BIOMECHANICS OF MICROCIRCULATORY BLOOD PERFUSION

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Abstract The microcirculation represents a region of the circulation in which blood vessels are directly surrounded by the tissue and cells to which they supply nutrients and from which they collect metabolites. The cellular elements that make up the microcirculation have now been identified, and a large body of evidence has become available that provides molecular definitions of these elements. The blood flow is in a domain in which viscous stresses dominate, but the viscoelastic and active properties of cells lead to nonlinear problems. The ability of cells to actively control cytoplasmic mechanical properties and shape, as well as their membrane adhesion, leads to unique cell behavior in microvessels that has a direct influence on organ transport and function. There is also increasing evidence that the properties of the cells are in turn influenced by fluid shear stresses. These issues have greatly expanded the scope of microvascular analysis. The microcirculation is one of the sites in which diseases manifest themselves at an early stage. The application of biomechanical analysis of the microcirculation is starting to focus on diseases. The field is rich with problems of high significance.

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INTRODUCTION

An average adult has $\sim 10^{11}$ blood vessels of which the great majority are capillaries. In spite of their large number, the capillaries are perfused with remarkable uniformity in all organs of the body. This article focuses on this network and the biomechanical mechanisms that control its perfusion.

In the last decade, an important expansion of thinking on microcirculation has taken place. The well-accepted interaction between models and experiments in physics and engineering has now been applied to problems in the microcirculation. The vascular network pattern, the biomechanical properties of the blood vessels, the blood, and its cellular components have been examined in several organs. Mathematical models, based on physical principles and with an increasing degree of complexity, have been developed, and predictions have been compared with independent experimental results. The result of this process has been discovery and development of improved microvascular models. Furthermore, instead of only asking how cell and tissue biology controls the mechanics of the microcirculation, we now ask how the mechanics controls the biology. This expansion has led to new approaches and a more detailed level of understanding that may have far-reaching implications for biology. The analysis is more often carried out at the molecular level.

The literature on microcirculation is large, and page limitation does not permit a full assessment of all recent developments in the field. The reader is referred to additional recent reviews (45, 51, 75, 76, 95, 100, 131, 133). The extensive experimental records of microvascular hemodynamics obtained in the 1970s and 1980s were reviewed by Zweifach & Lipowsky (158). Fung has summarized blood flow in the pulmonary microcirculation (42).

MICROVASCULAR NETWORK TOPOLOGY

The microvascular network in several organs has been reconstructed. In these reconstructions, each category of microvessels has been identified, and how each category is connected to its neighboring category has been clarified. The closer we study these networks, the more we appreciate the efficiency of their design to satisfy a diversity of functions, from a remarkable homogeneous capillary flow and well-defined pressure, to delivery and removal of physiological gases, nutrients/metabolites, proteins, and hormones, endothelial gene expression, and attraction of vascular cells. Network reconstructions were carried out after some visual enhancement with a contrast medium (polymers, colloidal carbon, staining of endothelial cells with lectins) in skeletal muscle (32, 33, 69, 118, 134, 147, 148),...
skeletal muscle fascia (136), and the coronary (59, 62–64) and retinal microcirculation (121, 123). A tumor microvessel topology has also been reconstructed (79). Each microvascular network has its own characteristics, but there are some general features that we discuss below.

Arteries and arterioles form either networks (also designated as arcades, plexuses, or collaterals) or bifurcating trees. Venules and veins have arrangements similar to those of their arterial counterparts, but they are wider in diameter and denser in their branching pattern. The networks are supplied with blood from several input arteries that in turn are connected to different central arteries, depending on the organ and vessel location. Similarly, the venules drain into several central veins. Arteriolar and venular networks are prominent in skeletal muscle and in the mesentery. In the porcine coronary circulation, they are present on the venular but not the arteriolar side (63, 64). Arteriolar and venular networks are essentially absent in the pulmonary circulation (155, 156) and in the retinal microcirculation (121). In skeletal muscle, two of the main feeder arteries are located at the proximal and distal end of the organ. These two feeder arteries are directly connected to each other by the largest arteriole in the muscle, the arcade bridge arteriole (118). Smaller arcade microvessels tend to be connected in a random pattern between larger microvessels in the network (Figure 1). Popel et al proposed a branching schema that is based on classification of microvascular loops (96).

The connections from the arteriolar and venular networks to the capillaries are provided by the terminal arterioles (also designated as transverse arterioles or meta-arterioles). The venular counterparts to the terminal arterioles are the collecting venules. Both classes of microvessels form asymmetric bifurcating trees and can be readily described by the Strahler branching pattern (137, 138). Chen (16, 17) and Chen & Prewitt (18) used an operator schema that takes into account spatial directions of the vessel.

In the Strahler branching schema, the capillary blood vessels are identified as the lowest order \( N_1 \); when equal-order vessels join at a bifurcation, a higher-order vessel is formed, and when vessels of unequal order join, the higher order is preserved. The number of vessels, \( N_I \), in each order \( I \) are then counted, and ratios between the number of vessels in one and its next lower order are determined by \( R_I = N_I/N_{I-1} \). The average of these ratios for all branching orders in microvascular trees is designated as the branching ratio \( R_B \). Typical values of \( R_B \) are in the range between 2.5 and 3.5. The Strahler schema has been applied to arteriolar and venular trees in several organs (34, 63, 64, 68, 147, 155, 156) and, in many cases, gives a satisfactory description of the branching pattern. In the retina arterioles, an improvement of the branching was achieved by defining a branching ratio function \( R_B \), which depends on the vessel order (123), instead of computing only an average branching ratio as proposed by Strahler. The number of branching orders is larger in organs without arcade arterioles (e.g. lung, porcine coronary vessels); it is smaller in organs with arteriolar or venular networks (e.g.
FIGURE 1 (top) Tracing of arcade arterioles (AA) and arcade venules (AV) in the rat spinotrapezius muscle. The arcade network spans the entire muscle, and there are multiple connections of this network to the central arteries. The side branches to the capillary network (bottom) are provided by the terminal (transverse) arterioles (TA), which form asymmetric trees and directly connect to the capillary meshwork. Capillaries are predominantly aligned with the muscle fibers and give rise to the collecting venules (CV), which return the blood to the arcade venules. From Skalak et al, Reference 134, and Schmid-Schönbein et al, Reference 118.

rat skeletal muscle) because fewer bifurcations are required to provide the connections to the capillary network.

The Strahler branching schema has also been applied to a description of average microvessel diameter and length. Diameters within a single-vessel order exhibit in first approximation a Gaussian distribution; the microvessel lengths exhibit lognormal distributions (34, 68). The branching ratio for the average diameter, $R_B$, is $\sim 1.5$, and for the average length, $R_L$, $\sim 2$. These ratios vary from organ to organ and even among animal strains (33).

The capillary network in all organs has the largest number of vessels (Figure 1). It consists of bifurcating endothelial tubes (with a basement membrane and pericytes) and is displayed in a polarized pattern between a terminal arteriole and
a collecting venule. In fact, in skeletal muscle, the capillaries are displayed in a repeated pattern in the form of capillary bundles, such that each terminal arteriole gives rise to two sets of capillary networks feeding into two collecting venules, and in turn each collecting venule collects blood from two terminal arterioles (134). The branching pattern in the capillaries can be described by a minimum set of seven independent network parameters to assure that all vessels we encounter are included in the branching schema. Many more network parameters can be introduced to provide additional details of the microvascular branching pattern. The more details we wish to provide, the more parameters we need to define.

Terminal arterioles and collecting venules are directly connected to the capillary network and have a polarity, such that arterioles feed into capillaries and from there on into a venule. In most organs, terminal arterioles supply several venules in their immediate vicinity, whereas venules receive capillary blood from several arterioles (121, 134).

**MICROVASCULAR GROWTH**

In addition to several angiogenic factors, the growth of microvascular networks is influenced by mechanical stresses. A number of hypotheses have been advanced about the mechanisms of network growth (optimal flow to provide metabolites, endothelial shear stress, pressure, etc), but only recent evidence has provided direct insight into the growth mechanisms. Price et al (97) have shown that direct capillary connections between neighboring terminal arterioles, which actually bypass the collecting venules (134), serve as a site for formation of new arterioles under the influence of elevated microvascular wall tension, with formation of new network arterioles (98). Wall tension is the key growth stimulus, and the arterioles originate in the capillary network. Simulations on entire microvascular networks suggest that stable structural adaptation requires a combination of endothelial wall shear stress, intravascular pressure, and flow-dependent metabolic stimulus, as well as a stimulus conducted from distal to proximal segments along microvascular walls (101). This may be a key mechanism that leads to the characteristic increase in the arteriolar network density in genetically hypertensive animals. In addition, hypertensive animals have a loss of capillary blood vessels in part caused by a humoral component involving the renal hormones renin and angiotensin, glucocorticoids, and apoptosis of capillary endothelium.

**MICROVASCULAR FLUID MECHANICS**

The motion of fluid in the microcirculation has a Reynolds number \( N_R = dU/\rho/\mu \) (based on vessel diameter \( d \), mean velocity \( U \), plasma viscosity \( \mu \), and mass density \( \rho \), which is \( 10^{-1} - 10^{-3} \), and a Womersley parameter \( N_W = d(\rho U/\mu)^{1/2} \) between 0.1 and 0.001, so that convective and transient inertia forces can be
neglected. Therefore, fluid motion is governed by the Stokes approximation of the equation of motion

$$\nabla \cdot \mathbf{p} = \mu \nabla^2 \mathbf{u},$$  \hspace{1cm} (1)

and, because at physiological pressures plasma and cells are incompressible,

$$\nabla \cdot \mathbf{u} = 0,$$  \hspace{1cm} (2)

where \( \mathbf{u} \) is the suspending medium velocity vector and \( p \) is the pressure. Without inertia forces and gravitation, the motion of freely suspended cells in plasma is governed by the "zero-drag" condition

$$\oint S \mathbf{T} dS = 0,$$  \hspace{1cm} (3)

with an equivalent condition for the moments produced by the surface traction \( \mathbf{T} \). This equation indicates that the motion of freely suspended cells and particulate matter in the blood is determined by the surface traction \( \mathbf{T} \), which in turn is determined in the blood by the motion of plasma. Therefore, the motion of blood cells in microvessels, which determines fundamental quantities like the hematocrit or the pathways taken by platelets or leukocytes in the microcirculation, is determined by the flow of plasma.

If cells adhere to the endothelium, Equation (3) has to take into account that the surface traction vector \( \mathbf{T} \) is determined on the lumen side by the fluid shear stress while it is determined by solid-surface traction in the membrane contact region with the endothelium mediated by adhesion molecules. The membrane attachment of blood cells is controlled by a set of specific adhesion molecules whose expression in turn is controlled by fluid shear stress. Adhesive and non-adhesive cells behave quite differently in the microcirculation; thus, biomechanical analysis is directly influenced by biosynthesis of membrane and cytoskeletal proteins and their interaction. Mechanics and biology are intimately intertwined.

To analyze the flow in microvessels, we define a mean velocity vector. The detailed flow velocity in microvessels is complicated owing to disturbances by endothelial cells and the blood cells and their deformation. Whereas, in some selected cases, the detailed blood flow around cells in microvessels has been computed (125, 157), in many cases it is expedient to define a mean flow field \( U, V, W \) and a disturbance \( u', v', w' \). In radial coordinates \( (z, r, \theta) \), the three velocity components are

$$u(z, r, \theta) = U(r, z) + u'(z, r, \theta)$$
$$v(z, r, \theta) = V(r, z) + v'(z, r, \theta)$$
$$w(z, r, \theta) = W(r, z) + w'(z, r, \theta)$$  \hspace{1cm} (4)

Here \( U \) is the average velocity and a function of \( r \) and \( z \) only, whereas \( V \) and \( W \) vanish if we assume axisymmetric flow and impermeable microvessels. The average velocity in axial direction is defined as
where $\Delta$ is a concentric ring region in the microvessel at radial position $r$. The ring region is assumed to be large enough to smooth out the velocity field at every position $r$ yet small enough to detect the average radial variations of the axial velocity. In practice, we assume it is of the order of 0.5 $\mu$m, or $\sim 1/10$th of a typical capillary diameter. The velocity components $u'$, $v'$, $w'$ have a mean value equal to zero.

Integration of the equation of motion [Equation (1)] over a cylindrical microvessel cross section with radius $a$ gives Poiseuille’s equation for the flow rate

$$Q = -\frac{\pi a^4}{8} \frac{\partial p}{\partial z}$$

where $\partial p/\partial z$ is the pressure gradient along the length of the vessel, $Q = \pi a^2 \bar{U}$, and $\bar{U}$ the average axial velocity over the vessel cross section. The average shear stress on the endothelium is

$$\sigma = -\frac{a}{2} \frac{\partial p}{\partial z} = \frac{4\mu}{a} Q.$$  

The prediction of a linear relationship between the pressure drop ($p_A - p_V$) along the length $L$ of a microvessel and the flow $Q$ by Poiseuille’s law can serve only as a first approximation. Experiments show that the relationship between pressure and flow in the microcirculation is nonlinear owing to a number of mechanisms, the deformability and adhesion of blood cells, the active contraction of the arterioles, and the passive distensibility of the blood vessels.

**VISCOELASTICITY AND SHAPE OF MICROVESSELS**

Because microvessels are distensible, the radius $a$ is a function of the transmural stress in the blood vessel wall. In the microcirculation, the predominant stress component is the pressure ($\sim 10^3$ dyn/cm$^2$ in venules, $10^5$ dyn/cm$^2$ in arterioles); shear stresses are much smaller ($50\sim100$ dyn/cm$^2$) (81). Therefore, the passive distension is dominated by the intravascular pressure $p$ and the external stress applied to the microvessels by the surrounding tissue. A number of microvessel classes have now been investigated in this regard. In pulmonary arterioles and venules, the diameter $d$ was found to be

$$d = d_0 \left[1 + \alpha (p - p_{Alb})\right],$$

where $p_{Alb}$ is the alveolar air pressure (153). Pulmonary capillaries, which, owing to their high network density, have been represented by Fung & Sobin (44) in
the form of a vascular sheet with thickness $h$, belong to the most distensible vessels in the circulation, such that the pulmonary sheet thickness

$$h = h_0 + \alpha (p - p_{ah})$$  \hspace{1cm} (9)

(43). In Equation (9), $\alpha$ is an empirical distensibility constant.

In skeletal muscle, the microvessels are significantly less distensible because they are tightly embedded between muscle cells and connective tissue fibers. They exhibit viscoelastic properties in form of a quasi-linear standard solid model of the form

$$p + \frac{\beta}{\alpha_1} \frac{\partial p}{\partial t} = \alpha_2 E + \beta \left( 1 + \frac{\alpha_2}{\alpha_1} \right) \frac{\partial E}{\partial t},$$  \hspace{1cm} (10)

where

$$E = \frac{1}{2} \left[ \left( \frac{d}{d_0} \right)^2 - 1 \right]$$  \hspace{1cm} (11)

is a nonlinear function of the diameter $d$ and $d_0$ is the reference diameter (135). In Equation (10), $\alpha_1$, $\alpha_2$, and $\beta$ are empirical coefficients that in rat skeletal muscle have been measured for all classes of arterioles, capillaries, and venules (135).

In response to a step pressure elevation, $p(t) = p_0 H(t)$, where $H(t)$ is the step function, microvessels exhibit a creep deformation. The short- and long-term elastic responses are

$$E = p_0 / (\alpha_1 + \alpha_2)$$  \hspace{1cm} (12a)

and

$$E = p_0 / \alpha_2,$$  \hspace{1cm} (12b)

respectively. For a step pressure, the creep rate in vessel radius to reach steady state is $\exp[-t/\tau_\alpha]$, where $\tau_\alpha$ is a time constant for capillaries that is an order of magnitude of 10 s. The time constants for arterioles and venules are of the same order of magnitude. Therefore, in the presence of a pulse pressure at 1 Hz, the time for creep deformation is short compared with the pressure periods, so that the initial elastic response [Equation (12a)] serves as a good approximation for capillary distensibility. Viscoelastic properties of microvessels have also been observed in the mesentery microcirculation (5).

The details of blood flow in microvessels depend critically on the shape of the lumen. The main cell that determines the lumen shape is the endothelial cell. In the capillary network at normal physiological pressure (~20 mmHg), the endothelial cell is deformed into a disc shape, providing a lumen that is close to a perfect cylindrical shape. If the pressure is reduced, noncircular lumens are produced with protrusions by the endothelial nuclei that start to become round at reduced (circumferential) stress in the endothelial cells (74). If the endothelial cells are stimulated (histamine, platelet activating factor, and many others), they
produce cytoplasmic projections owing to actin polymerization, which, especially in capillaries at low pressure, may grow to a size that significantly interferes with blood flow (74).

There have been repeated proposals that capillary endothelial cells and pericytes (which are positioned directly on capillary and venular endothelium) may be contractile, serving as a mechanism for capillary flow regulation (65, 104). Whereas the endothelial cells and pericytes have contractile cytoplasmic proteins and can spontaneously change shape (like in phagocytosis or angiogenesis), there is currently no conclusive evidence that these shape changes are sufficiently organized to result in a circumferential wall shortening at constant capillary pressures. Shape changes as seen after active pseudopod projections or passive protrusion of the cell nucleus, however, are common.

In arterioles, the shape of the endothelial cells is also determined by smooth-muscle contraction. Whereas, in larger arteries, the lumen shape is determined by the undulating shape of the elastica intima during contraction, in arterioles, the elastica intima is reduced to longitudinal fibers without undulations and the lumen shape is determined predominantly by compression of the endothelial cells into cuboidal shapes (115). The fluid shear stress on the endothelium in microvessels with noncircular cross sections is nonuniform, with lowest levels close to zero at the junction between endothelial cells and peak values at points that protrude into the lumen (115). The average wall shear stress in a vessel with a noncircular lumen shape is lower than the shear stress in a vessel with equal cross-sectional area but a cylindrical lumen shape.

Another important factor that determines the shape of the capillary network is the stress from cells surrounding the capillaries. In skeletal muscle, the capillary length is influenced by the shortening of the muscle fibers (31). During skeletal muscle contraction, the capillaries are cast into meandering shapes apparently without significant shortening (85).

THE MYOGENIC RESPONSE

The arterioles adjust their lumen diameter by contraction and dilation of the smooth muscle media in response to pressure (7, 60), shear stress [e.g. via release of nitric oxide from endothelial cells (46, 47) or prostaglandins (70)], to neurogenic [derived either from the nerve fiber plexus on the media (107) or via humoral mediators (such as norepinephrine)] and to metabolic stimuli (oxygen, pH, adenosine, and many others). The contraction is most pronounced in the arterioles of the microcirculation. The pressure-dependent (myogenic) contraction of the arterioles is derived from the inherent properties of smooth muscle to contract under tension even when applied to isolated smooth muscle cells (37). The myogenic contraction can be enhanced by neurogenic mechanisms and attenuated by endothelium-derived dilators (71, 72). Numerous studies are under way to examine molecular and cellular mechanisms of arteriolar contraction (87), but
there are few models that analyze the biomechanics of small arterioles (3, 9–11, 57, 67, 149).

One of the difficulties in formulating a self-contained theory of smooth muscle contraction, or for that matter a biomechanical theory of muscle contraction in general, has been the lack of a unique definition of “active stress” as well as the lack of a well-defined reference length in muscle. The separation of the total resultant stress of an actively contracting muscle into passive and active components, as defined by Hill’s model, is based on an arbitrary choice of the passive state and does not have a well-accepted structural counterpart in terms of the actual muscle morphology [see further discussion by Fung (41, Chapter 11), and (76)]. The actin-myosin complex is able to support a significant part of the stress in muscle during both shortening and passive distension, so that passive components (such as membranes or interstitial proteins) contribute only a part of the passive stress.

The definition of mechanical properties in any material depends on the choice of a reproducible reference state, irrespective of the strain measure one elects to use (stretch ratio \( l/l_0 \), Lagrangian strain \( E = [(l/l_0)^2 - 1]/2, \) etc). The reference length \( l_0 \), whether it is measured for the entire muscle or for any of its cellular or subcellular components, serves as a measure of tissue length that must be uniquely associated with a selected stress state. In traditional mechanics, the reference length \( l_0 \) is measured with respect to zero stress, \( l = l_0 \) at \( \sigma = 0 \), because it is convenient and reproducible. However, in actively contracting muscle, the reference length depends on the state of muscle stimulation, and thus there is no unique value of \( l_0 \) at any stress. For example, in isotonic contractions (\( \sigma = \) constant), the same stress is associated with a distribution of reference lengths. Thus, we need a new form of strain definition to define the mechanical properties of actively contracting smooth muscle. We will study this requirement for microvascular smooth muscle subject to myogenic contractions.

Let \( \lambda(t) \) be the instantaneous lumen radius and \( a_0 \) be the reference radius, which in passive arterioles is quite reproducible (135). Local details of the lumen shape (115) will be neglected. As discussed above, experiments on passive noncontracting arterioles suggest that the relationship between pressure \( p(t) \) and radius \( a(t) \) with its strain \( \lambda(t) = a(t)/a_0 \), from Equation (10), can be expressed in form of a hereditary integral

\[
p(t) = p(\lambda) + \int_0^t p(\lambda(t - \tau)) \frac{dG(\tau)}{d\tau} d\tau \tag{13}
\]

with the reduced creep function

\[
G_\lambda(t) = \frac{1}{\alpha_2} \left( 1 - \left( 1 - \frac{t}{\tau_0} \right) \exp \left[ - \frac{t}{\tau_0} \right] \right) H(t) \tag{14}
\]

and elastic response
\[ p^{\alpha_2}[\lambda(t)] = \frac{\alpha_2}{2} (\lambda^2 - 1). \] (15)

\[ \tau_e = \beta/\alpha_1 \quad \text{and} \quad \tau_a = \beta (\alpha_1 + \alpha_2)/\alpha_1 - \alpha_2 \] are time constants, based on the empirical coefficients \( \alpha_1, \alpha_2, \) and \( \beta. \)

In the active state, however, the reference radius \( a_0 \) at any stress will no longer be constant as in passive vessels. Thus, we need to replace the passive reference state, \( a_0, \) with a new reference state \( a_{\text{REF}}, \) which is subject to shortening under a myogenic contraction. In principle, we can use isotonic contraction records at constant arteriolar wall stress to identify the time course during a myogenic shift in radius \( a_{\text{REF}}(t). \) The passive stretch ratio \( \lambda(t) = a(t)/a_0 \) has to be replaced by an active stretch ratio \( \lambda(t) = a(t)/a_{\text{REF}}(t). \) The viscoelastic stretch during active contraction of the smooth muscle is described by

\[ \lambda(t) = \lambda_{ap}(t) \lambda_p(t) \] (16)

with an apparent stretch ratio \( \lambda_{ap}(t) = a_0/a_{\text{REF}}(t) \) and \( \lambda_p(t) = a(t)/a_0. \) Here \( \lambda_p(t) \) is the resultant stretch ratio that depends both on the active contraction of the smooth muscle and on passive viscoelastic stretch. By definition, in a myogenic contraction, the reference radius is a function of the arteriolar pressure \( p. \) Lee & Schmid-Schönbein (77) have proposed a linear relationship

\[ \lambda_{ap}(t) = \int_0^t G(t - \tau) \frac{d}{d\tau} p d\tau + a_m \] (17)

where \( a_m \) and \( b_m \) are two empirical contractile constants and \( G(t) \) is a delay function between the applied intravascular pressure \( p, \) and the radius response represented by the stretch ratio \( \lambda_{ap}(t) = a_0/a_{\text{REF}}(t). \) At steady state, Equation (17) approaches the form

\[ \lambda_{ap} = \frac{p + a_m}{b_m}. \] (18)

Current experimental results are closely approximated by the linear form of Equations (17) and (18) (77, 78); as more experimental details become available, the linear forms may need to be replaced by nonlinear forms.

If we assume that actively contracting smooth muscle in arterioles exhibits the same form of viscoelastic properties as passive arterioles [Equations (10) and (11)], the arteriolar radius owing to elastic distension and a shift of the reference state at steady pressures based on Equations (12b), (16), and (18) is

\[ \lambda_p = \frac{a}{a_0} = \frac{b_m(1 + 2p/\alpha_2)}{p + a_m}. \] (19)

Unsteady solutions of the myogenic response for several pressure histories are given elsewhere (76–78). The typical elastic expansion and subsequent myogenic
FIGURE 2 The diameter response of a skeletal muscle arteriole subjected to a step pressure (77). The initial elastic distension at the time of the step is followed by a transient myogenic contraction, which leads to a new shortened steady-state diameter. The theoretical prediction was computed from independent measurements of the viscoelastic properties and the reference length [Equations (10) and (18)] (Reference 78).

There is evidence that smooth muscle is strain-rate sensitive (23, 24), suggesting that $k_a$ may also depend on the rate of pressure change, $\frac{\Delta p}{\Delta t}$. Beach et al (8) have shown that capillaries may communicate with adjacent arterioles via endothelial cell contacts.

MICROVASCULAR PRESSURE–FLOW RELATIONSHIPS

If we express the radius $a$ for a distensible vessel as a function of the pressure $p$ in a general form as

$$a = a_o (1 + \alpha p)^n$$  \hspace{1cm} (20)

and substitute into Poiseuille’s formula [Equation (6)], we find, after integration along the vessel length $L$, the flow rate $Q$

$$Q = \frac{\pi a_o^4}{8(4n + 1)} \frac{1}{\mu L} \left[ \left(1 + \alpha p_u \right)^{4n+1} - \left(1 + \alpha p_d \right)^{4n+1} \right].$$ \hspace{1cm} (21)

where $p(z = 0) = p_u$ the upstream pressure, and $p(z = L) = p_d$ the downstream pressure. This is the fundamental pressure–flow equation for a distensible micro-
vessel with a Newtonian fluid. The flow in pulmonary arterioles/venules [Equation (20) with \( n = 1 \)] is then

\[
Q = \frac{\pi \alpha_0^4}{40 \mu \alpha L} \left[ \left( 1 + \alpha p_u \right)^5 - \left( 1 + \alpha p_d \right)^5 \right],
\]

(22)

although the flow in skeletal muscle microvessels for \( n = 1/2 \) and the empirical distensibility constant \( \alpha = 2/\alpha_2 \) [in Equation (12b)] is

\[
Q = \frac{\pi \alpha_0^4 \alpha_2}{48 \mu L} \left[ \left( 1 + \frac{2 p_u}{\alpha_2} \right)^3 - \left( 1 + \frac{2 p_d}{\alpha_2} \right)^3 \right],
\]

(23)

For comparison, the flow in pulmonary capillaries is (44)

\[
Q = \frac{1}{48 \mu \alpha L} \left[ \left( h_o + \alpha (p_u - p_d) \right)^4 - \left( h_o + \alpha (p_d - p_{Alv}) \right)^4 \right],
\]

(24)

The flow in all such distensible microvessels depends on both the upstream pressure \( p_u \) and the downstream pressure \( p_d \). Comparison between these pressure-flow relations shows that the more distensible vessels of the pulmonary microcirculation have a more nonlinear pressure-flow equation with a higher integer exponent. All microvessels are subject to the ‘‘waterfall effect’’ such that the flow \( Q \) depends predominantly on the arterial pressure and less on the venous pressure, because the first term on the right-hand side of Equations (22)–(24) with the upstream pressure \( p_u \) tends to dominate. The effect is more pronounced in the pulmonary circulation [with an exponent equal to 5 [Equations (22) and (24)]] than in the skeletal muscle microcirculation [with exponent 3 [Equation (23)]].

MICROVASCULAR FLOW DURING PULSATILE PRESSURES

In the microcirculation, time-dependent flows are caused by several mechanisms, including arterial pressure pulsation, arteriolar vasomotion (22, 88), the motion of individual blood cells (66, 117), and periodic compression of the microvessels by surrounding tissue structures. Pressure pulsations lead to a dynamic equilibrium between elastic stress in the wall of microvessel and the viscous fluid stress in the blood stream. Consequently, hemodynamic parameters on the arteriolar side are not in synchrony with the venular side, and local flows in selected capillaries are time dependent.

If we assume that the axial velocity components in the microvessels are significantly larger than the radial component, the equation of motion for plasma with a circular cross-section vessel is given by Poiseuille’s formula [Equation (6)]. Because the fluid escape across the blood vessel wall is significantly smaller than flow rate, the gradient of the flow rate \( Q(t, z) \) along the vessel length is
\[
\frac{\partial Q}{\partial z} = -\frac{\partial A}{\partial t}
\]

(25)

with the cross section \(A(z, t) = p - a^2\). The diameter strain \(E\) [Equation (11)] is then

\[
E = \frac{1}{2} \left( \frac{A(z, t)}{A_o} - 1 \right).
\]

(26)

Because pressure pulses are typically less than \(\sim 1\) s, the distension of the viscoelastic microvessels [Equation (10)] is dominated by the short-term elastic response with little time for viscoelastic creep, so that the pressure

\[
p(z, t) = \frac{\alpha}{2} \left( \frac{A(z, t)}{A_o} - 1 \right)
\]

(27)

with \(\alpha = \alpha_1 + \alpha_2\) [Equation (12)]. Combining Equations (25) and (27) yields

\[
\frac{\partial Q}{\partial z} = -\frac{2A_o}{\alpha} \frac{\partial p}{\partial t}.
\]

(28)

Noting that Poiseuille’s formula [Equation (6)] in terms of the lumen cross section \(A(z, t)\) is

\[
Q = -\frac{A_o^2}{8 \mu \pi} \left( \frac{2p}{\alpha} + 1 \right)^2 \frac{\partial p}{\partial z},
\]

(29)

so that, with Equation (25), the fundamental governing equation for fluid motion in a distensible microvessels under pulsatile pressure is

\[
\frac{\partial P}{\partial t} = \frac{C^2}{A^2} \frac{\partial^2 P^3}{\partial z^2}
\]

(30)

with the normalized pressure \(p(z, t) = [(2p/\alpha) + 1]\) and the constant \(C^2 = A_o\alpha/48 \mu \pi\). For an arteriole with a diameter of 140 \(\mu m\), \(\alpha = 700\) mmHg, and viscosity \(\mu = 0.04\) poise, \(C^2 = 95\) cm\(^2\)/s, whereas, for a capillary, \(C^2\) is only \(\sim 0.3\) cm\(^2\)/s. Thus, for a single capillary, \(\partial p/\partial t\) may be small, so that the left-hand side of Equation (30) may be neglected and signal propagation along the vessel in the blood is virtually instantaneous. In this case,

\[
\frac{\partial^2 P^3}{\partial z^2} = 0,
\]

(31)

which, on integration along the length of the microvessel, gives the steady-state pressure-flow relationship in Equation (23). In the microvascular network of an entire organ, however, unsteady viscous fluid motion is not negligible.

The solution to Equation (30) depends on the pressure history applied at the arterial and venous side of the microvessel. Numerical solutions of Equation (30)
show that, after a step arterial pressure, the arterial flow exhibits an overshoot followed by a gradual return to steady-state flow ($\dot{\partial p}/\dot{t} = 0$) [Equation (23)] in line with the experiments (114). The overshoot arises because the arterial pressure elevation leads to a rapid expansion of the arteriolar side of the microcirculation, whereas, in contrast, the venous flow rate asymptotically approaches the steady-state flow rate without overshoot. If, in contrast, a step flow is imposed, the arteriolar pressure increases asymptotically to its steady-state value.

A situation that is frequently encountered in experimental studies or during injury to blood vessels is the abrupt reduction of the arteriolar blood pressure from a normal physiological value to zero. For example, after a sudden ligation of an artery feeding the microcirculation, while the venous pressure is maintained, there is flow out of the venous side of the microcirculation. The magnitude of the outflow depends on the distensibility of the microvessels, $\alpha$, and on the viscosity of the blood. In the rat gracilis muscle, the transit time required to reach <5% of the initial flow rate is less than ~20 s in the presence of plasma and rises to ~40 s at a hematocrit of 27%, and there are much longer periods of time required if the erythrocytes form aggregates (141).

In the presence of oscillatory arteriolar pressures, the pressure–flow relationship exhibits hysteresis. For example, if the arterial inflow at constant venous pressure is oscillated between a physiological flow amplitude and zero flow, the hysteresis loop shifts with increasing frequencies toward elevated arteriolar pressures. The arteriolar pressure at the instant of zero arteriolar flow increases monotonically with oscillation frequency (141). Because the pressure–flow curve for a viscoelastic microvessel has a hysteresis loop that rotates counterclockwise but, at high frequency, rotates clockwise, there exists an intermediate frequency at which the pressure–flow curve assumes a figure-eight shape (76).

NON-NEWTONIAN PROPERTIES OF BLOOD IN THE MICROCIRCULATION

The flow rate $Q$ for plasma is inversely proportional to the plasma viscosity $\mu$ [Equations (22)–(24)], which in skeletal muscle was confirmed by detailed experiments over a range of viscosities (142). In the presence of red cells, blood behaves as a non-Newtonian fluid owing to the deformability of the red cells and their tendency to aggregate (19). The apparent viscosity of the flow in the tube is calculated from the relationship between the flow rate $Q$ and the pressure drop $\Delta p$ over the length $l$ of a cylindrical vessel with radius $a_0$

$$\mu_a = \frac{\pi a_0^4}{8Q} \frac{\Delta p}{L} \quad (32)$$

In the first approximation, the apparent viscosity $\mu_{app}$ measured in rigid glass tubes with diameters typical for vessels of the microcirculation can be described by Casson’s equations as
where \( k_1 \) and \( k_2 \) are two empirical coefficients that depend on the hematocrit (112).

The equation of fluid motion for a distensible microvessel with apparent viscosity \( \mu_{\text{app}} \) assumes the form

\[
\frac{dp}{dt} = -Q \frac{8}{\pi} \left( k_1 + k_2 \left( \frac{2 \pi a^2}{Q} \right)^{1/2} \right)^2.
\]

This equation can be readily integrated for vessels of different distensibilities with radius \( a(p) \). For example, for skeletal muscle at steady-state perfusion with radius \( \frac{1}{2} a_0 \) and constant arterial and venous pressure, the vessel distensibility will serve to raise the flow rate with Newtonian fluid, whereas the presence of red cells serves to raise the apparent viscosity and reduce the flow rate. The two effects counteract each other and at physiological microhematocrit almost annihilate each other.

The flow rates in the skeletal muscle microcirculation are inversely proportional to the hematocrit [Equation (23)]. In vivo experiments suggest that the apparent viscosity in the physiological range is a linear function of the hematocrit. For suspensions of pure red cells (after careful removal of all white blood cells and platelets), highly reproducible pressure–flow curves are obtained (Figure 3a) (144).

In contrast, when the skeletal muscle microcirculation is perfused with suspensions of whole blood (containing 30%–40% erythrocytes and ~5000 leukocytes/mm³, which is equivalent to <1% of the blood volume), a significant elevation of the hemodynamic resistance is encountered (12, 13, 143) in the renal and skeletal muscle microcirculation (Figure 3b) but less so in the pulmonary circulation (14). Despite the significantly higher additional pressure drop (the additional pressure drop per cell is equal to the difference in pressure drop across a flowing microvessel with and without the cell) by the stiffer and larger leukocytes compared with the smaller and highly flexible erythrocytes (119, 128), the shift of the microvascular resistance by leukocytes requires the presence of erythrocytes (54, 146) and is not observed for leukocytes themselves owing to their relatively small numbers in the circulation (150). In capillaries with a single file of cells at the same mean velocity, leukocytes move more slowly than red cells (86). As a consequence, the red cells are displaced from their preferred position along the center axis of the vessel into an eccentric position at which their axial velocity is reduced to the slower velocity of the leukocyte. Because cells in an eccentric position closer to the vessel wall have an elevated additional pressure drop compared with the same cells positioned along the axis of the vessel (139,
FIGURE 3  The pressure–flow relationship in the rat gracilis muscle at different hematocrits (a) and leukocyte counts (b) as measured with a high-precision perfusion pump (143, 144). In the absence of leukocytes, reproducible pressure–flow curves are present. After the addition of physiological numbers of leukocytes, a significant right shift of the pressure–flow curve occurs despite the fact that the leukocytes make up <1% of the cell volume. The strong right shift of the pressure–flow curve requires the presence of erythrocytes and is negligibly small in the absence of erythrocytes (54).
the apparent viscosity produced by the entire train of erythrocytes in the capillary is elevated [BP Helmke, M Sugihara-Seki, R Skalak, GWA Schmid-Schönbein, in press (55)]. Thus, the elevation of the organ resistance by a small number of leukocytes is detectable even without attachment of the leukocytes to the endothelium; the same effect is observed when the leukocytes are replaced by rigid (6-µm) microspheres, but it does depend on the hematocrit (54). The longer the capillaries, the more erythrocytes are affected by the presence of leukocytes; thus, the effect of leukocytes on whole-organ microvascular perfusion is larger in organs with greater capillary length and smaller in the pulmonary circulation with a dense network of very short capillaries. The apparent viscosity predicted from cylindrical glass tubes appears to underestimate the actual resistance encountered in the microcirculation (102), even for pure red cell suspensions (144). This has led to the hypothesis that a relatively thick glycocalyx on microvascular endothelium may serve to restrict red cell motion (26, 126).

DETAILS OF CAPILLARY FLOW

So far we have discussed average-velocity components in the microcirculation without regard to the actual details encountered in individual microvessels. Computations of the actual plasma velocity profile around the erythrocytes were presented originally by Zarda et al (157). They used membrane mechanical properties of the red cells, measured by independent micropipette experiments, and determined the typical parachute shapes of the red cells in capillaries subject to a pressure drop and deformed by fluid shear stress at the wall. The computed and observed red cell shapes in capillaries were quite similar. Models using the Reynolds equation of lubrication theory were applied to leukocytes (132), to red cells in symmetric and asymmetric positions in capillaries (139), and to capillaries with nonuniform cross sections caused by endothelial cell nuclei (124, 125). Endothelial cells protruding into the capillary lumen cause almost a twofold increase in hemodynamic resistance.

MICROCIRCULATION AFTER ACTIVATION

When leukocytes are activated (e.g. by administration of a stimulating agent such as endotoxin from bacterial surfaces, release of platelet-activating factor, or cytokines), a dramatic elevation of the microvascular resistance occurs (143). The muscle microcirculation perfusion shifts not only toward elevated resistances, but also the pressure–flow curves are no longer reproducible. This is especially important in the understanding of cardiovascular complications. A large number of investigations and reports are available in the medical literature. We discuss here some fundamental aspects of this important problem.
Activation of the microcirculation can be readily detected on endothelial cells, leukocytes, and platelets. An early indicator is active deformation of the cell cytoplasm by polymerization of actin (91, 92, 109), for example, in the form of pseudopods (116; Figure 4). These cytoplasmic projections with cross-linked actin are required for amoeboid migration, angiogenesis, phagocytosis, and many other cell functions, and, despite their relatively dynamic motion, at any instant of time, these projections are relatively rigid structures that exhibit reduced viscoelastic creep (110, 116). In the microcirculation, they cause impairment of flow and entrapment of leukocytes in capillaries (36, 52, 53, 106, 151, 152). For capillary endothelial cells, pseudopods may be projected into the lumen over a length of several micrometers, which causes a dramatic elevation of the hemodynamic resistance in such capillaries with greatly impaired ability of erythrocytes or leukocytes to pass through the lumen (74).

Another manifestation of cell activation is the expression of membrane adhesion molecules, which mediate attachment of platelets and leukocytes to the endothelium and to interstitial proteins and structures. Important members of these classes of adhesion molecules are the selectins (L, P, E), integrins (β1, β2), the immunoglobulin superfamily of glycoproteins (e.g. ICAM-1, -2, -3; VCAM-1, PECAM-1), and mucinlike adhesion molecules. The distribution of these molecules has a direct influence on the mechanics of cell adhesion and microvascular kinetics. Both L-selectin and ICAM-1 are constitutively expressed in the membrane of the circulating leukocytes (145) and on postcapillary endothelium (2, 58), respectively. Upon stimulation, L-selectin is shed by leukocytes, whereas the integrin CD11b/CD18 is transported from an intracellular granule membrane to the plasmalemmal membrane (89). P-selectin is constitutively expressed in postcapillary venular endothelium of many organs. It is stored in the Weibel-Palade bodies of the endothelial cytoplasm and, on stimulation, can be rapidly transferred into the plasmalemmal membrane, where it supports adhesion of the leukocyte membrane. Several of the adhesion molecules are produced de novo after stimulation. The identification of adhesion molecules and their counterreceptors, as well as their mechanics, is currently an active field of investigation (1, 15, 27, 40, 49, 73, 94, 103, 129, 130). The variety of membrane adhesion molecules and their counterreceptors provides the specificity for the attachment and migration of different leukocytes in different tissues. The use of antibodies against specific adhesion molecule epitopes and the use of transgenic animals with deletions of one or multiple adhesion molecules offer the opportunity to investigate the mechanisms at the molecular level (80). There is a high degree of complexity because several of these membrane adhesion molecules also regulate cell activation, and the expression of adhesion molecules, as well as the mechanical properties of the endothelial cells, is in turn controlled by fluid shear stress (20, 48, 108).

Other forms of cell activation, like oxygen free-radical formation, proteolytic enzyme release from cytoplasmic granules, expression of cytokines, and inflammatory mediators, affect the mechanical properties of the cells and therefore the biomechanics of the microcirculation in disease.
FIGURE 4 (top) Scanning electron micrograph and (bottom) transmission electron micrograph of human neutrophil after activation. In contrast to passive leukocytes, which are round, activated cells project pseudopods by polymerization of their cytoplasmic action. Such protrusions are accompanied by transport of adhesion molecules into the membrane as well as many other cell activities. This seemingly innocent transformation of the cells in the microcirculation leads to a significant rise in capillary resistance and accumulation of leukocytes on the endothelium of microvessels. The scale lengths of the cross bars are (top) 10 μm and (bottom) 1 μm.
THE LEUKOCYTE ADHESION CASCADE

One specific event that is influenced by cell activation is the adhesion of leukocytes to microvascular endothelium and emigration into the tissue by active motion. Leukocytes that are not activated pass through the microcirculation without prolonged attachment to any of the vessel segments, whereas, in contrast, activated leukocytes use the endothelium in microvessels as a mechanism to stop circulating, attach, and migrate into the tissue.

This cascade of events has its origin at the entry of the capillary network where leukocytes are compressed by the plasma lubrication pressure into cylindrical shapes (4, 132) without significant molecular attachment to the endothelium. In the capillary, the leukocyte has a cylindrical shape and travels with a lower velocity than the erythrocytes. The fluid lubrication pressure tends to centralize the leukocyte in the capillary lumen, but the collision with the red cells will displace both erythrocyte and leukocyte off the axial position. In postcapillary venules with wider lumen, leukocytes that are off the vessel axis will rotate and thereby pull plasma and red cells past themselves. As red cells pass the leukocyte, they apply a force on the leukocyte in the direction of the vessel wall sufficient to achieve molecular membrane attachment. This interaction is the first instance of leukocyte rolling on postcapillary endothelium during which leukocytes are passively deformed by the fluid shear stress into tear-drop shapes (61, 82). The rolling of the leukocyte is determined by the magnitude of the applied fluid shear stress, the details of the endothelial membrane surface contour, the distribution and density of membrane adhesion molecules, and the membrane contact area, especially tight contact regions and the viscoelastic properties of the cell cytoplasm (83).

One of the mechanisms to stop rolling is the active spreading of the leukocyte cytoplasm over the endothelium and stiffening of the cytoplasmic region underneath the contact region. Spreading can be triggered by integrin-ligand attachment (50) but is opposed by fluid shear stress (90). Fluid shear stress at modest levels induces a rapid retraction of pseudopods in circulating leukocytes, returning cells that actively spread on the endothelium into a round shape so that they are able to roll on the endothelium.

To migrate through the endothelium, leukocytes require pores in the endothelium. Endothelial cells can form pores after stimulation both at their junctions and inside the endothelium (6, 38, 93). The mechanism that leads to pore formation appears to involve tension produced by endothelial membrane curvature and local depolymerization of the actin cytoskeleton (113). Leukocytes project their pseudopods through such pores and crawl underneath the endothelium. Closure of the pore is brought about by repolymerization of the endothelial cytoskeleton. Migration through the basement membrane requires the action of proteolytic enzymes to break down the collagen mesh.
CELL DISTRIBUTION IN THE CAPILLARY NETWORK

The hematocrit in the microcirculation is lower than in the central circulation, which protects the more slowly flowing microvessels against an elevation of the apparent viscosity at reduced shear rates. The reduction of the microhematocrit is largely caused by two mechanisms that control the blood cell distribution in the microcirculation: radial migration of red cells (which leads to the Fahraeus effect) and the separation of blood cells at microvascular bifurcations. Both effects have received much attention and are reviewed elsewhere (100, 117, 127). For freely suspended cells flowing from a feed reservoir with hematocrit $H_F$ at a flow rate $Q = A \cdot U$ into a tube with average cell velocity $U_C$ and tube hematocrit $H_T$, conservation of the cells requires that the flux of cells into the tube ($Q_1 H_F$) is equal to the flux inside the tube ($A_1 U C_1 H_T$), so that

$$\frac{H_T}{H_F} = \frac{\bar{U}}{U_C}.$$  \hspace{1cm} (36)

Because the flowing erythrocytes are subject to radial migration away from the vessel wall, $U_C > \bar{U}$, the tube hematocrit $H_T$ is lower than the feed hematocrit $H_F$. In a cylindrical blood vessel, where the highest velocity of freely suspended erythrocytes on the center line (owing to the parabolic profile of Poiseuille flow) cannot be more than twice the average velocity, inspection of Equation (36) shows that $H_T$ cannot fall below $1/2$ of $H_F$. This limitation is clearly borne out by the experimental results in cylindrical tubes. However, in vivo the capillary hematocrit may fall below 50% of the central vessel hematocrit (84). Therefore, there exist other mechanisms to reduce the tube hematocrit in the microcirculation.

One important mechanism is caused by separation of blood cells at divergent bifurcations. At a narrow capillary bifurcation, erythrocytes or leukocytes are pulled by shear stresses and the pressure drop into the daughter vessel with the faster flow (99, 117, 154). At larger arteriolar bifurcations, the cells are carried along two well-defined flow tubes into the daughter vessel, with little cell mixing between the tubes. The two fluid tubes are separated by a dividing stream line (21, 39) that is almost planar at symmetric bifurcations but curved in nonsymmetric bifurcations with daughter vessels of unequal diameter. Because the hematocrit inside the parent vessel is not uniform (there are fewer cells at the wall than in the center of the stream), there is a nonlinear relationship between the flux of cells (cell volume per time) into any of the daughter vessels and the flow rate (cell and plasma volume per time). At low flow rates in terminal arterioles, the downstream capillaries receive a reduced hematocrit, and blood with a higher hematocrit is shunted into more quickly flowing arterioles. The mechanism serves to reduce the capillary tube hematocrit to almost zero values during vasomotor cycles.

In contrast to erythrocytes, leukocytes are easily trapped in the capillary network, leading to local obstructions (25, 35, 122). Reduction of blood flow (105) and activation of leukocytes serve to promote this entrapment (106, 111). The
entrapment of leukocytes in the pulmonary microcirculation depends more on the size and stiffness of the leukocytes (28, 29, 152) than on the action of membrane adhesion molecules (30), although activated leukocytes can be entrapped by a CD18-dependent adhesion mechanism (2). Hogg & Doerschuk (56) have reviewed leukocyte kinetics in the pulmonary microcirculation.

CONCLUSION

With the advent of molecular definitions of the membranes and cells that constitute the microcirculation, it will be possible to develop a more and more detailed picture of microvascular networks, organ perfusion, and transport. Biomechanics will play a central role in the analysis. Many organs have not been studied yet. There will be numerous applications to various diseases. It can be argued that analysis of disease is the most important application of biomechanical models of the microcirculation, i.e. to serve as the basis of a rational engineering analysis of cardiovascular diseases.


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