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A Review on Microvascular Hemodynamics: The Control of Blood Flow Distribution, and Tissue Oxygenation

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Introduction – Microcirculation at a glance

The microcirculation is a functionally independent entity which encompasses of arterioles, venules, and capillaries, with diameters that range from 5 μm to 100 μm. The primary goal of the microcirculation is to adjust blood flow to match the changing nutritional needs of parenchymal cells, and to remove byproducts of metabolism. While the primary purpose of the microcirculation is to facilitate the delivery of oxygen and nutrients to the tissues, its endogenous vasomotor activity also influences control of blood perfusion at all levels.

Living organisms have localized organs, such as the brain, lungs, heart, skin, etc. or complex, distributed systems, such as the circulation, nervous system, and immune system. The microcirculation belongs to the latter. The angiogenesis of the microvasculature seems to branch at random, and ultimately becomes a network whose smallest components, the capillaries, have a minimal internal diameter that allows passage of one blood cell. The circulation has a fixed design and structure, while the microcirculation's growth and changes are driven by local tissue factors.[1,2]

One of the principal determinants of microvascular structure is the rate of oxygen consumption. The configuration of blood vessels is optimized to achieve the most efficient blood flow distribution.[3] This optimization manipulates vessel diameter and length to minimize cardiac energy expenditure in order to ensure maximal oxygen delivery and

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removal of metabolic waste from the tissue.[4] The process of angiogenesis is controlled by chemical signals, such as vascular endothelial growth factor (VEGF), which bind to receptors on the surface of normal endothelial cells.[5]

Microcirculation – Arterioles and Venules

The structural integrity of the arteriole and venular vessels are composed of several layers. An inner layer of endothelial cells creates the lumen for the passage of fluids, cells and proteins. A thin sheet of smooth muscle composes the central part of the wall, and connective tissue outer layer that provides an inelastic outer boundary to the blood vessel.[6] The general structure is depicted in figure 1.

The microcirculation diverges into smaller branching points until it reaches the capillary network. The capillary network then converges back into progressively larger diameter vessels, through a network of venules, which are the starting point of the system of veins that returns blood to the heart. Arterioles are configured in two basic branching patterns, a dichotomous tree or arcading tree.[7] In the dichotomous tree, the main branch gives rise to two daughter branches that branch progressively until the capillary level is reached. In the arcading network, branch points can connect with other segments of the same tree, producing a polygonal network. Arcading networks are found in the intestinal mesenteric circulation, skeletal muscle, and the thermoregulatory cutaneous vasculature. Arcading structures are typical of organs that are subjected to significant deformation frequently, that may result in the occlusion of arterioles, in which case the arcading network provides alternative flow pathways for maintaining tissue nutritive flow, regulate temperature and equalizing blood pressure at specific arteriolar vessel size.[8]

The position, size, and configuration of blood vessels in the microcirculation is associated with regulatory functions beyond the simple distribution of flow. The process is centered on oxygen delivery by red blood cells (RBCs), where oxygen release to the tissues is determined by the O_2 affinity of hemoglobin within RBCs, and the local O_2 concentration gradient between RBCs and tissues.[9] As oxygen diffuses through the microvessels, it can diffuse radially to a distance ranging 100μm-200μm.[10] The first level of local regulation is governed by the arterioles, where the predominant cellular component is smooth muscle, they maintains vascular tone via a latch-bridge mechanism, which is a mechanism analogous to a ratchet-like apparatus.[11] The latch-bridge mechanism occurs as a result of Myosin Light Chain ATPase inhibition by phosphatases, thus preventing the hydrolysis of ATP.[12] Arterioles and venules maintain a dynamic state of partial constriction (i.e., vascular tone), regulated by smooth muscle cells (SMCs) which constitute much of the vascular wall. Smooth muscle cells are arranged in multiple layers embedded in a tough and elastic matrix of connective tissue, wrapping around the vessel in a low-pitch spiral, so that, when they shorten, the diameter of the vascular lumen decreases.

The layers of SMCs are separated from the blood by a monolayer of flat, polygonal endothelial cells. As blood flows over the endothelial cell lining, the shear stress applied to the endothelial cells by the flowing blood causes a release of nitric oxide (NO). NO has myogenic properties resulting in vasodilation. NO reacts with guanylyl cyclase in SMCs,

increasing the concentration of guanosine monophosphate (cGMP), and causing a decrease in intracellular calcium resulting in smooth muscle relaxation.[13]

Mechanotransduction and Nitric Oxide Regulation

A major source of NO production occurs as a result of endothelial mechanotransduction. The mechanical stimulus on the endothelial cells from the flowing blood is a potent signal to activate the endothelial derived nitric oxide synthase (eNOS) this is depicted in figure 1. Activation of eNOS results in the production of NO, L-citrulline from L-arginine, and O_2.[14,15] Mechanotransduction is sensitive to blood flow through local vessels, as well as blood viscosity. The greater the shear stress on the endothelial cells results an increase in eNOS production. NO in the vasculature, whether it be in the microcirculation or the macrocirculation, is concentration dependent. As NO stimulates the receptors of this G-protein coupled cascade, the smooth muscle cells become desensitized; NO receptors are endocytosed as the initialization step of the cascade, so the number of NO receptors diminish the rate of endocytosis exceeds the rate of receptor reappearance on the cell surface with increasing concentration.[16] As these receptors become saturated, the NO concentration increases in the lumen of the vessel. Due rapid and irreversible scavenging of NO by hemoglobin (Hb), cell-free Hb can effectively block NO bioactivity, resulting in vasoconstriction.[17–19] Hemoglobin is also known for its involvement in Nitrate Oxide Deoxygenation converting NO to Nitrate (NO_3) and met (ferric) heme when reacted with oxygenated heme.[20–22] Therefore, the NO reactions with Hb is dependent on the redox and ligation state of the heme iron modulated by O_2 levels. However, these reactions are slowed 1000x when the Hb is contained within the protective RBC membrane.[23,24] If not regulated, NO at high concentrations is toxic as it begins to target Aconitase and Cytochrome Oxidase, enzymes used in cellular respiration, thus making this process a natural defense against high concentrations of NO, but at low concentration a whole host of other side effects become apparent.[25,26]

Oxygen Exchange in the Microcirculation

Around 60–70% of the oxygen supply in the tissues occurs as oxygen diffuses through the microcirculation[27–29]. Oxygen is a major driving force for several biochemical processes. A significant amount of the oxygen transport occurs in the larger arterioles,[27–29] this is evident as studies have previously shown hemoglobin oxygen saturation decreased from 69.9% to 56.7% between large and small arterioles and the periarteriolar pO_2 decreased from 35 to 20 mmHg in the same vessels.[29] The continuous branching of the arterioles reduce the arteriole size, and reduces the arteriolar blood oxygen content proportional to the change in cross-sectional area.[30] An approach to understand oxygen delivery and consumption of the tissue, microvascular pO_2 and hemoglobin saturation must be coupled with the microvascular blood flow.[31] Traditional measurements of pO_2 are done using invasive methods such as oxygen-sensitive polarographic microcathodes or phosphorescence quenching microscopy another method that is not as invasive to determine hemoglobin saturation (SO_2) is spectrophotometry of hemoglobin.[32] Regardless of the measurement SO_2 and pO_2 are related via the hill equation so long as the hill coefficient of your oxygen carrier is known.

Microcirculation - Capillaries

As the microvasculature diverges from arterioles to capillaries, vessel diameter continues to decrease ultimately limiting transit to single RBCs. The capillary's inner diameter can be significantly smaller than the RBC diameter (~ 8 μm), particularly in tissues like the spleen and the liver where capillary diameters are as small as 4 – 5 μm, pushing RBC deformability to the extreme. The precise hydraulic radius of capillaries is not well defined due to the presence of the vascular endothelial glycocalyx, a glycoprotein layer that covers the luminal membrane of vascular endothelial cells, and occupies a significant cross-sectional area within the capillaries.[33] The outer structure of capillary is composed by a single layer of vascular endothelial cells supported on their basement membrane.[34]

The compliance of the capillary system is heterogeneous throughout the body, and is determined primarily by the organ or tissue the capillary network supplies. Capillaries in connective and muscle tissue are relatively rigid[35], whereas pulmonary capillaries tend to be more compliant, varying as a function of lung volume. The differences in the elasticity of the capillaries is thought to be associated with varying amounts of tissue surrounding the capillary bed.[36] For example, pulmonary capillaries are often represented as a tight three dimensional mesh of capillaries. The capillary bed around the alveoli is described as a parking garage with floors, ceilings and intervening collagen enriched posts that provides elastic support.[37,38] The idea of the sheet model is illustrated in figure 2. In contrast, muscle tissue capillaries are embedded in dense muscle fibers or connective tissue, which need significantly lower compliance to remain patent. The patency of the capillary is important, as the metabolic needs of the tissue can be matched only if blood is actively flowing through the tissue. Thus, capillary beds (networks) experience changes in perfusion according to the metabolic activity of the tissue. The adaptive behavior of the capillary bed preserves their ability to remain perfused regardless of the compression stress of the surrounding tissues.[39] However, it should not be over looked the sensitivity of the arteriole vascular smooth muscle to be sensitive to the change of pO_2.[38] The regulation of blood flow to the tissues can be dependent on the idea of precapillary sphincters to limit local blood flow and prevent over oxygenation of tissue.[40]

Microcirculation - Hemodynamics

The flow through the circulation, whether it be the arterial or venous end, experience similar phenomena. In the microcirculation blood and plasma flow is influenced by shear stress forces developed at the vessel walls, which result in partially blunted velocity blood profiles.[41,42] Unlike a normal parabolic profile with a peak indicating the maximum flow, this flow profile is blunted thus lacking a peak of max flow as a result of a core of fast-moving RBCs. Figure 3 portrays a comparititve view between a parabolic profile and a blunted profile. The degree of blunting is related to the dependent upon the ratio of tube diameter (D) and particle thickness (d), D/d. With increasing flow rates, the flow profile continues to become more parabolic as the shear rate on the particles increases. This is likely due to a shear dependent particle-particle interaction which results in an increase of particle size at higher shears by formation of rouleax or other aggregates.[42] With the same train of thought these blunted profiles tend to move closer to a normal parabolic profile as the diameter of the

vessel decreases.[42,43] The flow inside these vessels have another interesting characteristic, the presence of thin zone between the column of blood and the endothelial membrane, the cell free layer (CFL). The CFL is occasionally randomly intruded by RBCs and leukocytes and contains a gel like surface made of different sugars attached to the endothelial membrane known as the glycocalyx. The CFL is similar to a mechanical system that is generated due to dynamic conditions as cells and other formed elements draft away from the vessel wall due to the velocity gradient. The CFL works similar to a lubricating layer of moving mechanical parts as a viscous medium between blood and the vessel wall. Thus, the presence of the CFL significantly reduces the resistance to blood flow. The CFL is possible because of the Segre-Silberberg effect, which describes that the radial forces acting on the neutrally buoyant particles creating an equilibrium at approximately 60% of the tube's radii from the central axis.[44] The RBCs near the wall experience drag forces that drives cells along in the direction of the velocity vectors, and inertial forces which create lateral movement perpendicular to the velocity vectors. This lateral movement forces RBCs away from the vessel wall, leaving an annulus of plasma with very low concentration of cells near the wall.[45,46]

Microcirculation - Capillary Hemodynamics

To better understand the capillary hemodynamics, we will separate the analysis of how plasma flows from that of how RBC flow. An example of blood flow in a capillary is seen in figure 4. The flow of the incompressible Newtonian plasma, where the shear stress is proportionally related to shear velocity, is governed by Stokes flow, since plasma is mostly water.[47] As the plasma enters the capillary from a diverging arteriole branch it has a characteristic non-Poiseuillian profile, the pressure drop cannot be described across the capillary tube due to the viscosity of the fluid. Considering the radial velocities inside the capillary, the radial velocities can reach as much as 30% of the mean axial velocity.[47] As the plasma flows downstream, the flow reverts back to a parabolic profile that can be characterized as Poiseuille flow whose pressure drop can be characterized by the viscosity of the fluid (Figure 2). This occurs at a distance 0.65 times the diameter of the capillary tube from the entry section.[48]

Adding a layer of complexity, consider the deformable RBC entering the capillary. If two RBCs have a distance apart greater than 1.3x the capillary diameter, the plasma's velocity profile between the cells remains nearly parabolic.[48] This type of flow is named bolus flow.[49] As long as the distance between two consecutive RBCs is greater than the capillary diameter, the cells have very little interaction and the flow is essentially a superposition of two independent entry flows. There is a benefit in terms of reducing the resistance the RBCs experience in the capillaries by decreasing their distance apart. As the distance between RBCs in the capillary decreases, the interaction between the RBCs reduces the total resistance experienced by each RBC. Therefore, closely packing of RBC results in a lower hydrodynamic resistance than when RBC flow separately.[50]

Similarly, to the arterioles and venules capillaries have a CFL and a gel-like glycocalyx. The thin plasma layer between the endothelial lining of the capillary blood vessel and the RBCs experiences extremely high shear stress from the flowing RBCs in contact with it as the

diameter of the vessel is less than that of the RBC diameter. This CFL between the vessel wall and the RBC as previously mentioned can be thought of as the lubrication zone created by the CFL. Performing the proper analysis on this CFL can better characterize the flow of the RBC through the capillary. The thickness of the CFL or lubrication layer is related to RBCs velocity by the square root of the velocity and the resistance is related to the velocity by the inverse square of the RBC's velocity.[51,52] As the thickness of the CFL decreases, the RBC's velocity decreases, and can potentially "seize up" due to lubrication failure.

Assessing the flow of RBCs at bifurcations was extensively studied by Fung in 1972.[53] RBCs at bifurcations tend to move into the branch with higher velocity. The channel of a bifurcation with higher flow has a higher axial pressure gradient. The pressure gradient in both bifurcations drives plasma to skim past the RBC, resulting in uneven shear stress across the cell, which ultimately drives the RBC down the path with greater flow. As additional RBCs reach the same junction, they experience similar pressure and shear forces resulting in all RBCs following the same path at the bifurcation, assuming all RBCs were uniform. However, there is actual deviation in RBC flow due to randomness in the RBC shape and size, nonuniformity in vessel geometry, asymmetric flow, rotation of the RBC and other factors. As most things in nature, nature seeks balance and capillary flow is no different. Although, capillaries will favor one side of the bifurcation over another, the continuous flow of red cells down a particular path increases its resistance forcing a change in direction at the bifurcation.[53]

Microcirculation Dysfunction

The pathophysiology of the microcirculation can illuminate the intricacies involved with tissue perfusion. These hemodynamic alterations are known as circulatory shock, which includes variations in systemic hemodynamics, or endothelial dysfunction. Alterations in microcirculatory blood flow have been identified and the severity of these differences are associated with a poor outcome. For example, during hemorrhagic or septic shock, a dramatic drop in oxygen delivery to the tissues is seen.[54] Thus, the microvascular pressure decreases, reducing the density of functional capillaries (the number of capillaries perfused with RBCs) limiting the washout of metabolic by products that can lead to mitochondrial disfunction.[55] In the event of severe shock, some of the most apparent changes to the microcirculation are a reduction in oxygen carrying capacity, a decrease in blood viscosity, a decrease in vessel wall shear stress, and shedding of the protective glycocalyx barrier,[56] pathologic hyperfibrinolysis, and diffuse coagulopathy.[57,58] In the first few moments of shock, reduce in blood pressure, and an increase in the heart rate are observed. The decrease in blood pressure corresponds to a drastic reduction in hydrostatic pressure at the arteriolar end of the capillaries. The reduced hydrostatic pressure promoting interstitial fluid reabsorption in the capillaries.[59] The primary goal of resuscitation from shock is to restore balance via blood volume and microvascular pressure. Restoring microcirculatory function is a must to ensure a positive outcome following shock. The longer shock proceeds the longer an oxygen debt accumulates in the tissues, a debt that can only be repaid in the microcirculation.

Experimental Microvascular Measurements

To further understand the complexities of the microcirculation and its tendencies, a variety of techniques were developed to properly measure microcirculatory oxygen tension and hemodynamics. Better understanding of the intricacies of this complex network aids in engineering new techniques that promote more positive outcomes.

Intravital Microscopy

Observation of the microcirculation in humans is normally completed using laser doppler techniques or orthogonal polarization spectral imaging on the skin, nail flap or lip.[60] However, a common model to observe the microcirculation and oxygen delivery to the tissues utilizes hamsters and their dorsal skin flap. The skin is lifted from the animal, creating a skin fold, which is supported by two titanium frames with 12 mm circular openings. One frame is sutured on one side of the skin fold. The opposite skin layer is removed following the outline of the window leaving only a thin layer of retractor muscle, connective tissue, and intact skin. The exposed tissue is sealed with a glass cover held by the other frame creating an environment that allows for clear optical measurements of the microcirculation in vivo (Figure 5).[61] Furthermore, two blood vessels are typically cannulated: the carotid artery for monitoring blood pressure, and the femoral or jugular vein for the infusion of fluids and contrast agents. Hamsters are mammals that adapt to a fossorial environment, and in normal conditions have low central PaO_2 (57 mmHg corresponding to an Hb saturation of 84%) and a similar arteriolar pO_2 (57 mmHg corresponding to a Hb saturation of 81%). This suggests that hamsters are effective animals in delivering oxygen to the tissue in the microcirculation with minimal oxygen before reaching the microcirculation.[31]

Velocity Measurements

Velocity measurements in microvessels can be obtained via frame-by-frame analysis of short videos filmed through the high-magnification microscopy. Neither laser Doppler methods, nor ultrasound Doppler methods, have been refined to achieve reliable analytical results from vessels less than 100 μm in diameter.

The flow of blood in microvessels gives the appearance of the passage of a granular surface. This is quantified by placing a photo sensor over the microvessel videos and displaying the voltage of the photo sensor. This gives a time varying signal, dependent on the local light intensity in a small area of the microvessel image. The frequency and amplitude characteristics of this signal are directly related to the size of the objects that pass through the observed area and their velocity.

Previous iterations of this method used a single photometric sensor, however, a single sensor resulted in frequency ambiguity, and made determination of velocity difficult. As such, the method evolved to incorporate a second photometric sensor aligned along the axis of flow, allowing velocity to be determined by measuring the time delay between upstream and downstream signals. This is readily accomplished by measuring the time delay between the signals that maximizes their cross-correlation, a process that can be done on-line and in real

time. Wayland and Johnson in 1967 refined the two-slit photometric method into a convenient quantitative tool, capable of on-line presentation of velocity data for capillaries.[62–64]

Measurement of oxygen tension

High resolution microvascular pO_2 measurements can be made using phosphorescence quenching microscopy (PQM). PQM is based on the relationship between the phosphorescent decay of palladiummesotetra-(4-carboxyphenyl)-porphyrin bound to albumin, and the partial pressure of oxygen, according to the Stern-Volmer equation. A 10 mg/mL intravenous injection of the porphyrin dye is given approximately10 minutes before pO_2 measurements. A series of flashes causes phosphorescence of the dye, and the oxygen concentration is measured in an adjustable optical window.[65]

Phosphorescence is the emission of photons as the molecules of an excited phosphorescent material, such as Pd-porphyrin, falls from the excited triplet state back to the singlet ground state. The energy required to excite the electrons of molecular oxygen is approximately the same as the energy released by phosphorescent decay of Pd-porphyrin. O_2 can absorb this energy before a photon is released, and a much faster rate than a photon can be released, thus “quenching” the phosphorescence. Naturally, this is a concentration dependent effect, as the O_2 must be in close contact with the phosphorescent molecule. As such, a decrease in the rate of phosphorescent emission (a faster time constant), can be correlated with a higher local concentration of pO_2 via the Stern-Volmer equation.

Concluding Remarks

The microcirculation is an incredibly complex and vital network of vessels that are specifically designed to maintain the surrounding tissues. As this field of research continues to grow and new techniques are developed, questions revolving around oxygen transport will begin to be answered with clarity. As these questions are answered engineers can adapt these fundamental understands creating nonspecific blood substitutes. Furthermore, microcirculatory research also promotes further research on blood pathologies such as sickle cell and thalassemia. All in all, the microcirculation is a corner stone of the human body.

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Key Points

- Mechanotransduction produces Nitric Oxide to regulate the flow in the microcirculation.
- Unlike previously thought tissue oxygenation occurs in the arteriole end while capillary perfusion correlates to metabolite washout.
- Microvascular hemodynamics vary with the type of vessel, flow in the arterial and venous differs from the high shear stress environment of the capillaries.
- Microvascular measurements quantify the flow inside the microvasculature using a cross-correlating algorithm and oxygen tension is quantified using phosphorescence quenching microscopy.

Synopsis

The microcirculation is a complex network of vessels ranging from as large as 100 μm to as small as 5 μm. This complex network is responsible for the regulation of oxygen to the surrounding tissues and ensure metabolite washout. With a more complete understanding of the microcirculation's physiological and pathological tendencies engineers can create new solutions to combat blood pathologies and shock related diseases. Over the last number of decades a grown interest in the microcirculation has resulted in the development of fundamental techniques to quantify the microvasculature flow and the release of oxygen to tissues.

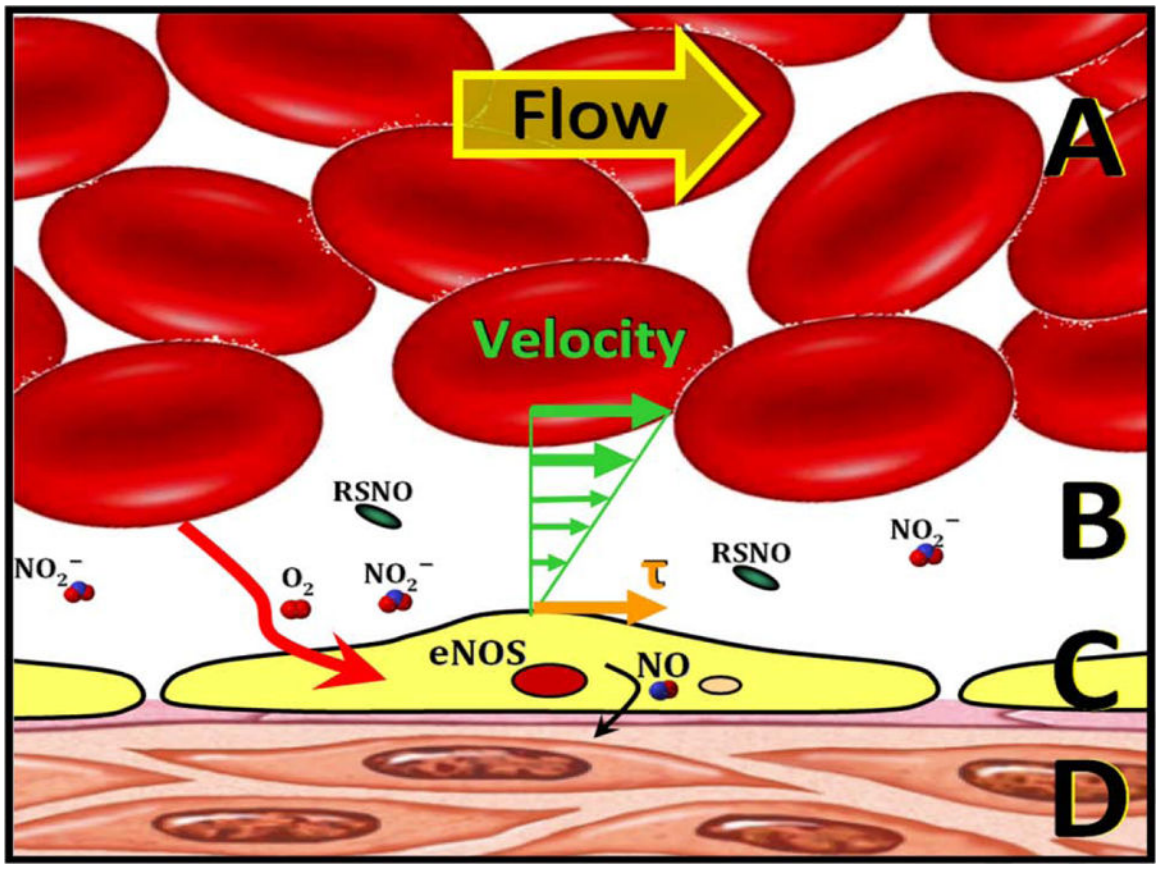

Figure 1:
Blood flow through arterioles or venules, A) The bluk of RBC flow B) Cell free layer generated by the Segre-Silberberg effect with various biochemical proteins C) Endothelial cell lining generating eNOS from mechanotransduction D) Smooth muscle layer encapsulating the entire vessel.

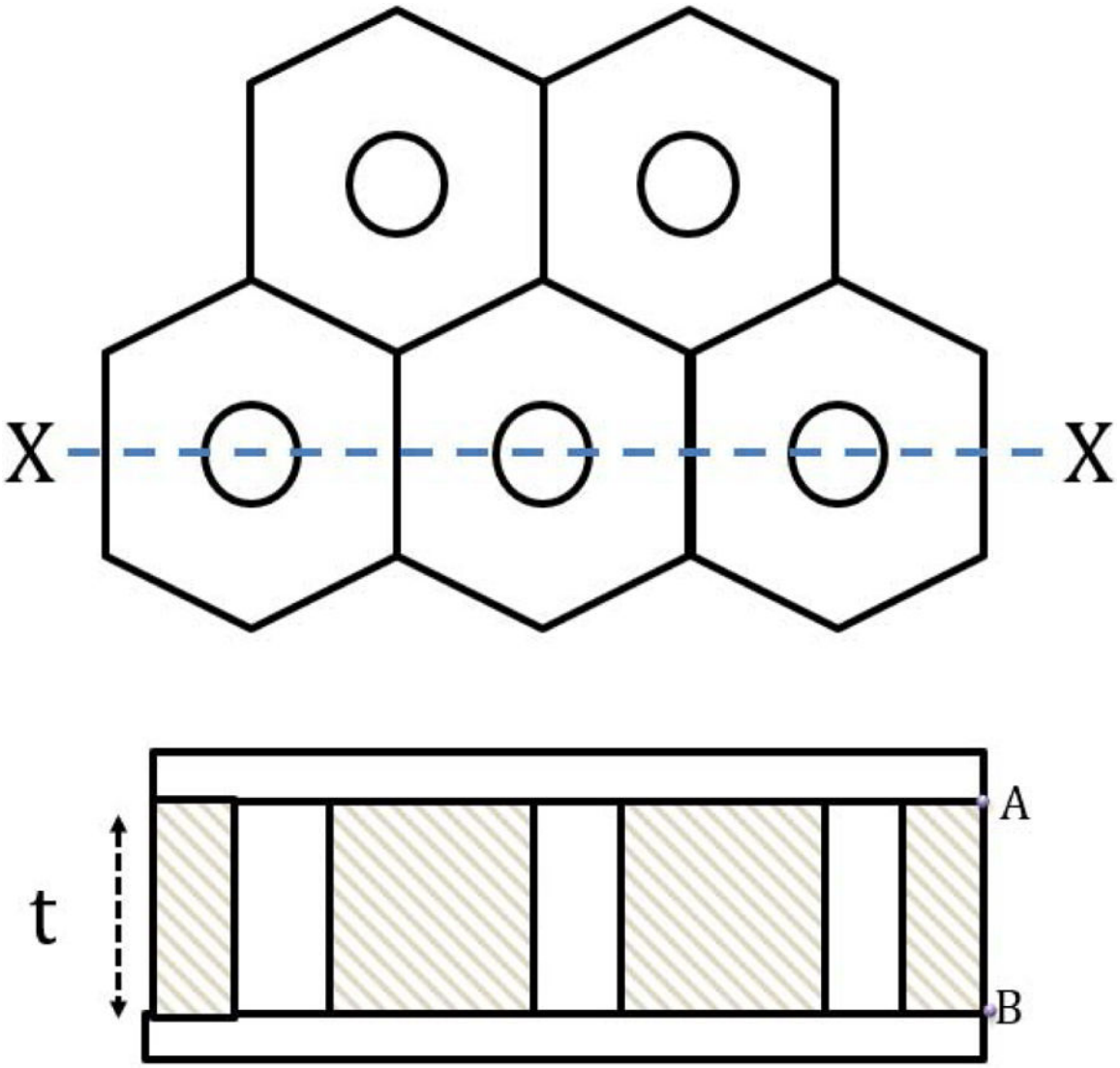

Figure 2:

Sheet fold model. *Top.* Plain View *Bottom. Cross section view from X- - -X.*

The clear rectangular spaces are the nonvascular posts. The striped areas indicate the flow channels. Sheet thickness = t. A and B are contact of posts with endothelial surface.

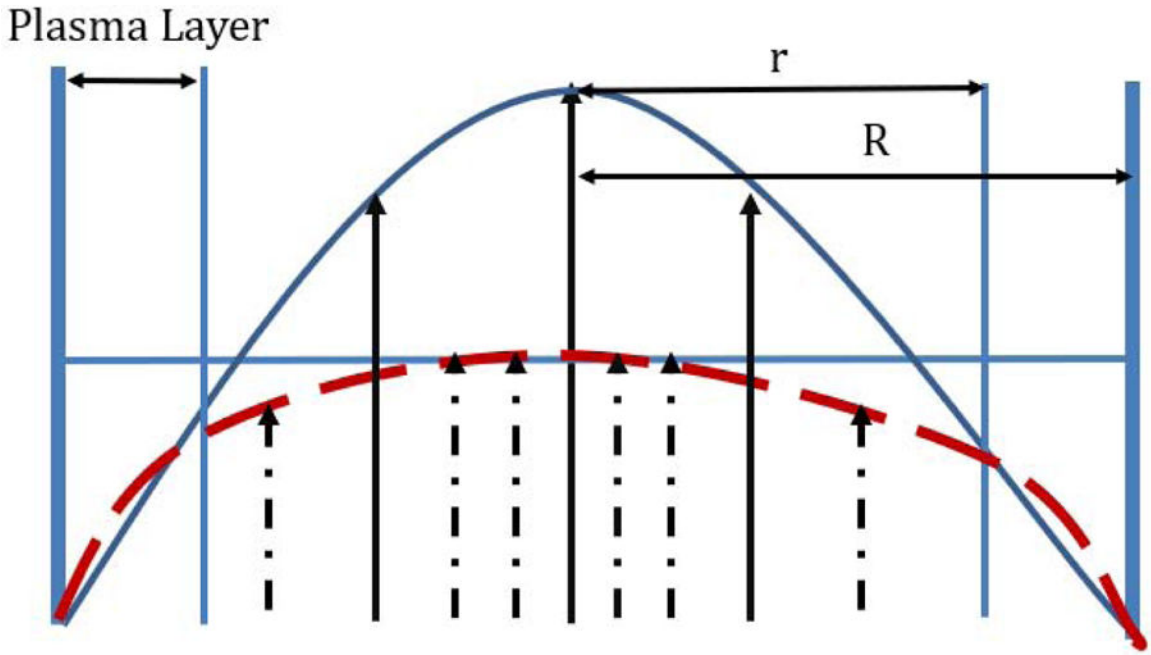

Figure 3:
Parabolic and blunted flow profiles R is the vessel radius, r is the flow radius and the plasma layer illustrates the CFL.

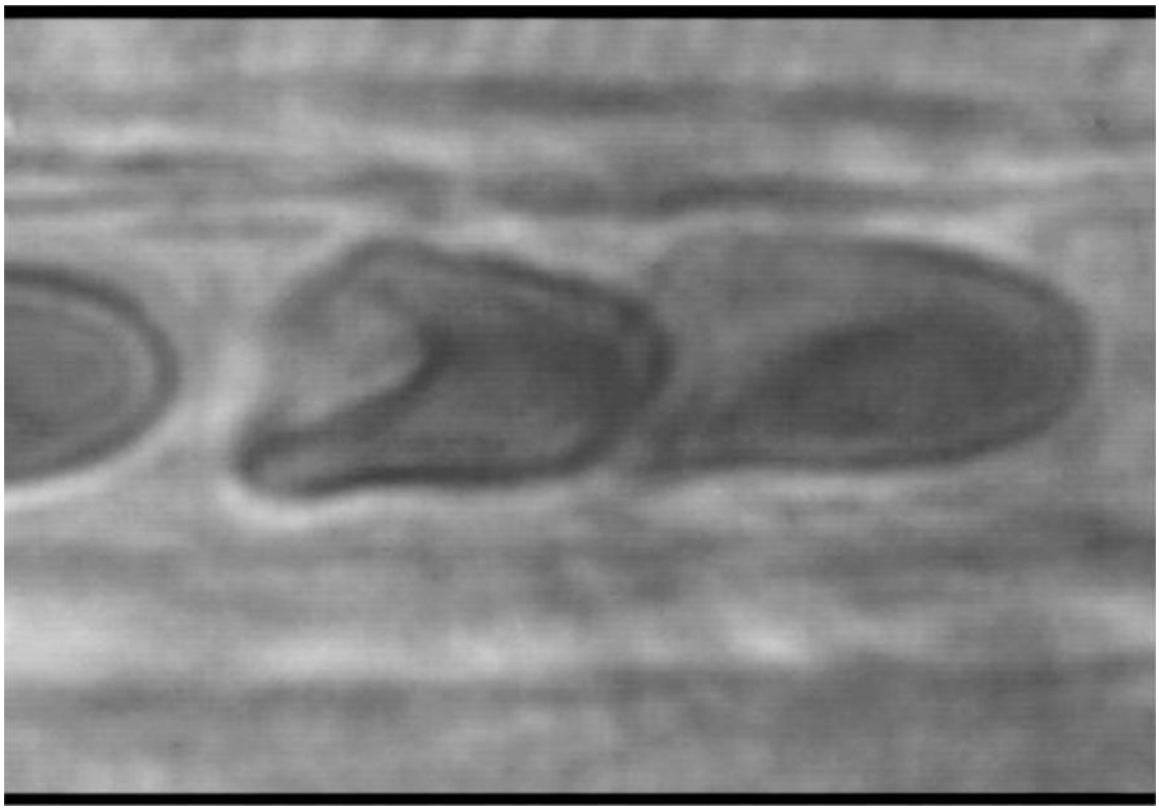

Figure 4:
RBCs flowing through a narrow capillary channel.

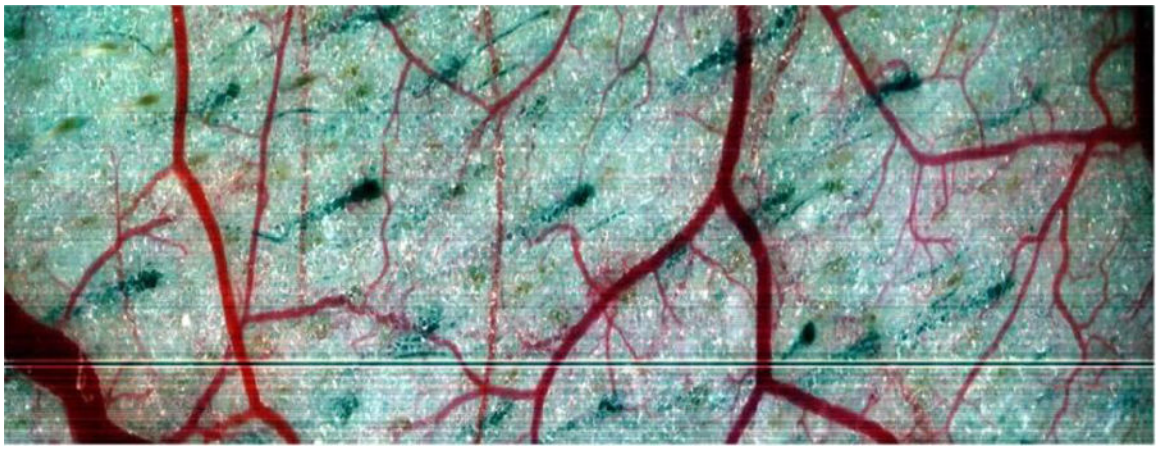

Figure 5:
Microcircualtion of a hamster using intravital microscopy on the skinfold technique.