Hemodynamics and Vascular Remodeling

1

Timothy W. Secomb

Contents

Abstract

The flow of blood in the vasculature generates forces that act on vessel walls. Blood pressure generates circumferential stresses within the walls, while the endothelial lining of vessels experiences shear stresses as a consequence of blood's motion over it. Both types of stress can elicit biological responses from cells in the walls, including growth and remodeling that are required for the normal function of the vasculature, and the development of vascular diseases. The main objective of this review is to summarize the dynamical features of blood flow as they affect the stresses that act on vessel walls. A second objective is to

T. W. Secomb (✉)
Department of Physiology, University of Arizona, Tucson, AZ, USA
e-mail: secomb@u.arizona.edu

M. Hecker, D. J. Duncker (eds.), *Vascular Mechanobiology in Physiology and Disease*, Cardiac and Vascular Biology 8,
https://doi.org/10.1007/978-3-030-63164-2_1

summarize the relationship between these stresses and the resulting structural responses in normal and disease states.

1.1 Introduction

The human circulatory system includes blood vessels with a total length of about 10^7 m [1]. They form a network of more than 10^9 segments with diameters ranging from a few μm to a few cm. Adequate and efficient distribution of blood flow throughout the body in accordance with tissue requirements depends on the structural characteristics of the vascular system and the flow behavior of blood as it traverses this network.

The structure of the vasculature is not static. The locations of the major arteries and veins are largely predetermined, but all blood vessels are subject to significant structural changes during development, in response to changing functional demands in health, and due to the effects of the disease. It is obvious that the structural characteristics of the vast number of vessel segments cannot be controlled on an individual basis by genetic information. Instead, the structure of the vasculature must emerge as the collective result of vascular growth and remodeling by each segment in response to the conditions and stimuli that it experiences [2]. These stimuli include the forces acting on vessel walls resulting from blood pressure and flow, namely the circumferential wall stress generated by blood pressure and the wall shear stress generated by blood flow.

In the following sections, the concept of stress in continuum mechanics is presented, followed by a review of the fluid dynamics of blood flow, with emphasis on the stresses acting on vessel walls. The effects of these hemodynamic stresses on vessel wall structures in normal and disease conditions are then discussed.

1.2 Mechanical Stress in Materials

In studies of fluid and solid mechanics, a continuum approach is generally used, in which relevant properties of the material, such as density and velocity, are considered as continuous functions in space, without analyzing the positions or motion of the individual molecules or other particles in the material or the forces acting on them. To describe the forces acting in a continuum, a mathematical entity known as the stress tensor is used. Here, the concepts underlying the stress tensor are described without using mathematical notation. More rigorous expositions are provided in textbooks [3, 4]. Despite the importance of biological responses to mechanical stress in the field of mechanobiology, understanding the concept of stress and its expression as a tensor presents a challenge for many biologists. The following discussion is intended to help bridge this gap.

As a starting point for defining mechanical stress, the forces acting across a hypothetical small planar surface lying within a material or on its boundary are considered. The traction (or stress vector) is defined as the force per unit area acting

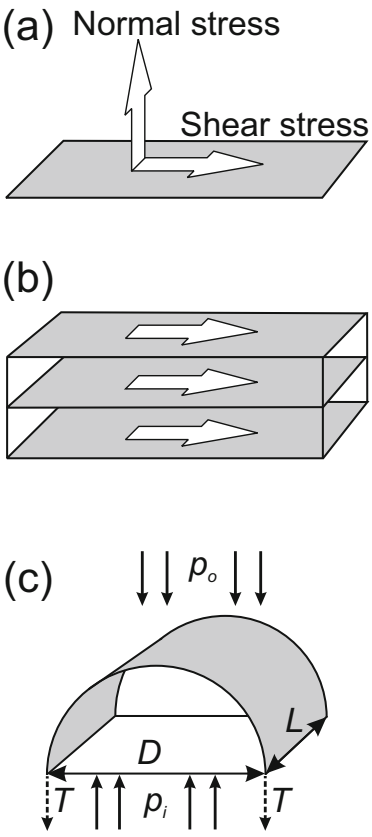

Fig. 1.1 Schematic illustration of basic concepts relating to mechanical stress. (**a**) Normal and shear components of stress acting on a surface (shaded) within or on the boundary of a material. (**b**) When a shear stress acts on the surface of a planar structure of finite thickness, such as a monolayer of endothelial cells, then the shear stress is transmitted uniformly through the thickness of the structure. (**c**) Estimation of the tension in a cylindrical structure subjected to a fluid pressure difference across its wall (shaded). The pressure difference across the wall generates a net force that is balanced by the force generated by tension in the walls

on one side of the surface. More precisely, the traction at a point is defined by considering such a surface containing the given point and taking the limit of force divided by area as the area of the surface approaches zero. Being a vector, traction requires three components to represent its magnitude and direction.

The traction generally depends on the orientation of the surface, represented by the unit vector normal (i.e., perpendicular) to it. For instance, a material may be under tension in one direction and under compression in an orthogonal direction. It can be shown that the dependence of the traction on surface orientation can be fully defined by specifying the tractions acting on three mutually orthogonal coordinate surfaces. The combination of these three traction vectors forms a tensor, which can be expressed as a 3×3 matrix of components in any given coordinate system. In this matrix, the elements on the diagonal are normal stress components, i.e., forces acting normal to a surface (Fig. 1.1a). The off-diagonal elements are shear stress components, i.e., forces acting parallel to a surface (Fig. 1.1a). However, it should be noted that these definitions depend on the orientation of the coordinates. Normal stresses in one coordinate system may appear as shear stresses in a rotated system.

By convention, the outward normal vector to a surface experiencing a traction is used to represent its orientation. It follows that positive diagonal elements in the stress tensor represent tensile forces in the material, while negative diagonal elements represent compressive forces. In the special case of hydrostatic pressure, the only non-zero elements of the stress tensor are on the diagonal, and all are equal to $-p$, where p is the pressure. For any traction acting on a surface with a given normal vector, the force acting on a surface with the opposite normal vector must be equal and opposite, since it represents the reaction force according to Newton's third law of motion.

The stress tensor discussed here is more precisely called the Cauchy stress tensor. In this form of the stress tensor, all quantities are referred to coordinates in the current, possibly deformed, state of the material. For analysis of large-deformation elasticity, other stress tensors (e.g., Piola-Kirchhoff) are often used [5], in which quantities are referred to coordinates in an initial undeformed or reference configuration.

1.3 Conditions for Equilibrium of Mechanical Stress

According to Newton's second law of motion, the force acting on an object equals the product of mass and acceleration. To apply this principle in a continuum, the forces acting on a small volume within the material are considered. For convenience, a cuboidal region is assumed. If the stress in the material is uniform in space, then according to the above discussion, equal and opposite forces act on each pair of parallel surfaces of the cuboid, since their outward normal vectors point in opposite directions. In this case, the zero net force is generated. In general, therefore, the resultant forces generated by a stress field within a continuum must depend on the spatial variations of the stress tensor. The size of the cuboidal region is then considered to approach zero. In this limit, it is found that the resultant force per unit volume of the material is proportional to a particular combination of the spatial derivatives of the stress tensor. If the acceleration of the material is zero or its inertia is negligible, then this combination of derivatives (specifically, the divergence) must be zero to satisfy the mechanical equilibrium of the material.

This result has significant implications for the mechanotransduction of shear stress. Consider a situation in which a multilayer planar structure is subjected to a uniform shear stress on its upper surface, and is immobilized so that its acceleration is zero. According to the condition of mechanical equilibrium, the shear stress (possibly averaged over a surface parallel to the upper surface) must be uniform through the thickness of the structure (Fig. 1.1b). In a curved geometry, such as a blood vessel wall, the same result applies to a good approximation if the structure is thin relative to the vessel radius. This argument can be applied to the endothelial cells lining blood vessels, with the implication that the same (average) shear stress is experienced by the luminal surface, the interior cellular structures such as the cytoskeleton, and the structures connecting the endothelial layer to the basement

membrane. All of these structures are therefore potential sites for mechanotransduction of shear stress by endothelial cells.

The conditions of mechanical equilibrium can also be used to calculate the tension generated in a cylindrical blood vessel wall as a result of the difference between the internal and external pressures acting on the vessel. In this case, the analysis can be simplified by considering the total forces acting on a semicircular part of a vessel segment of length L and diameter D, as shown in Fig. 1.1c. The wall is considered to be thin relative to the radius, and only forces acting in the vertical direction are considered. The pressure difference across the wall, $\Delta p = p_i - p_o$, generates an upward force ΔpLD, which must be balanced by a downward force of $2LT$ generated by tension in the walls, where T is the tension per unit length of the vessel. Equating these forces gives

$$T = r\Delta p \tag{1.1}$$

which is known as the Law of Laplace for a cylinder, where $r = D/2$ is the tube radius. If the wall has thickness h, then the average circumferential stress in the wall is

$$\sigma = \frac{r}{h}\Delta p \tag{1.2}$$

The ratio r/h is generally larger than 1, and it follows that the dominant stress in vessel walls is circumferential stress, not the radial stress generated by blood pressure acting on the walls. Furthermore, r/h varies substantially with vessel type and size [6], being relative small (as low as about 2) in capillaries, and increasing with vessel size up to values of about 10 in arteries and about 50 in veins.

Some caution is needed with regard to the interpretation of Eq. (1.2) in the context of mechanotransduction. Because the circumferential wall stress is a normal component of stress acting in the circumferential direction, it can be variable and even discontinuous with the position in the radial direction (unlike shear stress). The levels of stress carried by the various components of the vessel wall (endothelial cells, basement membrane, smooth muscle cells, elastin, and collagen) may vary widely according to the mechanical stiffness and the degree of stretch (strain) of each component. Also, if r/h is not large, the thin-wall theory presented above may not be a good approximation and a more elaborate theory is needed [7]. The components of the vessel wall that are primarily responsible for responses to changes in intravascular pressure, particularly vascular smooth muscle, may experience levels of stress significantly different from the estimated average given by Eq. (1.2).

1.4 Hemodynamics

For the purposes of this review, we define hemodynamics as "the physical study of flowing blood and of all the solid structures (such as arteries) through which it flows" [8]. This differs from the medical usage of the term, where it generally refers to

parameters such as arterial blood pressure and cardiac output in patients. More detailed discussions of this field are presented in several books [8–12] and articles [7, 13]. In the following presentation, the dependence of wall shear stress on fluid mechanical effects is emphasized, in recognition of the fact that shear stress is an important determinant of vascular remodeling.

1.4.1 Flow in a Cylindrical Tube

The analysis of fluid flow along a cylindrical tube is central to the study of hemodynamics. A first step in this analysis is the determination of the distribution of shear stress in the fluid and at the tube wall, which can be obtained readily under some simplifying assumptions [3, 4]. The tube is assumed to have diameter D and length L, with pressures p_1 at the upstream end and p_0 at the downstream end. The distribution of flow velocity across the tube is assumed to be uniform along the tube and also constant in time. Effects of gravity are neglected. We consider a cylindrical region of fluid with radius $r \leq D/2$, centered on the axis of the tube, and define τ as the shear stress acting in the upstream direction on the curved surface of this region. According to the stated assumptions, τ is uniform over the curved surface. Because there is no acceleration of the fluid, Newton's second law of motion implies that the sum of the forces acting on the cylinder is zero, i.e.,

$$\pi r^2 p_1 - \pi r^2 p_0 - 2\pi r L \tau = 0 \tag{1.3}$$

where each of the stresses, p_1, p_0, and τ, is multiplied by the area of the surface on which it acts. Therefore

$$\tau = \frac{r\Delta p}{2L} \tag{1.4}$$

where $\Delta p = p_1 - p_0$ is the driving pressure. This result shows that the shear stress in the fluid varies in proportion to the distance from the tube axis and that the shear stress acting on the tube wall is

$$\tau_w = \frac{D\Delta p}{4L} \tag{1.5}$$

It is noteworthy that these results do not depend on any assumption about the viscous properties of the fluid.

For the further analysis of flow in tubes, we assume that the fluid is Newtonian, meaning that the shear stress is proportional to the gradient of fluid velocity:

$$\tau = -\mu \frac{du}{dr} \tag{1.6}$$

where μ is a constant, the fluid viscosity, and $u(r)$ describes the variation of fluid velocity with the radial position. (The minus sign appears here because τ was defined with respect to the direction opposite to the flow.) From Eqs. (1.4) and (1.6), it can be shown that

$$u(r) = \frac{\Delta p}{4L\mu}\left(\frac{D^2}{4} - r^2\right) \tag{1.7}$$

i.e., the profile of velocity across the tube has the form of a parabola. Flow in a tube with this velocity profile is known as Poiseuille flow. This solution satisfies the "no-slip" condition for a viscous fluid, which states that the velocity of the fluid adjacent to a solid boundary must match the velocity of the boundary, i.e., $u(D/2) = 0$ in this case. Integration of the velocity over the vessel cross section leads to the equation generally known as Poiseuille's law or the Hagen–Poiseuille equation:

$$Q = \frac{\pi}{128}\frac{\Delta p D^4}{L\mu} \tag{1.8}$$

where Q is the volume flow rate along the tube.

The fourth power dependence of flow rate on diameter, for a given fluid viscosity and for fixed tube length and pressure drop along the tube, was established experimentally in the nineteenth century by J.L.M. Poiseuille [14]. Equation (1.8) was obtained subsequently by theoretical analysis [15].

The derivation of Poiseuille's law depends on a number of assumptions that are generally not satisfied in the vascular system, and its applicability in any given situation has to be carefully evaluated. Even so, it provides a starting point for more detailed analyses and has important physiological implications. In particular, the proportional dependence of Q on D^4 implies that the blood flow rate is very sensitive to changes in vessel diameters. Therefore, blood flow rates can be modulated over a wide range by moderate changes in vessel diameter, and controlled distribution of blood flow according to local tissue needs can be achieved only with relatively precise control of vessel diameters.

Combining Eqs. (1.5) and (1.8) yields the following result:

$$\tau_w = \frac{32}{\pi}\frac{\mu Q}{D^3} \tag{1.9}$$

This relationship is significant with regard to understanding how vascular responses to wall shear stress influence network structure, as discussed below.

1.4.2 Bulk Viscosity of Blood

Blood is a complex fluid, consisting of a suspension of cells in plasma. The mechanical properties of blood are strongly affected by the presence of a high

volume fraction (hematocrit) of red blood cells (erythrocytes), typically in the range of 40–45% for healthy individuals [16].

The bulk viscosity of blood can be measured by placing a sample in a viscometer where it is subjected to a shear flow with a controlled shear rate, defined as $\dot{\gamma} = du/dz$, where u is the fluid velocity and z is a coordinate perpendicular to the flow direction. The shear stress τ on a surface bounding the flow is measured, and the viscosity is computed as $\mu = \tau/\dot{\gamma}$. The viscosity of blood is found to increase as a function of hematocrit [17], as would be expected since the presence of suspended particles tends to oppose the variations of flow velocity within the fluid. Also, blood exhibits shear-thinning behavior and viscosity increases substantially when the shear rate is decreased to low levels [17]. This behavior can be understood as the result of two main effects [16]. Firstly, red blood cells are highly deformable, and this deformation allows them to accommodate to the flow and reduce their contribution to the suspension viscosity. However, this effect is reduced at very low shear rates, because the cells are deformed less at the resulting low levels of shear stress. Secondly, red blood cells of many species, including humans, aggregate at low shear rates, forming larger structures called rouleaux which interfere more strongly with the flow. With increasing shear rates, aggregates are broken up and the viscosity decreases. It is important to note that this dependence on shear rate occurs mainly at shear rates below about 100 s^{-1} [17], whereas shear rates in normally flowing vessels are generally above this range and viscosity shows only slight variations with shear rate. For many purposes, e.g., when analyzing blood flow in arteries, the dependence of viscosity on shear rate can be neglected and blood can be treated as a Newtonian fluid as defined above.

1.4.3 Viscosity of Blood in Microvessels

The preceding discussion is based on the assumption that blood can be represented as a continuum, in the sense that viscosity is considered as an average property over a region containing a large number of red blood cells. This approximation is valid for vessels with diameters of about 300 μm or more. However, in vessels with smaller diameters, the effects of the particulate nature of blood become significant. In particular, red blood cells show a tendency to migrate away from vessel walls, as a result of fluid mechanical interactions between the deformable cells and the imposed flow in the vessel. This phenomenon, which does not involve active motion by the cells, results in the formation of a cell-free or cell-depleted layer near the vessel walls, which causes a significant reduction of resistance to flow relative to what would be expected based on the bulk viscosity of blood [18].

A convenient method to quantify this effect is to define the apparent viscosity, from Eq. (1.8):

$$\mu_{\text{app}} = \frac{\pi}{128}\frac{\Delta p D^4}{LQ} \tag{1.10}$$

where Δp and Q are now measured quantities. Based on an analysis of multiple experimental studies of blood flow in glass tubes, Pries et al. [19] obtained an empirical formula for the dependence of apparent viscosity of blood in vitro on tube diameter and hematocrit, for tube diameters from 3.3 μm up to 2 mm and hematocrits up to 90%. These results show a strong Fåhraeus–Lindqvist effect [20]: apparent viscosity decreases with decreasing diameter down to a minimum at about 7 μm. For hematocrit 45%, the bulk viscosity is $3.2\mu_p$, where μ_p is the viscosity of plasma, whereas the apparent viscosity in a 7-μm tube is $1.25\mu_p$.

Observations of blood flow in microvessel networks of the rat mesentery were, however, found to be inconsistent with model predictions based on the above in vitro estimates of blood viscosity [21]. Based on such observations, a different empirical formula was developed to describe the apparent viscosity of blood in microvessels in vivo, as a function of tube diameter and hematocrit [22]. According to this formula, the apparent viscosity in large vessels matches the in vitro result, but the apparent viscosity is substantially higher than the in vitro estimate in smaller vessels. For example, the estimated apparent viscosity in a 7-μm capillary at hematocrit 45% is about $8.4\mu_p$, almost seven times higher than would be expected based on data from glass tubes.

The shear stress acting on the walls of microvessels can be estimated from the flow rate Q according to Eq. (1.9), setting the viscosity μ equal to μ_{app}. Therefore, the finding of relatively high values of apparent viscosity in microvessels implies that the estimates of wall shear stress in microvessels based on observations of blood flow rate or blood flow velocity are significantly higher than would be obtained if the calculation was based on values of apparent blood viscosity obtained in vitro.

Several potential causes for the high apparent viscosity of blood in microvessels relative to values in glass tubes were identified by Pries et al. [21]. Subsequent studies showed that the main cause for the higher apparent viscosities in vivo is the presence of a layer of macromolecules on the inner wall of blood vessels, termed the endothelial surface layer (ESL) or glycocalyx [23]. This gel-like layer has a very low volume fraction of membrane-bound molecules, but the resistance to fluid motion through the layer is sufficient to reduce the flow velocity of plasma to a much lower value than the velocity in the lumen, outside the ESL.

An important implication of this finding is that the endothelial cell membrane does not experience a significant level of fluid shear stress due to plasma flow over its surface. Instead, shear stress is transmitted to the endothelial cells via the attachment points of the macromolecules that anchor the ESL, including syndecans and glypicans [23, 24]. Being transmembrane proteins, these molecules may in turn transmit the shear stress to the internal cytoskeleton, consistent with an important role for the cytoskeleton in mechanotransduction of shear stress [25, 26].

1.4.4 The Reynolds Number

The flow of fluids is governed by Newton's laws of motion, such that the acceleration of any small part of the fluid, multiplied by its density, is equal to the net force per unit volume acting on it. When the velocity field is viewed in a fixed frame of reference, the fluid acceleration includes a component, known as the advective acceleration, given by a product of the fluid velocity and a spatial gradient of velocity. This represents, for instance, the acceleration experienced by a fluid moving from a region of low velocity to a region of higher velocity, as in a nozzle. The forces acting on the fluid include body forces (i.e., gravity), forces due to gradients in pressure, and forces due to viscosity.

In the study of fluid mechanics, dimensionless parameters are defined that provide indications about the characteristics of the flow under consideration. The most important of these is the Reynolds number [11], defined as the ratio of the inertial effect to the viscous effect. Here, the inertial effect is estimated as the density multiplied by the advective acceleration, while the viscous effect is estimated as the viscous force per unit volume. Suppose that U is a typical fluid velocity and L is a typical length over which the velocity varies. According to the above information, the inertial effect has a typical magnitude $\rho U^2/L$, where ρ is the fluid density. From Eq. (1.6), the shear stress has typical magnitude $\mu U/L$, and the resultant force per volume, which depends on the spatial gradient of stress, has typical magnitude $\mu U/L^2$. The Reynolds number (Re) is then defined as the ratio

$$\mathrm{Re} = \frac{\rho U^2/L}{\mu U/L^2} = \frac{\rho UL}{\mu} \tag{1.11}$$

For flow in tubes, the most relevant spatial dimension is the diameter and the Reynolds number is defined as $\mathrm{Re} = \rho UD/\mu$.

1.4.5 Flow at Low Reynolds Number

Values of the Reynolds number vary widely in the circulatory system, from values below 10^{-3} in the capillaries to values above 10^3 in major arteries. At very low Reynolds numbers, the effects of fluid inertia on the flow are negligible and the flow is dominated by effects of viscosity. This regime is known as Stokes flow. The governing equations of fluid flow are then linear in velocity and pressure, allowing the use of a range of classical mathematical techniques to analyze problems of Stokes flow [27]. Because effects of inertia are negligible, the flow readily adjusts to changes in direction, and vessel curvature or tortuosity does not result in substantial changes in the magnitude of flow or the distribution of wall shear stress. When the pressure gradient driving the flow varies in time, the flow rate varies approximately in proportion to the instantaneous pressure gradient. Irregularities such as bifurcations or changes in vessel diameter produce local perturbations to velocity distributions, which quickly recover their previous characteristics once the

irregularity is passed. The velocity profile of fluid entering a vessel approaches its final form within a short distance. For a Newtonian fluid, this profile is the characteristic parabolic profile of Poiseuille flow. In these respects, fluid flow at low Reynolds number is somewhat simpler than flow at high Reynolds number, as discussed below.

However, when the flow of blood is considered, additional complexity arises because blood is a concentrated suspension of cells, whose dimensions are comparable to microvessel diameters. As mentioned earlier, red blood cells show a tendency to migrate away from microvessel walls. The fluid mechanical mechanisms underlying this behavior depend on the deformability of the cells and on the fluid dynamical interactions of cells with the walls and are only partially understood [18, 28–33]. The distribution of red blood cells across the vessel cross-section affects the distribution of hematocrit in each branch when the flow reaches a diverging microvascular bifurcation [34], and the theoretical understanding of this phenomenon is a challenging problem in the low Reynolds number flow [35–37].

1.4.6 Flow at High Reynolds Number

When the Reynolds number is high, in the range of hundreds or thousands, the flow exhibits very different behavior to that at a low Reynolds number. The phenomena discussed in this section have been considered in more detail in several books [9, 12, 38]. At high Reynolds number, effects of fluid inertia have dominant effects on the fluid motion in most of the flow domain. Even so, viscosity has important effects as a consequence of the no-slip condition, as defined above. This condition is often satisfied through the appearance of a narrow region adjacent to a solid surface in which velocity changes rapidly with the position, known as a boundary layer. A region of rapidly changing velocity can also appear in the interior of the flow, in which case it is referred to as a "shear layer."

An example of a boundary layer is provided by the flow of an (initially quiescent) fluid entering a uniform cylindrical tube (Fig. 1.2a) at high Reynolds number. In the entrance region of the tube, the fluid has a uniform distribution of velocity, except for narrow boundary layers at the tube walls where the velocity drops to zero to satisfy the no-slip condition. This results in a relatively high wall shear stress in this region. As the fluid progresses downstream, this layer gradually thickens until eventually the velocity profile approaches the parabolic shape discussed above. The distance to achieve an almost parabolic profile, known as the "entrance length," is proportional to the Reynolds number. Beyond this point, the flow is considered to be fully developed. For the aorta and major arteries, the entrance length is typically comparable to or longer than the actual length of the artery, and so fully developed flow is never achieved, and the distribution of wall shear stress differs significantly from the estimate based on Poiseuille flow.

The flow of blood through a region of local narrowing of a blood vessel, i.e., a stenosis, provides further examples of phenomena occurring in high-Reynolds flow (Fig. 1.2b). At the stenosis itself, the blood flow velocity must increase as a

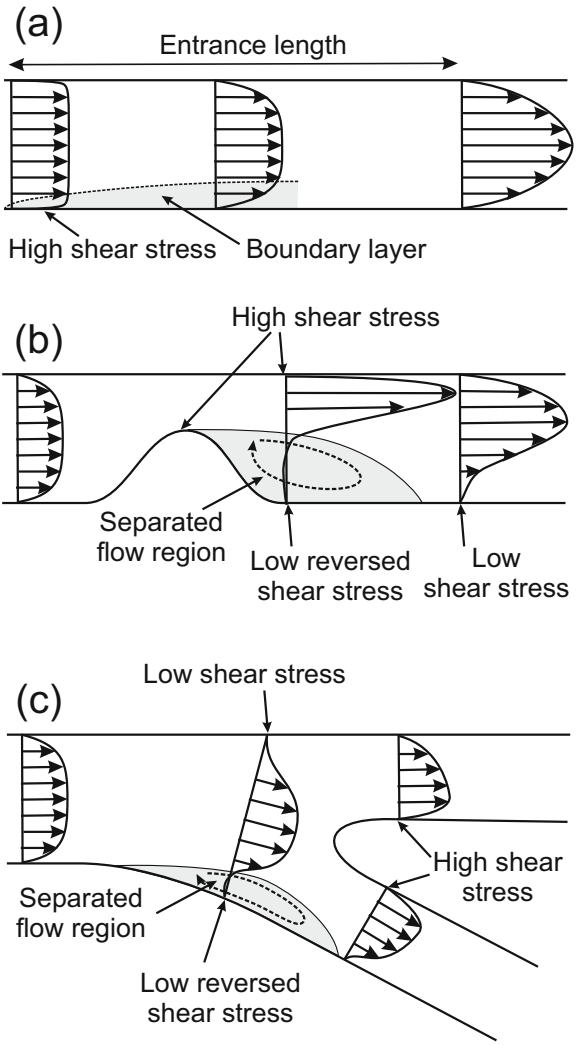

Fig. 1.2 Schematic illustration of phenomena associated with laminar flow in blood vessels at high Reynolds numbers. (**a**) Entrance effects. When steady laminar flow with an initially flat velocity profile enters a tube, a boundary layer is formed in which the flow velocity is progressively retarded. This layer thickens with distance downstream, and eventually the velocity profile approaches the parabolic form of Poiseuille flow. (**b**) Flow past a stenosis (narrowing) in a vessel, exhibiting flow separation. The region between the separating streamline and the wall is shaded and typically exhibits slow recirculating blood flow. Wall shear stresses are increased in some regions and reduced in others, relative to the shear stress in the upstream region. (**c**) Flow through a diverging arterial bifurcation. As in (**b**), the shaded region represents flow separation. Wall shear stress is increased in some regions and decreased in others

consequence of the reduced cross-sectional area of the vessel lumen in the stenosis. The flow exiting the narrow region tends to continue moving parallel to the vessel axis, rather than following the profile of the wall. This sets up a phenomenon known as flow separation, in which fluid streamlines (paths aligned with the flow direction) that are adjacent to the wall in the stenosis separate from the wall, typically reattaching to the wall at some distance downstream, as shown in Fig. 1.2b. In the region between the separating streamline and the wall, shown in gray in Fig. 1.2b, a region of recirculating flow is set up, in which the flow velocities are generally much lower than elsewhere in the vessel.

A similar phenomenon can occur in a diverging arterial bifurcation. In this case, the widening of the parent vessel at the entrance to the bifurcation sets up fluid mechanical conditions analogous to those immediately downstream of a stenosis. The wall shear stress is reduced in the region of widening, and flow separation may occur, leading to the reversal of the wall shear stress in the region of recirculating flow (Fig. 1.2c).

When fluid flows through a curved vessel, the fastest moving fluid, which is near the centerline in a straight tube, is displaced toward the wall at the outside of the curve, and the shear stress is increased there and decreased on the wall at the inside of the curve [9].

Flows at high Reynolds number may be subject to instability, i.e., spontaneous development of time-dependent fluctuations in the flow field. The conditions for instability depend both on the Reynolds number and on the characteristics of the flow. Poiseuille flow, with a parabolic flow profile, is stable up to Reynolds numbers of about 2300 [9]. However, the flow profiles occurring downstream of a stenosis or in the entrance to a bifurcation (Fig. 1.2b, c), which include one or more inflection points, can lead to flow instability at much lower Reynolds numbers, in the range of a few hundred. One result of flow instability is the generation of audible sounds, known as "bruits" when they occur in arteries. The flow in such cases is often referred to in medical literature as "turbulent." In the fluid mechanics literature, however, turbulence has a stricter definition, including the presence of highly random flow perturbations on a range of length scales. Unstable blood flow at Reynolds numbers in the hundreds is more properly described as "disturbed flow," with the possibility of true turbulence occurring at higher Reynolds numbers [38]. The term "laminar flow" is used to describe flow that is not turbulent and can include flows that exhibit instability and disturbances.

The pulsatile nature of blood flow in arteries introduces additional fluid mechanical phenomena that influence the stresses experienced by vessel walls, particularly in arteries. Arterial flow has an oscillatory component superimposed on the mean flow rate. The fluctuating flow can cause reversal of the direction of the wall shear stress during part of the cardiac cycle. Flow instabilities may appear and disappear during each cycle, depending on the Reynolds number and the frequency of the cardiac pulsation [12].

In summary, the shear stresses generated by blood flow in the arteries depend in a complex manner on the geometry of the vessels and the characteristics of the flows through them. In general, straight unbranched segments experience a relatively high unidirectional shear stress, with the possibility of reversal during part of the cardiac cycle. However, variations in vessel width, caused, for instance, by stenosis or by bifurcations, can result in regions of low shear stress, with reversals of stress direction associated with flow separation, and fluctuations in stress resulting from flow instability.

1.5 Functional Demands on the Vasculature

The primary function of the circulatory system is the transport of substances from one part of the body to another. This transport is accomplished mainly by two physical processes, convection, and diffusion. Convection refers to the transport of materials carried by the motion of flowing blood, and diffusion refers to random thermal motion of individual molecules which generates net fluxes down gradients of solute concentrations or, more precisely, down gradients of the solutes' thermodynamic potentials. At the cellular level, active transport across cell membranes is also required for many solutes.

Transport of oxygen is a critical function of the circulation. Being a non-polar molecule, it has relatively low solubility in water and in tissue. Its transport from the atmosphere to mitochondria occurs by purely passive mechanisms down gradients in oxygen partial pressure [39]. The necessity for adequate transport of oxygen and other substances places stringent demands on the structure of the circulatory system. As a result of the low concentration of oxygen in tissue, oxygen transport by diffusion is effective only over very short distances, about 100 μm or less in most oxygen-consuming tissue. Therefore, it must be delivered by convective transport within such a distance of all cells that require oxygen. This requires a dense network of tiny vessels throughout the tissue. On the other hand, viscous resistance to blood flow is very high in vessels with very small diameters. For mechanical efficiency, the vascular system must include hierarchical branching structures feeding the microvessels, such that convective transport over larger distances can be achieved by vessels with larger diameters and lower resistance to flow. In effect, the vascular system must solve a complex patterning problem, generating a structure in which a dense meshwork of capillaries is combined with a hierarchical structure of arteries, arterioles, venules, and veins of varying lengths and diameters so that all parts of the tissues are adequately supplied with blood flow [40]. A central challenge in vascular biology is to understand the mechanisms that control the structure of the vasculature in health and disease.

The need to satisfy the metabolic requirements of the tissue suggests that hypoxia is a stimulus for vessel growth and remodeling. The stimulation of angiogenesis (growth of new vessels) mediated by hypoxia-inducible factor 1α (HIF1α) and vascular endothelial growth factor (VEGF) is well established [41]. However, local growth of new vessels in a hypoxic region can have only limited effectiveness in overcoming hypoxia unless it is accompanied by enlargement of the corresponding feeding and draining vessels to allow increased perfusion. This implies the need for mechanisms to coordinate structural adaptation along flow pathways, beyond the region experiencing hypoxia. Structural responses to changes in wall shear stress generated by flowing blood provide such a mechanism, as discussed below. Moreover, the vessel walls must be able to support the forces generated by blood pressure. The dominant stress in the wall is circumferential tension, and the wall must be able to respond to increases in this tension, typically by increasing wall thickness. Evidently, vascular remodeling must involve responses to several different stimuli, including mechanical forces generated by blood flow.

1.6 Role of Hemodynamic Signals in Vascular Remodeling

Evidence for the influence of wall shear stress on vessel diameters can be deduced from a consideration of the relationship between diameter and blood flow rate in the circulation. In the arterial tree, including arteries and capillaries, it has been observed experimentally that flow rate scales approximately as the cube of diameter across a wide range of scales [42, 43]. This scaling is consistent with the optimality theory known as Murray's law [44], which is based on the assumption that vessel diameters are adjusted to minimize a cost function consisting of a linear combination of viscous energy dissipation and blood volume. A potential mechanism by which such a scaling could be achieved is suggested by Eq. (1.9), which states that the wall shear stress is proportional to the ratio of blood flow rate to the cube of diameter (neglecting variations in blood viscosity). If it is assumed that a set point of wall shear stress exists, such that shear stresses above this level stimulate diameter enlargement, and vice versa, then a vessel with a given flow rate will adjust its diameter so as to conform to the cubic dependence of flow on diameter [42, 45]. Indeed, direct experimental evidence supports such a response to changes in wall shear stress [46].

However, some limitations to this theory are apparent. Firstly, veins are consistently larger in diameter than paired arteries carrying the same blood flow rate [42], and levels of wall shear stress are correspondingly lower in veins than in arteries. This implies that other factors besides wall shear stress must affect diameters. Detailed analyses of hemodynamics in microvascular networks of the rat mesentery showed a trend of decreasing wall shear stress with decreasing intravascular blood pressure, which was consistent across arterioles, capillaries, and venules [47]. Such behavior can be accounted for by assuming that intravascular pressure, or more precisely the circumferential stress generated by that pressure, also acts as stimulus for structural remodeling [47, 48]. According to this theory, an increase in intravascular pressure causes inward remodeling with the thickening of the vessel wall. This is consistent with observations of decreased internal diameters of small arteries in hypertension [49].

A second limitation of the theory of diameter adaptation based on shear stress alone becomes apparent when the behavior of vascular networks is simulated [50, 51]. If a flow is divided between two segments connected in parallel, both segments experience the same pressure drop. According to Eq. (1.5), the shear stress in each is proportional to its diameter. Suppose that an initial condition is imposed in which both segments have the same wall shear stress. A small enlargement of one segment would result in an increase in its wall shear stress, in turn stimulating further enlargement, while the other segment would shrink. In other words, such an initial configuration would be unstable.

These considerations imply that other factors in addition to wall shear stress and intravascular pressure must influence the control of vessel luminal diameters through structural remodeling. Pries et al. [52, 53] developed theoretical models for structural adaptation that include a metabolic growth stimulus: if low flow in a given vessel segment leads to reduced oxygen levels, then this stimulates diameter enlargement,

presumably through increased expression of growth factors. Also, these models include effects of convected and conducted responses, such local hypoxia in a given segment generates a growth stimulus in the vessels in the flow pathway upstream and downstream of the given segment. Here, convected responses refer to effects of metabolic signal substances carried downstream from hypoxic regions and simulating growth of downstream vessels [54], and conducted responses refer to signals propagated upstream along the walls of blood vessels by endothelial and smooth muscle cells, which communicate via gap junctions [55, 56]. It was shown that such a model can predict stable network structures with hemodynamic properties consistent with corresponding in vivo observations.

In summary, vascular responses to wall shear stress play an essential role in generating the hierarchical structure of vascular networks, in which the decreases in flow rate in successive branches of the arterial and venular trees are accompanied by corresponding decreases in vessel diameter. Responses to circumferential wall tension generated by intravascular pressure have the effect not only of controlling the thickness of vessel walls but also of generating the asymmetry between the arterial and venular trees, in which venous vessels are systematically larger than corresponding arterial vessels, with lower levels of wall shear stress. These responses, working in concert with responses to metabolites and growth factors, and with upstream and downstream propagated responses, provide a sufficient set of mechanisms to account for the observed structures of vascular networks.

1.7 Conclusions and Translational Perspectives

According to Poiseuille's law, the flows in blood vessels are sensitively dependent on the vessel diameters. At the same time, the structure of the vessels, and in particular their diameters, are capable of continuous adjustment in response to a number of stimuli, including the forces generated by blood flow. These interacting processes are largely responsible for establishing and maintaining the geometric structure of the healthy vasculature so that it can meet the body's requirements. Interactions between hemodynamics and structure also contribute to the development of vascular diseases.

Table 1.1 lists hemodynamic forces acting on vessel walls and some normal and pathological behaviors that are influenced by these forces. The primary structural response of blood vessels to elevated circumferential wall stress is the thickening of the vessel wall, which tends to reduce this stress, according to Eq. (1.2). This response underlies the adaptation of veins used for coronary bypass grafts to arterial blood pressure [57]. It should be noted that circumferential wall stress does not approach a unique set point independent of vessel size; instead, average circumferential stress levels increase with vessel diameter [58]. A second structural response to increased circumferential stress is the reduction of the vessel lumen (inward remodeling). This response may play a role in the development of hypertension [6, 59]. If peripheral resistance is initially increased for some reason, this stimulates an increase in blood pressure in order to maintain flow. The inward modeling of

Table 1.1 Hemodynamic forces acting on vessel walls and biological effects

Hemodynamic property	Role in normal vascular remodeling	Role in disease processes/ responses
Blood pressure, causing circumferential wall stress	Matching of wall thickness to pressure	Adaptation of vein grafts to arterial pressure
Elevated blood pressure		Increased peripheral resistance in hypertension
Wall shear stress	Matching of vessel diameter to flow rate	Enlargement of collateral vessels
Elevated wall shear stress		Initiation of cerebral aneurysms
Low/fluctuating wall shear stress		Initiation of atherosclerotic lesions

arterial vessels in response to this increased pressure has the effect of further increasing peripheral resistance, in a positive feedback loop.

With increased wall shear stress, the primary structural response is increased luminal diameter. This has the important effect of matching vessel diameters to flow rates. When arteries or arterioles become blocked, if collateral flow pathways are available, these vessels may become enlarged and take over the supply of the affected region [60]. This depends on the response to increased shear stress in the collateral vessels. Hemodynamic effects have long been thought to influence the development of atherosclerosis [61]. Normal to high levels of wall shear stress with consistent flow directions promote a stable phenotype in endothelial cells, which inhibits the development of atherosclerosis [62]. However, low and fluctuating levels of shear stress tend to destabilize endothelial cells, and atherosclerosis typically appears initially at regions with such flow conditions, as for example, around arterial bifurcations. It has also been proposed that the complex distributions of pressure-induced wall stresses in such regions may also cause vulnerability to atherosclerosis [63–65], although this hypothesis has not received wide acceptance. Elevated levels of wall shear stress are considered to be a factor leading to the initiation of cerebral aneurysms [66].

In summary, biological responses to stresses acting on vessel walls generated by blood flow are important for the growth and maintenance of functionally adequate and efficient vasculature, and also for the development of diseases of blood vessels. Progress in this area of mechanobiology requires the integration of knowledge of hemodynamics, vessel wall mechanics, mechanotransduction, and growth and remodeling of vessel walls, on scales ranging from molecular and cellular to whole-organ and systemic. Improved understanding of the mechanisms governing vascular structure has the potential to lead to new strategies for preventing or treating diseases of the vasculature.

Acknowledgments This work was supported by NIH Grant HL034555.

Compliance with Ethical Standards The author has no conflicts of interest with regard to the present work.

References

1. Secomb TW, Pries AR (2016) Microvascular plasticity: angiogenesis in health and disease—preface. Microcirculation 23(2):93–94. https://doi.org/10.1111/micc.12262
2. Zakrzewicz A, Secomb TW, Pries AR (2002) Angioadaptation: keeping the vascular system in shape. News Physiol Sci 17:197–201
3. Fung YC (1993) Biomechanics. Mechanical properties of living tissues, 2nd edn. Springer, New York
4. Humphrey JD, Delange SL (2004) An introduction to biomechanics. Solids and fluids, analysis and design. Springer, New York
5. Bonet J, Wood RD (1997) Nonlinear continuum mechanics for finite element analysis. Cambridge University Press, Cambridge
6. Pries AR, Secomb TW, Gaehtgens P (1999) Structural autoregulation of terminal vascular beds: vascular adaptation and development of hypertension. Hypertension 33(1):153–161
7. Secomb TW (2016) Hemodynamics. Compr Physiol 6(2):975–1003. https://doi.org/10.1002/cphy.c150038
8. McDonald DA (1974) Blood flow in arteries, 2nd edn. Edward Arnold, London
9. Caro CG, Pedley TJ, Schroter RC, Seed WA (1978) The mechanics of the circulation. Oxford University Press, Oxford
10. Milnor WR (1989) Hemodynamics, 2nd edn. Williams and Wilkins, Baltimore
11. Fung YC (1997) Biomechanics: circulation, 2nd edn. Springer, New York
12. Nichols WW, O'Rourke MF (1998) McDonald's blood flow in arteries. Theoretical, experimental and clinical principles, 4th edn. Arnold, London
13. Secomb TW, Pries AR (2007) Basic principles of hemodynamics. In: Baskurt OK, Hardeman MR, Rampling MW, Meiselman HJ (eds) Handbook of hemorheology and hemodynamics. IOS Press, Amsterdam, pp 289–306
14. Poiseuille JLM (1846) Recherches expérimentales sur le mouvement des liquides dans les tubes de très-petits diamêtres. Mémoires presentés par divers savants à l'Académie Royale des Sciences de l'Institut de France IX:433–544
15. Hagenbach E (1860) Uber die Bestimmung der Zähigkeit einer Flüssigkeit durch den Ausfluss aus Röhren. Poggendorf's Ann Phys Chem 108:385–426
16. Chien S (1975) Biophysical behavior of red blood cells in suspension. In: Surgenor DM (ed) The red blood cell, vol II. Academic Press, New York, pp 1031–1133
17. Chien S, Usami S, Taylor HM, Lundberg JL, Gregersen MI (1966) Effects of hematocrit and plasma proteins on human blood rheology at low shear rates. J Appl Physiol 21(1):81–87
18. Secomb TW (2017) Blood flow in the microcirculation. Annu Rev Fluid Mech 49:443–461. https://doi.org/10.1146/annurev-fluid-010816-060302
19. Pries AR, Neuhaus D, Gaehtgens P (1992) Blood viscosity in tube flow: dependence on diameter and hematocrit. Am J Phys 263:H1770–H1778
20. Fahraeus R, Lindqvist T (1931) The viscosity of the blood in narrow capillary tubes. Am J Phys 96:562–568
21. Pries AR, Secomb TW, Gaehtgens P, Gross JF (1990) Blood flow in microvascular networks. Experiments and simulation. Circ Res 67(4):826–834
22. Pries AR, Secomb TW, Gessner T, Sperandio MB, Gross JF, Gaehtgens P (1994) Resistance to blood flow in microvessels in vivo. Circ Res 75(5):904–915
23. Pries AR, Secomb TW, Gaehtgens P (2000) The endothelial surface layer. Pflugers Arch 440 (5):653–666
24. Secomb TW, Hsu R, Pries AR (2001) Effect of the endothelial surface layer on transmission of fluid shear stress to endothelial cells. Biorheology 38(2–3):143–150

25. Davies PF (1995) Flow-mediated endothelial mechanotransduction. Physiol Rev 75 (3):519–560
26. Wang N, Tytell JD, Ingber DE (2009) Mechanotransduction at a distance: mechanically coupling the extracellular matrix with the nucleus. Nat Rev Mol Cell Biol 10(1):75–82. https://doi.org/10.1038/nrm2594
27. Happel J, Brenner H (1973) Low Reynolds number hydrodynamics, 2nd edn. Noordhoff, Leyden
28. Kaoui B, Ristow GH, Cantat I, Misbah C, Zimmermann W (2008) Lateral migration of a two-dimensional vesicle in unbounded Poiseuille flow. Phys Rev E 77(2):021903
29. Fedosov DA, Caswell B, Popel AS, Karniadakis GE (2010) Blood flow and cell-free layer in microvessels. Microcirculation 17(8):615–628
30. Kumar A, Graham MD (2012) Mechanism of margination in confined flows of blood and other multicomponent suspensions. Phys Rev Lett 109(10):108102. https://doi.org/10.1103/PhysRevLett.109.108102
31. Grandchamp X, Coupier G, Srivastav A, Minetti C, Podgorski T (2013) Lift and down-gradient shear-induced diffusion in red blood cell suspensions. Phys Rev Lett 110(10):108101
32. Freund JB (2014) Numerical simulation of flowing blood cells. Annu Rev Fluid Mech 46:67–95
33. Hariprasad DS, Secomb TW (2014) Two-dimensional simulation of red blood cell motion near a wall under a lateral force. Phys Rev E 90(5):7. https://doi.org/10.1103/PhysRevE.90.053014
34. Pries AR, Ley K, Claassen M, Gaehtgens P (1989) Red cell distribution at microvascular bifurcations. Microvasc Res 38(1):81–101
35. Lykov K, Li XJ, Lei H, Pivkin IV, Karniadakis GE (2015) Inflow/outflow boundary conditions for particle-based blood flow simulations: application to arterial bifurcations and trees. PLoS Comput Biol 11(8):e1004410
36. Yin X, Thomas T, Zhang J (2013) Multiple red blood cell flows through microvascular bifurcations: cell free layer, cell trajectory, and hematocrit separation. Microvasc Res 89:47–56. https://doi.org/10.1016/j.mvr.2013.05.002
37. Balogh P, Bagchi P (2019) Three-dimensional distribution of wall shear stress and its gradient in red cell-resolved computational modeling of blood flow in in vivo-like microvascular networks. Physiol Rep 7(9):e14067. https://doi.org/10.14814/phy2.14067
38. Pedley TJ (1980) The fluid mechanics of large blood vessels. Cambridge University Press, Cambridge
39. Weibel ER (1984) The pathway for oxygen: structure and function in the mammalian respiratory system. Harvard University Press, Cambridge, MA
40. Secomb TW, Alberding JP, Hsu R, Dewhirst MW, Pries AR (2013) Angiogenesis: an adaptive dynamic biological patterning problem. PLoS Comput Biol 9(3):e1002983. https://doi.org/10.1371/journal.pcbi.1002983
41. Semenza GL (2001) Regulation of hypoxia-induced angiogenesis: a chaperone escorts VEGF to the dance. J Clin Invest 108(1):39–40. https://doi.org/10.1172/JCI13374
42. Rodbard S (1975) Vascular caliber. Cardiology 60(1):4–49
43. Mayrovitz HN, Roy J (1983) Microvascular blood flow: evidence indicating a cubic dependence on arteriolar diameter. Am J Phys 245:H1031–H1038
44. Murray CD (1926) The physiological principle of minimum work. I.The vascular system and the cost of blood volume. Proc Natl Acad Sci USA 12:207–214
45. Kamiya A, Bukhari R, Togawa T (1984) Adaptive regulation of wall shear stress optimizing vascular tree function. Bull Math Biol 46(1):127–137
46. Langille BL, O'Donnell F (1986) Reductions in arterial diameter produced by chronic decreases in blood flow are endothelium-dependent. Science 231:405–407
47. Pries AR, Secomb TW, Gaehtgens P (1995) Design principles of vascular beds. Circ Res 77 (5):1017–1023
48. Pries AR, Reglin B, Secomb TW (2005) Remodeling of blood vessels: responses of diameter and wall thickness to hemodynamic and metabolic stimuli. Hypertension 46(4):725–731

49. Heagerty AM, Aalkjaer C, Bund SJ, Korsgaard N, Mulvany MJ (1993) Small artery structure in hypertension. Dual processes of remodeling and growth. Hypertension 21(4):391–397. https://doi.org/10.1161/01.hyp.21.4.391
50. Hacking WJG, VanBavel E, Spaan JAE (1996) Shear stress is not sufficient to control growth of vascular networks: a model study. Am J Phys 270:H364–H375
51. Hudetz AG, Kiani MF (1992) The role of wall shear stress in microvascular network adaptation. Adv Exp Med Biol 316:31–39
52. Pries AR, Secomb TW, Gaehtgens P (1998) Structural adaptation and stability of microvascular networks: theory and simulations. Am J Phys 275(2 Pt 2):H349–H360
53. Pries AR, Reglin B, Secomb TW (2001) Structural adaptation of microvascular networks: functional roles of adaptive responses. Am J Physiol Heart Circ Physiol 281(3):H1015–H1025
54. Reglin B, Secomb TW, Pries AR (2017) Structural control of microvessel diameters: origins of metabolic signals. Front Physiol 8:813. https://doi.org/10.3389/fphys.2017.00813
55. Segal SS, Duling BR (1986) Flow control among microvessels coordinated by intercellular conduction. Science 234(4778):868–870
56. Maibier M, Bintig W, Goede A, Hopfner M, Kuebler WM, Secomb TW, Nitzsche B, Pries AR (2019) Gap junctions regulate vessel diameter in chick chorioallantoic membrane vasculature by both tone-dependent and structural mechanisms. Microcirculation 27(1):e12590. https://doi.org/10.1111/micc.12590
57. Carrel A, Guthrie CC (1906) Results of the biterminal transplantation of veins. Am J Med Sci 132:415–422. https://doi.org/10.1097/00000441-190609000-00006
58. Pries AR, Reglin B, Secomb TW (2001) Structural adaptation of vascular networks: role of the pressure response. Hypertension 38(6):1476–1479
59. Folkow B (1990) "Structural factor" in primary and secondary hypertension. Hypertension 16 (1):89–101. https://doi.org/10.1161/01.hyp.16.1.89
60. Gruionu G, Hoying JB, Gruionu LG, Laughlin MH, Secomb TW (2005) Structural adaptation increases predicted perfusion capacity after vessel obstruction in arteriolar arcade network of pig skeletal muscle. Am J Physiol Heart Circ Physiol 288(6):H2778–H2784
61. Caro CG, Fitz-Gerald JM, Schroter RC (1971) Atheroma and arterial wall shear. Observation, correlation and proposal of a shear dependent mass transfer mechanism for atherogenesis. Proc R Soc Lond B Biol Sci 177(1046):109–159. https://doi.org/10.1098/rspb.1971.0019
62. Malek AM, Alper SL, Izumo S (1999) Hemodynamic shear stress and its role in atherosclerosis. JAMA 282(21):2035–2042
63. Salzar RS, Thubrikar MJ, Eppink RT (1995) Pressure-induced mechanical stress in the carotid artery bifurcation: a possible correlation to atherosclerosis. J Biomech 28(11):1333–1340. https://doi.org/10.1016/0021-9290(95)00005-3
64. Thubrikar MJ, Robicsek F (1995) Pressure-induced arterial wall stress and atherosclerosis. Ann Thorac Surg 59(6):1594–1603. https://doi.org/10.1016/0003-4975(94)01037-d
65. Chatzizisis YS, Giannoglou GD (2007) Coronary hemodynamics and atherosclerotic wall stiffness: a vicious cycle. Med Hypotheses 69(2):349–355. https://doi.org/10.1016/j.mehy.2006.11.053
66. Sforza DM, Putman CM, Cebral JR (2009) Hemodynamics of cerebral aneurysms. Annu Rev Fluid Mech 41:91–107. https://doi.org/10.1146/annurev.fluid.40.111406.102126