Published in final edited form as:
Comput Methods Appl Mech Eng. 2009 September 15; 198(45-46): 3514–3523. doi:10.1016/j.cma.2009.02.004.

Open Problems in Computational Vascular Biomechanics: Hemodynamics and Arterial Wall Mechanics

C.A. Taylor[1] and **J.D. Humphrey**[2]

[1]Departments of Bioengineering and Surgery, Stanford University, Stanford, CA, USA, taylorca@stanford.edu

[2]Department of Biomedical Engineering and M.E. DeBakey Institute, Texas A&M University, College Station, TX, USA, jhumphrey@tamu.edu

Abstract

The vasculature consists of a complex network of vessels ranging from large arteries to arterioles, capillaries, venules, and veins. This network is vital for the supply of oxygen and nutrients to tissues and the removal of carbon dioxide and waste products from tissues. Because of its primary role as a pressure-driven chemomechanical transport system, it should not be surprising that mechanics plays a vital role in the development and maintenance of the normal vasculature as well as in the progression and treatment of vascular disease. This review highlights some past successes of vascular biomechanics, but emphasizes the need for research that synthesizes complementary advances in molecular biology, biomechanics, medical imaging, computational methods, and computing power for purposes of increasing our understanding of vascular physiology and pathophysiology as well as improving the design of medical devices and clinical interventions, including surgical procedures. That is, computational mechanics has great promise to contribute to the continued improvement of vascular health.

Keywords

computational biofluid mechanics; wall shear stress; intramural stress; biomechanical aspects of vascular disease; patient-specific modeling

1. Introduction

Despite significant progress in clinical care and public education, cardiovascular diseases remain the leading cause of death and disability in industrialized nations. Continued advances in molecular and cell biology, biomechanics, medical imaging, computational methods, and computational power promise, however, to revolutionize our understanding and thus treatment of these devastating diseases. There is a pressing need, therefore, to synthesize these many advances into a consistent clinically useful tool.

The goal of this paper is to review biomechanical aspects of some of the primary diseases that affect the vasculature, to note briefly the state of the art in vascular biofluid and biosolid mechanics, and to identify important open problems in both basic research and clinical care. That mechanics plays a fundamental role in cardiovascular health and disease has been known for centuries (e.g., see Young [1], who considered the hemodynamics, or Roy [2], who

Corresponding Author: J.D. Humphrey, Ph.D., Department of Biomedical Engineering, 337 Zachry Engineering Center, 3120 TAMU, Texas A&M University, College Station, TX 77843-3120, (P) +1-979-845-5558, (F) +1-979-845-4450, jhumphrey@tamu.edu.

considered wall mechanics), yet it has only been since the mid-1970s that we have understood why mechanics is truly important. Experiments on vascular cells isolated in culture – both the endothelial cells that line every blood vessel and the smooth muscle cells that endow these vessels with an ability to dilate and contract and thereby control local blood flow – reveal that altered mechanical loading can induce changes in gene expression. It is, of course, the associated changes in cellular activity (e.g., proliferation, migration, differentiation, synthesis and degradation of proteins, programmed cell death) that result in both appropriate adaptations during development, maturity, and exercise and maladaptive consequences during disease progression. Let us begin, therefore, with a brief discussion of the normal vasculature.

2. Brief on Vascular Organization and Structure

The vasculature serves as a conduit for blood flow. It thereby facilitates the exchange of oxygen/carbon dioxide, hormones, nutrients, and waste products between the blood and tissues throughout the body; it facilitates immune and reparative processes; and it aids in the regulation of body temperature. Consisting of a complex network of billions of nearly cylindrical branching tubes, the vasculature can be divided into five types of vessels: arteries, arterioles, capillaries, venules, and veins. Each vessel serves a unique function and consequently possesses unique structure and properties. We focus on arteries in this paper, but emphasize the importance of understanding the biomechanics of each part of the vasculature (e.g., see [3]), particularly the veins which are often used as arterial substitutes in coronary bypass surgeries. Moreover, biomechanical conditions in arteries are strongly affected by the microcirculation downstream and, via coupling through the heart, the venous return upstream.

There are two arterial systems: systemic (blood flow to the body) and pulmonary (blood flow to the lungs). In the absence of congenital malformations, these two systems act in series and their volumetric flows (~5 L/min for an average adult) are matched closely via the Frank-Starling mechanism whereby increased filling of a ventricle increases myocardial fiber length and thereby increases the force of contraction. In the absence of hypertension, blood pressures are approximately 6 times higher in the systemic than in the pulmonary circulation. Both systems are often described as having fractal geometry (i.e., self-similarity across spatial scales), but branch geometry changes with successive generations of the arterial tree, thus resulting in increases in cross-sectional area from the aorta and main pulmonary artery to their respective microcirculations. This increasing cross-sectional area reduces the resistance to flow within the vasculature as compared to an area-preserving branching network. Furthermore, many vascular beds include either pre-existing collateral pathways that serve to minimize tissue ischemia or pathways that develop in response to the onset of disease. Regardless of whether parts of the arterial tree are truly fractal, they are space filling – continually branching to ever smaller vessels until the level of the capillaries.

Direct representation in a numerical model of all vessels from a major artery to the pre-capillary arterioles would be a daunting task, resulting in tens to hundreds of millions of vessels. As discussed later in this paper, the vastness of the vascular tree necessitates methods that “lump” all of these vessels into a small number of empirically-derived components or, at a minimum, utilize simplified hemodynamic equations with anatomically representative models of the entire system. Alternate approaches have been used to describe the branching patterns of arteries, ranging from symmetric and asymmetric binary fractal trees [4] to diameter-defined Strahler systems that accommodate branching systems with small side branches coming off a larger trunk as frequently seen in the arterial system [5]. More on basic arterial physiology and hemodynamics can be found in Nichols and O'Rourke [6].

The arterial wall consists of three layers: the intima, media, and adventitia. The innermost layer, or intima, consists primarily of a monolayer of endothelial cells and an underlying basal lamina

composed of mesh-like type IV collagen and adhesion molecules (e.g., fibronectin and laminin). In addition to being a smooth, non-thrombogenic interface between the blood and contents of the arterial wall, the endothelium is biologically active. In response to chemical and mechanical stimuli, endothelial cells produce vasoactive molecules (which dilate or constrict the vessel), growth factors (which promote cell replication or the synthesis of proteins), adhesion molecules (which control local recruitment of blood-borne cells essential to the immune response), and factors that regulate the blood clotting process. Moreover, the endothelium can modify lipids for transport into the wall, which thereby plays an important role in atherosclerosis. Realization that many functions of the endothelium are controlled by blood flow induced shear stress [7] provided important motivation for studying the hemodynamics and guidance for treating many vascular disorders. The middle layer, or media, consists primarily of smooth muscle cells embedded in a plexus of elastin, collagens (e.g., types I, III, V), and proteoglycans. In general, the closer arteries are to the pulsating heart the more elastin, and the farther away the more smooth muscle. Regardless, overall wall thickness tends to be regulated so as to maintain the circumferential wall stress near a target value, hence motivating the study of wall mechanics. Whereas smooth muscle is primarily responsible for synthesizing matrix proteins during development, it endows the mature vessel with its ability to constrict or dilate and thereby regulate blood flow locally. Smooth muscle hypertrophy (increase in size), hyperplasia (increase in number), apoptosis (cell suicide), and migration each play essential roles in diseases such as aneurysms, atherosclerosis, and hypertension. Accumulation of matrix, particularly collagen, occurs in atherosclerosis and hypertension; loss of matrix, particularly elastin, occurs in aneurysms, vascular dissections, and aging. The outermost layer, or adventitia, often connects with perivascular tissue. It consists primarily of fibroblasts and diagonally-to-axially oriented type I collagen, but includes admixed elastic fibers, nerves, and in some cases its own small vasculature, the vasa vasorum (which can remodel significantly in disease states such as hypertension and atherosclerosis and thus is fundamental to understanding biochemomechanics of the wall in general). Fibroblasts regulate the adventitial matrix, particularly collagen, but are increasingly recognized as potential contributors to changes in the media and sub-intima as well [8]. Nevertheless, it is thought that the adventitia serves, in part, as a protective sheath that prevents over-distension of the media (like all muscle, smooth muscle contracts maximally at a certain length, above and below which the contractions are less forceful). More on arterial wall structure and function can be found in Levy and Tedgui [9] and Humphrey [10].

3. Biomechanical Aspects of Disease and Injury

Diseases of the vasculature are manifold and it is impossible in a brief review to provide details sufficient for biomechanical modeling. Hence, we merely identify salient features of a few important disease conditions and cite some key references in each case. The goal of this section, therefore, is primarily to demonstrate the ubiquitous importance of biomechanics in vascular research and to motivate new computational investigations on vascular disease.

3.1 Aging

Aging is a natural consequence of living and not a disease per se. Nevertheless, age related changes in structure and function increase the susceptibility of the arterial wall to many diseases and thus is an important topic of biomechanics. Conspicuous changes in aging include the gradual loss of elastin, loss of smooth muscle contractility, and increase in collagen density and/or cross-linking. Elastin tends to endow the wall with elastic recoil and resilience whereas collagen tends to provide overall stiffness. Hence, increases in the collagen-to-elastin ratio in aging yields stiffer, enlarged arteries, which dramatically affects the propagation of pressure waves to distal vessels and thereby affects their structure and function. Moreover, elastin contributes significantly to both the normal residual stress within the arterial wall (which tends

to homogenize the transmural gradient in wall stress) and the axial prestress (which arises during development and affects the biaxial state of stress in the wall), and thereby plays an important role in governing local wall mechanics and thus the mechanobiology. Aging is thus a risk factor for and predictor of other vascular diseases [11,12].

3.2 Hypertension

High blood pressure, or hypertension, affects over 50 million Americans alone and is a significant risk factor for many other diseases, including heart attack, stroke, and end stage kidney disease. Hypertension is primarily a disease of arteries and arterioles; it manifests differently in the systemic and pulmonary systems and thus should be studied separately in these cases. Regardless, the most conspicuous change to arteries is a thickening of the wall due to an increase in smooth muscle mass and extracellular matrix, primarily collagen and proteoglycans. This structural stiffening affects the hemodynamics, which in turn affects wall stress and the associated mechanobiology, and may set into motion a complex feedback process that leads to increased hypertension or other vascular disease processes.

Normal blood pressure is 120/80 mmHg (systolic/diastolic). Systemic hypertension is generally revealed by a blood pressure of 150/90 mmHg, or higher, but it is unclear whether the systolic, diastolic, mean, or pulse (difference between systolic and diastolic) pressure is most detrimental [13]. Regardless, an increased pressure can distend the deformable arterial wall, which will decrease mean wall shear stress (which is often estimated via $4\mu Q/\pi a^3$, where μ is viscosity, Q is volumetric flow, and a is the luminal radius) but further increase mean circumferential wall stress (often estimated via $P\,a/h$, where P is pressure and h the wall thickness). This decreased shear stress would be expected to be returned toward normal via a downregulation of endothelial derived vasodilators (e.g., nitric oxide) and an up-regulation of vasconstrictors (e.g., endothelin-1). Not only do these vasoactive substances change the biomechanical state of the artery in which cells and matrix turnover in response to the increased intramural stress, they also influence the rate of turnover [14]. Hence, understanding both the hemodynamics and wall mechanics is fundamental to understanding hypertension and both its local and global affects.

The normal pulmonary vasculature is a high-flow, low-pressure system; it delivers blood to the lungs where oxygen is absorbed and carbon dioxide is released. Arterial pressures are normally 24/10 mmHg and the arterial wall is correspondingly thin and highly distensible. The term pulmonary hypertension encompasses multiple disease manifestations, including pulmonary arterial hypertension, which is characterized by an increased pressure and resistance to flow within the pulmonary arteries. This form of the disease occurs primarily due to an increased vasoconstriction followed by significant remodeling of the walls of medium- and small-diameter arteries. As in systemic hypertension, arterial remodeling includes smooth muscle hypertrophy, hyperplasia, and increased collagen deposition. Pulmonary hypertension increases the load on the right ventricle, which can lead to heart failure, and is associated with various conditions, including chronic obstructive pulmonary disease, adult respiratory distress syndrome, and high altitude (hypoxic) hypertension (see [15,16]). There has been much less work on pulmonary artery wall mechanics, perhaps because of their shorter lengths due to the highly branched morphometry within a short distance. Because of the importance of pulmonary vascular diseases as well as recent advances in modeling both the complex geometry of and blood flow within the pulmonary vasculature (e.g., [17,18]), there is ample motivation to advance our understanding of pulmonary artery wall mechanics and associated growth and remodeling in disease progression and clinical interventions.

3.3 Atherosclerosis

The dominant form of acquired cardiovascular disease, atherosclerosis, results in part from the chronic buildup of fatty material (i.e., bad cholesterol) within the intimal layer, often in arteries supplying blood to the heart, brain, kidneys, digestive system, or lower extremities. Risk factors, including physical inactivity, obesity, smoking, and a high cholesterol diet, can affect all arteries of the body, yet atherosclerosis tends to localize at branches and bends within the arterial tree. This observation led to the now widely accepted hypothesis that local hemodynamic factors play a critical role in atherogenesis [19-21]. Indeed, hemodynamic loads appear to play equally important roles in the progression of the disease and its devastating end-point – plaque rupture. Atherosclerotic plaques can develop over extended periods from initial "fatty streaks" to small obstructions, consisting primarily of foam cells, proliferating smooth muscle cells, and extra collagen, to large obstructions that also contain calcium deposits and necrotic debris [10]. It is thought that changes in both wall shear stress and intramural wall stress affect the rate and extent of such structural changes, including a "compensatory" atrophy of medial smooth muscle (which helps reduce the extent of the obstruction) due to stress shielding by a stiff plaque cap. Most important clinically, however, is rupture of the so-called "vulnerable" plaque, which exposes highly thrombogenic material to the flowing blood and results in an intraluminal thrombus. Such a thrombus can directly obstruct the lumen (which in a coronary artery results in a heart attack), dislodge and travel downstream where it can obstruct a smaller vessel (which in a cerebral artery results in a stroke), or continue to replenish over time and cause a localized chronic inflammation (e.g., in an abdominal aortic aneurysm). Understanding plaque rupture requires knowledge of the applied loads (hemodynamics) and the structure of the plaque (wall stress); similarly, an understanding of the development and dissolution of a thrombus requires knowledge of the hemodynamics and the chemomechanical properties of the clot.

Whereas considerable effort has been devoted to understanding hemodynamics in locations prone to atherosclerosis (e.g., the carotid sinus, infrarenal abdominal aorta, aortic bifurcation, and coronary arteries), quantification in regions relatively free of atherosclerosis (e.g., the upper extremity arteries as well as cerebral and pulmonary circulations), may provide further insight and thus is needed. Similarly, understanding hemodynamic conditions that are athero-protective (e.g., resulting from exercise) may yield more insight into hemodynamic risk factors for atherosclerosis than merely studying the disease state. Finally, there is a need for mechanistic models that relate hemodynamic factors to cell-mediated biochemomechanical processes that are responsible for atherosclerosis.

3.4 Aneurysms

Manifesting as focal dilatations of the arterial wall, aneurysms arise, in part, from the degeneration of constituents within the arterial wall, often medial elastin and smooth muscle. The two most common types of aneurysms are intracranial saccular aneurysms [22] and abdominal aortic aneurysms [23]. The former occur in or near the circle of Willis, the major network of arteries that supplies blood to the brain; the latter occur in the infrarenal aorta, the primary conduit that supplies blood to the legs. The etiology differs for these two types of lesions, but genetics, risk factors, and biomechanical factors play important roles in their natural histories and must be understood better in combination [24]. Thoracic aortic dissections and aneurysms similarly merit increased study.

Intracranial saccular aneurysms tend to be thin-walled and to consist primarily of remnant fibroblasts and fibrillar collagen having a layered structure. These lesions can be classified mechanically as anisotropic membranes. Clinical intervention (e.g., surgical clipping or intraluminal coiling) is often based on the maximum dimension of a lesion even though many large aneurysms do not rupture and many small ones do rupture. Simple biomechanical

arguments reveal that curvature, not overall size, is more important in the mechanics of membranes [10]. Such considerations are now being addressed in patient-specific models, which promise to help resolve the controversy over the role of size. Two longstanding hypotheses concerning enlargement and rupture-potential implicated structural (limit point) and dynamic (resonant) instabilities, but studies based on nonlinear biomechanics suggest that these are unlikely. Rather, it appears that these lesions enlarge and rupture via a growth and remodeling process wherein resident fibroblasts / myofibroblasts turnover fibrillar collagen (production and removal) in an attempt to restore the wall stress toward normal. Indeed, it appears that such turnover can explain, in part, the remarkable biological stability of many cerebral aneurysms (cf. [10,25,26]). Nevertheless, rupture occurs when wall stress exceeds wall strength, the latter of which depends on local protease activity and rates of collagen synthesis, both of which are controlled by cellular responses to local hemodynamic loads. Because many saccular aneurysms remain biologically stable, however, there is a pressing need to distinguish clinically those lesions that require intervention and those that should only be monitored periodically.

Abdominal aortic aneurysms are more complex than their cerebral counterparts in many ways. Although there is a similar loss of medial elastin and smooth muscle, with associated increases in fibrillar collagen, these lesions often have significant atherosclerotic involvement and an associated intraluminal thrombus (70% of cases). Hence, one must account for the complex layered structure of the wall and thrombus, not invoke the membrane assumption. Although precise roles of atherosclerosis and thrombus in the natural history are not known, they affect the chemomechanical environment experienced by the remnant cells and thus affect disease progression. For example, a growing thrombus increases the diffusion distance between blood borne oxygen and cells within the arterial wall; localized hypoxia can alter collagen turnover directly or promote neovascularization from the vasa vasorum, which in turn can bring monocytes in addition to oxygen into the wall. Monocytes can differentiate into macrophages, which via the release of proteases can alter the balance of local collagen production and removal within the wall and thereby alter local wall stress and strength. As in their cerebral counterparts, abdominal aortic aneurysms rupture when stress exceeds strength. Because clinical decisions to intervene are based primarily on lesion size, there is a need to predict better the rate of enlargement; because hemodynamic factors affect both the rate of enlargement and rupture-potential, there is a need to understand these effects better. For example, because increased wall shear stress appears to be atheroprotective within “favored” segments of the vasculature, the potential of exercise (i.e., increasing infrarenal flow) in slowing the rate of enlargement of aneurysms merits study [27]. Finally, there is a need to understand better and model the evolving perivascular boundary conditions appropriate for both intracranial and aortic aneurysms, not just the luminal boundary conditions (tractions) resulting from the hemodynamics.

3.5 Thrombosis

Blood clotting is essential for normal hemostasis, yet it is also responsible for significant death and disability. For example, clots form on implanted medical devices, from which they can dislodge, travel downstream, and cause distal ischemia (in severe cases resulting in stroke, pulmonary embolism, or heart attack); clots form on ruptured atherosclerotic plaques, whereby they can obstruct the lumen or shed emboli that cause distal ischemia; and clots form on the outer surface of otherwise normal cerebral arteries following the rupture of cerebral aneurysms and cause cerebral vasospasm, the most common cause of death or neurological deficits in these patients. Understanding the biochemomechanics of clot formation, progression, and dissolution in a flowing bloodstream or the cerebral spinal fluid thus merits careful study. For information on some recent advances, see [28-30].

3.6 Medical Devices

Advances in biomaterials have enabled many different classes of implantable medical devices for treating vascular diseases. Of these, one of the most widely used is the “stent.” Stents are delivered from a distal artery (often the femoral artery in the groin) via a catheter system to the vessel of interest (e.g. coronary, carotid, renal, iliac, or femoral artery) where they are balloon-expanded or self-expanded (e.g. for nitinol stents). Computational mechanics is broadly used in stent design and evaluation [31,32]. Although stents represent a significant advance over balloon angioplasty alone, this technology suffered from problems of thrombosis and in-stent restenosis when first introduced [33]. The first problem, stent thrombosis, was largely alleviated by using high-pressure balloons to ensure that the devices were apposed to the vessel wall and by using dual antiplatelet therapy. The second problem, in-stent restenosis, is an over-exuberant proliferative response by smooth muscle cells arising to heal the damage to the vessel wall resulting from angioplasty and stenting. In recent years, this problem has been reduced significantly with the introduction of drug-eluting stents. While many variants exist, most technologies utilize a metallic stent coated with an anti-proliferative drug contained within a polymer coating on the surface of the stent. While largely solving the problem of in-stent restenosis, the first generation drug-eluting stents experienced an increased incidence of stent thrombosis, often occurring just months after deploying the device [34].

Stent technologies have also been employed to treat aortic aneurysms, although in these cases the stents (generally self-expanding nitinol structures) are covered with a fabric to isolate the weakened vessel wall from arterial blood pressure. Such “stent grafts” are rapidly replacing open surgical techniques for the treatment of abdominal and thoracic aortic aneurysms [35]. Stent graft technology has been less successful for the treatment of cerebral aneurysms largely due to risk of emboli to the smaller cerebral arteries, or the possibility of occluding small branch arteries, which can be debilitating or even life-threatening. In treating cerebral aneurysms, intravascular coils are often placed within the lesions to trigger intra-aneurysmal clotting with the hope that the thrombus will remodel and be endothelialized so as to isolate the lumen from arterial blood pressure and thereby lessen the risk of rupture [36].

Artificial heart valves, while used clinically for decades, are still evolving. A large number of alternate mechanical valves have been used, including tilting disk, bi-leaflet, and ball and cage valves. More recently, “bioprosthetic” valves have been harvested from animals or explanted from deceased human beings. While such natural valves lessen the need for anticoagulation therapy, they suffer from the buildup of calcium deposits and are less durable than artificial valves. Complex hemodynamic loads on the valves are thought to contribute either directly or indirectly to such complications [37].

Ventricular assist devices augment blood flow and pressure in patients with a failing heart [38]. Although developed as a bridge to heart transplantation, they are increasingly being viewed as “destination therapies” due to their increasing success in allowing the heart to heal / recover and a shortage of donor organs. Most such devices perform left ventricular assist (LVADs), but devices to assist the right heart (RVADs) are under development as well. Recently, smaller, steady flow assist devices have begun to replace bulkier pulsatile flow devices, but concerns have arisen about consequences of reduced arterial pulsation on normal arterial wall structure. Computer-aided engineering of ventricular assist devices presents extraordinary challenges to computational biomechanics, including issues of flow stagnation, blood damage, thrombosis, device efficiency, and device durability to name a few.

4. Foundations of Vascular Mechanics

4.1 Hemodynamics

Constitutive Relations—Blood is a complex suspension of cells in plasma, with the concentration of cells ~50% by volume and the plasma consisting of ~90% water, 8% proteins, 1% inorganic substances, and 1% emulsified fat. There are three major types of cells in blood: erythrocytes, leukocytes, and platelets. Erythrocytes, or red blood cells, are the most abundant cells in blood; they transport oxygen and carbon dioxide. Mammalian erythrocytes are disk shaped (due to the absence of a nucleus) with a diameter of approximately 8 μm and a thickness of 2 μm. Leukocytes, or white blood cells, represent less than 1% of blood cells, but they have a critical role in producing antibodies and identifying and disposing of foreign substances. Monocytes and lymphocytes are two particular types of leukocytes that have been implicated in early stages of atherosclerosis, consistent with the view that chronic inflammation is important [39]. Platelets control the conversion of the plasma-borne protein fibrinogen to fibrin, a key structural element in a blood clot. Activation, aggregation, and accumulation of platelets depends on local hemodynamic loads and are critical in both the normal processes of vessel healing / hemostasis and the abnormal events that cause thrombosis.

Although the suspension fluid, plasma, consists primarily of water, the large concentration of cells in whole blood results in a non-Newtonian rheological behavior. Specifically, blood exhibits a shear-thinning behavior, with a higher overall viscosity at any shear rate in the presence of increased cell concentration. Non-Newtonian models, including Carreau-Yasuda and modified Cross, are often used in computational modeling of blood flow [40]. Nevertheless, it is generally assumed that blood flow in large arteries (e.g., the aorta), where the shear rate is high, can be modeled reasonably well using a Newtonian fluid approximation. The potential importance of non-Newtonian effects on hemodynamics in complex domains, as, for example, within atherosclerotic regions, aneurysms, and medical devices (wherein shear rates may be low even though the vessels are large), warrants further investigation however. Finally, it is likely that more sophisticated models (e.g., treating blood as a suspension of cells in plasma or accounting for clotting effects) will be needed to develop mechanistic models that relate hemodynamic conditions to vascular disease.

Navier-Stokes Equations—The governing equations for the three-dimensional theory of blood flow, under the assumptions of an incompressible, homogeneous, Newtonian fluid flow in a fixed domain, consist of continuity and Navier-Stokes equations plus suitable initial and boundary conditions. Blood flow is laminar under baseline conditions in human arteries, but can become weakly turbulent in some arteries under high flow conditions or with the development of disease. Due to the pulsatile nature of blood flow, signs of turbulence generally appear after peak flow as the flow decelerates and, in many cases, disappear during the diastolic phase of the cycle as flow diminishes prior to the bolus of blood being ejected from the heart. In rare cases, with the most severe disease, evidence of turbulent flow is apparent throughout the cardiac cycle.

Since the pioneering work of Perktold [41], much of the research in modeling blood flow in human arteries has focused on the solution of the three-dimensional equations using numerical methods, particularly finite elements. Such methods are well suited to the investigation of phenomena difficult to describe using in vitro techniques, including wall compliance [42,43], mass transport [44], and realistic anatomic models [45]. An overview of contemporary experimental and computational methods for quantifying hemodynamics can be found in Taylor and Draney [46].

Boundary Conditions—There are three primary surfaces of interest in hemodynamics: the inlet surface for the flow, the outlet surface(s), and the lateral surface (i.e., inner surface of the

vascular wall). Traditionally, hemodynamic studies have prescribed a velocity profile at the inlet, a combination of velocity profiles and traction-free conditions at the outlet(s), and a zero-velocity no-slip condition on the lateral surface. A variant of this approach involves prescribing a pressure waveform at one or more surfaces. These boundary conditions are sufficient for cases wherein the flow distribution is known a priori, only the velocity fields and wall shear stress are of interest, and the wall is assumed to be rigid. For many other problems, however, wherein the wall is compliant or the velocity and pressure fields are to be predicted, boundary conditions need to be specified so that the computational domain for the blood can be coupled to reduced-order models at inlet or outlet boundaries and deformable wall models at the lateral surfaces. This more general approach leads to new challenges where parameters of the reduced-order models need to be assigned, the mechanics of the wall needs to be considered, and the fluid-solid interactions between the blood and the blood vessel need to be modeled.

4.2 Wall Mechanics

Constitutive Relations—The arterial wall is a complex composite of consisting of three primary types of constituents: structural proteins, resident cells, and a ground substance matrix. The primary structural proteins are elastin and fibrillar collagen. Elastin is the most biologically stable protein in the body (with a half life on the order of the lifespan of the organism) and it is the most elastic; it is capable of recoverable extensions of over 100%. Amongst the many members of the collagen family, particularly types I, III, IV, V, and VIII in arteries, the fibrillar types I and III dominate overall wall stiffness. Finally, smooth muscle cells are capable of generating large, sustained contractile forces, which regulate the caliber of the artery and thus local blood flow.

Significant advances in modeling the complex biomechanical behavior of the arterial wall began in the late 1960s and continue to this day. Although arteries exhibit viscoelastic characteristics (creep, stress relaxation, and hysteresis), the assumption of (hyper)elasticity is sufficient in most physiologic and pathophysiologic cases. All constitutive relations must capture the nearly incompressible, nonlinear, anisotropic responses under finite deformations, however. Briefly, two general classes of relations have found most use: purely phenomenological relations in terms of the Green strain (cf. [10,47]) and structurally-motivated phenomenological relations (cf. [48,49]). Although both types of relations are sufficient for computing wall stress in general, structurally-motivated relations using a rule-of-mixtures approach for the stress response are particularly useful in modeling stress-mediated vascular growth and remodeling (G&R) in normal arteries as well as disease situations such as aneurysms and cerebral vasospasm [25,49]. Mathematical models of arterial G&R are discussed in detail below. It should be noted, however, that there is considerable need for improving all structurally motivated models, as, for example, to begin to account for important interactions amongst the structural constituents (e.g., roles of collagen V or proteoglycans in developing strong collagen I fibers).

Elastodynamics—Arteries are subjected to complex time-varying internal pressures, yet the associated inertial forces tend to be negligible in many cases and one usually can treat the initial-boundary value problem as quasi-static. Hence, one must solve classical linear momentum balance. Because of theoretical, experimental, and computational convenience, most of the literature focuses on stresses in short segments of select vessels (e.g., the common carotid arteries) that are reasonably straight and of uniform diameter and thickness. Notwithstanding the tremendous insight that has been gleaned from such studies, most of the important in vivo problems entail complex geometries and hemodynamic loads, thus necessitating numerical (finite element) solutions. Examples of such models can be found in [31,50,51]. Fortunately, standard finite element methods suffice in most cases, thus focusing one's attention on prescribing well the geometry, mechanical properties, and applied loads.

Boundary Conditions—There are three primary surfaces of importance in arterial wall mechanics: the inner surface, in contact with the blood or implantable device, the outer surface, in contact with perivascular tissue, and the "ends". The need to know traction boundary conditions on the inner surface of the artery (pressure and wall shear stress) reveals yet again the importance of knowing the hemodynamics. Fortunately, considerable information on this inner surface boundary condition can be gleaned from experiments, clinical measurements, or formal fluid-solid interaction (FSI) models. In contrast, tractions acting on the ends of the segment of interest (giving rise to the important, aforementioned axial prestress) and the adventitial surface are not amenable to measurement in animal studies or the clinical setting. Fortunately, it was discovered in the 1970s that arteries exhibit a remarkable property – the axial force needed to maintain the vessel at its in vivo axial stretch does not change during normal cyclic pressurizations. This constraint can be used in parameter estimations based on in vivo data [52] and it enables the semi-inverse method of finite elasticity to be used effectively. The outer boundary condition due to perivascular tissue is much more difficult to address, and only recently has received increased attention (cf., [53]). As in outlet boundary conditions for the hemodynamics, lumped parameter models will likely remain the best approach to address perivascular effects provided that the vascular wall properties are well known.

4.3 Fluid-Solid Interactions

Given the importance of hemodynamics on intramural stresses and wall properties on the character of the blood flow, it is remarkable that most research in vascular biomechanics has been pursued separately by those in biofluid mechanics and biosolid mechanics. Nevertheless, there has been recent progress in solving coupled blood flow – vessel wall interaction problems. The traditional approach to solving fluid-structure interaction problems in the arterial system has been the Arbitrary Lagrangian Eulerian (ALE) method whereby equations governing mesh movement, involving flow in a moving domain, and accounting for elastodynamics of the wall are solved using either a fully-coupled or a staggered approach [54]. Considerable progress has been made in solving such problems as evidenced by other papers in this volume. An alternative to the ALE approach is the Coupled Momentum Method (CMM) of Figueroa et al. [42]. In this approach, wall motion is assumed to be small so that the fluid mesh is not updated, a membrane model for the vessel wall is employed, and node-on-node compatibility between the lateral surface of the fluid mesh and the vessel wall is enforced. These simplifications enable the elastodynamic equations for the wall to be embedded within the fluid dynamics equations, hence the only additional degrees of freedom are the (nonzero) velocities of the nodes on the lateral surface. The CMM is highly efficient for large scale fluid-structure interaction and wave propagation problems wherein underlying assumptions of small deformation and thin walls are valid. Indeed, the thin wall assumption is generally applicable (if the bending stiffness is accounted for appropriately) if the focus is on the hemodynamics because the fluid only needs to "know" the structural stiffness of the wall that constrains its motion, not detailed stress distributions throughout the wall.

4.4 Other Coupled Phenomena

Oxygen Transport—Large elastic blood vessels are too thick to rely on advection and diffusion from the luminal surface to provide oxygen and nutrients to cells deep within the wall, which thereby need their own blood supply – the vasa vasorum. Thus, beyond approximately 30 lamellar units, normal blood vessels have a vasa vasorum in the outer medial and adventitial layers. The inner avascular zone has been observed to be a constant thickness along the length of the aorta [55]. A hallmark of advanced vascular diseases that thicken the wall (e.g., occlusive atherosclerotic plaques) or increase the distance between the flowing blood and intramural cells (e.g., intraluminal thrombus) is the development of new blood vessels, or

neovascularization, which likely occurs due to chemokines released in response to the local inflammation and/or hypoxic conditions.

Lipid Transport—The transport of atherogenic molecules, for example low density lipoproteins (LDLs), between the blood stream and the vessel wall is an essential part of the atherosclerotic process [56]. Computational methods have an important role in modeling lipid transport and testing hypotheses related to the role of biomechanical forces and atherogenesis [44]. Challenges include characterizing residence time in complex three-dimensional pulsatile flow [57], modeling shear-dependent changes in the endothelial permeability, and modeling convective-diffusive transport between the intimal and medial layers including porohyperelastic models and changes in permeability due to pulsatile pressure. Excellent reviews of these issues and theoretical and computational methods for analyzing lipid transport can be found in Tarbell [56] and Ethier [44].

Vasoactive Molecules—Two of the most important vasoactive molecules are nitric oxide (NO), a potent vasodilator, and endothelin-1 (ET-1), a potent vasoconstrictor. Production of these molecules by the endothelium depends strongly on local wall shear stress, with shears above baseline promoting the production of NO and values below baseline promoting ET-1. These molecules are not only important in modulating vasodilatation or vasoconstriction in response to acute increases or decreases in flow, respectively, they play a two-fold role in arterial G&R in response to sustained alterations in hemodynamics [58]. First, altered vasoactivity changes the configuration of the vessel in which subsequent cell and matrix turnover occur. Second, NO is an inhibitor of smooth muscle proliferation and synthesis of collagen whereas ET-1 promotes both proliferation and matrix synthesis. In other words, shear stress induced changes in endothelial production of vasoactive molecules not only changes the state in which smooth muscle cells function, it also changes the rate at which they remodel the wall. Recent studies have begun quantifying the diffusion of NO within the arterial wall and its rate of consumption by the vascular smooth muscle cells [59]. Such data will enable us to use reaction-diffusion equations to include detailed effects of hemodynamically controlled NO, ET-1, and similar endothelial derived molecules on intramural smooth muscle and fibroblast responses, which will move us closer to the multiscale approaches that will enable molecular level information to be exploited in tissue level computations. The potential of this approach further reinforces the utility of mixture theory based constitutive relations for the wall.

Mitogens, MMPs, and More—As noted earlier, the endothelial cells that line all blood vessels, the smooth muscle cells within the media, and the fibroblasts within the adventitia all respond to alterations in mechanical loading via altered gene expression [14]. Among the many different molecules produced by these cells, growth factors (mitogens), cytokines (inflammatory mediators), matrix metalloproteinases (MMPs), and tissue inhibitors of MMPs (or TIMPs) play particularly important roles in vascular biology. For example, it is becoming increasingly clear that both the production and activation of transforming growth factor-beta (TGF-β), a potent stimulator of collagen synthesis, are regulated strongly by changes in intramural stress. Indeed, the activity of TGF-β is affected by the availability of angiotensin-II, a potent vasoconstrictor, which is also controlled locally by altered intramural stresses. Similarly, MMPs are upregulated during the progression of both intracranial saccular and abdominal aortic aneurysms, likely due to direct mechanotransduction mechanisms related to altered intramural stresses as well as indirect effects of altered wall shear stress on endothelial cells (e.g., endothelial cells upregulate adhesion molecules that capture circulating monocytes from the blood stream, which then migrate into the arterial wall where they differentiate into macrophages that produce MMPs). A related, important role of a replenishing intraluminal thrombus is that it is a source of plasmin, an activator of MMP activity. There are many more examples wherein regulation of growth factors, cytokines, and proteases depends strongly on

both fluid and pressure induced changes in stress, hence there is an increasing need to include the effects of these molecules via appropriate reaction-diffusion equations.

4.5 Biological Growth and Remodeling

Arteries retain a remarkable ability to adapt to changing hemodynamic conditions throughout life. The best known examples are that arteries increase (or decrease) in caliber in response to sustained increases (or decreases) in blood flow induced wall shear stresses [7] and they increase (or decrease) in thickness in response to sustained increases (or decreases) in blood pressure [9]. Indeed, perhaps the most important application of arterial wall mechanics is in understanding better how arteries adapt or maladapt under normal conditions, in disease, in injury, and in response to treatments that may include the use of implanted medical devices. To date, two primary approaches have been proposed to address arterial G&R: the concept of kinematic growth (e.g., [60,61]) and the concept of a constrained mixture [62,63]. Whereas the former can predict many cases of arterial adaptations, it models the consequences of G&R, not the means by which such changes occur. In contrast, the constrained mixture approach enables one to model the different rates of turnover of individual types of cells and matrix based on individual mass density production and removal (constitutive) functions. Such an approach promises to enable information on the mechanobiology to be incorporated directly.

From a computational perspective, one has many options for modeling the kinematics of G&R. One can employ as a computational reference an original unloaded mixture (tissue) configuration, evolving unloaded configurations, the original loaded (in vivo) configuration, or evolving loaded configurations. Each of these configurations can be related via appropriate deformation gradient tensors. Regardless of approach, different constituents (e.g., collagen and smooth muscle) are incorporated within extant matrix under stress, but this stress need not equal that of the tissue. Rather, individual constituents appear to possess a preferred “deposition stretch” or “deposition stress” and thereby possess individual natural configurations that can evolve as the overall artery adapts. It is essential, therefore, to incorporate individual natural configurations within the constitutive theory. See, for example, [25,49].

We recently suggested that a comprehensive model of vascular mechanobiology and biomechanics must synthesize analyses of the hemodynamics, wall mechanics, and growth and remodeling kinetics ([24,64], and that such models can be referred to as Fluid-Solid-Growth (FSG) models. Because of the very different time scales between the cardiac cycle (i.e., seconds, for which FSI models hold) and periods of arterial adaptation (i.e., days to months, for which G&R models hold), such models can be formulated in a loosely coupled fashion. We present in another paper in this volume [65] a basic framework for implementing such a FSG model for arterial adaptation.

5. Open Problems

In summary, computational biomechanics holds significant promise in advancing health care. Many important open problems remain, however, a few of which are discussed below:

5.1 Patient-Specific Geometric Modeling

Development of image-based modeling technologies for simulating blood flow began in the late 1990s [45,66,67]. Since that time, many groups have developed and utilized these techniques to investigate the pathogenesis of occlusive or aneurysmal disease in the carotid artery [68,69], coronary arteries [70], aorta [71], and cerebral circulation [72-74]. Patient-specific modeling techniques have also been applied in solid mechanics analyses to predict rupture risk of aneurysms [23].

Open problems related to patient-specific geometric modeling include the development of more robust techniques to segment the vessel lumen and create analytic or discrete geometric models. Three competing approaches have been utilized to create computational models from medical images to date. The first approach is based on re-sampling the three-dimensional image data on two dimensional image planes, segmenting the lumen boundary on this plane to obtain a closed-curve, lofting adjacent curves to create a tubular model of a single vessel, and then using geometric union operations to create a complete model [75]. This approach works particularly well for image data within regions of poor contrast or resolution, but is time consuming and user intensive. On the other end of the spectrum, direct three-dimensional image segmentation and geometric construction methods have been employed [76,77]. In these methods, a discrete surface mesh is obtained from the segmentation, a volume mesh is generated directly or an analytic surface is fit, then a geometric model is formed and a volume mesh created. The direct-3D approach has the advantage of being more automated and it can more faithfully represent complex geometries, yet it can present challenges with image data where contrast with adjacent tissues is poor. An intermediate approach is that of fitting template geometries to image data [78]. Further advances in patient-specific geometric modeling are needed to create accurate geometric models with minimal user-intervention even for challenging image data sets.

Another open problem in patient-specific geometric modeling is to create models that include the thickness of the vessel wall. While the solution to this open problem will have to await further advances in medical imaging, new image segmentation and geometric modeling techniques will be needed as well. Finally, little work has been devoted to validating image-based modeling methods and assessing the uncertainty of measurement data and sensitivity of solutions. Validation of image-based modeling methods is particularly challenging because the vessel wall is moving in response to the pulsatile pressure and, until recently, only time-averaged three-dimensional image data have been available. Although there have been some attempts to assess the sensitivity of hemodynamic solutions to image reconstruction techniques [79], much more work is needed.

5.2 In Vivo Material Characterization

Fundamental to any analysis in continuum biomechanics is a basic knowledge of material behavior under conditions of interest. Such constitutive relations are formulated most easily in vitro wherein geometry, applied loads, and responses can be well controlled and measured. Yet, our primary motivation in biomechanics is to understand the in vivo condition, that is, to help patients who are in need. There are five basic steps in the formulation of any constitutive relation: delineating the general characteristic behaviors, establishing an appropriate theoretical framework, identifying specific functional forms, calculating best-fit values of the material parameters, and evaluating the predictive capability of the final relations. Fortunately, it appears that we can formulate general constitutive relations for the arterial wall based on in vitro data and then focus primarily on identifying best-fit values of the associated material parameters from in vivo data, which requires accurate information on the geometry (from medical imaging) and hemodynamic loads (from imaging, pressure measurements, and CFD of FSI). Because of the potentially large number of material parameters in constitutive relations for the wall, particularly structurally motivated ones, there is also a need to restrict the allowable parameter search space. Again, however, this can be accomplished based on in vitro findings, including bounds on typical mass fractions, orientations of individual constituents, extents of residual and axial prestress, and so forth [53]. One of the main challenges, therefore, is prescribing the perivascular boundary conditions in vivo.

5.3 In Vivo Fluid and Solid Boundary Conditions

As noted previously, most prior biomechanical analyses have employed simple boundary conditions, including parabolic velocity profiles at inlets, traction-free outlets, and no perivascular support. Most problems of clinical interest require more realistic conditions, however, with the computational domain for the fluid embedded within a closed-loop circulatory model and interactions included between the fluid and a solid that is constrained by perivascular tissue. This complexity presents new challenges related to prescribing boundary conditions. First, there is the need to estimate parameters in reduced-order models of the distal resistance beds and to couple these models to the computational domain for the fluid. For the case of distributed network models, this involves specifying anatomic and physiologic parameters (e.g. branching patterns, vessel diameters and lengths) that cannot be resolved using standard noninvasive imaging (because of the micron diameter vessels). For lumped parameter models of downstream or upstream portions of the circulation excluded from the computational domain, this necessitates assigning bulk resistances, impedances, compliance, or inertial terms. In either the distributed or the lumped-parameter reduced-order models, parameter values need to be “tuned” so the combined model matches available physiologic data, including measured blood pressures and flows. Without question, fluid-solid interactions in the arterial system depend strongly on the tissue or fluid outside the vessel of interest. For example, many portions of the vasculature are embedded in soft tissue (e.g., epicardial coronary arteries of the heart) or lie adjacent to hard tissues such as bones. Such support can have a dramatic stabilizing influence on wall dynamics and should be modeled when possible. A second challenge, therefore, is the need to model the perivascular support and extract information on the degree of support via noninvasive imaging methods.

5.4 Multiscale Modeling From Molecule to Manifestation

Whereas clinical symptoms and most interventional treatments, including those involving implanted medical devices, occur at the tissue level, the fundamental mechanisms that cause the disease or dictate the response of the artery to treatment depend on molecular processes. Parallel advances in molecular biology and systems biology promise to enable modeling of the underlying mechanobiology (i.e., mechano-transduction, transcription, and translation). Hence, there is a need to begin to develop multiscale models that combine knowledge of molecular mechanisms with clinical manifestation. Although it is unrealistic to think that a single model could incorporate all of the incredible complexity of the different cell types and matrix constituents within geometrically accurate patient-specific, fluid-solid-growth models, subclasses of such models are possible and should be pursued for specific clinical problems based on dominate underlying processes (e.g., endothelial dysfunction).

5.5 Surgical Planning and Medical Device Development

Computational methods for modeling hemodynamics and wall mechanics offer an opportunity to predict potential benefits of alternate treatment strategies. A new era in clinical care could be created whereby interventionalists and surgeons utilize simulation-based methods, initialized with patient-specific anatomic and physiologic data, to design optimal treatments for individuals based on predicted outcomes. In the last several years, a few groups have started to apply image-based modeling techniques to the assessment of surgical procedures to treat congenital heart defects [80,81]. Exciting opportunities are on the horizon, for example, with the introduction of formal optimization methods to modify vascular graft geometry for the purpose of improving hemodynamic outcomes [82].

In addition to enabling physicians to devise better treatments for individual patients, computational methods could enable cardiovascular device manufacturers to predict the performance of their devices in virtual patients prior to deployment in human trials. These virtual clinical trials prior to animal and human studies could result in safer designs, reduced

development costs, and shorter time-to-market. Furthermore, pharmaceutical and biotechnology manufacturers could utilize simulation to model the transport of drugs through the circulatory system and determine local concentrations to use in pharmacokinetic models of drug metabolism. This new frontier in computational mechanics has an almost limitless number of open problems to challenge investigators for many years to come and combines both the successes and the challenges of most aspects of vascular mechanics discussed throughout this paper.

6. Closure

The past four decades have brought forth tremendous advances in vascular biology, mechanics, computational capabilities, medical imaging, pathophysiology, and interventional technologies. Nevertheless, the potential to synthesize these many advances within a common conceptual and theoretical framework could revolutionize clinical care. Attention in computational vascular mechanics should focus on patient-specific analyses of disease progression, device-tissue interactions, and interventional and surgical planning based on appropriate couplings of advection-reaction-diffusion formulations and fluid-solid-growth models. Models should be as simple as possible, yet include complexities that enable the underlying mechanobiology and chemomechanics to be modeled well.

Acknowledgments

This review was first presented as a Workshop on “Computational Methods in Cardiovascular Mechanics” at the 9th US National Congress on Computational Mechanics at San Francisco in August 2007. Our research on which this work is based has been supported, in part, by grants from the National Science Foundation (BES-0084644 – JDH; ITR-0205741 – CAT) and the National Institutes of Health (HL-64372, HL-80415 – JDH; U54 GM072970 – CAT). We also acknowledge expert contributions to research in our laboratories by S. Baek, L. Cardamone, C.A. Figueroa, R.L. Gleason, H.J. Kim, R.L. Spilker, A. Valentin, and I.E. Vignon-Clementel.

References

1. Young T. Hydraulic investigations, subservient to an intended croonian lecture on the motion of the blood. Phil Trans Roy Soc (London) 1808;98:164–186.
2. Roy CS. The elastic properties of the arterial wall. J Physiol 1881;3:125–159.
3. Pries AR, Secomb TW, Gaehtgens P. Design principles of vascular beds. Circ Res 1995;77(5):1017–23. [PubMed: 7554136]
4. Olufsen MS. Structured tree outflow condition for blood flow in larger systemic arteries. American Journal of Physiology 1999;276(1 Pt 2):H257–68. [PubMed: 9887040]
5. Kassab GS, Rider CA, Tang NJ, Fung YC. Morphometry of pig coronary arterial trees. Am J Physiol 1993;265(1 Pt 2):H350–65. [PubMed: 8342652]
6. Nichols, WW.; O'Rourke, MF. Mcdonald's blood flow in arteries: Theoretical, experimental and clinical principles. 5. Oxford University Press; 2005.
7. Davies PF. Flow-mediated endothelial mechanotransduction. Physiol Rev 1995;75(3):519–60. [PubMed: 7624393]
8. Strauss BH, Rabinovitch M. Adventitial fibroblasts: Defining a role in vessel wall remodeling. Am J Respir Cell Mol Biol 2000;22(1):1–3. [PubMed: 10615057]
9. Levy, BI.; Tedgui, A. Biology of the arterial wall. Kluwer Academic Publishers; Dordrechht: 1999.
10. Humphrey, JD. Cardiovascular solid mechanics: Cells, tissues, and organs. Springer; New York: 2002.
11. Greenwald SE. Ageing of the conduit arteries. J Pathol 2007;211(2):157–72. [PubMed: 17200940]
12. O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: A clinical perspective. J Am Coll Cardiol 2007;50(1):1–13. [PubMed: 17601538]
13. Laurent S, Tropeano AI, Boutouyrie P. Pulse pressure reduction and cardiovascular protection. J Hypertens Suppl 2006;24(3):S13–8. [PubMed: 16723861]

14. Humphrey JD. Vascular adaptation and mechanical homeostasis at tissue, cellular, and sub-cellular levels. Cell Biochem Biophys 2008;50(2):53–78. [PubMed: 18209957]
15. Jeffery TK, Wanstall JC. Pulmonary vascular remodeling: A target for therapeutic intervention in pulmonary hypertension. Pharmacol Ther 2001;92(1):1–20. [PubMed: 11750034]
16. Mandegar M, Fung YC, Huang W, Remillard CV, Rubin LJ, Yuan JX. Cellular and molecular mechanisms of pulmonary vascular remodeling: Role in the development of pulmonary hypertension. Microvasc Res 2004;68(2):75–103. [PubMed: 15313118]
17. Burrowes KS, Hunter PJ, Tawhai MH. Anatomically based finite element models of the human pulmonary arterial and venous trees including supernumerary vessels. J Appl Physiol 2005;99(2): 731–8. [PubMed: 15802366]
18. Spilker RL, Feinstein JA, Parker DW, Reddy VM, Taylor CA. Morphometry-based impedance boundary conditions for patient-specific modeling of blood flow in pulmonary arteries. Ann Biomed Eng 2007;35(4):546–59. [PubMed: 17294117]
19. Caro CG, Fitz-Gerald JM, Schroter RC. 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 1971;177(46):109–59. [PubMed: 4396262]
20. Friedman MH, Hutchins GM, Bargeron CB, Deters OJ, Mark FF. Correlation between intimal thickness and fluid shear in human arteries. Atherosclerosis 1981;39(3):425–36. [PubMed: 7259822]
21. Zarins CK, Giddens DP, Bharadvaj BK, Sottiurai VS, Mabon RF, Glagov S. Carotid bifurcation atherosclerosis. Quantitative correlation of plaque localization with flow velocity profiles and wall shear stress. Circ Res 1983;53(4):502–14. [PubMed: 6627609]
22. Humphrey JD, Canham P. Structure, properties, and mechanics of intracranial saccular aneurysms. J Elast 2000;61:49–81.
23. Vorp DA. Biomechanics of abdominal aortic aneurysm. J Biomech 2007;40(9):1887–902. [PubMed: 17254589]
24. Humphrey JD, Taylor CA. Intracranial and abdominal aortic aneurysms: Similarities, differences, and need for a new class of computational models. Annu Rev Biomed Eng 2008;10:221–46. [PubMed: 18647115]
25. Baek S, Rajagopal KR, Humphrey JD. A theoretical model of enlarging intracranial fusiform aneurysms. J Biomech Eng 2006;128(1):142–9. [PubMed: 16532628]
26. Kroon M, Holzapfel GA. A model for saccular cerebral aneurysm growth by collagen fibre remodelling. J Theor Biol 2007;247(4):775–87. [PubMed: 17482213]
27. Dalman RL, Tedesco MM, Myers J, Taylor CA. Aaa disease: Mechanism, stratification, and treatment. Ann N Y Acad Sci 2006;1085:92–109. [PubMed: 17182926]
28. Anand M, Rajagopal K, Rajagopal KR. A model for the formation, growth, and lysis of clots in quiescent plasma. A comparison between the effects of antithrombin iii deficiency and protein c deficiency. J Theor Biol 2008;253(4):725–38. [PubMed: 18539301]
29. Guy RD, Fogelson AL, Keener JP. Fibrin gel formation in a shear flow. Math Med Biol 2007;24(1): 111–30. [PubMed: 17018571]
30. Wootton DM, Ku DN. Fluid mechanics of vascular systems, diseases, and thrombosis. Annu Rev Biomed Eng 1999;1:299–329. [PubMed: 11701491]
31. Kiousis DE, Gasser TC, Holzapfel GA. A numerical model to study the interaction of vascular stents with human atherosclerotic lesions. Ann Biomed Eng 2007;35(11):1857–69. [PubMed: 17647105]
32. LaDisa JF Jr, Guler I, Olson LE, Hettrick DA, Kersten JR, Warltier DC, Pagel PS. Three-dimensional computational fluid dynamics modeling of alterations in coronary wall shear stress produced by stent implantation. Ann Biomed Eng 2003;31(8):972–80. [PubMed: 12918912]
33. Rogers C, Edelman ER. Endovascular stent design dictates experimental restenosis and thrombosis. Circulation 1995;91(12):2995–3001. [PubMed: 7796511]
34. Finn AV, Nakazawa G, Joner M, Kolodgie FD, Mont EK, Gold HK, Virmani R. Vascular responses to drug eluting stents: Importance of delayed healing. Arterioscler Thromb Vasc Biol 2007;27(7): 1500–10. [PubMed: 17510464]
35. Fogarty TJ, Arko FR, Zarins CK. Endograft technology: Highlights of the past 10 years. J Endovasc Ther 2004;11:II192–9. [PubMed: 15760266]

36. Linfante I, Wakhloo AK. Brain aneurysms and arteriovenous malformations: Advancements and emerging treatments in endovascular embolization. Stroke 2007;38(4):1411–7. [PubMed: 17322071]
37. Yoganathan AP, He Z, Casey Jones S. Fluid mechanics of heart valves. Annu Rev Biomed Eng 2004;6:331–62. [PubMed: 15255773]
38. Simon MA, Watson J, Baldwin JT, Wagner WR, Borovetz HS. Current and future considerations in the use of mechanical circulatory support devices. Annu Rev Biomed Eng 2008;10:59–84. [PubMed: 18647112]
39. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med 1999;340(2):115–26. [PubMed: 9887164]
40. Gijsen FJ, Allanic E, van de Vosse FN, Janssen JD. The influence of the non-newtonian properties of blood on the flow in large arteries: Unsteady flow in a 90 degrees curved tube. J Biomech 1999;32 (7):705–13. [PubMed: 10400358]
41. Perktold K, Resch M, Peter RO. Three-dimensional numerical analysis of pulsatile flow and wall shear stress in the carotid artery bifurcation. J Biomech 1991;24(6):409–20. [PubMed: 1856241]
42. Figueroa CA, Vignon-Clementel IE, Jansen KC, Hughes TJR, Taylor CA. A coupled momentum method for modeling blood flow in three-dimensional deformable arteries. Computer Methods in Applied Mechanics and Engineering 2006;195(4143):5685–5706.
43. Perktold K, Rappitsch G. Computer simulation of local blood flow and vessel mechanics in a compliant carotid artery bifurcation model. Journal of Biomechanics 1995;28(7):845–856. [PubMed: 7657682]
44. Ethier CR. Computational modeling of mass transfer and links to atherosclerosis. Ann Biomed Eng 2002;30(4):461–71. [PubMed: 12085998]
45. Taylor CA, Hughes TJR, Zarins CK. Finite element modeling of blood flow in arteries. Computer Methods in Applied Mechanics and Engineering 1998;158:155–196.
46. Taylor CA, Draney MT. Experimental and computational methods in cardiovascular fluid mechanics. Annual Review of Fluid Mechanics 2004;36:197–231.
47. Fung, YC. Biomechanics: Motion, flow, stress, and growth. Springer; New York: 1990.
48. Holzapfel GA, Gasser TC, Ogden RW. A new constitutive framework for arterial wall mechanics and a comparative study of material models. J Elast 2000;61:1–48.
49. Valentin A, Cardamone L, Baek S, Humphrey JD. Complementary vasoactivity and matrix remodelling in arterial adaptations to altered flow and pressure. J R Soc Interface. 2008
50. Alastrue V, Pena E, Martinez MA, Doblare M. Assessing the use of the “Opening angle method” To enforce residual stresses in patient-specific arteries. Ann Biomed Eng 2007;35(10):1821–37. [PubMed: 17638082]
51. Delfino A, Stergiopulos N, Moore JE Jr, Meister JJ. Residual strain effects on the stress field in a thick wall finite element model of the human carotid bifurcation. J Biomech 1997;30(8):777–86. [PubMed: 9239562]
52. Stalhand J, Klarbring A, Karlsson M. Towards in vivo aorta material identification and stress estimation. Biomech Model Mechanobiol 2004;2(3):169–86. [PubMed: 14767677]
53. Masson I, Boutouyrie P, Laurent S, Humphrey JD, Zidi M. Characterization of arterial wall mechanical behavior and stresses from human clinical data. J Biomech. 2008
54. Hughes TJR, Liu WK, Zimmermann TK. Lagrangian–eulerian finite element formulation for incompressible viscous flows. Comput Methods Appl Mech Engrg 1981;29:329–349.
55. Wolinsky H, Glagov S. Comparison of abdominal and thoracic aortic medial structure in mammals. Deviation of man from the usual pattern. Circ Res 1969;25(6):677–86. [PubMed: 5364644]
56. Tarbell JM. Mass transport in arteries and the localization of atherosclerosis. Annu Rev Biomed Eng 2003;5:79–118. [PubMed: 12651738]
57. Shadden SC, Taylor CA. Characterization of coherent structures in the cardiovascular system. Ann Biomed Eng 2008;36(7):1152–62. [PubMed: 18437573]
58. Dajnowiec D, Langille BL. Arterial adaptations to chronic changes in haemodynamic function: Coupling vasomotor tone to structural remodelling. Clin Sci (Lond) 2007;113(1):15–23. [PubMed: 17536999]

59. Buerk DG. Can we model nitric oxide biotransport? A survey of mathematical models for a simple diatomic molecule with surprisingly complex biological activities. Annu Rev Biomed Eng 2001;3:109–43. [PubMed: 11447059]
60. Rachev A. A model of arterial adaptation to alterations in blood flow. J Elast 2000;61:83–111.
61. Taber LA. A model for aortic growth based on fluid shear and fiber stresses. J Biomech Eng 1998;120 (3):348–54. [PubMed: 10412402]
62. Humphrey JD, Rajagopal KR. A constrained mixture model for growth and remodeling of soft tissues. Math Model Meth Appl Sci 2002;12:407–430.
63. Watton PN, Hill NA, Heil M. A mathematical model for the growth of the abdominal aortic aneurysm. Biomech Model Mechanobiol 2004;3(2):98–113. [PubMed: 15452732]
64. Baek S, Gleason RL, Rajagopal KR, Humphrey JD. Theory of small on large: Potential utility in computations of fluid-solid interactions in arteries. Comp Meth Applied Mech Engrg 2007;196:3070–3078.
65. Figueroa CA, Baek S, Taylor CA, Humphrey JD. A computational framework for coupled fluid-solid growth modeling in cardiovascular simulations. To appear in Computer Methods in Applied Mechanics and Engineering. 2009
66. Moore JA, Rutt BK, Karlik SJ, Yin K, Ethier CR. Computational blood flow modeling based on in vivo measurements. Annals of Biomedical Engineering 1999;27(5):627–640. [PubMed: 10548332]
67. Taylor CA, Draney MT, Ku JP, Parker D, Steele BN, Wang K, Zarins CK. Predictive medicine: Computational techniques in therapeutic decision-making. Comput Aided Surg 1999;4(5):231–47. [PubMed: 10581521]
68. Long Q, Xu XY, Ariff B, Thom SA, Hughes AD, Stanton AV. Reconstruction of blood flow patterns in a human carotid bifurcation: A combined cfd and mri study. J Magn Reson Imaging 2000;11(3): 299–311. [PubMed: 10739562]
69. Steinman DA. Image-based computational fluid dynamics modeling in realistic arterial geometries. Ann Biomed Eng 2002;30(4):483–97. [PubMed: 12086000]
70. Gijsen FJ, Wentzel JJ, Thury A, Lamers B, Schuurbiers JC, Serruys PW, van der Steen AF. A new imaging technique to study 3-d plaque and shear stress distribution in human coronary artery bifurcations in vivo. J Biomech 2007;40(11):2349–57. [PubMed: 17335832]
71. Tang BT, Cheng CP, Draney MT, Wilson NM, Tsao PS, Herfkens RJ, Taylor CA. Abdominal aortic hemodynamics in young healthy adults at rest and during lower limb exercise: Quantification using image-based computer modeling. Am J Physiol Heart Circ Physiol 2006;291(2):H668–76. [PubMed: 16603687]
72. Cebral JR, Castro MA, Burgess JE, Pergolizzi RS, Sheridan MJ, Putman CM. Characterization of cerebral aneurysms for assessing risk of rupture by using patient-specific computational hemodynamics models. AJNR Am J Neuroradiol 2005;26(10):2550–9. [PubMed: 16286400]
73. Jou LD, Wong G, Dispensa B, Lawton MT, Higashida RT, Young WL, Saloner D. Correlation between lumenal geometry changes and hemodynamics in fusiform intracranial aneurysms. AJNR Am J Neuroradiol 2005;26(9):2357–63. [PubMed: 16219845]
74. Shojima M, Oshima M, Takagi K, Torii R, Hayakawa M, Katada K, Morita A, Kirino T. Magnitude and role of wall shear stress on cerebral aneurysm: Computational fluid dynamic study of 20 middle cerebral artery aneurysms. Stroke 2004;35(11):2500–5. [PubMed: 15514200]
75. Wilson NM, Wang KC, Dutton RW, Taylor CA. A software framework for creating patient specific geometric models from medical imaging data for simulation based medical planning of vascular surgery. Lecture Notes in Computer Science 2001;2208:449–456.
76. Bekkers EJ, Taylor CA. Multiscale vascular surface model generation from medical imaging data using hierarchical features. IEEE Trans Med Imaging 2008;27(3):331–41. [PubMed: 18334429]
77. Cebral JR, Castro MA, Appanaboyina S, Putman CM, Millan D, Frangi AF. Efficient pipeline for image-based patient-specific analysis of cerebral aneurysm hemodynamics: Technique and sensitivity. IEEE Trans Med Imaging 2005;24(4):457–67. [PubMed: 15822804]
78. Zhang Y, Bazilevs Y, Goswami S, Bajaj CL, Hughes TJR. Patient-specific vascular nurbs modeling for isogeometric analysis of blood flow. 2007;196(2930):2943–2959.

79. Moore JA, Steinman DA, Ethier CR. Computational blood flow modeling: Errors associated with reconstructing finite element models from magnetic resonance images. Journal of Biomechanics 1998;31(2):179–184. [PubMed: 9593213]

80. Marsden AL, Vignon-Clementel IE, Chan FP, Feinstein JA, Taylor CA. Effects of exercise and respiration on hemodynamic efficiency in cfd simulations of the total cavopulmonary connection. Ann Biomed Eng 2007;35(2):250–63. [PubMed: 17171509]

81. Migliavacca F, Dubini G, Bove EL, de Leval MR. Computational fluid dynamics simulations in realistic 3-d geometries of the total cavopulmonary anastomosis: The influence of the inferior caval anastomosis. J Biomech Eng 2003;125(6):805–13. [PubMed: 14986405]

82. Marsden AL, Feinstein JA, Taylor CA. A computational framework for derivative-free optimization of cardiovascular geometries. Computer Methods in Applied Mechanics and Engineering 2008;197 (2124):1890–1905.