

Structure and cell biology of the vessel wall

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INTRODUCTION

A healthy heart pumps about 6000-8000 liters of blood around the body each day. Blood is carried through the body via blood vessels. The blood vessels form a closed system that begins and ends at the heart. In mammals blood circulates through two separate circuits: the pulmonary circuit and the systemic circuit (Fig. 1.1).

- Pulmonary circuit: the right ventricle of the heart pumps blood into the lungs, where waste gases are exchanged for oxygen, after which the blood is transported back to the left atrium of the heart.
- Systemic circuit: the left ventricle pumps oxygenated blood to all tissues and organs of the body via the aorta after which deoxygenated blood is transported back to the right atrium of the heart.

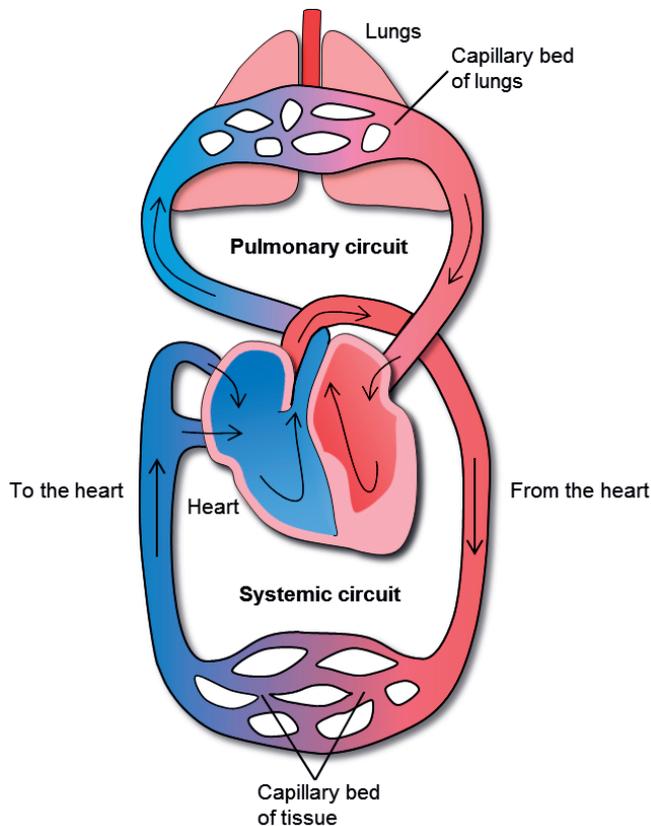


Figure 1.1: Schematic overview of the cardiovascular circulatory system. Note that arteries and oxygenated blood are depicted in red and veins and deoxygenated blood are depicted in blue.

Figure 1.1 gives a simplified overview of the blood flow through the body, where deoxygenated blood is depicted in blue and oxygenated blood is depicted in red. Note that somewhat counterintuitively, deoxygenated blood does not refer to blood without oxygen. Rather, it refers to a lower oxygenation grade than that of oxygenated blood because a certain amount of oxygen has been delivered to tissues. As a result, deoxygenated blood still contains about 75% of oxygen compared to oxygenated blood.

A well-functioning cardiovascular system is essential for all vertebrates. The blood vessels are a conduit for a variety of molecules, such as nutrients, oxygen and waste products, to and from all parts of the body. Blood vessels have several main functions:

1. Distribution of blood containing nutrients (e.g. glucose and amino acids), oxygen (O_2), water and hormones to all the tissues and organs of the body.
2. Removal of metabolic waste products and carbon dioxide (CO_2) from the tissues to the excretory organs and the lungs, respectively.
3. Regulation of blood pressure.
4. Maintenance of constant body temperature (thermoregulation).

Distribution of nutrients, gases and removal of waste products

The primary function of blood vessels is to transport blood around the body, thereby supplying organs with the necessary O_2 and nutrients. At the same time, the vessels remove waste products and CO_2 to be processed or removed from the body.

Regulation of blood pressure

Blood vessels control blood pressure by changing the diameter of the vessel through either constriction (vasoconstriction) or dilation (vasodilation). Variations in blood pressure occur in various parts of the circulation depending on the diameter of the vessel.

Maintenance of constant body temperature (thermoregulation)

Blood vessels help maintain a stable body temperature by controlling the blood flow to the surface area of the skin. To prevent overheating, blood vessels near the surface of the skin can dilate, allowing excessive heat of the blood to be released to the surroundings. In contrast, blood vessels near the skin's surface can constrict, reducing heat loss through the skin when needed under cold circumstances.

STRUCTURE OF THE VESSEL WALL

Blood vessels need to be well-constructed, as they have to withstand the pressure of circulating blood through the body every day. The vessel wall is arranged in three distinct layers,

termed tunica: an inner layer (tunica intima), a middle layer (tunica media) and an outer layer (tunica adventitia) (Fig. 1.2). These layers mainly contain endothelial cells, vascular smooth muscle cells and extracellular matrix, including collagen and elastic fibers.

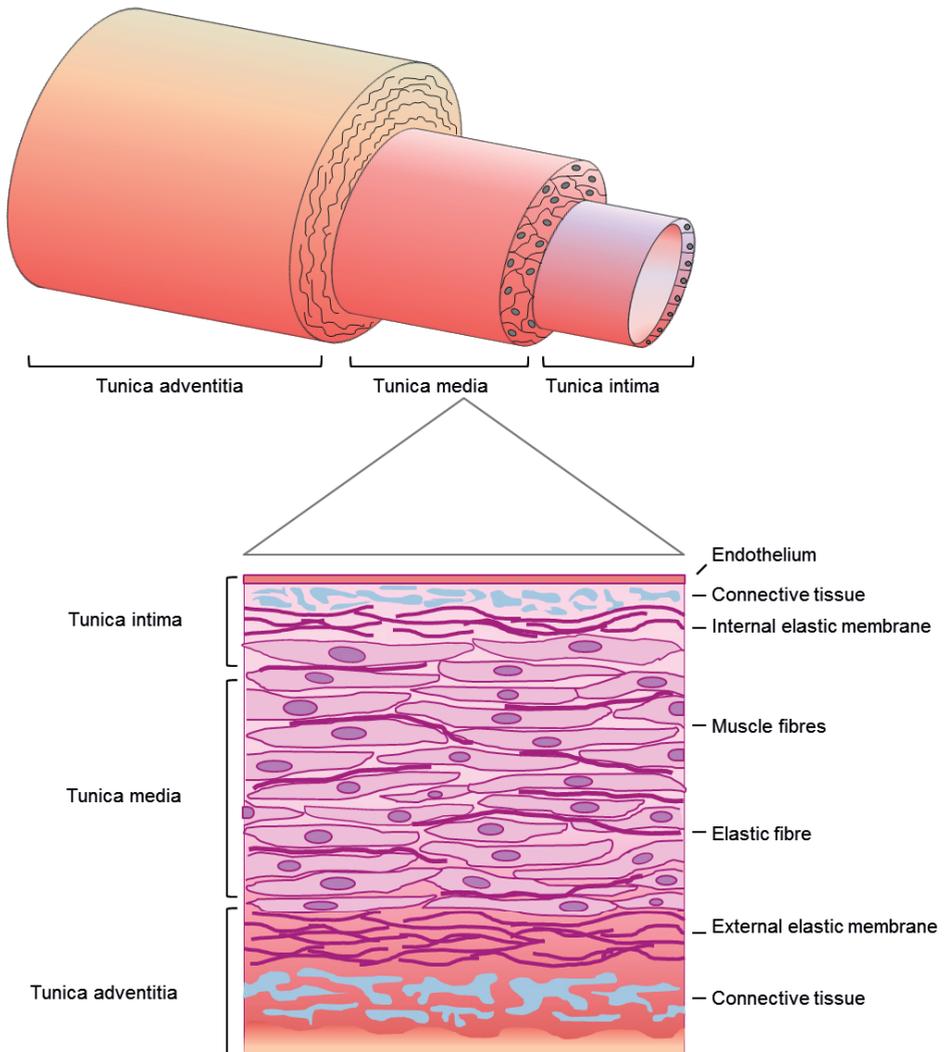


Figure 1.2: General structure of the vessel wall, showing the tunica intima, tunica media and tunica adventitia and a close-up depicting the different structures within these layers.

Tunica intima

The tunica intima ('inner coat') is the innermost layer of a blood vessel. In healthy vessels, it consists of a thin single layer of endothelial cells, which are in direct contact with the blood in the lumen, as well as a subendothelial layer made-up mostly by connective tissue. The single layer of endothelial cells, called endothelium, has a smooth surface that minimizes the friction of the blood as it moves through the lumen. The endothelium plays a role in vascular permeability, inflammation, coagulation and vascular tone, which refers to the maximal degree of contraction by vascular smooth muscle cell relative to its maximally dilated state. The subendothelial layer, also called basal lamina, provides a physical support base for the endothelial cells and flexibility of the vessel for stretching and recoil. Moreover, it guides cell and molecular movement during tissue repair of the vessel wall. The tunica intima is the thinnest layer of the blood vessel and minimally contributes to the thickness of the vessel wall. In arteries and arterioles, the outer margin of the tunica intima is separated from the surrounding tunica media by the *internal elastic membrane*, a thick layer of elastic fibers. The internal elastic membrane provides structure and elasticity to the vessel and allows diffusion of materials through the tunica intima to the tunica media. Microscopically, the lumen and the tunica intima of an artery appear wavy because of the partial constriction of the vascular smooth muscle cells in the tunica media, the middle layer of the blood vessel, whereas the tunica intima of a vein appears smooth.

Tunica media

The middle layer, tunica media, is considered to be the muscular layer of the blood vessel as it primarily contains circularly arranged smooth muscle fibers together with extracellular matrix, mostly elastin sheets. It is often the thickest layer of the arterial wall and much thicker in arteries than in veins. The tunica media provides structural support as well as vasoreactivity (the ability of blood vessels to contract or to relax in response to stimuli) and elasticity to the blood vessel. The primary role of the vascular smooth muscle cells is to regulate the diameter of the vessel lumen. Concerning blood pressure regulation, the vascular smooth muscle cells in the tunica media can either contract causing vasoconstriction, or relax causing vasodilation. During vasoconstriction, the lumen of the vessel narrows, leading to an increase in blood pressure, whereas vasodilation widens the lumen allowing blood pressure to drop. Both vasoconstriction and vasodilation are partially regulated by nerves (nervi vasorum). The tunica media is separated from the tunica adventitia by a dense elastic lamina called the *external elastic membrane*. Under the microscope, these laminae appear as wavy lines. This structure is usually not apparent in small arteries and veins.

Tunica adventitia

The tunica adventitia (also known as tunica externa) is the outermost layer of the vessel wall, surrounding the tunica media. The adventitia is predominantly made-up by extracel-

lular matrix (collagen and elastic fibers), nutrient vessels (vasa vasorum) and autonomic nerves (nervi vasorum). Fibroblasts and numerous macrophages are also present in this layer. The tunica adventitia is often the thickest layer in veins, sometimes even thicker than the tunica media in larger arteries. The tunica adventitia helps to anchor the vessel to the surrounding tissue and provides strength to the vessels as it protects the vessel from overexpansion.

Vasa vasorum

Characteristic of the adventitial layer is the presence of small blood vessels, called the vasa vasorum. The vasa vasorum supplies blood and nourishment to the tunica adventitia and outer parts of the tunica media, as these layers are too thick to be nourished merely by diffusion from blood in the lumen, and removes 'waste' products. Because of the thick and muscular walls of the arteries, the vasa vasorum are more frequent in the wall of arteries than in the wall of veins.

COMPONENTS OF THE VASCULAR WALL

The vascular wall is composed of many cell types and constituents that influence the diameter and functional control of the vessel wall. Several main cell types include endothelial cells, vascular smooth muscle cells and immune cells (Fig. 1.3). Interaction between these

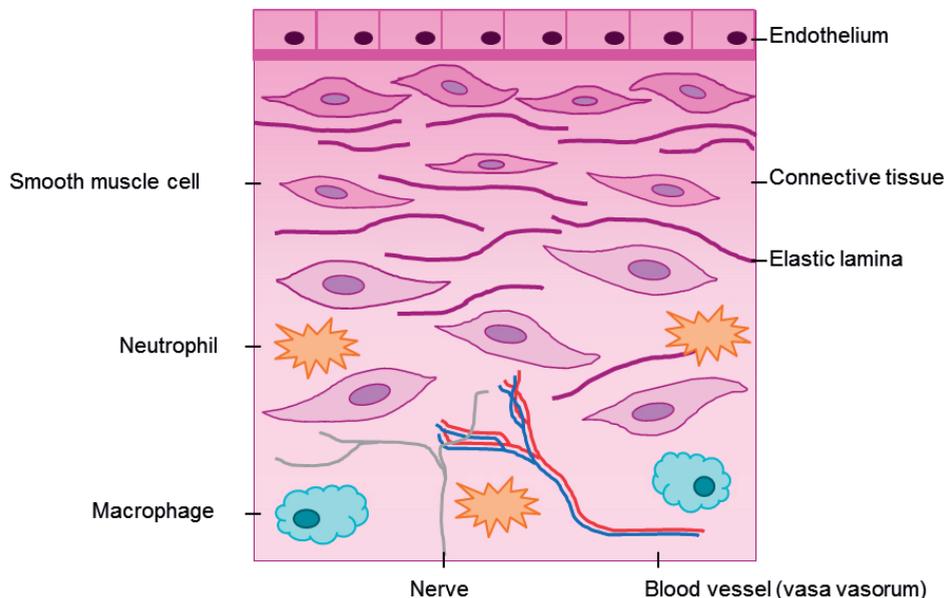


Figure 1.3. Summary of the major components of the vessel wall.

cell types allows the vessel to adapt to alterations in pressure and various physical stimuli by either dilation or contraction.

Endothelium

Vascular endothelial cells lining the entire circulatory system, from the heart and arteries to the small capillary beds, are in direct contact with blood. They form a single-cell layer (monolayer) called the endothelium, which has been estimated to cover a surface area of more than 1000 m² in humans. The morphological shape of endothelial cells varies across the circulatory system (Flaherty et al. 2012). In large arteries, endothelial cells are aligned and elongated in the direction of the blood flow, whereas in region of disturbed flow, e.g. near bifurcations, endothelial cells are more round and do not align in a specific direction. Varying among the vascular tree, endothelial cells are between 0.2 to 2.0 µm thick and 1 to 20 µm long. They are joined together by tight junctions, which restrict the transportation of large molecules across the endothelium. Endothelial cells are active contributors to a variety of vessel-related activities, including permeability, vascular tone and hemostasis. Vascular endothelial cells have several important functions (Box 1.1).

Box 1.1 Vascular endothelial cell function

1. Providing a semi-permeable barrier between the vessel lumen, containing the blood, and the surrounding tissues. Selective material, electrolytes, macromolecules, fluid and cells can pass the barrier entering or leaving the bloodstream.
2. Regulating vascular tone, by secreting vasoactive substances that stimulate the smooth muscle cells of the tunica media to relax or contract, thus widening or narrowing the vessel.
3. Modulating cellular adhesion and inflammation of the vasculature, as endothelial cells regulate lymphocyte and leucocyte adhesion and transendothelial migration, from the bloodstream across the barrier into the vessel wall, by expression of surface adhesion molecules.
4. Modulating haemostasis and coagulation. Under normal conditions, endothelial cells express a wide variety of non-thrombogenic factors that maintain blood fluidity and help prevent inappropriate blood clotting.
5. Involved in the formation of new blood vessels (angiogenesis). Angiogenesis is in part regulated by the endothelial cell, which is important in wound healing.

The endothelium has a strategic position in the vessel wall, right between the circulating blood and the vascular smooth muscle cell. From this position, the endothelium plays a vital role in controlling vascular function, as it is able to respond to mechanical and hormonal signals and receive information from cellular constituents of the vessel wall. Endothelial cells are highly dynamic as they need to interpret changes in blood composition and mechanical changes, and respond properly to several stimuli, either physical or chemical, by producing a variety of factors that contribute to the control of vascular tone, vascular inflammation, cellular adhesion, hemostasis and coagulation. For instance, the endothelium serves as a semi-permeable barrier, restricting and controlling the move-

ment of fluids, molecules and cells across the blood vessel wall. This movement across the endothelial lining can occur via different mechanisms, either through the endothelial cells (transcellular) or by passing the junction between two adjacent endothelial cells (paracellular). The permeability of the barrier can be altered in response to specific stimuli that act on endothelial cells. Also, endothelial cells themselves can secrete different vasoactive substances that influence the activity of the underlying vascular smooth muscle cell, and thereby the contractile state of the vessel. For instance, endothelial cells can secrete nitric oxide which causes the vascular smooth muscle cells to relax, consequently leading to vasodilation. Moreover, endothelial cells tightly regulate the expression of adhesion molecules on their surface. These adhesion molecules not only modulate cell migration but are also important in response to local injury, as platelets and other inflammatory cells are recruited to the site of damage in need of defense or repair. Furthermore, endothelial cells are required to maintain blood fluidity and prevent thrombus formation. They bind and display tissue factors that have anti-coagulant properties thereby preventing the initiation of coagulation.

Injury and dysfunction of the endothelium directly or indirectly plays a vital role in the initiation and development of most of human vascular diseases. Endothelial dysfunction not only leads to an imbalance between vasoconstriction and vasodilation but also causes coagulation disorders and can be involved in the malignant growth of tumors. It is also involved in numerous other physiological and pathological conditions such as hypertension, septic shock, diabetes and hypercholesterolemia. Moreover, endothelial dysfunction is seen as the initial step in the atherosclerotic process.

Vascular smooth muscle cells

Vascular smooth muscle cells are the most prominent cell type of an artery and, depending on the size of the artery, may comprise several layers. Vascular smooth muscle cells are typically 2 to 5 μm in diameter, and vary from 100 to 500 μm in length. Yet, as the vascular smooth muscle cells can either relax or contract, their actual length depends on the physiological conditions and functioning of the cell. The vascular smooth muscle cells exert different functions, which translates into two different phenotypes of the vascular smooth muscle: contractile or synthetic. The contractile smooth muscle cells are long spindle-shaped cells that contain a single centrally positioned elongated nucleus, whereas the synthetic vascular smooth muscle cells are less elongated and have a more cobblestone morphology. Each smooth muscle cell is enclosed by a variable amount of extracellular matrix, containing collagen, elastin and various proteoglycans. Smooth muscle cells are arranged in different orientations, either circumferentially or helically, along the longitudinal axis of the vessel. Smooth muscle cells are connected to each other by tight- and gap-junctions. These junctions permit the transfer of signaling molecules between cells and increase the tensile strength of the medial layer, respectively, allowing the control

of the diameter of the vessel. Smooth muscle cells are normally quiescent cells that do not divide. However, damage to the vessel wall can drive the smooth muscle cells into a proliferative state in which they will divide and migrate.

In the artery, almost all smooth muscle cells are present in the tunica media. The primary function of smooth muscle cells is to regulate the diameter of the vessel lumen, as it directly controls vessel tone and regulates blood pressure by either contraction or relaxation. In the small arteries (less than 300 μm in diameter) and veins, contraction of the vascular smooth muscle cell is responsible for the regional distribution of the blood flow as it gives a reduction in lumen diameter and thereby increases vascular resistance, leading to a higher blood pressure. Vasoconstriction in the larger arteries has a different hemodynamic effect and mostly affects the stiffness (compliance) of the blood vessel, increasing the impedance to move blood through the artery.

Regulation of the vascular diameter by activation/deactivation of vascular smooth muscle cells is primarily under control by the autonomic nerves in the adventitial layer that act on specific receptors present on the outside of vascular smooth muscle cells. Yet, other locally produced and blood-borne factors can also act directly on the vascular smooth muscle cell and thus play an important role in its function. Smooth muscle cell contraction can be initiated by electrical, chemical or mechanical stimuli. Contractility of smooth muscle cells is controlled by actin and myosin filaments of the cytoskeleton, which make up a substantial portion of the cytoplasm of smooth muscle cells. Besides contractility, vascular smooth muscle cells also perform other functions such as migration, proliferation, proinflammatory and secretory, responses that become progressively important during vessel remodeling, injury and disease. For example, the smooth muscle cells produce a variety of extracellular matrix components, including collagen and elastin. Activated vascular smooth muscle cells also secrete matrix metalloproteinases (MMPs), which facilitate extracellular matrix remodeling. The ratio between vascular smooth muscle cells and the amount of extracellular matrix determines the overall mechanical properties and structural integrity of the vessel. The phenotype of the vascular smooth muscle cell can range from contractile to synthetic. These two phenotypes of smooth muscle cells not only differ in morphology but also in expression levels of different genes and their proliferative and migratory properties. Contractile smooth muscle cells are most often quiescent whereas synthetic smooth muscle cells have a high proliferation and migratory rate. The vascular smooth muscle cells can switch between these two phenotypes in response to changes in environmental cues, therefore these cells are not only important in short-term regulation of the lumen diameter but also in long-term adaptation of the vessel through structural remodeling.

There is clear evidence that vascular smooth muscle cells are involved in the pathogenesis of several vascular diseases, including atherosclerosis, restenosis, hypertension,

asthma and vascular aneurysms. Upon vascular injury, the smooth muscle cells undergo a phenotypic switch from contractile to synthetic, which most often includes increased proliferation, migration to the site of damage and increased excretion of extracellular matrix proteins. These characteristics play an important role in vascular repair, however, when occurring in high degrees, it predisposes the cell to acquire characteristics that contribute to the development of vascular diseases. The most acknowledged disease, in which smooth muscle cells play a key role, is atherosclerosis. However, the precise role of smooth muscle cells in atherosclerotic disease progression most likely depends on disease stage, as smooth muscle cells play a disadvantageous role in lesion development and progression, whereas they have a beneficial role in stabilizing the fibrous cap and consequently prevent plaque rupture.

Pericytes

Pericytes are the contractile cells of the capillaries and venules, whereas vascular smooth muscle cells are the contractile cells of other blood vessels (arteries, arterioles and veins). The size and morphology of pericytes greatly depends on location and type of vessel, and may be irregular in a single vessel. Generally, they have an elongated shape with a prominent round nucleus, and are surrounded by basal lamina material that is continuous with the basement membrane of the tunica intima. These pericytes are wrapped around the endothelial cells on the luminal side of the basement membrane. Pericytes have been associated with regulating capillary blood flow and stabilization of microvessels.

Cytoskeleton proteins

Cytoskeletal proteins are structural elements surrounding the cell membrane and are important to maintain cellular shape and integrity. These proteins play an active role in the interaction between blood vessels and the surrounding environment. Key cytoskeleton proteins include actin filaments, microtubules and intermediate filaments. Actin filaments are important in cell-cell control and cell-matrix interactions as they can bind to plasma membrane proteins. Actin filaments surrounding the endothelial cell are therefore involved in fluid and molecule exchange between the tissue and the circulating blood, by tightly regulating the vascular barrier. Furthermore, actin filaments are involved in cell motility, particular in the contraction of the vessel wall through association with the motor protein myosin. As such, when vascular smooth muscle cells become activated, the cytoskeleton proteins actin and myosin rapidly reorganize, creating membrane bound, parallel-organized units termed 'stress fibers'. In this complex, myosin slides along the actin filaments, which produces an increased intracellular tension leading to contraction of the cell. The microtubules not only support the cellular structure, but also are involved in cell division, as they facilitate the formation of spindles during mitosis. Intermediate

filaments appear to have a structural role in maintaining cellular integrity but might also provide an anchoring for contractile proteins.

Vascular extracellular matrix

The extracellular matrix is a highly-organized network of proteins containing collagen and elastin fibers and a loose network of proteoglycans. Foremost, the extracellular matrix provides structural support and elasticity to the vessel wall, keeping cells in place and allowing adaptation of the vessel wall to high blood pressure. Endothelial cells of the tunica intima, vascular smooth muscle cells of the tunica media and fibroblasts of the tunica adventitia all produce extracellular matrix proteins that have a different function in each tunica. The extracellular matrix proteins of the tunica intima make up the sub-endothelial basement membrane, which provides flexibility of vessels for stretching and recoil, whereas the extracellular matrix of the tunica media is responsible for strength and stretch of the vessel wall, as well as for transmission of muscle contraction. The tunica adventitia is made up principally by extracellular matrix, and contains a limited number of cells. This layer adds further strength to the vessels wall. Additionally, the extracellular matrix provides specific informational cues to vascular cells, thereby regulating cellular adhesion, proliferation, differentiation and migration.

Collagen

Physical properties of the blood vessel wall largely depend on collagen fibers. These collagen fibers provide a supporting framework that anchors smooth muscle cells in place. When internal pressures are high, the collagen network becomes rigid, limiting elasticity of the vessel wall. Collagen types I, III, and IV are present in the adventitia, tunica media and basement membranes, respectively. Veins tend to have a higher collagen content than arteries. Once blood vessels start to lose their collagen, tiny ruptures can occur in the vessel wall.

Elastin

Elastin provides vessels with the ability to stretch and recoil in response to hemodynamic forces resulting from alterations in blood pressure. Many elastin molecules are cross-linked and connected to each other and other molecules, including microfibrils, fibulins and collagen, to form an elastic fiber. These elastic fibers allow the vessels to expand during the contractile phase of the heart and then recoil during the filling phase of the heart, keeping the blood flowing forward. These elastic fibers are mainly found in the tunica media of arteries, where smooth muscle cells and collagen fibers are present between these elastic layers. Depletion of elastin is often due to destruction rather than reduced production.

Integrity of the extracellular matrix is essential to maintain both physical and biological properties of the vessel, as changes in the extracellular matrix affect the local environment that vascular cells are embedded in. As a result, cellular adhesion, prolif-

eration, migration, differentiation, and gene expression of several vascular cells will be affected. Moreover, disruption and/or deletion of these extracellular matrix proteins has deleterious effects on the structure and function of vessels, as it contributes to weakening of the vessel wall. Maintaining a proper balance between the different matrix components depends on new synthesis of matrix proteins and on matrix degradation by enzymes, such as MMPs. An imbalance of extracellular matrix proteins in favor of matrix degradation is for instance seen in vascular diseases like aneurysms, where it leads to vessel wall rupture, and atherosclerosis, where it is involved in plaque destabilization.

Infiltrating immune cells

Endothelial cells and vascular smooth muscle cells are able to produce a variety of immune and inflammatory mediators, such as tumor necrosis factor- α (TNF- α), interleukins (IL), platelet-derived growth factors (PDGF). These factors stimulate migration of immune cells and inflammatory cells from the blood into the tissue. As a result, different immune cells can be found in the vessel wall, including macrophages and lymphocytes. For instance, activated endothelial cells can express adhesion molecules that allow mononuclear leucocytes, such as monocytes and T-cells, to attach to the endothelium and penetrate into the tunica intima. Penetration of these cells into the tunica media by endothelial cells is seen as one of the early steps in the development of atherosclerotic lesions.

TYPES OF BLOOD VESSELS

Blood vessels are found throughout the body and can be categorized by function and by composition of the wall. There are five general types of blood vessels: arteries, arterioles, capillaries, venules and veins (Fig. 1.4). As these types of blood vessels have to withstand different degrees of blood pressure, the composition of the wall varies among these types (see Table 1.1).

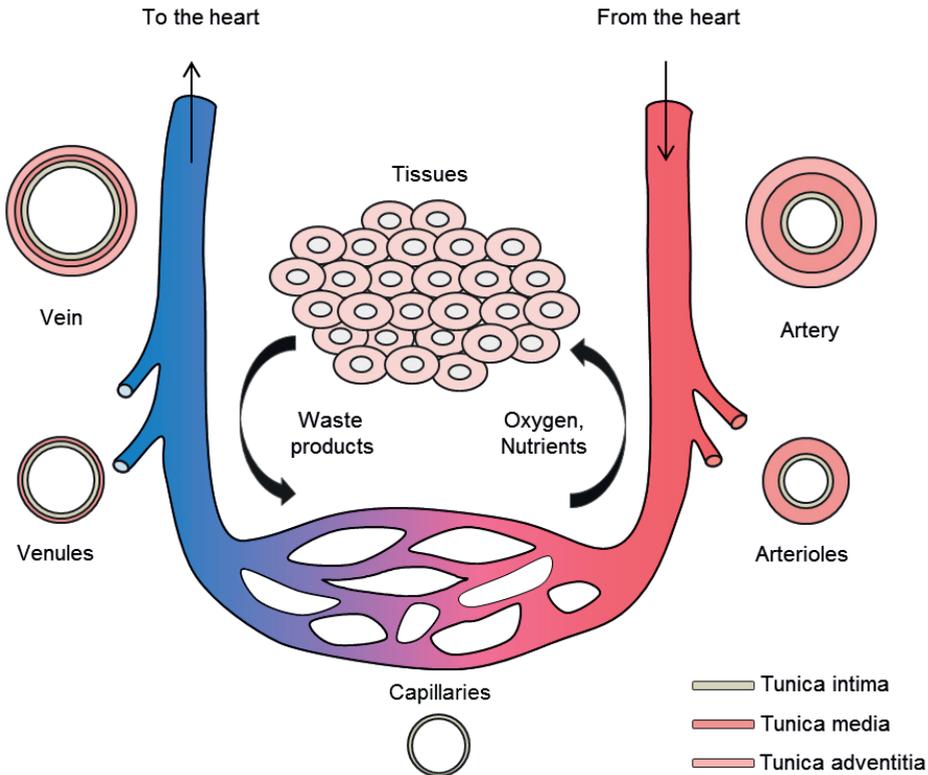


Figure 1.4: Schematic drawing showing major structural characteristics of the different types of blood vessels.

Arteries

Arteries carry highly pressurized oxygen rich blood away from the heart to other organs of the body. Because arteries experience high blood pressure and pulsatile flow as blood is ejected from the heart, they must be strong, elastic and flexible and therefore have a much thicker wall than veins. Arteries consist of three layers, tunica intima, media and adventitia. The tunica media of an artery is very thick and contains more smooth muscle cells and elastic fibers than that of veins, allowing the arteries to be more contractile and elastic, respectively. The large arteries of the body contain a lot of elastic laminae that allows the artery to stretch and accommodate to high blood pressure. The arteries branch repeatedly into smaller and smaller vessels, eventually becoming arterioles. According to size and function, arteries can be divided into two groups.

Table 1: Summary of the characteristics of different blood vessels.

Type of vessel	Actions	Structure vessel wall	Structure fits function
Artery	Carries blood away from the heart to the arterioles at high pressure	Three-layer thick wall (endothelial lining, middle smooth muscle and elastic tissue layer, outer connective tissue layer; strong, elastic and flexible; narrow lumen)	Strong, elastic walls and narrow lumen help to maintain high blood pressure
Arteriole	Helps control blood flow from arteries to capillaries	Similar three layers as arteries but thinner; very narrow lumen	Vessel wall helps control blood flow by constricting or dilating
Capillary	Supply tissue with nutrients and gases and removal of waste products	Single thin layer of endothelium	Thin wall brings blood into close contact with tissue; allowing diffusion
Venule	Connects capillaries to veins	Thinner wall than arterioles, less smooth muscle and elastic tissue; extremely porous wall	Porous wall makes it easy for fluids and blood cells to pass through
Vein	Carries relatively low-pressure blood from venules to the heart	Similar layers as arteries but thinner; thin middle layer but thicker outer layer; contains valves; wide lumen	Thin wall and wide lumen allow housing of a large volume of blood and offers less resistance to blood flow

1. Elastic arteries

Elastic arteries are found close to the heart and receive blood directly from the heart. These arteries are called elastic because the tunica media is dominated by elastic laminae that give the vessel wall great elasticity, helping the artery to stretch in response to high pulsatile blood pressures during each heartbeat. The aorta, pulmonary trunk and the larger arteries that originate from them, are types of elastic arteries. Their tunica intima is thicker than that of muscular arteries and is surrounded by an internal elastic lamina, which is less well defined because of the abundance of elastic laminae. The tunica media of elastic arteries is much thicker compared to other arteries. It is primarily made up of multiple elastic laminae alternating with thin layers of smooth muscle cells and collagen fibers, which together form a lamellar unit. The external elastic lamina is difficult to distinguish from other elastic lamellar units in the tunica media. The tunica adventitia appears thinner than the tunica media and contains vasa vasorum, as the walls of these arteries are too thick to receive enough oxygen and nutrients from blood flow in the vessel lumen. The vasa vasorum supplies both the tunica media and the tunica adventitia with oxygen.

2. Muscular arteries

Muscular arteries are medium-sized arteries, which distribute the blood to various tissues and organs. These types of arteries include the femoral, brachial and coronary arteries. The diameter of the muscular artery lumen is on average 0.1 mm to 10 mm. The tunica intima of muscular arteries is thinner than those of elastic arteries. The tunica media

consists mostly of multiple layers of smooth muscle cells and less of elastic laminae. The elastic laminae are confined to two circumscribed rings: the internal elastic laminae and the external elastic laminae. The thickness and appearance of the tunica adventitia is variable. The greater amount of smooth muscle cells combined with less elastic laminae results in less elasticity but a better ability to constrict and dilate.

Arterioles

Arterioles are the smallest arteries of the body and have the same three layers as the larger arteries. The critical endothelial lining of the tunica intima is intact, and it still rests on the internal elastic laminae, which is not always well defined in histological sections. The tunica media generally consists of less than six layers of smooth muscle cells and there is no external elastic lamina. The tunica adventitia is about the same size as the tunica media. The arteriole lumen is around 10-100 μm in diameter. As arterioles have a small diameter, they generate a great resistance to blood flow and are critically involved in slowing down blood flow. Smooth muscle cells of the tunica media form concentric rings that control distribution of blood flow by either contracting or dilating lumen size. Normally, smooth muscle cells are slightly contracted, causing the arterioles to maintain a consistent vascular tone.

Capillaries

Blood moves from the arterioles into the capillaries, which are tiny, narrow, thin-walled vessels that connect arteries with veins. Capillaries are the smallest of all blood vessels, about 5-8 μm in diameter, and blood pressure further drops as it encounters extra resistance flowing through the capillaries. Their walls consist of a single layer of endothelial cells and an underlying basement membrane, often accompanied by pericytes. The basement membrane keeps cells in place and is largely made up of proteins. Capillaries have no tunica media or tunica adventitia. The diameter of a capillary is just wide enough to allow single red blood cells (erythrocytes) to pass through. The thin wall of the capillaries facilitates its primary function: exchange of oxygen, nutrients and other substances, between blood and the underlying tissue. Most capillaries are organized into a network called capillary bed. Based on the morphology of their endothelial layer, capillaries can be classified into three different types.

1. *Continuous capillaries* consist of an uninterrupted, continuous lining of endothelial cells, which are joined by tight non-permeable junctions, and a complete basement membrane. The continuous capillaries have a low permeability to molecules; it only allows small molecules, like water and ions, to diffuse through the tight junctions, which have gaps of unjoined membrane called intercellular clefts. They are commonly found in skin, muscles, lung and central nervous tissue.

2. *Fenestrated capillaries* have leakier intracellular junctions and perforations in the endothelial cell body, called fenestrae or pores. The fenestrae are present at both the luminal and basal surface of the cell, and the endothelial cells are surrounded by a continuous basement membrane. Fenestrated capillaries are much more permeable compared to continuous capillaries, and allow larger molecules and a limited amount of proteins to bypass the endothelial cells. The extent of fenestra may depend on the physiological state of the surrounding tissue, as their numbers may depend on the need to absorb or secrete. They are found in tissues that participate in fluid exchange including endocrine glands, intestinal villi and kidney glomeruli.
3. *Discontinuous capillaries*, also called sinusoids, are the largest of all capillaries and have larger, open spaces in the endothelium, containing a lot more intracellular clefts. They are very permeable (leaky) and allow large molecules, including red and white blood cells and various serum proteins, to pass through the intracellular spaces of the endothelium. Discontinuous capillaries contain a basement membrane that is often incomplete. These discontinuous capillaries are found in areas where the exchange of substances is advantageous, i.e. in the liver, hematopoietic organs (spleen and bone marrow) and some endocrine organs.

Venules

Blood flows from the capillary beds into very small veins called venules (10-200 μm in diameter). Venules allow deoxygenated blood to return from the capillary beds to the larger blood vessels called veins. Venules consist of a tunica intima, a thin tunica media and a tunica adventitia. The vessel wall of venules is thinner than arterioles and is extremely porous, making it easy for fluids and blood cells to pass through their walls. Venules can be further subclassified into muscular (50-200 μm) and post-capillary venules (10-50 μm). The post-capillary venule starts where two capillaries from the capillary bed come together. It is a non-muscular vessel, as the tunica media consists of an incomplete layer of pericytes and scattered smooth muscle cells. Instead, the post-capillary venule has a thin very permeable endothelial layer, making them the preferred site of white blood cell (leucocyte) adhesion and transmigration. Hence, the response of the vasculature to inflammation is generally localized in the post-capillary venules. During inflammatory responses, vasoactive substances act on the endothelium which results in extravasation of fluid and the migration of leucocytes into the tissue. Post-capillary venules join together, forming larger muscular venules. In the muscular venules, the pericytes are replaced by one or two layers of smooth muscle cells.

Veins

Multiple venules unite to form veins. Veins carry deoxygenated blood back from tissues and organs towards the heart. One difference between veins and arteries is the direction of

blood flow. As in arteries, veins have three layers. However, veins have much thinner walls than arteries as they are distant from the heart and subsequently experience less pressure from the blood flow. The tunica intima and tunica adventitia are similar in structure to arteries though the tunica media is much thinner. The tunica intima consists of the endothelial lining with its basement membrane, and surrounding internal elastic laminae. The tunica media of veins is thin and only contains a few smooth muscle cells and elastic laminae, whereas the tunica adventitia is much thicker, containing collagen and occasionally some smooth muscle cells and elastic fibers. In general, veins are larger in diameter (varying from 1 mm to 15 mm), containing a wide lumen, which together with the thin walls allows the accommodation of a large blood volume. Most of the blood volume of the body, around 60%, is contained within veins at any time. Because of these thin walls and a small medial layer, veins do not have the same elasticity and vasoconstriction capacities as arteries. Blood is displaced through veins by contraction of the surrounding muscles and pressure gradients that are created during inhalation and exhalation. Compared to arteries, veins are frequently irregular of shape and softer. Some veins also contain valves, particularly veins in the legs, which prevent backflow of blood as it travels back to the heart. Veins can be classified into four main types as shown in Box 1.2.

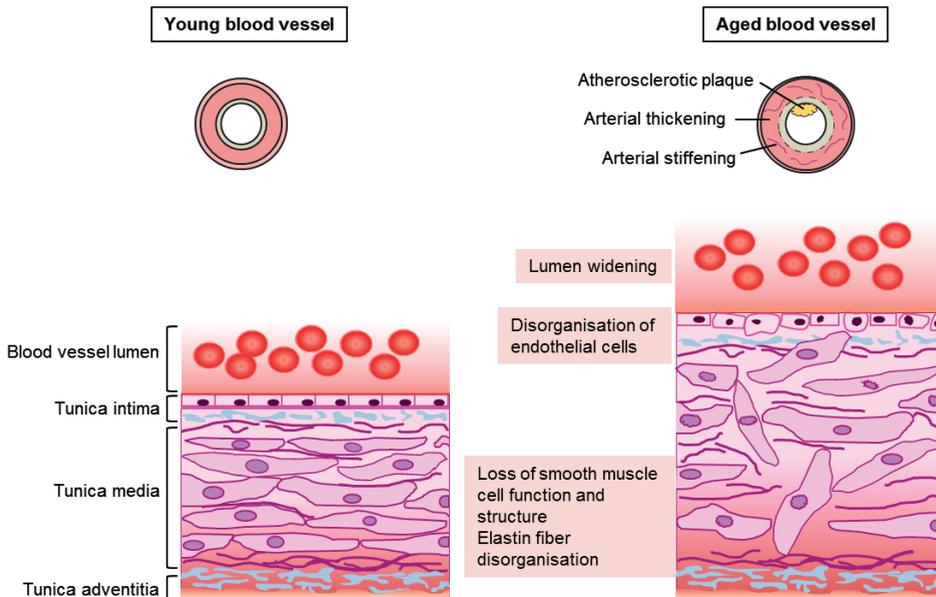


Figure 1.5. Schematic view of the structural changes of the vessel wall during aging.

Box 1.2 Classification of veins

1. *Pulmonary veins* carry oxygenated blood from the lungs to the left atrium of the heart
2. *Systemic veins* return deoxygenated blood from the rest of the body to the right atrium of the heart.
3. *Superficial veins* are located close to the surface of the skin and are not located near a corresponding artery.
4. *Deep veins* are located within muscle tissue and typically near a corresponding artery.

Lymphatic vessels: secondary drainage system

The general structure of lymphatic vessels is based on the three tunica described above. Lymphatic vessels are lined by endothelial cells and have a thin layer of smooth muscle cells followed by the adventitia. They are part of the lymphatic system that transports fluid away from tissues and plays an important role in the body's defense system. The fluid that lymphatic vessels carry is not blood, but is clear fluid, called lymph, that comes from blood plasma that exits blood vessels at the site of the capillaries.

AGING AND THE VASCULAR WALL

The prevalence of cardiovascular disease increases progressively with age. To understand why aging is closely linked to cardiovascular disease, it is essential to know what happens to our vessels during normal aging. Aging is a natural biological process that begins as soon as adulthood is reached and it causes diverse detrimental changes in cells and tissues. A series of structural, architectural and compositional modification take place in the vasculature during aging (Fig. 1.5). As such, with increasing age, blood vessels lose their flexibility and structural integrity, which diminishes the ability of blood vessels to expand and contract efficiently. In addition, age-related vascular alterations lead to loss of adequate tissue perfusion (ischemia), insufficient vascular growth or excessive remodeling. Eventually these changes affect cardiovascular performance and set the stage for the onset of several cardiovascular diseases including hypertension (high blood pressure), atherosclerosis, stroke and aneurysm formation.

Age-related structural changes

At a microscopic level, principal age-related structural changes of the vasculature include an increase in vessel lumen size and thickening and stiffening of the intimal and medial layer. Important structural changes causally related to vessel wall thickening and stiffening include vascular smooth muscle enlargement and relocation to the subendothelial space, increased extracellular matrix accumulation (particularly rich in glycosaminoglycans), and increased deposition of lipids and calcium salts. While the content of collagen increases, elastin fibers become disorganized, thinner and fragmented.

As an individual grows older, the endothelial barrier of the tunica intima becomes damaged and some of its specialized functions are blunted. The endothelial barrier becomes porous (leaky), the self-renewal process weakens and endothelial signaling is modified. For example, with increasing age endothelial cells produce substances that signal blood cells to adhere to the endothelial layer of the tunica media instead of smoothly flowing through the blood vessel lumen. Additionally, endothelial cells transmit signals to the underlying vascular smooth muscle cells in the tunica media that prompt these cells to change. These changes result in vascular smooth muscle cells to translocate and move towards the site of injury, where they reposition in the tunica intima just beneath the endothelial layer. At this site, the vascular smooth muscle cells multiply and produce matrix proteins, which eventually results in thickening of the tunica intima. Moreover, with age, some of the vascular smooth muscles of the tunica media die, increasing the workload of the remaining vascular smooth muscle cells and causing them to grow larger. Some changes cause vascular smooth muscle cells to switch from a contractile state to a state in which they produce excessive amounts of collagen proteins and other matrix substances, thereby creating imbalance between the elastin and collagen content of the tunica media. The ratio of collagen to elastin increases in favor of collagen, which is a 100 to 1000 times stiffer than elastin, resulting in a stiffer wall and a less compliant blood vessel. Moreover, vessel wall stiffening has been associated with the formation of cross-links between glucose and collagen. Growing levels of cross-links reduce elasticity of the vessel wall, as these cross-links glue together important proteins of the extracellular matrix thereby degrading its primary structure, preventing it from functioning correctly. Aging also affects elastin, as it becomes overloaded with calcium, stretches out, and eventually becomes fragmented and disorganized.

Related diseases

Due to structural changes in the vessel wall with age, many of the arteries are less able to withstand the forces of pulsating blood. High systolic blood pressure, which is commonly observed in the elderly, may exacerbate this problem. As a result, the vessel wall becomes weakened and more prone to develop several vascular diseases, including aneurysms. Moreover, aging increases incidence and severity of atherosclerosis, as the age-related changes of the vessel wall make it easier for fatty substances to accumulate inside of the blood vessel. Several studies suggest that exercise, good nutrition and therapeutic interventions can slow down the aging process occurring within blood vessels. For example, it in elderly who regularly exercise arterial stiffening is less pronounced.

SUMMARY

The vessel wall consists of three different layers termed tunica intima, tunica media and tunica adventitia. The main components of these layers include endothelial cells, vascular smooth muscle cells, cytoskeleton proteins and extracellular matrix proteins. Interaction between these components of the different layers determines the biological and physical properties of the blood vessel. Changes and damage to these components and cellular constituents contribute to the pathogenesis and progression of several vascular diseases, as well as to aging of the vasculature. The subsequent chapters in this book will cover, in greater detail, related diseases of the vasculature.

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