Overview

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Anatomy and Physiology of Blood Vessels

The blood vessels conduct blood from the heart to the tissues and back, thus achieving continuous supply of oxygen and nutrients, removal of waste products, and – when needed – delivery of leukocytes to the organs. In one overall circulation cycle, the heart is passed two times in order to pump the blood through the other tissues and lungs (see chapter "Overview" under part "Heart"). Starting in the left ventricle of the heart, oxygenated blood flows into the systemic circulation through the aorta, and then into the large conduit arteries, which subsequently divide into smaller conduit arteries, resistance arteries, and the microcirculation. There, arterioles branch out into capillaries, the smallest blood vessels and site of solute and gas exchange. Capillaries merge into venules, and those merge into veins, conducting the blood toward the right heart. From the right heart, blood flows into the pulmonary artery to enter the pulmonary circulation, where it is reoxygenated. The blood then returns to the left heart.

All large blood vessels are composed of three layers: the tunica intima, tunica media, and tunica adventitia. The intima of healthy arteries is mainly a continuous layer of endothelial cells (ECs), which prevents intravascular clotting of the blood, regulates fluid and solute transport from the blood to the tissues and back, and controls leukocyte recruitment and vascular tone [1]. The media consists of multiple layers of smooth muscle cells (SMCs) embedded in collagen, alternated by layers of elastin. The adventitia is a loose fibrous tissue that contains fibroblasts as well as small vessels (*vasa vasorum*) that nourish the outer cells of large arteries and can harbor leukocytes, mast cells, and mesenchymal stem cells. At its outside, it continues diffusely into a layer of perivascular adipose tissue (PVAT) that provides vasoregulatory adipokines to the arteries and arterioles (Fig. 1). In atherosclerotic arteries, the intima is thickened by accumulation of lipoproteins and lipid-laden cells underneath the endothelium (see chapter "Atherosclerotic heart disease").

The aorta and large arteries are characterized by a thick layer of SMCs in their media, which maintains a rather constant blood pressure. The elasticity (windkessel function) of arteries helps not only to dampen the blood pulse generated by each heart beat but also – by recoil – to continue propelling the blood toward the tissues during diastole.

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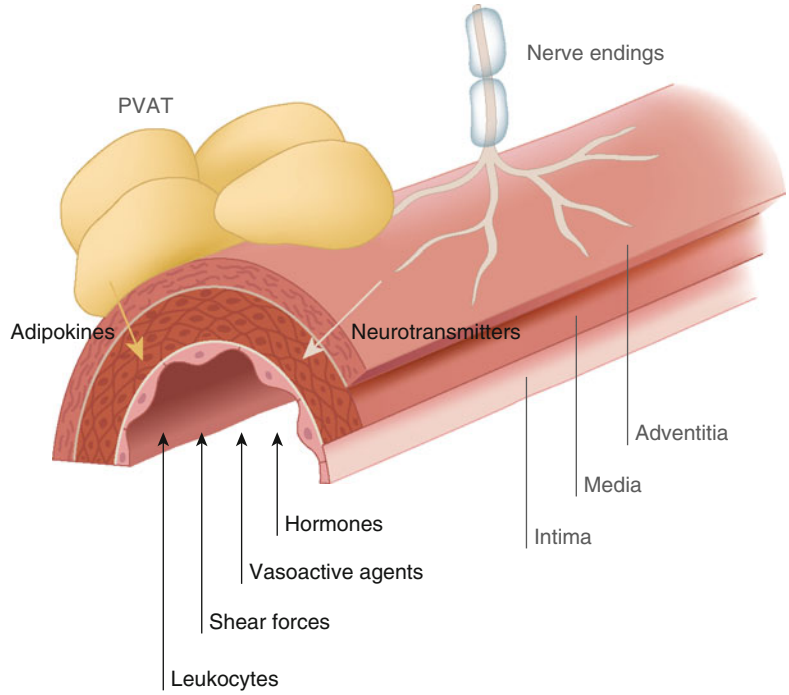

Fig. 1 External mediators acting on blood vessels. The arterial wall consists of three main layers: the intima, which in healthy vessels mainly consists of the endothelium; the media that harbors concentric smooth muscle cells, alternated by collagen and elastin layers; and the adventitia. Many exogenous factors act on the wall of arteries. From the luminal side, hormones and vasoactive agents bind to cellular receptors and regulate the interplay between endothelium and smooth muscle cells; shear forces influence the endothelial behavior; and leukocytes, platelets, and their products also interact with the vessel wall. From the outside, sympathetic nerve endings release neurotransmitters and the perivascular adipose tissue (*PVAT*) releases adipokines that contribute to vasoregulation

The small arteries and arterioles are the major site of resistance to blood flow. The collective diameter of all resistance vessels together is a main determinant of blood pressure (see chapter "Hypertension"), together with cardiac output. In addition to regulation of blood pressure, these "resistance vessels" determine and regulate the perfusion of the connected capillary bed, depending on the local demand, e.g., preferential perfusion through the skeletal muscle during exercise or to the splanchnic bed after meals. Neuronal factors, hormones, and tissue-derived paracrine factors modulate the perfusion of a tissue in order to meet its metabolic demand.

Delivery of oxygen and nutrients as well as removal of waste products occurs in the capillary bed [2], as the surface area of the capillary endothelium available for diffusion is large and transport distance from blood to the tissue is low. In most tissues, the capillary ECs are in contact with pericytes and form a continuous endothelium. However, in specific tissues, such as liver and adrenal glands, they have large pores (so-called fenestrae) to allow rapid penetration of cholesterol-containing lipoproteins required for bile and steroid production, respectively. In contrast, in the brain, a tight endothelial barrier known as the blood-brain barrier is formed by interplay between endothelium, pericytes, and astrocyte foot ends [3]. However, upon a thrombotic stroke, the site distal to the occluded vessel becomes hypoxic and leaky (see chapter "Stroke").

The walls of postcapillary venules, which collect the blood from the capillaries, consist of endothelium only and are the first to respond to vasoactive agents and noxious stimuli by temporarily allowing protein leakage to the interstitium and facilitating the first recruitment of phagocytes after injury or infection.

Walls of veins are considerably thinner than those of arteries, especially their media. Limb veins contain valves, facilitating conduction of the blood back toward the heart despite a low blood pressure. No valves are encountered in the smallest veins, the great collecting veins, and the veins of viscera and the brain. Veins are easily distended and contain the larger portion of blood in the circulatory system. In chronically overdistended veins in the legs, so-called varicose veins (see chapter "Varicose veins"), the valves are no longer competent to sustain blood movement toward the heart, and, subsequently, a higher pressure on the distal valves arises, creating a vicious cycle, eventually resulting in stasis and ankle edema.

Inside-In: Paracrine Signals Acting Within the Vessel

SMC contraction occurs after stimulation of Ca^{2+} influx and subsequent activation of the enzyme myosin light chain (MLC) kinase [4]. The phosphorylated MLC initiates movement of myosin along F-actin fibers leading to cell contraction. MLC phosphatase activity undoes MLC phosphorylation and prevents contraction [4].

Many vasoactive agents, such as norepinephrine and substance P released from neurons (see below) and bradykinin (formed from a blood plasma protein), enhance cytoplasmic Ca^{2+} levels in SMCs leading to contraction, when applied to SMCs in the absence of endothelium. However, when a healthy endothelium is present, these vasoactive agents often also activate the endothelium prompting the generation of nitric oxide (NO) by endothelial NO synthase (eNOS), prostacyclin or prostaglandin E2 via cyclooxygenase, and occasionally endothelium-derived hyperpolarization factor (Fig. 2a). These factors, of which NO is the most potent one, cause "endothelium-dependent" relaxation of SMCs. NO activates guanylate cyclase in SMCs and (the resulting) cGMP activates protein kinase G, which, among others, limits the influx of Ca^{2+} ions into the cytoplasm and subsequent contraction of SMCs [5]. Prostacyclin and prostaglandin E2 cause elevation of cellular cAMP level, which by protein kinase A-mediated phosphorylation and inhibition of myosin light chain kinase (MLCK) also leads to reduced actin-myosin interaction. In contrast, endothelin-1 is secreted by activated endothelium to stimulate vascular contraction (Fig. 2b).

The effects of NO and prostacyclin extend beyond SMC contraction. These mediators also reduce the activation and aggregation of blood platelets (Fig. 2). Furthermore, NO reduces inflammatory activation (see below) in the healthy arterial endothelium itself by interference with nuclear factor κB signaling that is required for the transcription of inflammation-specific genes [6].

SMCs also respond to pressure and radial strain, directly. Prolonged changes in blood pressure can induce remodeling of SMCs and adaptation of the vessel diameter. Another physical factor that affects vascular functioning is vascular stiffening. Calcification due to deposition of calcium phosphate in arteries causes media stiffening in conduit arteries of elderly people, by which the vessel wall becomes less compliant. However, arterial stiffening can also be caused by formation of advanced glycation end products (see chapter "Diabetes mellitus") that cross-link proteins within the vessel wall. Stiffening results in a reduced dampening of the pulse wave and thus a higher pulse pressure. This can promote vascular damage in brain and microvasculature of diabetic patients (see chapter "Diabetes mellitus").

Inside-Out: Vascular Factors Affecting Other Tissues

In addition to local vasoregulation, ECs in specific organs can also affect distant tissues by the conversion and catabolism of vasoactive agents [7]. In particular, the lung vasculature plays an important role through the production of angiotensin-converting enzyme (ACE), which converts angiotensin I into angiotensin II, thus influencing systemic blood pressure and volume via the renin-angiotensin-aldosterone-system (see chapter "Overview" under part "Kidney"). The lung vasculature also inactivates bradykinin, an important vasodilator, and takes up and degrades serotonin, a vasoconstrictor terminating their effects.

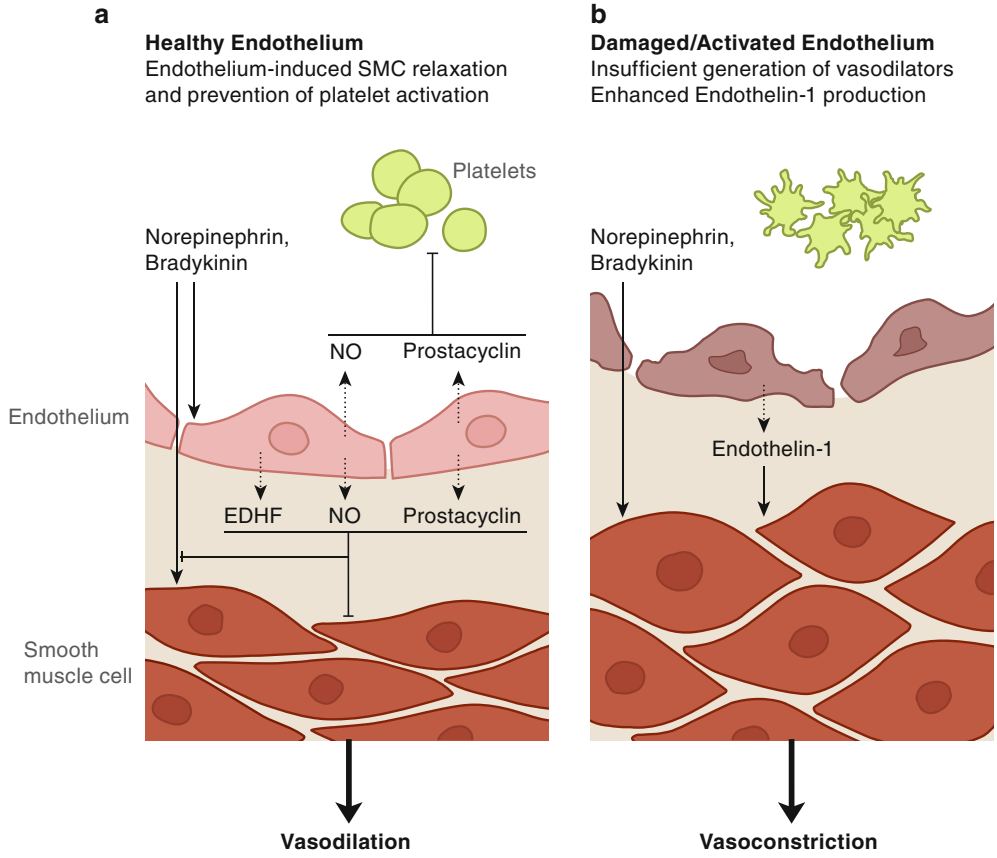

Fig. 2 Paracrine interaction between endothelium and smooth muscle cells. (**a**) After stimulation with vasoactive agents or neural factors (e.g., norepinephrine and bradykinin), the healthy endothelium releases nitric oxide (*NO*), prostacyclin, and endothelium-derived hyperpolarization factor (*EDHF*), which counteract smooth muscle contraction by various intracellular mechanisms and therewith contribute to vasodilation. Prostacyclin and NO also counteract platelet activation. (**b**) In disease, the production of these vasodilating agents can decrease, while production of the protein endothelin-1 can increase. Additionally, direct effects of vasoactive agents on smooth muscle cells are no longer suppressed, inducing vasoconstriction

The endothelium of healthy vessels produces several proteins that prevent thrombus formation (see chapter "Overview" under part "Blood") [8]. It interrupts the coagulation cascade by providing antithrombin III that neutralizes thrombin and by thrombomodulin-facilitated activation of the anticoagulant protein C. It binds a metalloproteinase called ADAMTS13 that proteolytically cleaves von Willebrand factor multimers limiting platelet adhesion and activation. Furthermore, the endothelium reduces platelet activation and aggregation (Fig. 2a). Finally, it releases tissue-type plasminogen activator, a fibrinolysis-catalyzing enzyme. These antithrombotic activities ensure undisturbed circulation. If the balance between pro- and antithrombotic/coagulant factors is disturbed, thrombus formation or bleeding will occur. While thrombus formation is required for limiting blood loss after wounding, it can also lead to adverse events, such as deep vein thrombosis or stroke (see chapter "Stroke").

Inflammatory cells in atherosclerotic vessels (see chapter "Atherosclerotic heart disease") produce cytokines, such as tumor necrosis factor-α (TNF-α), that alter the properties of ECs. This results not only in a reduction of antithrom-

botic properties and activity of eNOS but also in the expression of leukocyte adhesion molecules, such as vascular cell adhesion molecule-1 and E-selectin, as well as chemo- and cytokines, such as monocyte chemotactic protein-1 and interleukin-8 that stimulate influx of various leukocyte types [9]. Moreover, atherosclerotic arteries are associated with a subtle elevation of circulating C-reactive protein, reflecting a weak activation of the acute phase response in the liver (see chapter "Overview" under part "Liver").

Outside-In: Factors from Other Tissues Affecting Conduit and Resistance Vessels

Neural factors, such as norepinephrine and substance P, and hormones, such as epinephrine, insulin, and estrogen, are important regulators of vascular tone (Fig. 1). However, the effect of a specific factor can vary among the vascular beds of different organs because of different receptor isoforms, receptor sensitivities, or tissue-specific receptor distributions. In addition to primary effects on the vasculature, inflammatory cytokines and hypoxia can change gene expression in ECs [9]. Furthermore, shear stress by laminar flowing blood on arterial ECs causes a gene induction pattern within these cells that reduces inflammatory activation, while disturbance of the laminar flow pattern in arteries alters endothelial functioning and contributes to atherosclerotic lesion generation [10].

Hormones have to pass the endothelium to reach tissue cells and usually also act directly on blood vessels. In muscle or heart tissue, insulin has to pass the endothelium, while activating insulin receptors on the endothelium simultaneously. Insulin receptor activation in the proximal resistance vessels of tissues that store nutrients usually causes vasodilation by activation of eNOS via a pathway that involves insulin receptor susbstrate-1, phosphatidylinositol-3-kinase, and Akt (also called protein kinase B). In obesity, this effect is diminished, while endothelin-1 favors vascular contraction. Other hormones also act on blood vessels. For example, estrogens interact with an endothelial membrane-bound estrogen receptor variant, which induces NO production and vasodilation (see chapter "Overview" under part "Reproductive system") [11].

The vessel wall is approached not only from its luminal side by endocrine mediators but also from its outside by products of the surrounding PVAT acting in a paracrine fashion (Fig. 1). In obesity and type 2 diabetes (see chapters "Metabolic syndrome" and "Diabetes mellitus", respectively), PVAT expands and becomes inflamed. While lean PVAT produces adipokines like adiponectin that facilitate vasodilation both in conduit arteries and insulin-stimulated resistance arteries, the expanded fatty PVAT loses this ability and shifts toward the production of nonesterified fatty acids, the pro-inflammatory cytokine TNF-α, leptin, and other factors that favor the contractile pathway induced by insulin [12]. These events affect, for example, the white adipose tissue and illustrate the mutual interrelationship between metabolism, inflammation, and vessel functioning.

Final Remarks

Blood vessels distribute fuel for metabolism, control tissue perfusion by vasoregulation, and deliver tissue products and leukocytes to the sites where they are needed. Being critically important for the organism, blood vessels have a high capacity to adapt to various stresses and local needs. This can occur by short-term responses, such as acute adaptation of the vessel tone or release of factors that contribute to hemostasis, or by the induction of new genes, as in inflammation or hypoxia. Normally, this response is temporary. However, this adaptability can be overstretched by chronic activation or injury, leading to chronic or acute adverse responses. Within the book, three frequently encountered clinically relevant blood vessel-based diseases are covered: atherosclerosis (see chapter "Atherosclerotic heart disease"), stroke (see chapter "Stroke"), and varicose veins (see chapter "Varicose veins").

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