MICROCIRCULATION

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Contents

Summary

Microcirculation represents the smallest functional unit of the vascular system. Microvessels are directly surrounded by the tissue and parenchymal cells to which they supply nutrients and from which they collect metabolites. This region of the circulation includes the arterioles, blood capillaries, and venules, as well as the lymphatic capillaries and interstitial spaces. There are numerous factors controlling microcirculation through changes in the diameter of microvessels. Local control (myogenic, metabolic, shear stress) allows the matching of blood flow to tissue needs. The major function of neural control is to maintain systemic blood pressure by altering vascular resistance and capacitance. So in microcirculation there are two opposing control systems: local control, which aims to maintain blood flow at the level necessary

for optimal function of each of the organs, and neural control, which may restrict blood supply to the tissue, especially to less essential organs, in order to increase blood supply to organs essential for survival of the body.

The exchange of materials between the blood and the tissue occurs throughout the microvascular bed: for example, significant amounts of oxygen pass from blood to the tissues though the arteriolar wall. However the capillaries are best designed for the exchange process, with their large surface area, thin walls, and high permeability; thus they are primary area of exchange of nutrients, hormones, and wastes.

There is a great diversity in the microvascular organization of different organs as well as in the effectiveness of local and neurohormonal control mechanisms; even within consecutive sections of the same microvascular tree a very large heterogeneity is clearly observed in respect to the regulatory mechanisms.

During the 1990s there were considerable advances in our general knowledge of vesicular transport, of transendothelial exclusive water channels, of the role of glycocalyx in transcapillary exchange, and of some particular control mechanisms. The microcirculation is one of the sites in which diseases manifest themselves at an early stage. A great variety of diseases are inseparably linked to microvascular disorders. This field is rich with problems of high significance. The current trends in microvascular researches are in understanding the molecular basis of microcirculatory events; in investigation of the complex interactions between the multiple control mechanisms involved, including second messenger systems; and in studying the pathophysiology of microcirculation that can give a unique perspective on the disease process, providing the link between fundamental research and clinical and molecular medicine. This research field is under vigorous investigation.

1. Introduction

The term “microcirculation“ is the collective name of the smallest channels of the cardiovascular system: the arterioles, the capillaries, and the venules, as well as the lymphatic capillaries and the interstitial spaces. It is also often called the “microvascular bed.” Each component of the microcirculation has its own characteristic structure and function. So there are a variety of patterns of microvascular beds dictated primarily by the function of the tissues that they serve.

In broad operational terms, the purpose of the microcirculation is to deliver blood (oxygen and nutrients) to the parenchymal cells of the body in accordance with their metabolic activity and to remove metabolic waste products. Because parenchymatous organs differ in structure and display a range of activities, their microcirculation differs greatly. Nevertheless, there are certain common organizational and functional features. These common features of microcirculation, including structure, function, control mechanisms, and transmicrovascular exchange will be briefly outlined in this article, and some remarks on the role of microcirculation in a number of diseases will be presented.

2. Classification and Structure of Microvessels

Small arteries entering tissue branch into the arterioles, which form a network of capillaries that are drained by venules. Microvessels can be defined as vessels less than 300 μm in diameter. The arterioles more than 100–150 μm have 4–6 layers of smooth muscle cells. They decrease in diameter progressively up to 30–50 μm where they have a continuous single layer of smooth muscle cells and are called "terminal arterioles." Smaller side branches of the terminal arterioles exhibit discontinuous contractile muscle elements in the wall and are identified as "metarterioles." The distal portion of the metarteriole without muscle and receiving tributaries from the adjacent capillary net is called the "preferential channel" or "thoroughfare channel." These microvascular structures are considered as microscopic shunts. The last smooth muscle cell (or group of cells) on a terminal arteriole, which determines blood flow through the capillaries as well as the number of open capillaries, is termed "the precapillary sphincter." Precapillary sphincters have a contractile activity of a myogenic nature and are almost completely devoid of direct control by the autonomic nervous system; local factors are primary in controlling their contractile activity, and they do not contribute significantly to the regulation of peripheral resistance that participates in determining systemic blood pressure.

In a number of tissues (for example, the skin and liver) there are arteriovenous anastomoses (or shunts) representing direct connections between arterioles and venules, which allow arterial blood to enter the venous circulation without passing through exchange vessels. These short unbranched anatomic shunts have a good muscle coat and a dense sympathetic innervation.

The blood capillaries are the smallest ramifications of the arterioles, with an inner diameter of 5–10 μm and a wall consisting of endothelium, basement membrane (or basal lamina) and a few pericytes. The exchange of materials between the blood and tissues occurs primarily at the capillaries. There are basically three types of capillary based on their ultrastructure: continuous, fenestrated, and discontinuous. The continuous capillaries are the most common type and are found in skeletal and cardiac muscle, skin, connective tissue, lungs, and the nervous system. The endothelium and basal lamina are of the continuous type. Endothelial cells contact each other at junctional areas, mostly tight junctions, and contain plasmalemmal vesicles and transendothelial channels, which are pathways for transcapillary exchange. Basal lamina may split to enclose the pericytes. The fenestrated capillaries have endothelial cells containing openings or pores (fenestrae) with an average diameter of about 60–80 nm. These pores are usually closed by a diaphragm or may be an open channel across the endothelial cell. The fenestrae facilitate transendothelial exchange by increasing permeability. These capillaries are found in connective tissue, intestines, glands, and the kidneys. The discontinuous capillaries (sinusoids) have wide lumens, large gaps between the endothelial cells, or large pores in the endothelial cell itself. Basal lamina are either discontinuous or absent. These capillaries are present in the liver, spleen, and bone marrow. The large holes allow large molecules and even erythrocytes to escape from the blood stream.

The endothelial tube of the capillaries continues as an endothelial tube of venules, in which all endothelial cells have a continuous cytoplasm with a varying numbers of cytoplasmic vesicles. Venules are usually divided into five basic subgroups: venous capillary, 5–8 μm in diameter with occasional pericytes around the endothelium and

basement membrane, devoid of smooth muscle cells; postcapillary venules, 8–30 μm in diameter with an increased number of pericytes and fibroblasts; collecting venules, 30–50 μm in size with a complete layer of pericytes and fibroblasts; muscular venules, 50–150 μm in size with one or two layers of smooth muscle cells; and small collecting veins, 150–300 μm in size with a number of layers of smooth muscle cells, intervening bundles of collagen, and elastic membranes. One of the most characteristic properties of venules is their relatively high permeability for large molecules as well as their high sensitivity to a number of vasoactive substances.

From the functional point of view, the arterioles are the major regulators of the local blood flow and total peripheral resistance. The terminal arterioles and precapillary sphincters are the major determinants of a number of open (perfused) capillaries and hence the total capillary surface area available for exchange. The venules not only drain the capillary bed but also perform the capacitance function and are an important site for fluid and macromolecular exchange. By modulating the pre-to-postcapillary resistance ratio, the arterioles and venules are able to control effectively the mean capillary hydrostatic pressure and hence, transcapillary exchange.

3. Control of Microcirculation

3.1. General Considerations

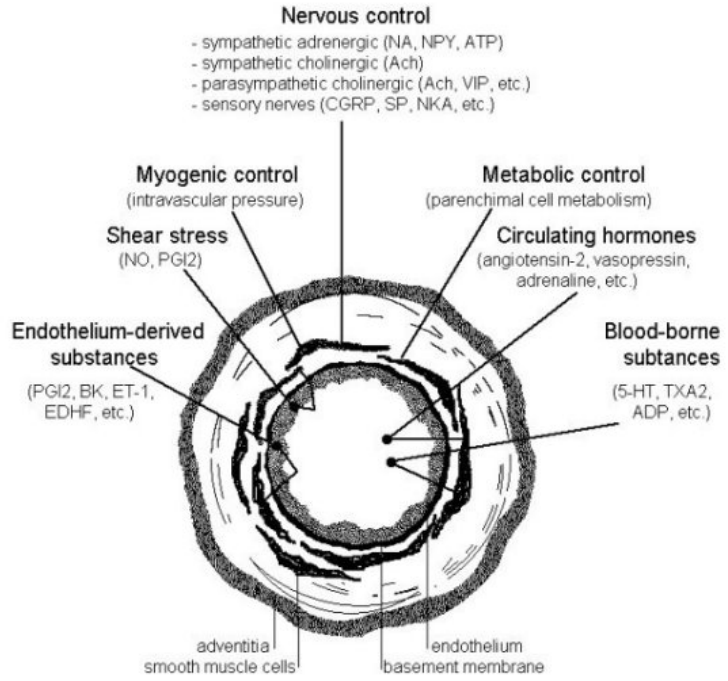

Figure 1. Various factors affecting microvascular tone (see text for abbreviations and explanations)

The factors that control microcirculation through changes in diameter of microvessels are myogenic, metabolic, humoral, and neural. Local control (myogenic, metabolic), which occurs in the microvasculation, allows the matching of blood flow to tissue needs.

The major function of neural control is to maintain systemic blood pressure by altering vascular resistance and capacitance (through changes in venous return to the heart). So in microcirculation there are two opposing control systems: local control, which aims to maintain blood flow at the level necessary for optimal function of each of the organs, and neural control, which may restrict blood supply to the tissues. The effectiveness of neural mechanisms varies greatly from organ to organ. Blood flow to less essential organs may be temporarily reduced through neural control in order to increase blood supply to organs essential for survival of the body. The effectiveness of local mechanisms also varies greatly in different organs. Redistribution of cardiac output is achieved through the integration of local and neural mechanisms. The predominant effect on the organ blood flow depends on the intensity of stimuli of each controlling factor and its particular effectiveness in the various organs. Various factors affecting microvascular tone are summarized in Figure 1.

3.2. Local Control

3.2.1. Myogenic Control

About a century ago, Bayliss was the first to demonstrate that distension of blood vessels produces the contraction of smooth muscle cells in the vessel wall. According to the myogenic hypothesis an increase in the luminal pressure causes vascular constriction, whereas a decrease in pressure evokes partial relaxation of the blood vessels. This effect (which is known as “the Bayliss effect”) is endothelium-independent and can be seen even under conditions of no innervation or exposure to blood-borne vasoactive agents. Thus it is myogenic in nature.

This intrinsic property of smooth muscle cells is more prominent in arterioles of about 50–100 μm. Myogenic responses may play a critical role in determining the basal microvascular tone, and represent an important mechanism of autoregulation of capillary hydrostatic pressure, keeping it within a physiological level.

Microvascular pressure is one of the determinant factors for transmicrovascular fluid and substrate exchange. An excessive increase in pressure may result in tissue oedema, while too low pressure may impair the nutrient supply to the parenchymal cells.

The mechanisms of the myogenic response have not yet been fully established; however, great progress has been achieved. The recent data in this respect are summarized in Figure 2.

A sustained rise of intracellular Ca^{2+} is related to myogenic responses and smooth muscle contraction (Figure 2A), hyperpolarization being a compensatory mechanism (Figure 2B).

Although the sensor for the microvascular pressure has not yet been identified, a mechanosensitive (stretch-activated) nonselective cation channel, phospholipase C, and protein kinase C (Figure 2) are among the possible mediators for myogenic responses.

3.2.2. Metabolic Control

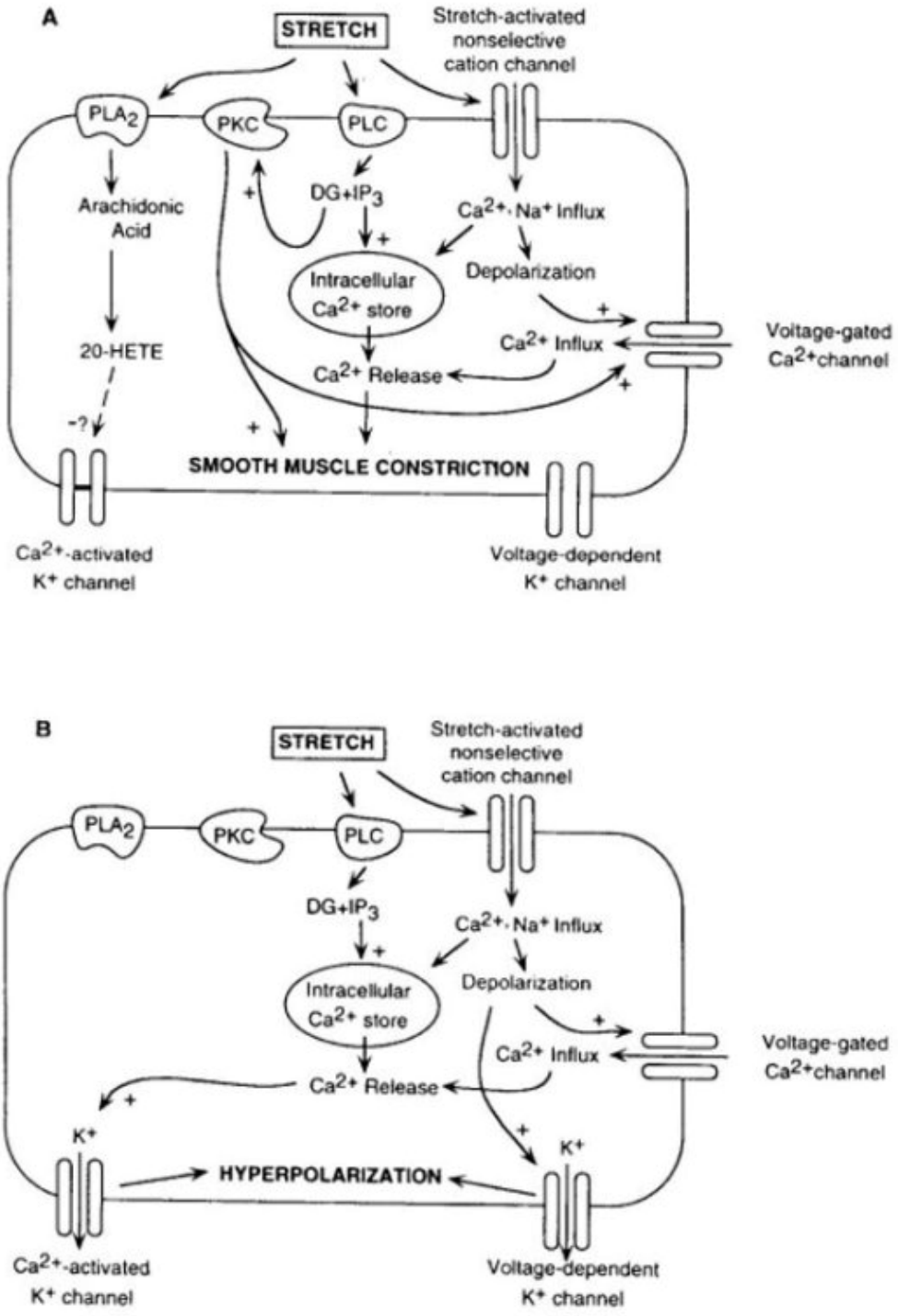

Figure 2. Schematic illustrations for the possible mechanisms of the myogenic constriction of microvessel (A) and its compensatory mechanisms (B) Abbreviations: PLC – phospholipase C; PLA_2 – phospholipase A_2; PKC – protein kinase C; DG – diacylglycerol; 20-HETE – 20-hydroxyeicosatetrenoic acid; IP_3 – inositol triphosphate. Source: Komaru, Kanatsuka and Shirato (2000), reproduced by permission.

Most metabolites produced by the parenchymal cells have a potent vasodilatory property. Metabolite production is an important coupling mechanism between the tissue needs and blood supply. An increase in the amount of metabolites can result from an increase in tissue activity or a decrease in the blood supply to the tissue. The accumulation of metabolic by-products around the microvessels causes their dilatation and an increase or restoration of blood flow through the capillary network, resulting in an increased delivery of oxygen and removal of metabolites. This will allow blood flow to reach a new level, matching the tissue needs.

The metabolic control of blood flow is independent of extrinsic innervation and even enables the tissue to oppose the vasoconstrictor effects of the sympathetic nervous system. Many substances resulting from an increased metabolic rate have been proposed as principal mediators of metabolic vasodilatation.

They include oxygen, carbon dioxide, hydrogen ions, potassium, phosphate, adenine nucleotides, adenosine, lactate, kinins, prostaglandins, hyperosmolarity, and some vasoactive polypeptides. None of them can completely account for metabolic vasodilatation in any tissue. For this reason multiple factor hypotheses have been developed, usually with one or two factors dominant (different in various tissues), which can better account for metabolic vasodilatation.

3.2.3. Flow-Induced Vasodilation

If perpendicular stress caused by intraluminal pressure leads to stretching of the vascular wall followed by myogenic responses, the other physical force – shear stress – acts on the endothelium in the longitudinal direction, due to friction between the blood stream and endothelium. Twenty years ago, one of the 1998 Nobel winners, Robert Furchgott, with his coworker discovered an endothelium-derived relaxing factor, subsequently identified as nitric oxide (NO), the first representative of a new class (gaseous) of signaling molecules. As was further demonstrated by another 1998 Nobel winner, Louis Ignarro, a simple free radical NO is formed from the amino acid L-arginine by endothelial NO synthase in a calcium-, calmodulin-, and NADPH-dependent manner. Penetrating rapidly into smooth muscle cells, NO evokes vasodilatation via stimulation of the enzyme soluble guanylate cyclase and formation of cyclic guanosine monophosphate (GMP) from GTP. Shear stress is a potent physiological stimulus for NO release, and the basal NO release by shear stress exerts a continuous inhibition of vascular tone opposing the tonic vasoconstrictor effect of the sympathetic nerves. The vasoconstrictor effects of noradrenaline, serotonin, vasopressin, angiotensin-II, and endothelin are also opposed by the NO system.

Endothelium-derived NO is the most potent endogenous vasodilator known. However, there is great heterogeneity from one vascular bed to another in the production and vasodilatory potency of NO. In general, endothelium-dependent relaxations are more prominent in arteries than in veins. Even among arterial microvessels the magnitude of flow-induced dilatation is heterogeneous. For instance, in coronary macrovasculature, arterioles 80–130 μm in diameter are much more sensitive to shear stress than arterioles of other sizes. Not only is NO a potent vasodilator, it also inhibits platelet adherence and aggregation, reduces adherence of leukocytes to the endothelium, and suppresses

proliferation of vascular smooth muscle cells. A number of disorders are closely associated with impaired endothelial production of NO, including atherosclerosis, hypertension, diabetes mellitus, and thrombosis. Mechanoreceptors through which endothelial cells sense shear stress and transform the appropriate signal into the biochemical cascade have not yet been identified.

3.2.4. Autoregulation

Perturbations in systemic blood pressure lead to corresponding changes in blood flow and microvascular pressure, which in many organs are compensated for by local readjustments so as to restore flow and pressure to control levels. The term “autoregulation” is applied to processes that maintain a constant microvascular blood flow (and also intracapillary hydrostatic pressure) in the face of changes in perfusion pressure. Although the sympathetic nervous system may modulate the range of pressure over which an organ may autoregulate, the presence of the sympathetic nerves is not necessary for this phenomenon to occur. The combined effects of myogenic and metabolic control mechanisms are responsible for the phenomenon of autoregulation. Their relative contribution may vary between organs to a degree that can be rather difficult to assess. When arterial pressure is reduced, flow decreases, and at the same time microvascular pressure falls, so that either of these mechanisms would be expected to cause vasodilation. If, however, venous pressure is elevated, the two mechanisms are put into opposition, because microvascular pressure rises, favoring a myogenic constriction, while blood flow falls, favoring a metabolic vasodilation.

Autoregulation has been reported in most organs and tissues of the body. However, the magnitude of autoregulation varies greatly from organ to organ. In the skeletal muscle, capillary blood flow remains relatively constant over a mean arterial pressure range of 8–17.3 kPa (60–130 mmHg). Blood flow in the kidney is essentially independent of the arterial pressure over a substantial pressure range.

Also, the coronary vascular bed has good autoregulatory control between arterial pressures of 8 and 25.3 kPa (60 and 190 mmHg). The autoregulatory capability of the gastrointestinal circulation is less pronounced; however, in the villus vessels a relatively constant blood flow can be seen over a perfusion pressure range of 13.3–4 kPa (100–30 mmHg). Flow autoregulation is very limited in the cutaneus vasculature and almost absent in the lungs. Autoregulation is an important defense mechanism for the prevention of both tissue ischemia and oedema formation.

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Biographical Sketch

Sergey A. Polenov, M.D., D.M.Sc., was born in 1941 in Leningrad. He studied from 1959–1962 at the Institute of Physical Culture and Sport, St. Petersburg, and from 1962–1967 at the First Pavlov Medical Institute, St. Petersburg, gaining his M.D. in 1967. From 1967–1987 he was at the Laboratory of

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He has received recent long-term research grants from the International Science Foundation (ISF) (USA, 1994-1995), Russian Foundation for Basic Research (RFBR) (Russia, 1995–1997, 1999–2000, 2000–2002), Civilian Research and Development Foundation (CRDF) (USA, 1996–1998), ASGL-Research Laboratories (Russia, 1999–2000), and INTernational ASsociation (INTAS) (EC, 2001–2003), for research into physiology, pathophysiology, and experimental medicine. He has been a member of the Physiological Society of the USSR (Russia) since 1970 and of the International Society for Autonomic Neuroscience since 1998. He has produced 160 publications including 60 abstracts and 15 books, book chapters, or reviews.