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Open problems in computational vascular biomechanics: Hemodynamics and arterial wall mechanics

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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.

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 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

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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 six 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 acute 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.