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Role of Arterial Wall Mechanics in Cardiovascular Regulation

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Abstract:

Cardiovascular tissue comprises of large and small arteries, heart chambers, and valves, playing several pivotal roles in cardiac health and diseases. The ability to work under a constant cyclic mechanical environment throughout life is a fundamental property of cardiac and vascular tissues. From an engineering perspective, an up-to-date knowledge of the mechanical behavior and material properties of vascular tissues is essential to our understanding of cardiovascular disease pathophysiology and the development of therapeutic strategies. Therefore, this review focuses on the current state of knowledge on the passive and active biomechanical properties of blood vessels, and the key experimental and computational techniques used to quantify small artery vasoactive responses in cardiovascular control. We started with a brief, general discussion of the structure and composition of the small atrial wall, the passive and active properties of vascular tissues, smooth muscle mechanics, and the difference between small and large artery biomechanics. Then the measurement techniques used to study biomechanics of small arteries and mathematical modeling approaches were discussed. We concluded with the clinical implications of altered vessel biomechanics in aging, hypertension and atherosclerosis, and the future directions.

Keywords: *Arterial Wall; Biomechanics; Cardiovascular Regulation; Active and Passive Properties; Aging, Hypertension; Atherosclerosis; Computational Modelling*

Introduction

The human body is a beautiful conglomerate of complex and intricate organs and organ systems with a well-defined workline distribution. The cardiovascular system mainly includes the heart and blood vessels of different lumen sizes that continuously circulate oxygenated and deoxygenated blood. The vascular system comprises large and small arteries, arterioles, capillaries, venules, and veins with distinct cardiovascular regulatory functions[1]. As a consequence, arterial structure and biomechanical behavior is different depending on its location in the vascular system. Arteries carry oxygenated blood away from the heart to the tissues, except for pulmonary arteries, which carry blood to the lungs for oxygenation. They carry blood that is oxygenated after it has been pumped from the heart. Arteries have a blood pressure higher than other parts of the circulatory system. The pressure in arteries varies during the cardiac cycle. It is highest when the heart contracts and lowest when heart relaxes. The variation in pressure produces a pulse, which can be felt in different areas of the body, such as the radial pulse. Arteries have the highest pressure and have narrow lumen diameter[2], [3].

In contrast, small arteries and arterioles form the crucial part of the circulatory system, the microcirculation, where they help control vascular resistance in an intricate manner for efficient delivery of nutrients to host tissues[4]. It is the ability of the cardiovascular system to adjust the resistance of each arterial segment by controlling its lumen diameter to meet the metabolic demand of the tissues. The arterial diameter is, in turn, a function of the amount and arrangement of the vascular wall materials and, in particular, of the level of tone in the vascular

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smooth muscle[1], [5], [6]. Therefore, a thorough, up-to-date understanding of the structure and function of small arteries is essential to study the relationship between mechanical and chemical properties underlying vasoregulation in cardiovascular diseases.

Structure of Arteries in Cardiovascular System

The arteries in the cardiovascular system show significant diversity in terms of their structure, size and functions in the vasculature. The wall of an artery comprises of three layers. The innermost layer, tunica intima (also called tunica interna), surrounded by a connective tissue basement membrane with elastic fibers[1], [7]. The intima consists of connective fibrous tissue covered by of endothelial cells and further divided into endothelium, basal lamina, and the internal elastic lamina. Endothelium is a layer of endothelial cells made up of simple, squamous epithelium. The cells are spindle-shaped and have a rounded nucleus. It provides structural integrity to the vessel's inner walls and a smooth surface for easy blood flow. The endothelial cells rest on a thin glycoprotein layer called the basal lamina, followed by a thin sub-endothelial connective tissue layer. Internal elastic lamina separates the tunica indicia to tunica media, and it has fenestrated structures that allow the inner part of the artery to get nutrition from the oxygenated blood.

The middle layer is called tunica media, which is primarily smooth muscle and is usually the thickest layer (shown in Figure 1B). It contains smooth muscle, elastin, collagen fibers, and a ground substance matrix, making majority of the arterial wall thickness. It not only provides support for the vessel but also changes vessel diameter to regulate blood flow and blood pressure. Additionally, the smooth muscle layer also secretes extracellular matrix. The elastin and collagen fibers play a structural and mechanical role in the arteries and their essential function is to provide elasticity and resilience to the tissues. The External elastic lamina separates the tunica media from tunica adventitia[1].

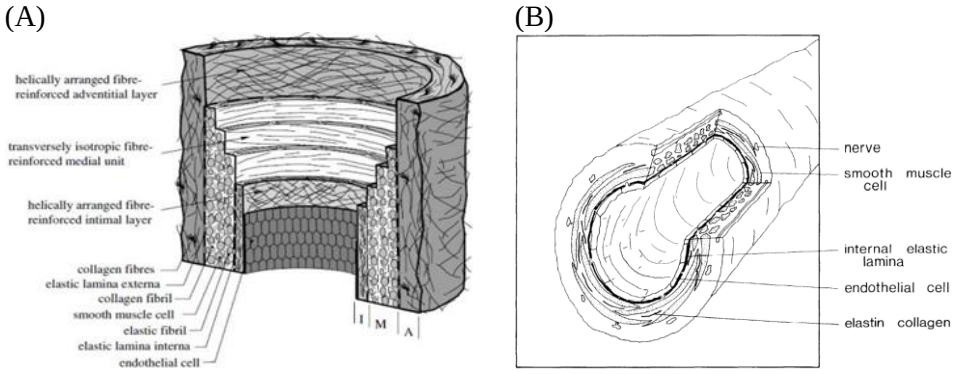

Fig. 1. Schematic showing the cross-sectional views of (A) large and (B) small artery structure and cellular composition (from[1], [8], [9]).

The external elastic lamina separates the tunica media from tunica adventitia. This layer is not very porous because the cells present get their nutrition from the blood vessels that are present in the tunica adventitia. The outermost layer, which attaches the vessel to the surrounding tissue, is the tunica externa or tunica adventitia. It consists of a network of connective tissue including collagen fibers, elastin, nerves, fibroblasts, and the vasa vasorum. The tunica adventitia provides a limiting barrier, protecting the vessel from overexpansion. The collagen serves to anchor the blood vessels to nearby organs, giving it stability.

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Similar to large size arteries, the vascular wall of small arteries consists of an outer tunica adventitia, a central tunica media, and inner tunica intima, as shown in Figure 1B. Several aspects of small artery structure are of importance for determining the contractile response characteristics of the blood vessels for microcirculatory functions. As in larger arteries, the adventitia of the small arteries contains connective tissue (elastin and collagen), mast cells, macrophages and Schwan cells with associated nerve endings. The tunica media of small arteries is bounded on the luminal side by a well-defined internal elastic lamina, but the external elastic lamina is fragmented or absent, and there are no elastic laminae within the media. The number of smooth muscle cell layers within the media of small arteries decreases with decreasing vessel diameter from approximately six layers in 300~pm vessels to a monolayer in 30 to 50 pm arterioles[1]. Within the media, the smooth muscle cells are circumferentially arranged, and difference in sizes of smooth muscles can account for the functional differences observed between small and large arteries in most species. The endothelial cells of small arteries, have a squamous structure and form a continuous cover. In arterioles, the cells are reported to be ~2µm thick and oriented with the long axis parallel to the direction of flow. An important morphological observation is that the endothelial cells of small arteries frequently project through fenestrations in the internal elastic lamina to interact with the vascular smooth muscle cells within the tunica media[9].

More recently, there have been extensive focus on small arteries functions in different vasculatures, which mainly depends on both vascular and extravascular mechanical and chemical factors. It is well known to contribute to the regulation of local vasomotor tone and global peripheral vascular resistance. Under resting conditions and other *in vivo* conditions, these vessels have a pronounced active tone regardless of the presence of other microcirculatory stimuli. However, variations of physiological pressure along the vasculature plays a vital role in small artery responses to various stimuli. Variation of arteriolar pressure profile along the vasculature strongly affect small artery regulatory functions. Although pressure profiles are difficult to measure, studies in hamster cheek pouch vasculature clearly demonstrate, the small arteries and arterioles are exposed to high pressure gradient in the vasculature. Experimental data reveals the intravascular pressure of small arteries is substantially less as compared to actual systemic pressure and therefore, a large part of peripheral resistance lies in small arteries itself. Specifically, cheek pouch vasculature shows a pressure gradient of 0.7mmHg/mm. In the study of Meininger [2] it was shown that the measured blood flow velocities and small artery diameters in the rat cremaster muscle varies between 117-65 µm with a pressure gradient of 1-2.5 mmHg/mm. Figure 2 shows the pressure sensed by arteries of hamster cheek pouch vasculature.

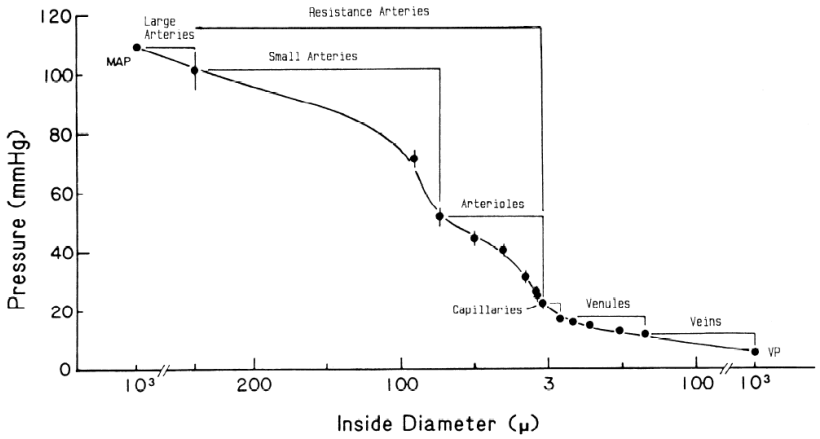

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Fig. 2. Shown here is the arterial nomenclature used to represent observed pressure gradient in hamster cheek pouch circulation. (adopted from[10]); MAP: mean arterial pressure measured near femoral artery; VP: venous pressure measured around maxillary vein).

Thus, understanding vascular tone regulation requires a quantitative understanding of physiological pressure sensed by the blood vessels at different locations and under stress conditions. Therefore the main focus of this review to summarize the recent advancements in arterial mechanics and their relationships between vascular regulatory response in a given tissue and their method of assessment.

Mechanical Properties of Arterial Wall in Health

Passive and Active Vessel Wall Mechanics:

The passive mechanics of blood vessel wall is mainly governed by the material compositions of the vessels wall, which are basically due to the passive components elastin and collagen fibers. However, the artery also has active components allowing it to respond to local demands by contracting and relaxing, which is mainly the vascular smooth muscle cells[4], [6], [11], [12]. It is well known that the artery walls are anisotropic and behave in a highly nonlinear fashion (soft at low blood pressure with an increasing stiffness at higher pressures). This peculiar behavior is a result of the elastin and collagen microstructures and is associated with the anisotropy.

The arterial wall is typically represented as a contractile element, a Parallel Elastic Component (PEC), and a Series Elastic Component (SEC)[5], [12], [13], [14]. The PEC represents the elastic behavior of the vessel wall when the contractile element is completely relaxed. The PEC is made up of one spring, which represents elastin, and a number of much stiffer springs of different lengths, which represent collagen. Collagen is a basic structural protein in animals. It gives strength and stability and appears in almost all parts of the body. The collagen molecule consists of three helically wound chains of amino-acids. These helices are collected together in micro fibrils, which in their turn form sub fibrils and fibrils. Bundles of fibrils form fibers. The fibers are normally arranged in a wavy form. Due to this waviness the stress-strain relationship shows a very low stiffness at small stretch ratios.

The contractile element is the smooth muscle. The smooth muscle is coupled in series with the SEC. The SEC is made up of collagen fibers of differing lengths that are increasingly recruited in proportion to smooth muscle activation. When the contractile element is activated, the combined smooth muscle–SEC increases isometric wall stress and wall stiffness [3]. Smooth muscle cells in the vascular system are responsible for control of short-term changes in lumen diameter and of long-term changes in the extracellular matrix turnover, in which fibroblasts play a key role. The gradient of the circumferential stress in the radial direction decreases, and the circumferential stress tends to a homeostatic value due to SMC activation, a value that is approximately constant over each layer of the wall. In a homeostatic state, SMCs are partially contracted, thus forming the basal tone of the artery. Vascular smooth muscle in small resistant arteries regulates blood pressure by adjusting the lumen diameter. In large arteries the contraction of smooth muscles contributes to the resistance in the vascular wall. The contracting mechanism in smooth muscle cells involves cross bridge interaction between myosin (thick filaments) and actin (thin filaments). Calcium ions (Ca^{2+}) initiate contraction, and to regulate the concentration of Ca^{2+}, a complex network of signaling pathways is used[5], [15]. Figure 3 shows the stress-stretch relationships in an isolated arterial segment under zero

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calcium condition (passive) and in the presence of calcium alone, and in the presence of calcium and other chemical stimulus.

The smooth muscles are contracted in two different ways: a) by membrane depolarization, b) by receptor activation. When activated through membrane depolarization, the initiation of contraction take place due to changes in the cell surface membrane potential, which trigger the influx of Ca^{2+} by voltage-dependent Ca^{2+} channels. In contrast, receptor activation activates the contraction using a more complex signaling pathway. Activation of receptors by agonists at the cell surface results in Ca^{2+} increase, either from release of intracellular stores or through signaling mechanisms that increases the Ca^{2+} sensitivity of the contractile apparatus. Upon starting a contraction Ca^{2+} binds to the protein calmodulin (CaM). The CaM activates the myosin light chain (MLC) kinase, which phosphorylate the regulatory light chain of myosin. When the myosin has been phosphorylated the interaction between myosin and actin takes place through load bearing cross bridges. Energy released from ATP result in cycling of the myosin and actin cross bridges to produce force for contraction [3], [14], [15], [16], [17].

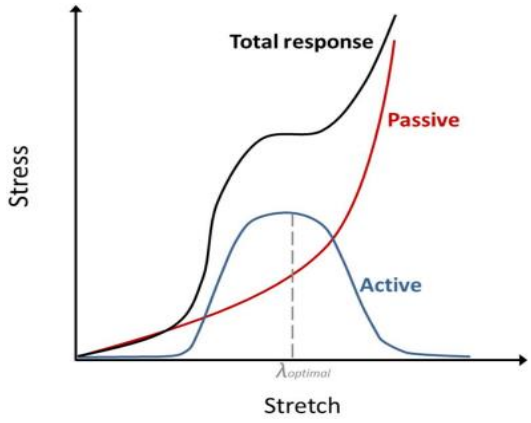

Fig. 3. Schematic showing (A) passive, active and total length-tension characteristic curves of small artery wall, observed in various tissues.

Experimental Approaches to Arterial Biomechanics:

Small arteries are commonly classified in terms of their lumen diameters, but the conditions under which diameter is measured vary from experiment to experiment *in vitro*. Wire myograph is the first apparatus, for the determination of the contractility of isolated small arteries to agonist stimulation, which was mainly developed by Bevan and Osher [18]. They showed it was possible to mount segments of arteriole or artery as ring preparations on two fine wires, with the wires being clamped at each end to ensure that the responses were isometric. The basic principles of isometric and isobaric myography have been reported long ago, both in large vessels , isometric tension measurement of small arterioles and arteries[1], [4], [18], [19], isobaric diameter measurement of smaller arteries (Halpern et al., 1984) as well as of very small arterioles[11], [18], [19], [20]. More recently, isovolumic myography was used to measure the vasoactive response in near physiologic conditions[21]. Here we emphasize the importance of existing myography data in different size of preparations, measured under various conditions to quantify tone in any small arteries. A number of techniques have been introduced that utilize the ability of wire and pressure myographs to make simultaneous

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measurements of contractility and of various aspects of the excitation-contraction coupling in vascular smooth muscles[5], [22], [23]. Thus, small arteries are mostly preferred for studies of vascular smooth muscle excitation-contraction coupling in general[24]. We complement these facts with our insights on cellular mechanisms and latest modeling approaches to quantify these mechanical regulatory responses.

Computational Approaches to Arterial Biomechanics:

Mathematical modeling of cardiovascular systems have shown great advancements in numerical techniques and their efficient application in understanding the biomechanical origin of many cardiovascular diseases[9], [25], [26], [27], [28]. Computational modeling is being used in a wide variety of ways in cardiovascular research, including assessment of effects of wall shear stress on atherogenesis, prediction of risks for aneurysm rupture, interpretation of medical images, and quantification of vascular tones in response to diverse physical and chemical stimuli[8], [25], [28], [29].

From an engineering standpoint, understanding hemodynamic patterns in large arteries of diverse species have been extensively studied using finite element modeling approaches because of their important role in vascular diseases such as atherosclerosis and intimal hyperplasia. Several biomechanics modeling studies used idealized arterial geometry to study arterial functions of healthy and stenosed arteries. More recently, the combination of high-resolution medical imaging (typically, magnetic resonance angiography, x-ray angiography and ultrasound imaging), sophisticated image segmentation techniques, and high-performance computers has made it possible to simulate physiologically pulsatile flow patterns in anatomically realistic arterial geometry with computational fluid dynamic (CFD) modeling techniques. Such image-based CFD analyses have clearly demonstrated the importance of subject-specific geometry, and to a lesser extent subject-specific flow rates[5], [28], [30], [31]. For example, many efforts have focused on quantifying the relationship between local hemodynamic factors and the presence or absence of vessel abnormalities by coupling CFD with wall material properties. The goal of these lines of studies is to demonstrate an association between low wall shear stress and high wall mechanical stress at the bifurcation or other anatomical region that are thought to responsible for plaque formation[13], [29], [31]. Model predicted wall thickness in the various vessel branches can be validated using vascular image or ultrasound data.

Cardiovascular tissues are viscoelastic, exhibiting behaviors that combine features of elastic solids and viscous fluids. Elasticity, viscosity, and viscoelasticity can be quantified from mechanical testing techniques that relate the dynamics of a tissue's deformation to an applied load. A common parameter of material elasticity is the elastic modulus, E, which is the slope of the stress-strain curve, and can be easily defined at any point along the stress-strain curve. In arteries, for example, it is often convenient to probe the behavior in low and high strain regions separately and to calculate low and high strain moduli, respectively. Viscoelastic materials dissipate energy upon deformation, which can be observed through hysteresis in the stress-strain curve. Viscoelastic material behavior is also time-dependent, the loading-unloading stress-strain behavior also depends on strain rate. To measure viscoelasticity, the strain rate, frequency, or time-dependent mechanical behavior of a material are measured. Sometimes, a sinusoidal input (stress or strain) is applied to tissue, and an output signal (the

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corresponding strain or stress) is measured[25], [30]. The output signal is in phase with the input signal for a purely elastic material and out of phase for a viscoelastic material.

Classical models of viscoelastic materials use combinations of spring and dashpot elements to characterize stress-strain behavior, as shown in Figure 4[16], [28], [29], [30], [32]. Spring elements represent elastic behavior, where the spring constant of proportionality, directly relates the applied force, F, to the resulting deformation, x. Dashpot elements represent viscous behavior, where the applied force is related to the rate of deformation, $\dot{x}$, by the viscosity, μ. Spring and dashpot elements are arranged in series in Maxwell models and in parallel in Kelvin-Voight models. Since the elements are arranged in parallel, force in a Kelvin-Voight model is a sum of the two individual element forces, and elements share the same deformation. The elements in a Maxwell model share the same force, and the total deformation is the sum of the individual element deformations. The combination of spring and dashpot elements in these two models can be used to construct more complex viscoelastic solid models[8].

More recently, multicellular biophysical models of single vessel vasoreactivity have shown molecular level interaction of various pathways that controls active tone on the top of passive mechanics of vessel wall. These mechanistic models provides in-depth insights into many complex mechanisms underlying small artery tone regulation, both under normal and pathological conditions. A detail discussion about cellular mechanisms of arterial tone regulation to change in blood pressure or flow can be found elsewhere [15], [23], [24].

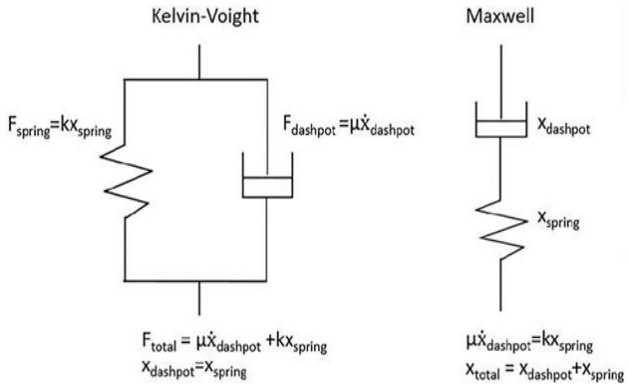

Fig. 4: Schematic representation of classical Kelvin-Voight and Maxwell models for passive and active responses[8], [25].

Overall, computational modeling of cardiovascular system provides a powerful tool to quantify the transient and steady-state biomechanical and biochemical vasoactive responses in isolated arteries in vitro. In most times, computational modeling combines synergistically with in vitro vasoactive response data to provide information that is otherwise difficult (or impossible) to get, and it enables us to study how mechanical forces may induce arterial disease via mechanosensitive pathways of vasoregulation, and may one day be routinely used for therapeutic planning. Based on our brief review of existing computational and experimental methods, we hope that anatomical-based computational models of arterial biomechanics and cellular-level models of vascular function will provide a new way of diagnosis of cardiovascular disorders using patient-specific computer simulations.

Mechanical Properties of Arterial Wall in Disease

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Aging and Arterial Wall Mechanics

It is generally believed that age-related arterial stiffening leads to several cardiovascular pathologies[13]. As elastin is long-lived with a half-life of several years, age-related changes are generally qualitative rather than quantitative. Qualitative changes involve changes in cross-linking. Although an optimal degree of peri-natal cross-linking is essential for the physiological function of scleroproteins, age-related crosslinking (glycation, nitration) and calcification have a negative effect of scleroprotein mechanics. Many studies have reported an increase in elastin fiber fluorescence with age and related this to glycation and nitration[13], [33], [34], [35]. Many factors including Di tyrosine, products of lipid peroxidation and reactive carbonyl compounds and quinines modify elastin fluorescence. Elastin fluorescence can also be caused by the extraction procedure used. Elastin can incorporate glucose and ribose and form ages. Cross-linking can also be affected by nitrite. In contrast to elastin, the collagen concentration in three layers of arterial wall increases with age, affecting the ration of elastin to collagen. For example, medial fibrosis occurs as a consequence of the replacement of vascular smooth muscle by collagen fibers. Similarly, aged endothelial cells have morphological changes to depict vascular smooth muscle phenotype, indicating they may also deposit collagen that contributes to intimal thickening[33].

Hypertension and Arterial Wall Mechanics

Two different but interrelated mechanisms may play a central role in the pathophysiology of the hypertensive crisis[4], [36]. The first is the failure in autoregulatory mechanism in the vascular bed. The autoregulation system is a key factor in the pathophysiology of hypertension and hypertensive crisis. Autoregulation is defined as the ability of the organs (brain, heart, and kidneys) to maintain a stable blood flow irrespective of alterations of perfusion pressure[12]. If the perfusion pressure drops, the corresponding blood flow decreases temporarily, but it returns to normal values after the next few minutes. In case of autoregulation malfunction, if the perfusion pressure drops, this leads to decrease in blood flow and an increase in vascular resistance[23].

In hypertensive crisis, there is a lack of autoregulation in vascular bed and blood flow and so an abrupt increase of blood pressure and systemic vascular resistance can occur, which often leads to mechanical stress and endothelial injury. The second mechanism is the activation of renin–angiotensin system, leading to further vasoconstriction and thus generating a vicious cycle of continuous injury and subsequently ischemia[37], [38]. Hypertension increases intraluminal pressure so promoting elasto-calcinosis suggesting that global degeneration of the arterial wall of which elasto-calcinosis may be one facet is due to the fatiguing effects of cyclic stress on medial elastic fibers followed by fracture. As pulse pressure increases in hypertension (especially so in isolated systolic hypertension), cyclic wall stress is increased and so elasto-calcinosis and fracture of elastic fibers would be expected to occur earlier than in normotensive individuals[39].

Atherosclerosis and Arterial Wall Mechanics

Atherosclerosis is a chronic, progressive disease in which plaques build up in the walls of arteries[40]. These plaques are formed by deposits of cholesterol and other lipids, calcium,

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and large inflammatory cells called macrophages. Once a plaque is present in an artery, it can interfere with blood flow in arteries, even in the early stages of the disease, i.e. during atherogenesis[41]. Development of atherosclerosis is directly related to hemodynamic factors and an important parameter in biomechanics of this disease. The onset of plaque usually occurs in the low wall shear stress area, and the plaque development alters the local walls shear stress distribution. While low wall shear stress promotes atherosclerosis, high wall shear stress prevents atherosclerosis, and it is often associated with the formation of vulnerable plaque phenotype[41], [42], [43]. Overall, wall shear stress can potentially indicate the onset of initial lesion formation and progression to more advanced lesions, playing an important role in regulating cardiovascular responses in disease[44]. Therefore, quantitative understanding of the underlying mechanisms by which arterial wall mechanics control flow-mediated cardiovascular disease may help elucidating the pathogenesis of atherosclerosis and develop potential therapeutic strategies. Yet the regulatory role of wall shear stress remains to be a topic of intense research.

Conclusions

The wall of the artery is basically characterised by a complex microstructure that controls the mechanical properties of vascular tissues [45]. The arterial wall components consist of collagen and elastin fibres, proteoglycans, vascular smooth muscle cells and endothelial cells. While smooth muscle cells play a fundamental role in the active mechanical response, collagen and elastin controls the passive response in vasoregulation. Several experimental methods have been designed to qualitatively and quantitatively assess the changes in these properties. Computational models, combined with *in vitro* experimental data on vascular microstructure and vasoreactivity to mechanical stimuli may provide deeper insights into the mechanical basis of many cardiovascular diseases.

In conclusion, a quantitative understanding of arterial biomechanics and its association with biochemical processes of vascular cells in arterial walls is the key to underpinning the pathophysiology vascular diseases. Combining experimental data with mathematical models of cardiovascular tissue mechanics including lumped parameter models, cellular models, and patient-specific models of arterial wall functions may help understanding the cellular mechanisms of altered biomechanical responses in several diseases. Based on this brief review of arterial biomechanics, it is clear that understanding vascular regulation requires a thorough understanding of the interaction between arterial wall properties, blood rheology, fluid mechanics and intracellular pathways controlling cardiovascular responses *in vivo*. Thus, one future direction is that the cardiovascular regulation in disease state can be better understood by combining experimental data on single cell ion channel kinetics, single vessel *ex vivo* vasoreactivity and whole organ/vascular morphometry with multi-scale computational model of vascular and cardiac tissues. The nonlinear correlations between key biomechanical factors and disease phenotype require new experimental methods that can measure combined effects of multiple physical and chemical stimuli (e.g., pressure, flow, blocking agents, agonists etc.) stimuli on vasoreactivity and biomechanics of arterial walls in various tissues. Overall, this review shed the lights on the significance of passive vessel wall mechanics in controlling active vasoregulatory responses to diverse stimuli of tissue microcirculation, which are ultimately controlling whole-body cardiovascular functions in disease states.

Ethical Approval:

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This review did not involve any human or animal subjects and hence ethical approval was not required.

Conflict of Interest:

The author declares that there is no conflict of interest.

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