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# A short review on the vascular endothelial surface layer

## Abstract

The established knowledge concerned with the vascular wall lack the functional detailed evidence of the Endothelial layer function. Latest studies confirmed the importance of vascular endothelial layer mainly in capillaries circulation that lack the presence of middle smooth muscles layer. In this short review we confirm the importance of the vascular endothelial layer in the homeostatic function including oxygen and carbon-dioxide transfer as well as maintaining hydro-static pressure, maintaining the acid base balance, absorption of nutrients and extraction of wastes.

Volume 13 Issue 3 - 2025

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**Received:** August 18, 2025 | **Published:** October 10, 2025

## Introduction

The walls of arteries and veins consist of three distinct layers. Starting from the inner lumen, the layers are: The Tunica intima, the Tunica Media, and the Tunica Externa. Arterial and venous blood flow contacts the endothelium lined by a Glycocalyx, which is a gel-like layer of glycoproteins and polysaccharides on the luminal surface. the Glycocalyx-lined tunica intima, is the only layer that forms the capillary wall, Capillaries are unique because they lack the outer tunica media and tunica adventitia found in larger blood vessels, making their wall extremely thin to facilitate the necessary exchange of substances between the blood and surrounding tissues, Glycolcalyx, composed of macromolcules, reaching a thickness of tens of nanometers . Within it, there are numerous prolongations that passes nerves impulses to the underlying intermediate smooth muscle layer in arteries and veins. This layer is followed by a vascular endothelial layer, ranging in thickness from 0.5 to 1.00 microns. These messages trigger acute and chronic responses in the vascular wall through the interaction of smooth muscle, which is responsible for vasoconstriction, dilation, and remodeling as required by blood flow to them. The role of Glycolcalyx membrane layer is to facilitate the movement of blood flow, which consists of plasma, red and white blood cells, platelets, and various large molecules.

The vascular endothelial layer provides a large surface area for the exchange of substances carried in the bloodstream and the tissues as it passes through. It plays a critical role in many other vital processes, including blood flow regulation, inflammatory responses, and blood coagulation. The middle layer extends deep to the intima, consisting of vascular smooth muscle cells, elastic lamellae separate the endothelial cells from the smooth muscle cells, with mayo epithelial junctions located across structural openings in the middle layer. In this study, we review the relationship of these components to blood flow and the physiological mechanism that controls this function.

## Evidence for the existence of (Glycocalyx)

Information derived from microscopic histological anatomical studies indicates that the area of the human endothelium is estimated at 350 square meters, and the weight of this endothelial mass is estimated at approximately 110 grams. This endothelium is not inert or merely a physical barrier between the bloodstream and the arterial lining. Rather, it performs numerous vital functions, such as regulating vascular tone, regulating the exchange of salts and electrolytes, hemostasis, coagulation, and inflammatory responses. These functions depend precisely on the physical and chemical state of the vascular endothelium and its interaction with the bloodstream. This layer is called the glycocalyx and is composed of polysaccharides that protrude from the endothelial cell body as microscopic extensions composed mainly of glycoproteins and proteoglycans, carrying a negative electrostatic charge and having penetrating and mechanical sensory transmission activities between cells in the blood vessel walls. The glycocalyx separates the blood flow within the lumen of the vessels from the endothelial cell layer. Its components, including Sialic acid, Glycan-1, Heparan Sulfate, and Hyaluronan, contribute to the transmission of mechanical sensation generated by the friction of red blood cells generated by the parallel longitudinal blood layer lamellae within the blood flow, as microscopic extensions composed mainly of glycoproteins and proteoglycans, carrying a negative electrostatic charge (Figure 1).

**Figure 1** Electron microscopic section of a blood vessel showing the Glycocalyx layer.

## The theory of the existence of (Glycocalyx) as an acellular endothelial layer lining the vessel walls

Advanced studies indicate the presence of very fine, transparent fibers resulting from desquamation of the vascular endothelial layer. Electron microscopy has demonstrated the presence of a thin, irregular capillary layer up to 20 nanometers thick, appearing as a fluffy, cotton-like layer. Further research has demonstrated that this superficial vascular endothelial layer is the stable plasma layer composed of interconnected molecules consisting of proteoglycans and glycoproteins, which has been called the Glycocalyx (Figure 2).

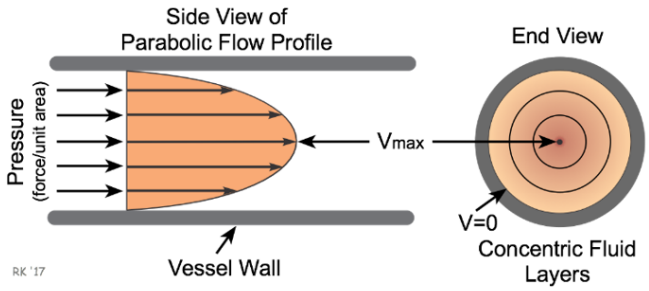


**Figure 2** A longitudinal and transverse section showing the layers of blood flow and explaining the mechanism of friction between the layers of laminar blood flow.

Thus, blood vessels, arterioles, and capillaries are covered with a very fine fibrin capillary layer of Glycocalyx, with an average thickness of up to 110 nanometers, in the form of spaces separated by gaps with a diameter of up to 50 nanometers, and crossed by fibrin capillary bridges of varying lengths, composed of fine molecules that hang across the vascular lumen. The total thickness of these layers reaches more than 200 nanometers. Electron microscopic studies have also proven the presence of fibrin plugs, which include fibrin capillaries, the number of which ranges between 20 and 40 fibrin capillaries per fibrin plug, and their lengths reach 350 nanometers. They appear to perform the function of closing the fine pores in the lining of vessels, which are microscopically covered with the glycocalyx membrane, and between them are molecules of glycolipids and molecules of proteoglycans and glycoproteins that carry electrical charges. Negative. The functions of the vascular endothelium are manifested by inflammatory reactions, thrombosis, and fibrinous thrombosis, which may have immunological or genetic biochemical relationships. Glycosylcholine plays a vital role in thrombotic conditions due to the presence of heparan sulfate in the vascular endothelial layer. This compound consists of protein-like sugar chains called heparan sulfate glycoproteins (Figure 3), and is released from the vascular endothelium under the stimulation of active phospholipase enzymes.

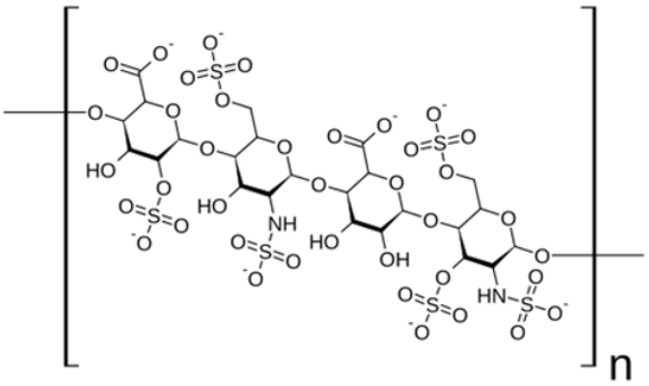


**Figure 3** The biophysical function of the endothelial vascular layer.

## The endothelial Glycocalyx

Heparan sulfate glycoprotein also participates in regulating vascular permeability and modulating inflammatory responses, including the activity of red and white blood cells. The results of Glycocalyx activity include the generation of nitric oxide, which stimulates vasodilation, facilitating blood flow through the vessels, and the extravasation of plasma and blood cells into the interstitial spaces between cells. Through its structural structure and negative charge, Glycocalyx prevents large molecules weighing more than 70 k Da from leaking out of the vascular endothelium. The physical resistance of the vascular endothelium increases as the blood flow approaches the capillaries and their lining, leading to a slowdown in capillary flow. Depending on the differential pressure, fluids migrate out of the arterial capillaries in response to the hydrostatic pressure generated by systolic arterial tension (cardiac origin) versus the resistance of the capillary endothelium, which gradually thins toward the periphery. This explains the occurrence of microscopic cracks and fissures that lead to the migration of plasma and blood cells through the endothelial cell layer and the gradual metabolic inflammatory reaction in the vessel walls (arterioles), as these represent foreign bodies within the vascular layers, which can develop with age into vascular sclerosis (Figure 4). By the same mechanism, it also prevents the infiltration of pathogens such as bacteria, viruses, and cancer cells. Hence, the endothelial glycocalyx undergoes a continuous resorption and renewal process, and this process continues automatically unless the glycocalyx is exposed to some disturbances that disrupt the physiological balance, such as in cases of atherosclerosis through the vascular endothelium, which ends in manifestations of atherosclerosis following vascular aging, and thus increased arterial pressure following the increased stiffness of the vessel walls associated with aging. The vascular endothelial layer may also be exposed to diabetic vasculopathy and the spread of cancer cells through it.

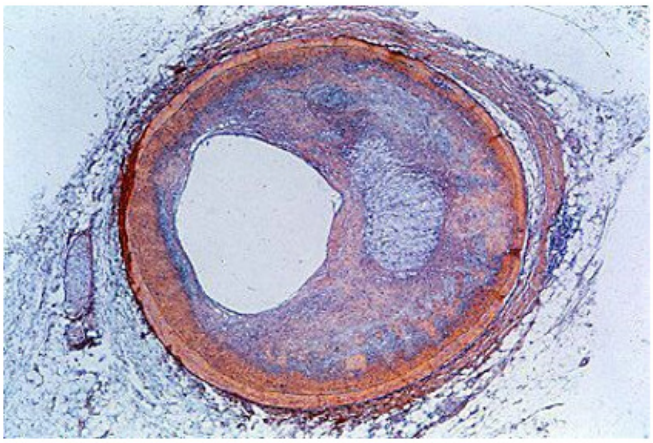

**Figure 4** Formation of atherosclerotic plaques within the vascular endothelium.

## Glycocalyx structure

It is well established that the endothelial Glycocalyx plays a pivotal role in blood vessel function, particularly in the mammalian cardiovascular system. The vessels that transport blood throughout the body can be divided into three distinct main chambers: the arterial chamber, the capillary chamber, and the venous chamber (Figure 5). Each chamber has a distinct physiological function. The role of the arteries is to transport blood and metabolites to successive capillary chambers, where most metabolites and components are exchanged between the blood and tissues. The venous circulation then receives the blood and metabolites and delivers them to the right heart to be pumped into a subsequent cycle.

Arterial currents are exposed to internal rheological pressures resulting from the friction of the graded layers of liquid plaques that make up the blood flow, whose speeds increase within the vessel from the periphery to the center, such that the speed of the central plaques exceeds the speed of the frustrating plaques, ending at the

Glycocalyx layer lining the vessel lining. This is accompanied by a clear slowdown in the speed of the arterial side at its ends (the arterial chamber) until it reaches the capillary circulation in the capillary chamber. The hydrostatic pressure values at the end of the arterial phase reach 32 mmHg, which explains the stability of the arterial flow from the center (the heart) to the periphery (the distal end of the arterial phase 32 mmHg). This pressure remains higher than the pressure within (the capillary chamber) 25 mmHg, which allows room for the displacement of arterial flow fluids through the capillary chamber to the interstitial space, depending on the effectiveness of the hydrostatic pressure, which will lead to physical filtration of the water and ion components outside the capillary chamber towards the surrounding interstitial tissue. This includes the effectiveness of Albumin, which does not leave the capillary chamber, and which maintains the effectiveness of the osmotic pressure within the capillary chamber at a level of 25 mmHg, which is higher than that in the venous chamber (12 mmHg), which is associated with the presence of Albumin, which stimulates the path of venous return flow towards the center (right heart) (Figure 6).

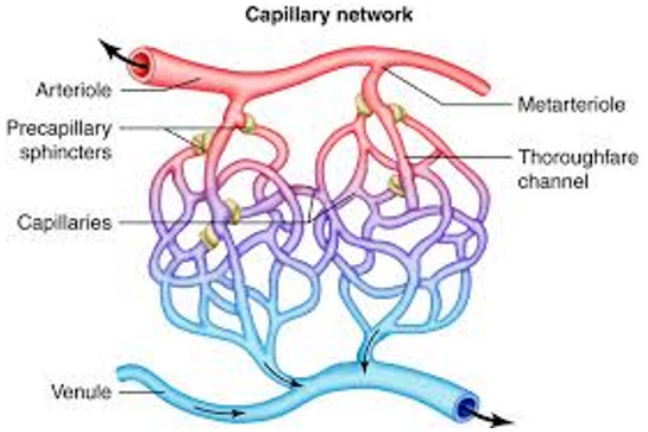


**Figure 5** Delineation of the capillary chambers.

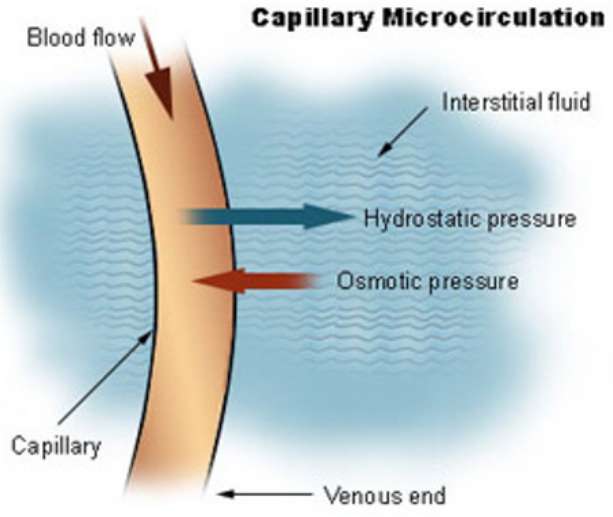


**Figure 6** Microscopic capillary circulation.

It is also expected that there will be differences in the shape and function of the endothelial Glycocalyx within the arterial circulation. This is related to the geometry associated with the distribution of arteries, as the Glycocalyx layer following the endothelium of the arteries at the arterial branches is exposed to direct pressure on the vascular endothelium, which ends in cracking and fissures in the arterial endothelium in the branching areas, leading to the displacement of some components of the blood flow, such as red blood cells, platelets, white blood cells, and various lipids (triglycerides / LDL / HDL), which play the role of foreign bodies if they leak through the vascular endothelium, generating physio pathological inflammatory reactions, which ultimately leads to the occurrence of atherosclerosis as a final result of these microscopic bruises, which will end, according to time, genetics, and other factors predisposing to the occurrence of stenosis of different locations and diameters within the arterial vascular tree, which physically leads to the occurrence of disorder and irregularity in the shape of the arterial flow.

## Regulation of arterial diameters

The medial layer of the arterial wall is primarily responsible for regulating arterial diameter. This is achieved through the contraction and relaxation of smooth muscle fibers. The combined activity of smooth muscle fibers results in vasodilation, vasoconstriction, and regular blood flow, synchronized with the heartbeat. The outer layer of blood vessels consists of collagen-rich connective tissue containing fibroblasts and vascular nerves. Its function is to support the growth and repair of arterial walls. Additional evidence suggests that it plays an important role in immune surveillance and migration of inflammatory cells, while also allowing communication between the local tissue environment, smooth muscle cells, and endothelial cells (Figure 7).

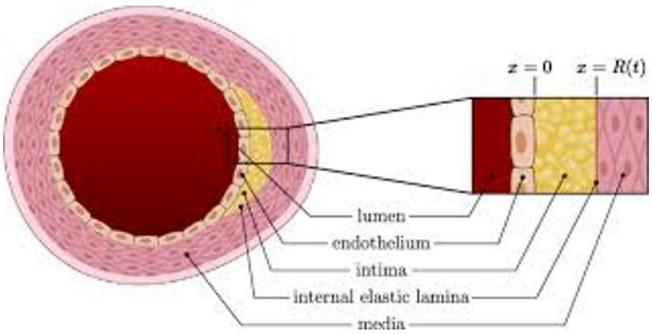


**Figure 7** Cross-section of the entire arterial vessel.

## Endothelial glycolysis and vascular permeability

The physical structure of blood vessels acts as a conduit for the delivery of oxygenated blood to meet the metabolic needs of body tissues. By design, healthy blood vessels continuously leak small molecules/solutes into surrounding tissues. In contrast, larger molecules (over 70 k Da) are prevented from passively moving out of the vessels under non-pathological conditions. Size and electrostatic charge are the two main physical factors regulating the leakage of molecules out of the vessels. The volume barrier depends primarily on the presence or absence of intercellular adherent's junctions and tight junctions at the interface of adjacent endothelial cells (endothelial cells) that line the lumen of the blood vessel. An additional factor contributing to the specific filtration volume of the barrier is the arrangement of extracellular extensions of basement membranes (endothelial glycolysis). Larger blood vessels are assumed to have limited permeability, partly due to their continuous endothelium. In contrast, the microvascular endothelium can be either continuous or discontinuous, with or without fenestrations, depending on the vascular layer. The presence of fenestrations facilitates the exchange of small-diameter molecules and the electrical charges they carry.

Thus, we can understand the mechanism of fluid movement through blood vessels based on Starling's principle and vascular fluid dynamics, and by understanding the balance between the total pressures that push fluid out of the vessel and those that re-enter the vessel. It has been established that the forces that push fluid out of the vessel are hydrostatic pressures within the lumen, while the force that opposes fluid displacement outside the lumen is the osmotic pressure resulting from the constant amount of albumin present in the vessel lumen. In this model, net forces on the arterial side push fluid outward through the inter capillary spaces, while fluid is forced back into the blood vessels (venous chambers) by the osmotic pressure caused by albumin within the blood fluid, which prevents it from leaving the tubule in all its chambers. The pressure within the venous chamber is maintained so as to effectively attract fluid into the venous chamber, keeping the pressure within the chamber at a constant level of 12 mm Hg. Between the pressures within the arterial and venous chambers, the pressures within the interstitial fluid (extra vascular) are physically aligned between the arterial and venous sides. The role of the Glycocalyx is to transport cells, proteins, and nutrients across the endothelial barrier through regulated processes. The extra vasation of immune cells outside the blood chambers is a specific receptor-mediated process in response to a local inflammatory response that induces leukocyte permeability, thus allowing immune cells to bind to the endothelium and infiltrate inflammatory tissues in general.

### Atherosclerosis

Atherosclerotic lesions are caused by the deposition of cholesterol-rich fatty materials within the walls of blood vessels, triggering an inflammatory response that leads to the formation of vascular lesions. These plaques, in turn, connect with each other over time, leading to microscopic tears in the arterial lining. This is followed by the accumulation of platelets and red blood cells that infiltrate beneath and on the surface of the vascular lining, leading to narrowing of the arterial lumen and impaired blood flow. One of the first steps believed to play a role in the development of atherosclerosis is the deterioration of the endothelial Glycocalyx structure within blood vessels. This deterioration is often caused by aging, genetic factors, and anatomical factors, as seen in areas of large vascular branches, such as the abdominal aorta, the common carotid artery, and other anatomical areas of the body. Among the consequences of atherosclerosis is increased blood pressure, the severity of which is further enhanced by genetic factors and various functional disorders.

### Sepsis

Local infections lead to a local inflammatory state, which may be followed by a systemic inflammatory state resulting from exposure to an infectious agent. This can result in a local inflammatory state or lead to septic shock and multi-organ failure in response to the direct release of cytokines resulting from the inflammatory response, or from a secondary infection resulting from immunosuppression in response to cytokine release. Sepsis is characterized by increased vascular permeability, which in turn leads to the leakage of proteins and molecules from the fluid phase of the blood. The resulting change in the concentration of solutes from within the lumen into the surrounding tissues leads to a decrease in osmotic pressure (colloid osmotic pressure), leading to decreased water absorption within the fluid phase, a major factor in sepsis-induced organ failure. The mechanism of edema caused by sepsis is thought to be due to increased vascular permeability resulting from the breakdown of the endothelial Glycocalyx.

## Conclusion

The endothelial Glycocalyx plays a pivotal role in maintaining vascular health by regulating its permeability and mechanical capacity, mitigating intercellular friction, and facilitating nitric oxide production. Furthermore, these processes work in tandem to maintain vascular homeostasis and act as a barrier against inflammation, a major cause of the development and progression of cardiovascular disease.

## Acknowledgements

None.

## Conflicts of interest

The authors declare that there are no conflicts of interest.

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