The vascular system and associated disorders

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The heart is the principal organ that pumps blood around the body, and the vascular system transports the blood throughout the body. Arteries carry blood away from the heart and veins carry blood towards it. Blood flows through arteries and arterioles transporting oxygen, nutrients, and other substances essential for cellular metabolism and homeostatic regulation (**Chaudhry and Maio, 2022**). Veins and venules carry deoxygenated (oxygen-depleted) blood toward the heart. The exceptions to these are the pulmonary arteries (which carry deoxygenated blood) and the pulmonary veins (which carry oxygenated blood) (**Blanchflower and Peate, 2021**). Capillaries are tiny blood vessels that form a delicate network in close proximity to most parts of the body tissues and connect arterioles and venules. Their thin walls allow oxygen, nutrients, carbon dioxide and waste products to pass to and from tissue cells (**Jarvis, 2018**).

Blood vessels

Blood vessels are often described as channels that carry blood throughout the body, forming a closed circuit that begins and ends at the heart. Blood travels through the blood vessels following a pressure gradient (**Blanchflower and Peate, 2021**). The blood vessels, with the exception of capillaries, have three distinct layers, as identified in *Table 1*.

Table 1. Blood vessel layers

Layer	Name	Composition	Function
Outer	**Tunica externa or tunica adventitia**	**A tough protective layer made up of collagen and elastic fibres**	**It prevents the artery from overstretching and is involved in healing after injury, immunity, and vascular tone. It hosts a variety of cells such as macrophages, lymphocytes, dendritic cells (all involved in immune function), and fibroblasts and stem cells (involved in healing after injury). Cells can migrate from the tunica externa to the tunica media or tunica intima for repair after vessel damage (McCance et al, 2018)**
Middle	**Tunica media**	**A layer of smooth muscle and elastic tissue**	**It allows for the regulation of the size of the lumen of an artery to control blood flow and pressure. As blood vessels constrict or dilate, blood pressure increases or decreases, respectively**

Table 1. Blood vessel layers			
Layer	**Name**	**Composition**	**Function**
Inner	**Tunica intima**	**Lined with endothelium, making the inner surface smooth; forms the main part of the capillary wall**	**It plays roles in coagulation, antithrombosis (reducing the formation of blood clots), fibrinolysis (enzymatic breakdown of fibrin clots), immune function, vasodilation or constriction, tissue growth, and wound healing. In a healthy arterial network, the highly elastic walls and normal endothelial function ensure the sufficient flow of blood around the body**

Source: adapted from **Blanchflower and Peate, 2021**

Arteries

Arteries play a crucial and multifaceted role in the cardiovascular system, serving several important functions. First, they form an extensive network responsible for transporting oxygenated blood from the left ventricle of the heart to various tissues throughout the body. This delivery of oxygen is vital for sustaining cellular metabolism and maintaining tissue health (**Tucker and Arora, 2022**). Second, arteries contribute to the maintenance of adequate blood pressure and blood flow during diastole, ensuring efficient circulation throughout the body. Beyond these fundamental functions, arteries are integral to cardiovascular homeostasis, which involves the regulation of blood circulation to meet the dynamic demands of organs and tissues (**Tucker and Arora, 2022**). Through the adjustment of their smooth muscle walls, arteries can modulate blood flow by undergoing vasoconstriction or vasodilation, thereby redistributing blood as needed to support different physiological processes and adapt to changing conditions within the body.

Arteries can be classified into three main groups based on their structural and functional characteristics. First, elastic arteries, such as the aorta, possess thick walls and are located in proximity to the heart. These arteries accommodate the surge of blood ejected from the left ventricle during systole and aid in maintaining continuous blood flow during diastole (**Tucker and Arora, 2022**). Second, muscular arteries are characterised by a higher proportion of smooth muscle in their walls. They have the ability to undergo greater vasoconstriction and vasodilation, enabling them to distribute blood to specific organs and regions of the body based on demand (**Tucker and Arora, 2022**). Third, arterioles are the smallest branches of the arterial system. They connect muscular arteries to the capillaries and play a crucial role in regulating blood flow and pressure within specific tissues (**Tucker and Arora, 2022**). Understanding the multifaceted roles of arteries is essential in comprehending the intricate workings of the cardiovascular system and its significance in overall health and wellbeing. For more detailed descriptions of the aorta, arteries, and arterioles, please refer to *Table 2*.

Table 2. Aorta, arteries, and arterioles	
Term	**Descriptions**
Aorta	**The largest artery in the body, which starts from the left ventricle, distributing oxygenated blood to all parts of the body**

Table 2. Aorta, arteries, and arterioles	
Term	**Descriptions**
Arteries	**Vessels that carry blood away from the heart. As they get further from the heart, their lumen (the inner open space or cavity of a tubular structure) becomes smaller**
Arterioles	**The smallest vessels in the arterial system, which branch out from the arteries and lead to the capillaries**

Veins

The walls of veins are thinner compared with arteries and contain less elastic, collagenous tissue and smooth muscle. Veins have a larger lumen than arteries. Some veins, most commonly in the lower extremities, contain one-way paired semilunar bicuspid valves. Their function is to prevent any backwards reflux of blood towards the capillaries – allowing blood to flow only towards the heart. *Figure 1* illustrates a comparison of arteries, veins and capillaries, *Figure 2* illustrates the circulation of blood through the heart.

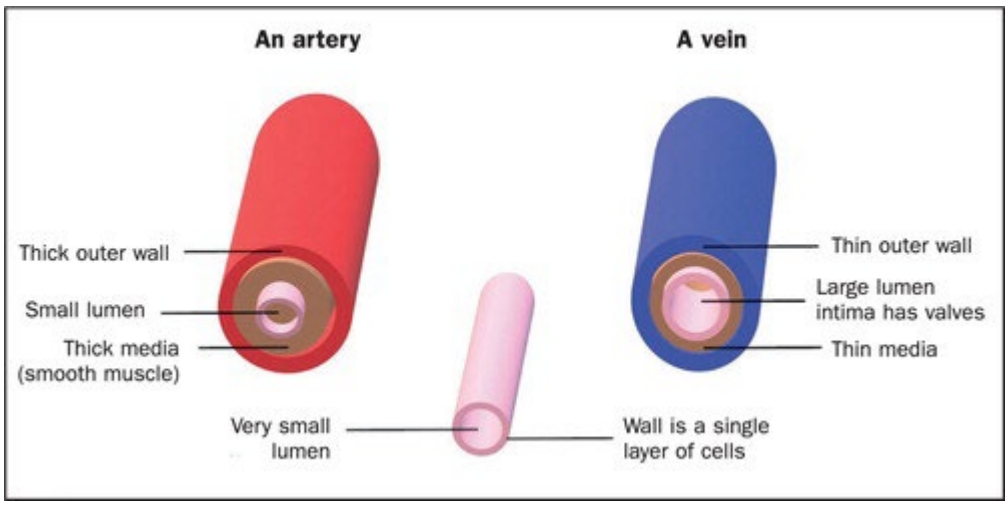

Figure 1. Comparison of artery, vein and capillary

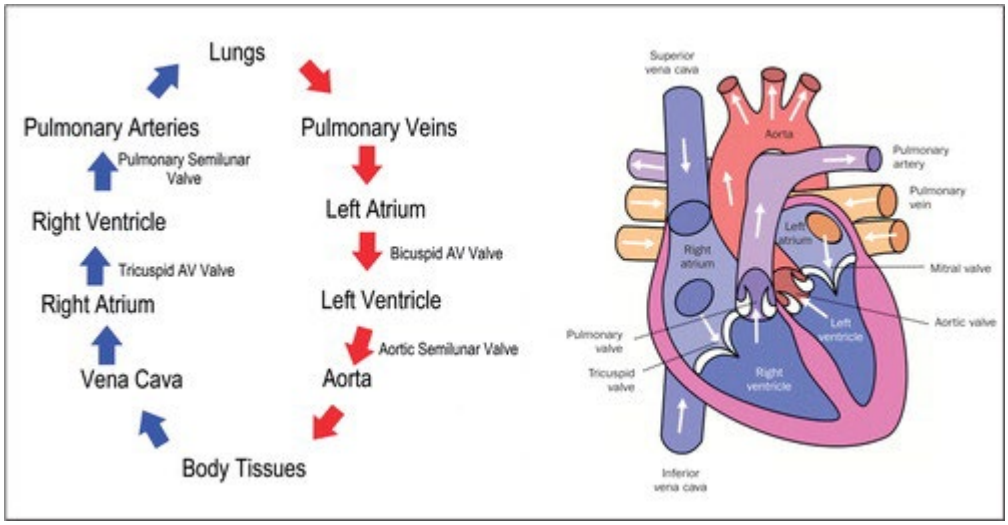

Figure 2. Circulation of oxygenated (red) and deoxygenated (blue) through the heart

Associated disorders

Hypertension

Hypertension is a sustained elevation in systemic arterial blood pressure (BP), either systolic or diastolic or both. The systolic pressure is the force at which the heart pumps blood around the body, whereas the diastolic pressure is the resistance to the blood flow in the blood vessels (**Shahoud and Sanvictories, 2022**). Normal BP can vary widely; a sustained BP over 140/90 millimetres of mercury (mmHg) is considered as high. The incidence rate of hypertension in England is 26.2% of the adult population (**Public Health England, 2017**). There are many classifications of hypertension based on severity eg mild or moderate (**National Institute for Health and Care Excellence (NICE), 2022a**)(*Table 3*).

Table 3. Types of hypertension	
Types	**Description**
Primary hypertension	**A type of hypertension influenced by a combination of genetic and environmental factors such as family history, obesity, and unhealthy diet, and not a result of a medical condition**
Secondary hypertension	**High blood pressure that is caused by another medical condition. Diseased organs can result in a raised pulmonary vascular resistance (PVR) and increased cardiac output**
Malignant hypertension	**Rapidly progressive hypertension where the diastolic pressure exceeds 120 mmHg. This can lead to encephalopathy, cerebral oedema, and loss of consciousness. It is life-threatening and is considered an emergency**
Isolated systolic hypertension	**This is often due to an increased cardiac output or PVR. It has a higher incidence in elderly people due to arterial rigidity caused by atherosclerosis**

Source: **NICE, 2022a**

View as image

Aneurysm

An aneurysm is a permanent dilation of an artery, or a chamber of the heart, caused by atherosclerosis. It can occur in arteries and veins. The aorta and arteries situated at the base of the vessels are most susceptible to aneurysms (**Blanchflower and Peate, 2021**). There are three types of aneurysms: abdominal aortic, thoracic aortic and cerebral (*Table 4*)

Table 4. Types of aneurysms	
Types of aneurysms	**Description**
Abdominal aortic	**Characterised by a bulge or swelling in the aorta, which is the main blood vessel running from the heart down through the chest and abdomen**
Thoracic aortic	**Refers to a weakened area in the aorta located in the chest (thoracic) region**
Cerebral	**Presents as a bulge or ballooning in a blood vessel in the brain. An example is a Berry aneurysm**

View as image

Peripheral arterial disease

It is estimated that approximately one in five people over 60 in the UK suffer from peripheral arterial disease (PAD) (**NICE, 2022b**). PAD is the failure of arteries to deliver sufficient blood to a particular part of the body, which results in oxygen starvation (tissue ischaemia) and cellular death (**NICE, 2020**). The legs are susceptible to arterial occlusion, which causes poor perfusion. Over a prolonged period, this will lead to poorly nourished skin that is vulnerable to infection and has a reduced ability to repair, progressing to arterial leg ulcers and in severe cases the development of gangrene (**Shammas, 2007**). *Table 5* outlines risk factors for PAD.

Table 5. Risk factors for peripheral arterial disease	
Risk factors	**Description**
Family history	**A family history of cardiovascular, cerebrovascular, peripheral arterial disease, or leg ulceration may predispose an individual to peripheral arterial disease (PAD)**
Medical history	**Diabetes mellitus, associated with early onset and rapid progression of atherosclerosis, is a significant risk factor for PAD. Hypertension can accelerate atherosclerosis progression, especially when coupled with other risk factors. High serum cholesterol levels enhance plaque formation, with low-density lipoprotein (LDL) cholesterol increasing the risk of atheroma, while high-density lipoprotein (HDL) cholesterol protects against plaque formation. Other arterial diseases, such as angina, myocardial infarction, cardiac bypass/angioplasty, transient ischaemic attack, stroke, and kidney disease, all present as risk factors for PAD**
Smoking	**Smoking is the most significant risk factor for PAD as it damages the vascular endothelium and accelerates the progression of atherosclerosis.**

Table 5. Risk factors for peripheral arterial disease	
Risk factors	**Description**
Exercise	**Regular exercise, specifically at least 150 minutes of moderate activity weekly, is thought to increase HDL ('good' cholesterol) levels, thereby offering protection against atherosclerosis**
Stress	**Biological and immune responses associated with stress may predispose individuals to atherosclerosis**
Age	**Increasing age is a significant risk factor for PAD**
Gender	**Atherosclerosis incidence appears to be higher in men under 70 years but is similar for both genders for people over 70. Oestrogen helps reduce LDL cholesterol, providing a protective effect**

Source: adapted from **Moffatt et al, 2007**

Skin changes in peripheral arterial disease

PAD is often characterised by a diverse array of skin changes resulting from reduced blood flow and oxygenation to the affected limb (**Conte et al, 2019**). These manifestations reflect the severity of the disease and can differ in individuals based on additional health factors. For instance, a limb affected by PAD may display a colour variation from pale to a mottled blue, indicative of deficient oxygenated blood supply. In certain individuals, the limbs could exhibit a deep red or purple hue, known as dependent rubor. This is attributed to arterial dilation in the foot to enhance oxygen supply, leading to arterial blood pooling (Rooke et al, 2021). Despite the possible resemblance to cellulitis or a well-perfused limb, dependent rubor is distinctive in that the leg is erythematous. When raised above the level of the heart, it will normalise in colour. This is suggestive of severe PAD due to chronic dilation (loss of vasoconstriction) of the dermal arterioles and capillaries despite increased hydrostatic pressure secondary to chronic ischemia (**Star, 2018**). Dependent oedema may also be a symptom of PAD. Of note are diminished or absent pedal pulses or monophasic sounds, whereas healthy vessels generate either triphasic or biphasic sounds, identifiable through a hand-held Doppler or Duplex scan (**Aboyans et al, 2018**).

Sensory changes such as numbness and tingling are frequently reported by patients with PAD, alongside physical signs of poor perfusion, including hair loss and thickened toenails (**Herrmann et al, 2020**). Muscle weakness or atrophy may occur in the calf or thigh, and skin can take on an atrophic, shiny appearance. In addition, arterial leg ulcers, often located on the lower parts of the limb, especially the foot or ankle, are common in PAD. These ulcers can be shallow or deep, exposing underlying structures, and often appear with a 'punched-out' look. Pale granulation tissue, slough, or necrotic tissue is frequently observed in these ulcerations (**McDermott et al, 2019**). It is crucial to note that these are general symptoms and may not present in all individuals diagnosed with PAD. The manifestation of specific symptoms may vary according to the severity of the disease and other individual health factors. Therefore, seeking consultation with a suitable health professional for a comprehensive diagnosis and tailored treatment plan is always advisable.

Atherosclerosis

Atherosclerosis is a common cause of arterial disease and involves the formation of fatty plaques in the interior wall of the arteries. This causes the narrowing of the lumen (stenosis), hardening of the artery and endothelial dysfunction due to lipid accumulation. This occurs mainly in the larger and medium-sized vessels, for example the aorta and its branches, and the coronary arteries (**Blanchflower and Peate, 2021**). These complications reduce pressure and the volume of blood reaching the arteries. This can also lead to heart disease and stroke. Symptoms are experienced when the lumen is occluded. Atherosclerosis affects different parts of the body in different ways.

Atheroma is the degeneration of the walls of the arteries caused by the accumulation of fatty deposits and scar tissue, resulting in reduced circulation. Atheromas may stay unchanged for large periods of time but can lead to further secondary complications such as expansion (ultimately the entire aorta is covered in atherosclerotic lesions), fibrosis and calcification (soft atheromas become hard and brittle) and aneurysmatic dilation (where atheromas weaken the vessel wall and destroy elastic tissue and smooth muscle) (**Damjanov, 2009**).

Acute arterial thrombus or embolism

Acute arterial thrombus or embolism occurs primarily in individuals with underlying atherosclerosis. The presence of fatty deposits leads to the progressive hardening and narrowing of arteries, thereby increasing the risk of clot formation. In this context, an unstable atheromatous plaque can serve as a thrombus origin point. Once mobilised, the thrombus can obstruct a smaller artery, causing occlusion. In addition, fat and air can also result in embolism (**Smith, 2023**). When evaluating patients suspected of acute arterial thrombus or embolism, it is crucial to assess the five Ps: pain, pallor, paraesthesia (burning or prickling sensation), pulseless, and perishing cold (**Smith, 2023**). These indicators provide valuable insights for diagnosing and managing this condition.

Inflammatory vascular disease (vasculitis)

This is a rare, progressive, degenerative disease that affects small and medium-sized arteries and veins. The artery wall becomes inflamed due to an occlusion that is surrounded by non-specific immune cells, which deprive healthy cells local to the occlusion of oxygen and nutrients. This results in tissue ischaemia and symptoms such as intermittent claudication – fatigue, cramping, numbness, pain, tingling and weakness in a muscle group (**Moffatt et al, 2007**). This is aggravated by exercise and relieved by rest. Chronic ischaemia is indicated by persistent ischaemic rest pain. Complications and diseases of the venous and arterial system can lead to changes in the lower limbs. Health professionals should be aware of changes to aid lower limb assessment, treatment, and diagnosis.

Venous insufficiency

Venous disease occurs when the calf muscle pump and foot muscle pumps are unable to effectively empty veins. This results in venous hypertension (increased pressure in the veins). This is often due to valve incompetence allowing blood to flow backwards or ‘reflux’ towards capillaries, and struggling to flow upwards towards the heart. Valve incompetence in the deep vein causes increased pressure on the valve below and the corresponding perforator vein valve. As a result, these valves also become incompetent causing the superficial veins to varicose and disease progression causing further damage to the vein (**Blanchflower and Peate, 2021**).

Risk factors for venous disease

Table 6 outlines some key risk factors. Please note that this is not an exhaustive list, and other risk factors can also contribute to venous disease. Individuals should consult health professionals for individual risk assessment and preventive strategies.

Table 6. Risk factors for venous disease	
Risk factors	**Description**
Family history	**Evidence suggests that venous disease can be hereditary. Patients should be asked if any relatives have had a history of venous disease or oedema**
Previous trauma	**Any leg injury, including fractures, soft tissue damage, drug use (particularly intravenous drug use), phlebitis, or other injuries that can damage veins, impair mobility, or cause deep vein thrombosis (DVT)**
Previous surgery	**Previous surgery on the leg, including those for fractures or flap procedures, can potentially damage veins or lymphatics, or affect ankle mobility or gait, thereby contributing to venous disease**
Deep vein thrombosis (DVT)	**DVT or a history of previous DVT is a risk factor for venous disease. A history of major surgery, such as abdominal or orthopaedic surgery, prolonged immobility, clotting disorders, extensive travel, pregnancy, and use of oral contraceptives can increase the risk of DVT, which can manifest effects decades after the event**
Varicose veins	**These are swollen and enlarged veins caused by dysfunctional valves. Varicose veins are a common sign of underlying venous disease**
Mobility	**Good ankle function is important for the calf muscle to effectively pump blood back to the heart through the veins. Impaired mobility can contribute to venous disease**
Obesity	**Overweight patients are more at risk of venous disease due to increased pressure on the valves in the lower limb, which elevates the hydrostatic pressure (pressure exerted by a fluid at rest due to gravity)**
Pregnancy	**Pregnancy increases abdominal pressure and hormonal changes can affect the muscle layer within veins, making them more prone to varicosities (Ropacka-Lesiak et al, 2012)**
Age	**Ageing can affect patient mobility. Reduced mobility impairs the calf muscle and foot pumps which aid venous return (Davies et al, 2008)**
Occupation	**Occupations that require prolonged sitting or standing can increase the risk of venous disease, presumably due to sustained pressure in the veins. Extensive travel also increases the risk (eg long-haul flights)**
Chronic constipation	**Chronic constipation increases pressure on the veins, which can lead to valve damage (Tafur and Rathbun, 2013)**

Source: **NICE, 2022c**; **2023**

Varicose veins

Varicose veins are veins that have been damaged by incompetent valves and venous reflux. The vessels become dilated and tortuous (**Bradbury, 2011**). Varicose veins over 3 mm in size are an early indication of venous insufficiency (**Lurie et al, 2020**). This mainly occurs in the saphenous veins, deep communicating veins and superficial veins.

Deep vein thrombosis

Deep vein thrombosis (DVT) manifests as the formation of a thrombus or clot within veins, a condition often triggered when blood flow is reduced. This reduction can occur due to stasis of blood in the vessels, a common phenomenon after immobility resulting from surgery, or obstruction to blood flow as a consequence of trauma. The sluggish blood flow activates the clotting cascade. Hypercoagulability of blood is a contributory factor and may be due to an array of conditions including surgery, hormone replacement therapy, contraception, malignancy, inflammation, infection, genetic factors, and heparin-induced thrombocytopenia (**Senst et al, 2022**). Intravenous cannula usage, when it damages the vein, can also result in clot formation.

Numerous factors potentially predispose individuals to DVT, and these can be divided into persistent and temporary risk factors. Persistent risk factors include a previous history of DVT, advanced age (over 60), and obesity. Both ageing and obesity, due to immobility and chronic inflammation respectively, reduce blood flow and impair fibrinolysis, the clot breakdown process (**Engbers et al, 2010**; **Blokhin and Lentz, 2013**). Furthermore, cancer, whether diagnosed or otherwise, can trigger clotting owing to the associated tissue damage. Similarly, systemic inflammation during acute infections and in inflammatory disorders such as vasculitis or inflammatory bowel disease is thought to promote clotting, although the specific pathophysiological mechanisms remain largely elusive (**Beristain-Covarrubias et al, 2019**). Interestingly, DVT prevalence is higher in males, the reasons for which remain to be unravelled (**Roach et al, 2014**). Heart failure, by reducing cardiac output and consequently slowing blood flow, can also predispose individuals to DVT. Varicose veins, due to bulging or twisting leading to sluggish blood flow, are also implicated in increasing clot risk (**Giannotta et al, 2015**). Other risk factors include acquired or familial thrombophilia, smoking, which increases platelet stickiness due to nicotine (**Cheng et al, 2013**), and use of oestrogen-containing oral contraceptives or hormone replacement therapy, which respectively increase clotting factor plasma concentration and disrupt haemostatic balance (**Solymoss, 2011**; **Busti, 2015**; **Gialeraki et al, 2018**). **NICE (2023)** has identified additional temporary risk factors for DVT including recent major surgery, hospitalisation, trauma, chemotherapy, prolonged travel, immobility, invasive procedures causing direct vein trauma, such as an intravenous catheter, pregnancy and postpartum period, dehydration, and hormone replacement therapy.

The most critical complication of DVT arises when a clot fragment dislodges and embolises to the lungs. Treatment modalities and patient outcomes are determined by clot size. A larger clot or one located in a major blood vessel can significantly obstruct blood flow, leading to severe symptoms and a greater risk of complications. For example, a large clot migrating from the leg to the lungs (pulmonary embolism), can block the main lung artery or its primary branches, a situation that can be life-threatening. Anticoagulant (blood-thinning) medications are routinely used to prevent clot enlargement and formation of new clots. More aggressive treatments may be required for larger clots or situations with significant complication risk, including thrombolytic therapy (medication to dissolve the clot) or, in more severe cases, surgical intervention to remove the clot. Therefore, although clot size is not the only determinant of treatment and outcome – a patient's overall health, age, and presence of other conditions also matter - it remains an essential consideration in managing DVT. Patients who have experienced an unprovoked DVT (not caused by trauma or surgery) face a 10% risk of recurrence in the first year following treatment (**Khan et al, 2019**). It is thus crucial for health professionals to have an in-depth understanding of the vascular system and its associated disorders, equipping them to effectively plan, deliver, and review care. Early assessment, diagnosis, and intervention can often enhance both patient outcomes and quality of life.

Case study

Melanie Smith (not her real name), a 40-year-old woman, had recently approached her local health centre complaining of a painful, swollen left leg. She has a sedentary office job and recently returned from a long-haul flight. She is a non-smoker, and her BMI is within the normal range. She has no personal or family history of blood clots but has been using oral contraceptives for the past 10 years. A full lower limb assessment was carried out by the district nurse (*Table 6*)

Table 6. Case study – assessment findings	
Assessment	**Findings**
History	**Melanie reported a recent long-haul flight, a risk factor for DVT, along with the use of oral contraceptives**
Leg pain and swelling	**Melanie reported pain in her left calf. The nurse noted that the calf was swollen and warm to touch**
Skin colour	**Melanie's left leg appeared redder compared with the right, which could indicate increased blood flow through smaller vessels closer to the skin, due to a clot in a deeper blood vessel**
Palpation of the leg	**The left calf was tender on palpation**
Palpate pedal pulses	**Pulses in Melanie's left foot were found to be slightly weaker than those in the right**
Homan's sign	**Melanie reported pain in her calf upon dorsiflexion of her foot, a positive Homan's sign, which can sometimes indicate DVT**
Measurement of limb circumference	**The nurse measured the circumference of both of Melanie's calves. The left calf was found to be 3 cm larger in diameter than the right**
Mobility	**Melanie reported difficulty walking due to pain in her left calf**
Capillary refill	**Melanie's capillary refill time in the left foot was normal**

The nurse suspected DVT due to the typical symptoms Melanie was displaying – a swollen, painful leg with warmth and redness – as well as her recent long-haul flight and use of oral contraceptives. She was referred for an urgent Doppler ultrasound scan to confirm the diagnosis. Melanie was educated about the signs of pulmonary embolism, a potentially life-threatening complication of DVT, such as sudden-onset shortness of breath and chest pain. She was instructed to seek immediate medical attention if she experienced any of these symptoms.

Conclusion

It is essential that health professionals have a good understanding of the vascular system in order to care for patients with related disorders. The key role of the health professional is to provide advice, prevent further complications and offer support to patients. Caring for patients with vascular disorders requires regular ongoing assessment, implementation, and evaluation of care.

KEY POINTS

- Arteries transport oxygenated blood to tissues throughout the body, veins return deoxygenated blood to the heart
- The smooth muscle walls of arteries mean they also maintain blood pressure and blood flow during diastole, and they modulate blood flow through vasoconstriction or vasodilation
- Some veins, most commonly in the legs, contain one-way paired valves to keep blood flowing in the direction of the heart
- Disorders affecting the arteries include hypertension, atherosclerosis, aneurysm and peripheral arterial disease

- Disorders affecting the veins include vasculitis, varicosities, venous insufficiency and deep vein thrombosis
- It is important for health professionals to have an in-depth understanding of the vascular system and associated disorders – early assessment, diagnosis, and intervention can often enhance both patient outcomes and quality of life

CPD reflective questions

- Which vascular disorder do you most frequently encounter in your nursing practice? Could you effectively describe its altered physiology to a patient, including symptoms and signs, and provide them with relevant educational information?
- After reviewing Melanie's case study, do you find yourself more informed about deep vein thrombosis? What, in your opinion, are the crucial insights that everyone should be aware of?

Declaration of interest: None

References

Aboyans V, Ricco JB, Bartelink MLEL et al; ESC Scientific Document Group. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. *Eur Heart J*. 2018;39(9):763–816.

Beristain-Covarrubais N, Perez-Toledo M, Thomas MR, Henderson IR, Watson SP, Cunningham AF. Understanding infection-induced thrombosis: lessons learned from animal models. *Front Immunol*. 2019;10:2569.

Blanchflower J, Peate I. The vascular system and associated disorders. Chapter 9 in: Peate I (ed). *Fundamentals of applied pathophysiology: an essential guide for nursing and healthcare students*. 4th edn. Chichester: Wiley; 2021

Blokhin I, Lentz S. Mechanisms of thrombosis in obesity. *Curr Opin Hematol*. 2013; 20(5): 437–444

Bradbury A. Pathophysiology and principles of management of varicose veins. In: Fitridge R, Thompson M (eds). *Mechanisms of vascular disease: a reference book for vascular specialists*; Adelaide: University of Adelaide Press; 2011. https://www.ncbi.nlm.nih.gov/books/NBK534256/

Busti A. The mechanism of oral contraceptive (birth control pill) induced clot of thrombus formation (DVT, VTE, PE). Evidence-Based Medicine Consult. 2015. https://tinyurl.com/yt3w74sw (accessed 26 July 2023)

Chaudhry R, Maio JH (Rehman A, ed). Physiology cardiovascular. StatPearls. 2022. https://www.statpearls.com/point-of-care/18942 (accessed 26 July 2022)

Cheng Y-J, Liu Z-H, Yao F-J et al. Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. *PLoS Med*. 2013;10(9):e1001515.

Conte MS, Bradbury AW, Kolh P et al; GVG Writing Group for the Joint Guidelines of the Society for Vascular Surgery (SVS), European Society for Vascular Surgery (ESVS), and World Federation of Vascular Societies (WFVS). Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg*. 2019;58(1 Suppl):S1-S109. e33.

Damjanov I. The blood vessels. In: Damjanov I (ed). *Pathology secrets*. 3rd edn. Mosby/Elsevier; 2009

Davies J, Bull R, Farrelly I, Wakelin M. Improving the calf pump using home-based exercises for patients with chronic venous disease. *Wounds UK*. 2008; 4(3): 48–58

Engbers MJ, Van Hylckama Vlieg A, Rosendaal FR. Venous thrombosis in the elderly: incidence, risk factors and risk groups. *J Thromb Haemost*. 2010;8(10):2105–2112.

Gialeraki A, Valsami S, Pittaras T, Panayiotakopoulos G, Politou M. Oral contraceptives and HRT risk of thrombosis. *Clin Appl Thromb Hemost*. 2018;24(2):217–225.

Giannotta M, Tapete G, Emmi G, Silvestri E, Milla M. Thrombosis in inflammatory bowel diseases: what's the link? *Thromb J*. 2015;13(1):14.

Herrmann J, Yang EH, Iliescu CA et al. Vascular toxicities of cancer therapies: the old and the new—an evolving avenue. *Circulation*. 2020;140(15):1282–1298.

Jarvis S. Vascular system 1: anatomy and physiology. *Nursing Times*. 2018;114(4):40–44

Khan F, Rahman A, Carrier M et al; MARVELOUS Collaborators. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. *BMJ*. 2019;366:l4363.

Lurie F, Passman M, Meisner M et al. The 2020 update of the CEAP classification system and reporting standards. *J Vasc Surg Venous Lymphat Disord*. 2020;8(3):342–352.

McCance KL, Huether SE, Brasher VL, Rote NS (eds). Pathophysiology: the biologic basis for disease in adults and children. 8th edn. St Louis: Mosby; 2018

McDermott MM, Guralnik JM, Tian L et al. Associations of lower extremity ischemia, lower extremity function, and functional decline in peripheral artery disease. *J Am Heart Assoc*. 2019;8(15):e010829.

Moffatt C, Martin R, Smithdale R. Leg ulcer management. Oxford: Wiley-Blackwell; 2007

National Institute for Health and Care Excellence. Peripheral arterial disease: diagnosis and management. Clinical guideline CG147. 2020 (updated from 2012). https://www.nice.org.uk/guidance/cg147 (accessed 26 July 2023)

National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. NICE guideline NG136. 2022a (updated from 2019) https://www.nice.org.uk/guidance/ng136 (accessed 26 July 2023)

National Institute for Health and Care Excellence. Peripheral arterial disease: How common is it? Clinical Knowledge Summary. 2022b. https://tinyurl.com/mr48u8dm (accessed 31 July 2023)

National Institute for Health and Care Excellence. Venous eczema and lipodermatosclerosis: What are the causes and risk factors? Clinical Knowledge Summary.

2022c. https://cks.nice.org.uk/topics/venous-eczema-lipodermatosclerosis/background-information/causes-risk-factors/

National Institute for Health and Care Excellence. Deep vein thrombosis: What are the risk factors? Clinical Knowledge Summary. June 2023. https://cks.nice.org.uk/topics/deep-vein-thrombosis/background-information/risk-factors/ (accessed 26 July 2023)

Public Health England. Hypertension prevalence estimates in England, 2017. 2020. https://tinyurl.com/ycxyhj47 (accessed 26 July 2023)

Roach REJ, Cannegieter SC, Lijfering WM. Differential risks in men and women for first and recurrent venous thrombosis: the role of genes and environment. *J Thromb Haemost*. 2014;12(10):1593–1600.

Rooke TW, Hirsch AT, Misra S et al; Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology; Society for Vascular Medicine; Society for Vascular Surgery. 2011 ACCF/AHA Focused Update of the Guideline for the Management of Patients with Peripheral Artery Disease (Updating the 2005 Guideline). *J Am Coll Cardiol*. 2011;58(19):2020–2045.

Ropacka-Lesiak M, Kasperczak J, Berborowicz G. Risk factors for the development of venous insufficiency of the lower limbs during pregnancy – part 1 [Article in Polish]. *Ginekol Pol*. 2012;83(12):939–942

Senst B, Tadi P, Basit A (Jan A, ed). Hypercoagulability. StatPearls. 2022. https://www.statpearls.com/point-of-care/23168 (accessed 26 July 2023)

Shahoud S, Sanvictories T (Aeddula N, ed). Physiology, arterial pressure regulation. StatPearls. 2022. https://www.statpearls.com/point-of-care/789 (accessed 26 July 2023)

Shammas NW. Epidemiology, classification, and modifiable risk factors of peripheral arterial disease. *Vasc Health Risk Manag*. 2007;3(2):229–234.

Smith D (Lilie C, ed). Acute arterial occlusion. StatPearls. 2023. https://www.statpearls.com/point-of-care/17146 (accessed 26 July 2023)

Solymoss S. Risk of venous thromboembolism with oral contraceptives. *CMAJ*. 2011;183(18):E1278–E1279.

Star A. Differentiating lower extremity wounds: arterial, venous, neurotrophic. *Semin Intervent Radiol*. 2018;35(5):399-405.

Tafur AJ, Rathbun S. Varicose veins. Chapter 54 in: Creager MA, Beckman JA, Loscalzo (eds) *Vascular medicine: A companion to Braunwald's heart disease*. 2nd edn. Saunders/Elsevier; 2013

Tucker W, Arora Y (Mahajan K, ed). Anatomy, blood vessels. StatPearls. 2022. https://www.statpearls.com/point-of-care/32153 (accessed 31 July 2023)