morphological abnormalities – such as venous dilation, and/or functional defects – such as venous reflux, may ultimately lead to blood failing to follow the normal path of venous return and flowing back down into the veins. Valvular incompetence may be involved and may be due to congenital defects or a weakening of the vein walls.

The most common risk factors for CVD are advancing age, high body mass index, smoking, family history of venous disease, a history of trauma to the lower extremities, previous venous thrombosis and pregnancy (Scovell, 2018).

The Clinical, Etiology, Anatomy and Pathophysiology (CEAP) classification (Eklöf et al, 2004) is used worldwide to diagnose, categorise and assess the severity of CVD (Table 1). Advanced CVD (CEAP grades 4-6) is associated with disability and reduced quality of life for patients, and a large cost burden for the health system (Mills and Armstrong, 2018).

Normal function of lower limb veins
To understand PVD and CVD, a good grasp of the venous system is needed. Unlike arteries, veins have thin walls that contain very little smooth muscle (Jarvis, 2018).
Deep veins – these include the tibial and peroneal veins (in the calf), the popliteal vein (at the back of the knee) and the femoral and iliac veins (in the thigh).

Perforating or communicating veins – these link the superficial veins and the deep veins.

Most veins have valves, and in the lower limbs – where veins such as the calf veins can be found – these delicate structures facilitate a one-way blood flow when structurally and functionally intact. In the superficial veins of the legs, where pressure is low, the valves are sited 5-10cm apart. When the leg moves, the large leg muscles compress the deep leg veins, thereby acting as a venous pump. The high pressure generated by muscle contraction helps the valves to open and close (Fig 1). When all aspects are functioning, the one-way blood flow system of the valves and the pump function of the leg muscles work together to drive venous blood back to the heart.

Varicose veins

When valves do not work properly, blood pools in the veins and raises the pressure in the venous system, causing venous distension. A persistent elevation of venous pressure in the lower limbs can lead to the development of varicose veins (dilated, elongated and tortuous subcutaneous veins), notably in the long and short saphenous veins (running from the inner ankle along the inside of the leg and joining the iliac vein in the groin) and short saphenous vein (running from the outer ankle along the back of the calf and joining the popliteal vein at the back of the knee).

Table 1. Basic CEAP classification of chronic venous disease

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Anatomy</th>
<th>Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0 – no visible or palpable signs of venous disease</td>
<td>Ec – congenital</td>
<td>Pr – reflux</td>
</tr>
<tr>
<td>C1 – telangiectasies or reticular veins</td>
<td>Ep – primary</td>
<td>Po – obstruction</td>
</tr>
<tr>
<td>C2 – varicose veins</td>
<td>Es – secondary</td>
<td>Pr,o – reflux and obstruction</td>
</tr>
<tr>
<td>C3 – oedema</td>
<td>En – no venous cause identified</td>
<td>Pn – no venous pathophysiology identifiable</td>
</tr>
<tr>
<td>C4a – pigmentation or eczema</td>
<td>As – superficial veins</td>
<td>Pn – no venous pathophysiology identifiable</td>
</tr>
<tr>
<td>C4b – lipodermatosclerosis or atrophie blanche</td>
<td>Ap – perforating veins</td>
<td></td>
</tr>
<tr>
<td>C5 – healed venous ulcer</td>
<td>Ad – deep veins</td>
<td></td>
</tr>
<tr>
<td>C6 – active venous ulcer</td>
<td>An – no venous location identified</td>
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</tbody>
</table>

*The advanced CEAP classification comprises the basic classification and 18 named venous segments that are used as locators for venous pathology.

CEAP = Clinical, Etiology, Anatomy, Pathophysiology.

Source: Adapted from Eklöf et al (2004)
saphenous veins and their tributaries. Varicose veins arise due to incompetence of the valves in the superficial, deep and/or perforating veins and are defined as permanently dilated vessels measuring >3mm in diameter when the person is standing.

At a microscopic level, the walls of varicose veins feature decreased levels of elastin, abnormalities in collagen pattern and smooth muscle fibres with increased fibrous tissues. Varicose veins may be explained by the ‘weak wall hypothesis’, which postulates that local factors had been affecting the vein wall before any valvular incompetence developed (Clarke et al, 1992). The diameter of varicose veins is larger than that of normal veins, but they also feature ‘skip lesions’, in which normal vein structure is interspersed with areas of abnormal vein structure.

From a cellular perspective, it is thought that changes in the extracellular matrix (a support structure of the vessels partly made of collagen) result in the development of varicose veins. Collagen may invade the smooth muscle layer of the blood vessel, affecting the contractility of its cells. Local hypoxia and inflammation may develop, leading to valvular incompetence (Ghaderian and Khodaii, 2012; Fan, 2005). In addition, the veins stretch abnormally, which can cause their delicate endothelial layer to tear. This exposes the subendothelial collagen, which can trigger the formation of a thrombus.

Ultimately, varicose veins lead to the reflux of blood. Patients with varicose veins will have a decreased ability to clear blood, which aggravates blood pooling and valve dysfunction. Many patients worry about the appearance of varicose veins, but they may also experience pain, swelling and, in more severe cases, tissue ulceration and loss (Jacobs et al, 2017).

### Chronic venous insufficiency

At a more severe level, persistently raised venous pressure can result in chronic venous insufficiency (CVI), a term signifying the functional changes that occur in the lower limbs due to dysfunctional veins. CVI affects around 7% of the population (Cesarone et al, 2002) and may occur due to either venous reflux or venous obstruction (for example, from deep vein thrombosis (DVT) or post-thrombotic changes), or secondary to both causes.

There is a clear relationship between CVI and DVT: around 50% of patients who have DVT will eventually develop CVI, usually within 5-10 years (Mills and Armstrong, 2018). DVT is explained later in this article.

### Venous thrombosis

Venous thrombosis is a cause of significant morbidity and mortality. A common clinical presentation of venous thrombosis is a deep vein thrombus, which can move into the lungs and create a pulmonary embolism (PE); the latter is potentially life-threatening (Bauer and Lip, 2018).

We still know little about the pathophysiology of thrombosis. In 1856, Rudolf Virchow proposed the Virchow trial to describe the factors that may precipitate the condition. The trial comprises:

- Changes in the constituents of blood that affect the blood’s coagulability and/or clotting characteristics;
- Changes to the blood vessel wall – for example, vascular endothelial injury;
- Altered blood flow or stasis.

Alterations in blood clotting components caused by thrombophilia are an important cause of thrombosis. For instance, increased levels of coagulation factors – in particular factor VII, factor VIII, von Willebrand factor and prothrombin – are associated with an increased risk of thrombosis. In factor V Leiden mutation, the most common thrombophilia, a mutation of factor V, renders it insensitive to the actions of protein C; this inherited mutation results in an increased risk of venous thrombosis. Furthermore, deficiencies in certain natural anticoagulants in the blood, such as proteins C and S, which may also be inherited, are associated with an increased risk of thrombus formation.

The formation of a thrombus involves the production of tissue factor, which normally triggers a coagulation response. An important cell adhesion molecule called P-selectin, which intervenes in cell-cell interactions, plays a role in the formation of a thrombus; experimental studies have shown that blocking the action of inhibitors of P-selectin prevents thrombus formation (Esmon, 2009).

Other risk factors for venous thrombosis include:

- Advancing age;
- Obesity (associated with increased levels of factors VIII and IX);
- Immobility;
- Frailty;
- Serious illnesses;
- Heart disease;
- Multiple comorbidities;
- Pregnancy;
- Puerperium (six weeks after childbirth);
- Drugs such as the contraceptive pill, those used in hormone replacement therapy, and some anticancer drugs.

A major risk factor for venous thrombosis is cancer. Having a cancer leads to an increased production of tissue factor, which starts the clotting pathway. Tumours such as pelvic tumours can compress the veins, which can lead to stasis and thrombus formation. Around 20% of patients who have a DVT may have an underlying malignancy (Sørensen et al, 2000).

### Superficial vein thrombosis

Superficial vein thrombosis, or superficial thrombophlebitis, is an inflammation of the superficial veins associated with thrombosis. Patients often present with pain and discolouration over the affected vein. This is a benign and self-limiting disorder that warrants supportive measures to reduce the symptoms (Di Nisio et al, 2013) and does not normally require treatment with anticoagulation.

Box 1 lists the different types of superficial vein thrombosis. The condition is considered less harmful than DVT, but it may progress to DVT if it occurs close to a junction with the deep venous system (Nasr and Scriven, 2015). It can also coexist with DVT.

### Deep vein thrombosis

A thrombus that forms in the deep veins of the leg is far more serious than one that forms in the superficial veins, the concern being that it may migrate to the lungs and create a PE. DVT is common, affecting one per 1,000 of the general population (Dinisio et al, 2013).

There are three types of DVT:

- Iliac;
- Femoral;
- Calf.

The features of the different veins in the

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**Box 1. Types of superficial vein thrombosis**

- Sterile – the most common type
- Traumatic – occurring after injury, intravenous cannulation or infusion, or treatment of varicose veins
- Infective – occurring after prolonged intravenous cannulation
- Migratory – recurring at various sites without an identifiable local cause; has been associated with malignancy such as pancreatic cancer

Source: Adapted from Nasr and Scriven (2015)
Clinical Practice

Systems of life

Box 2. Risk factors for CVT

<table>
<thead>
<tr>
<th>Transient</th>
<th>Permanent</th>
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<tbody>
<tr>
<td>Infection</td>
<td>Rheumatological</td>
</tr>
<tr>
<td>CNS and ear, nose and throat</td>
<td>Prothrombotic haematological states</td>
</tr>
<tr>
<td>Systemic infectious disease</td>
<td>Protein C, protein S and antithrombin deficiency</td>
</tr>
<tr>
<td>Pregnancy and puerperium</td>
<td>Factor V Leiden mutation</td>
</tr>
<tr>
<td>Drugs</td>
<td>G20210A gene mutation</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Antiphospholipid syndrome</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>Myeloproliferative disorders</td>
</tr>
<tr>
<td>Androgens</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Paroxysmal nocturnal haemoglobinuria</td>
</tr>
<tr>
<td>Steroids</td>
<td>Other haematological conditions</td>
</tr>
<tr>
<td>Head injury or trauma</td>
<td>Polycythaemia</td>
</tr>
<tr>
<td>Lumbar puncture or neurosurgical procedures</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Jugular vein catheterisation</td>
<td>Severe anaemia</td>
</tr>
<tr>
<td>Dehydration</td>
<td>CNS disorders</td>
</tr>
<tr>
<td></td>
<td>Dural fistulas</td>
</tr>
<tr>
<td></td>
<td>Congenital heart disease</td>
</tr>
<tr>
<td></td>
<td>Thyroid disease</td>
</tr>
</tbody>
</table>

CNS = central nervous system. CVT = cerebral venous thrombosis.

Source: Adapted from Ferro and Canhão (2018)

leg influence the likelihood of thrombus formation and the type of symptoms with which patients may present. Thigh veins comprise one thick vessel with only a few valves, while calf veins are often paired together and have many anastomoses (openings) and valves. Thrombus formation is therefore less likely in the thigh veins (where blood is less likely to stagnate) than in the calf veins (where venous stasis is more common).

A deep vein thrombus in the thigh veins means there may be symptoms of venous insufficiency in the distal leg, with redness and pain. Conversely, a deep vein thrombus in the calf veins is more likely to be due to venous stasis; it may extend proximally in the direction of the venous return, with no sign of venous insufficiency, and the patient may even be asymptomatic. The danger of a thrombus in the distal calf veins is that there is an increased risk of the thrombus emboliising via the inferior vena cava (toward the right side of the heart and the pulmonary vasculature) and creating a PE.

Muscle disuse can contribute to thrombus formation in the intramuscular veins. Studies have shown that the intramuscular vessels, particularly those in the soleus muscle of the calf, are responsible for 90% of DVT cases that cause a PE in patients confined to bed (Ro et al, 2017).

Deep vein thrombi and pulmonary emboli need to be treated with full anticoagulation - that is, low molecular weight heparin followed by an oral anticoagulant such as warfarin.

Cerebral venous thrombosis

The incidence of cerebral vein and dural sinus thrombosis (CVT) is two and five per million per year and is more common in women than men (Devasagayam et al, 2016). It is most often seen during pregnancy, in the post-partum phase and in women taking oral contraceptives. The risk factors are summarised in Box 2.

The mechanisms that contribute to the clinical features of CVT have been described by Ferro and Canhão (2018). Thrombosis of the cerebral veins or dural sinus impairs blood drainage from the brain tissues, which leads to increased venous pressure. This in turn can lead to:

- Increased pressure in venules and capillaries, which leads to reduced cerebral perfusion and blood flow (and potentially cytotoxic oedema), venous and capillary rupture (and potentially brain parenchymal haemorrhage), and disruption of the blood-brain barrier (and potentially vasogenic oedema);
- Impaired absorption of cerebrospinal fluid, which leads to raised intracranial pressure (and potentially tissue damage).

Patients presenting with CVT may have acute, subacute or chronic symptoms that may include a new headache, vomiting, or neurological symptoms. They may also present with features of raised intracranial pressure (such as morning headaches, vomiting, visual changes), seizures or encephalopathy. Patients with suspected CVT require urgent magnetic resonance imaging of the venous system (magnetic resonance venography); if confirmed, CVT requires full anticoagulation treatment.

References


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