

Chapter 2

Mechanisms of Arterial Stiffness

Abstract Current understanding for the mechanisms contributing to arterial stiffness is limited. The field is rapidly growing, however, and the complex process of functional, structural and signaling pathways working together to stiffen arteries is becoming increasingly clear. As such, arterial dilation and constriction, extracellular matrix accumulation and stiffening of individual cells via specific signal transduction pathways inter-connect providing numerous targets for potential therapeutic intervention. Herein we highlight the mechanisms that are largely implicated in arterial stiffness, and those that may be emerging as important targets.

Keywords Artery function • Smooth muscle • Adventitia • Endothelium • Collagen • Elastin • Advanced glycation end-products

Introduction

The mechanisms by which arteries stiffen include both physiological as well as cellular and molecular events that collectively contribute to the pathophysiology. Both functional and structural changes occur to stiffen arteries, which are due to the actions and interactions of the physiological and cellular/molecular events. In this chapter we will overview functional and structural changes, and highlight key cellular signaling mechanisms that promote these impairments. In order to gain greater insight for mechanisms contributing to arterial stiffness, we will use animal based studies to complement and to provide additional insight to support what is known from human-based literature. For example, aging mouse models are commonly used to study aortic stiffness, which demonstrate *in vivo* increases in aortic pulse wave velocity (aPWV) (Fig. 2.1a) and intrinsic stiffness assessed by *ex vivo* mechanical testing (Fig. 2.1b). Importantly, animal studies provide additional insight but the mechanisms do not always translate well to humans. A more in-depth understanding of mechanisms, however, ultimately leads to more efficacious treatments.

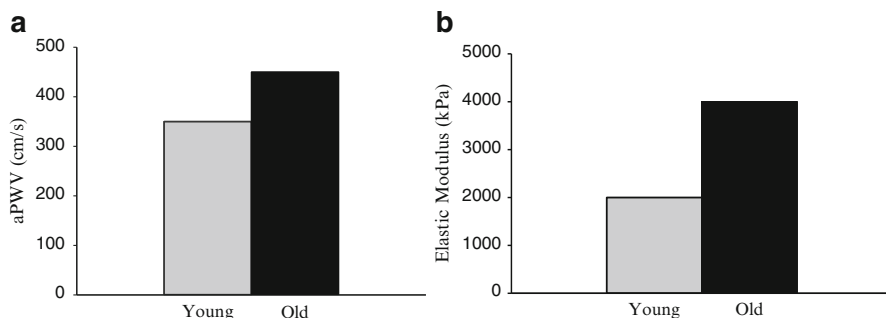


Fig. 2.1 A representative age-related increase of (a) in vivo arterial stiffness assessed by aortic pulse wave velocity (aPWV) and (b) ex vivo mechanical stiffness in isolated aortic segments of young (4–6 months) and old (26–28 months) mice

Functional Changes Contributing to Arterial Stiffness

Blood Pressure

Blood pressure is a traditional measure assessed clinically to determine risk for potential future cardiovascular events. Advancing age is associated with isolated systolic hypertension where current blood pressure control rates are suboptimal at ~50 % [1]. Aortic stiffness is considered to be a key mediator for controlling resistant hypertension. For instance, the Preterax in Regression of Arterial Stiffness (REASON) trial demonstrates that increased arterial stiffness is related to reduced blood pressure control, and decreases in arterial stiffness is a major contributor in the reduction and control of systolic blood pressure [2]. Additionally, other investigations have observed that increased aortic stiffness predicts incident hypertension and cardiovascular events [3, 4]. Collectively, current evidence indicates an effect for arterial stiffness to contribute to hypertension-related conditions.

In addition to the evidence for arterial stiffness to promote and regulate blood pressure, other data indicate blood pressure contributes to arterial stiffening. Recently, it has been proposed that “early vascular aging,” which is, in part, characterized by aortic stiffness is present in young hypertensive adults [5]. The changes in arterial stiffness that are observed in young hypertensive subjects are similar to what is seen in older non-hypertensive adults. As such, when blood pressure is reduced in young adults with hypertension arterial stiffness is also decreased, suggesting blood pressure does indeed contribute to arterial stiffness early in life [6]. The current evidence indicates arterial stiffness and blood pressure promote and/or decrease the expression of one another in a feedback loop. Thus, blood pressure is a key mechanism by which aortic stiffness may be modulated to reduce cardiovascular risk.

Impaired Smooth Muscle Function

Vascular smooth muscle cell dysfunction results in impaired vasodilation, increased vasoconstriction, increased proliferation and migration, and has been postulated to contribute to the overall impairments in blood pressure regulation and arterial stiffness. In a recent meta-analysis, it was shown that smooth muscle dysfunction occurs with advancing age in adults [7]. A limitation of this analysis is that the effect of dysfunctional smooth muscle is relatively small, and was observed in peripheral arteries. Due to current limitations in technology, assessing smooth muscle function of the central arteries, such as the aorta, in adults cannot be performed readily. However, aortic segments from animals in age- and hypertension-related models have shown that there are indeed impairments in smooth muscle function [8, 9]. Thus, there is evidence to support the notion for impaired aortic smooth muscle function to be associated with age- and blood pressure-related vascular dysfunction, including arterial stiffness. Importantly, it has been estimated that ~50 % of aortic stiffness with aging is due to smooth muscle cells [10], which has been attributed to signaling and structural events in smooth muscle cells [10, 11]. These findings collectively indicate smooth muscle dysfunction, as it relates to extracellular signaling and structural changes, significantly contributes to the development of arterial stiffness.

Impaired Endothelium-Dependent Dilation

The vascular endothelium is a monolayer of cells on the innermost side of arteries that responds to mechanical forces and receptor-mediated signaling, contributing to arterial homeostasis and pathophysiology. Smooth muscle function is influenced by the vasoactive factors released from the vascular endothelium with nitric oxide (NO) being a primary signaling molecule. It is important to note, as discussed in the previous section, that endothelium-independent dilation (EID), or smooth muscle dysfunction, contributes much less to arterial dysfunction in comparison to endothelium dependent dilation (EDD) [7, 12]. Studies demonstrating greater smooth muscle dysfunction have largely been reported in subjects with additional cardiovascular risk factors [12]. This is further supported in animal models of aging where EID, or smooth muscle cell relaxation, is largely unimpaired in old mice when arterial segments are treated with the NO donor sodium nitroprusside [13–15]. Taken together, age-related impairments in EDD influences smooth muscle function—rather than influencing the dilatory properties—that is related to signaling and structural changes of the cells. Thus, targeting EDD via improvements in NO bioavailability may improve structural changes in vascular smooth muscle cells, which would be critical for reducing arterial stiffness (Fig. 2.2).

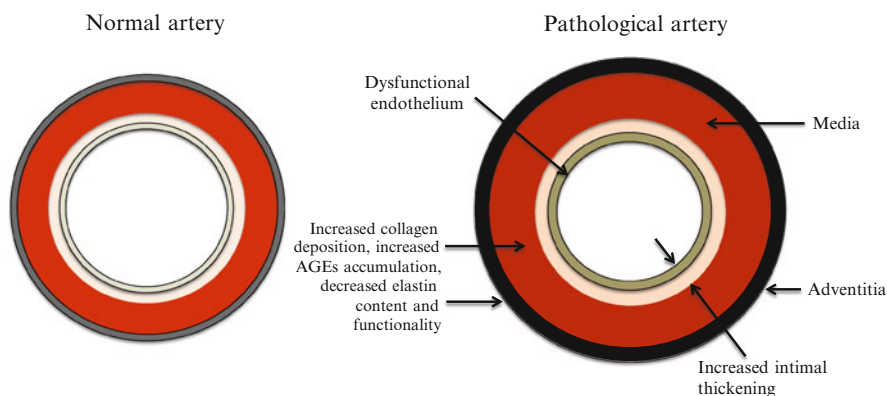


Fig. 2.2 A summary of the complex, multiple causes of arterial stiffness with aging and disease

Structural Changes Contributing to Arterial Stiffness

Aging results in multifaceted changes within the vasculature to promote arterial stiffness. These alterations include gross morphological remodeling and compositional changes within arteries that are not as readily identifiable in humans. Additionally, there are cell-specific changes that contribute to the overall decrements in arterial function and structure that have recently been elucidated. This section will highlight the importance of each structural component in the development of arterial stiffness (Fig. 2.2).

Gross Morphological Changes

Intima-media thickness (IMT) is a common clinical measure providing insight for an individual's vascular age and health. IMT increases as a product of aging, which is associated with increased stiffness and cardiovascular events [6]. IMT, a surrogate arterial stiffness measure is used clinically, but is more indicative of the gross changes in morphology rather than arterial stiffness. Moreover, IMT is not as sensitive of a predictor for major cardiovascular events in high-risk diabetic and/or hypertensive patients as other direct measures of arterial stiffness, [16] such as aPWV, because it only accounts for morphology, and excludes additional factors including material composition of the artery that is taken into account with aPWV [17]. The IMT thickening, however, is a relatively easy endpoint to assess for a trained clinical technician that provides additional insight for arterial health and future cardiovascular disease risk.

Compositional Changes

Collagen

Collagen is an important extracellular protein in arteries influencing arterial stiffness with over 20 identified isoforms to date [18]. The type I and III collagen isoforms are the most abundant in the aorta with type I having the greatest content throughout this large elastic artery [19]. This distribution pattern is important as type I collagen promotes strength leading to increased mechanical stiffness, whereas type III has greater elastic properties promoting elasticity. Type I collagen expression has an age-related increase in the three primary cell types of arteries: endothelial cells, vascular smooth muscle cells, and adventitial fibroblasts [20]. The compositional change for increased collagen I content and/or expression in each layer indicates the importance of this protein in arterial stiffening. For example, a collagenase-resistant animal model with the inability to decrease type I collagen was shown to have greater mechanical stiffness [21]. And, selective increases in adventitial collagen deposition, as observed with aging, may have even greater contributions to overall arterial stiffness compared to other arterial layers [22].

Type II collagen expression in arteries is an emerging isoform that may have important implications in age-related aortic stiffness. Arterial collagen II expression increases with aging in both rodents and humans [23]. This type II isoform is a matrix protein primarily found in cartilage, a biomaterial designed for strength. Thus, greater collagen II, in addition to increased collagen I protein expression in arteries is hypothesized to dramatically promote age-related arterial stiffening.

Elastin

The elasticity of arteries is primarily due to the extracellular protein elastin as it accounts for ~90 % of elastic fibers in arteries [18]. Aging and disease decrease elastin content and/or functionality leading to arterial stiffening as observed in the elastin haploinsufficient mouse model [24]. Elastin is expressed in all arterial cell types, but the medial smooth muscle cell layer expresses greater amounts of this protein [20]. Notably, arterial elastin expression progressively decreases with aging and is highest in early life. As elastin decreases, it is thought to be an irreparable process without the ability to re-form elastin in arteries. Prevention of elastin loss and functionality in early age would be of great importance in reducing arterial stiffness across the life span.

Advanced Glycation End-Products (AGEs)

Glycosylation, a post-translational modification of proteins, is also implicated in age- and disease-induced aortic stiffening. Non-specific accumulation and cross-linking of extracellular proteins by AGEs has been shown to contribute to arterial stiffness in

both aged rodents and adults [20, 25]. The greater cross-linking by AGEs results in increased stiffness, which is akin to a chain link fence with more links having less flexibility. AGEs accumulation is hypothesized to be the result of one of three primary mechanisms, which include: (1) increased circulating glucose concentrations, (2) greater oxidative stress within arteries, and (3) enhanced inflammatory signaling [26]. Although these factors are all considered primary pathways by which arterial AGEs are formed, greater mechanistic insight for each pathway requires further investigation. In addition to the cross-linking effect of AGEs to promote arterial stiffness, the cellular signaling of AGEs is also a potential mechanism for arterial stiffening that will be discussed later in this chapter.

Calcium

Rigid deposits of calcium mineral within the vascular wall increase in vivo stiffness [27]. Coronary calcium levels are associated with those of the aorta and both are shown to increase with advancing age [28]. In a middle-aged cohort without prevalent cardiovascular disease from the Framingham Heart Study, a correlation was found between aortic stiffness and vascular calcification [29]. The appearance of progressive aortic stiffness and aortic calcification appears as early as the fourth decade of life [30]. Thus, calcification is an important mechanism leading to aortic stiffness that warrants further investigation.

Cellular Changes

There are distinct changes in vascular smooth muscle cell (VSMC) and endothelial cell stiffness that contribute to the overall arterial stiffening process [11, 31]. Increased VSMC stiffness has been attributed to changes in the cytoskeletal protein actin, as reductions in this protein decreases age-related VSMC stiffness [11]. Intracellular structural changes, in part, begin to explain how nearly 50 % of arterial stiffness is due to VSMCs. For instance, focal adhesions link the contractile components of the cell, including actin, to the extracellular matrix, which have been shown to mechanistically promote arterial stiffness [10]. Thus, the actin cytoskeleton and focal adhesions seem to collectively coordinate the VSMC-contributions to overall arterial stiffening.

Endothelial cells have also been shown to increase cellular stiffness in an animal model of obesity [31]. In this model, endothelial cell stiffness increased ~5 fold, similar to what is observed in VSMCs. Few studies have examined endothelial cell stiffness, and, therefore, the mechanistic insight by which these cells become stiffer is limited. Notwithstanding, a senescent endothelial cell model has indicated that smooth muscle alpha actin and collagen I protein expressions increase with aging, which would implicate endothelial cells as a contributor to arterial stiffness. Importantly, the pro-inflammatory cytokine tumor necrosis factor

alpha was shown to recapitulate both smooth muscle alpha actin and collagen I protein expressions in non-senescent endothelial cells [32]. Hence, endothelial cell stiffness is an emerging contributor to arterial stiffness, which may be mediated by inflammatory processes.

In summary, cellular changes to both VSMCs and endothelial cells result in greater cell stiffness and provide novel insight for arterial stiffness. This novel area of investigation requires future study to determine the mechanisms by which VSMCs and endothelial cells stiffen with aging and disease.

Signaling Mechanisms

There are numerous potential signaling events that may contribute to age- and disease-related arterial stiffness. Our aim, however, is to highlight several key signaling and molecular mechanisms that have been shown to promote arterial stiffness. Thus, we present several important mechanisms shown to have a significant influence on arterial stiffness.

Oxidative Stress

Oxidative stress, which can be defined as increased reactive oxygen species (ROS) production or bioavailability in relation to the antioxidant buffering capacity, is greater in arteries of old animals. Increased NADPH oxidase (NOX) expression and/or activity is one oxidase system implicated in arterial ROS production with age, which is associated with decreased expression/activity of the superoxide dismutase (SOD) antioxidant defense system. As such, greater superoxide production within the aorta is associated with increased aortic stiffness observed with aging, and reductions in aortic superoxide bioavailability with antioxidant supplementation reverses arterial stiffening [13]. Importantly, antioxidant treatment is associated with an attenuation of age-related increases in the pro-oxidant NOX p67 subunit and reductions in the antioxidant manganese superoxide dismutase expressions [13–15, 33]. The oxidative stress process, however, is much more complex but currently there is little mechanistic evidence or insight. In short, greater oxidative stress within arteries promotes aortic stiffness via increased pro-oxidant superoxide production and reduced superoxide dismutation by the antioxidant system.

An important functional component of arterial stiffness is reduced nitric oxide (NO) bioavailability due to increased arterial ROS production with advancing age. Notably, antioxidant treatment reverses the age-related decrements in NO bioavailability, and is associated with reversal and/or attenuation with the structural and extracellular matrix components of arterial stiffening. For example, short-term (4-week treatment protocols) with SOD-specific boosting intervention, and less specific antioxidant interventions have been shown to modulate both collagen

and AGEs [13–15]. Yet, few interventions have shown attenuation of the age-related decrements in elastin content. Additionally, it is largely unknown if antioxidants influence vascular smooth muscle and/or endothelial cellular stiffness. It appears, however, antioxidant compounds are a potential treatment strategy to ameliorate arterial stiffness.

Inflammation

Large artery inflammation is emerging as an important aspect of arterial aging, and aortic stiffening. For instance, increased macrophage numbers, and pro-inflammatory cytokine expressions have been observed in aortas from older mice. Importantly, expression of the nuclear factor kappa B (NFκB) transcription factor is also greater in aortas with aging, which may mediate both monocyte recruitment and pro-inflammatory cytokine expression. Thus, examining the role of NFκB in arterial stiffness, and identifying novel interventions to modulate NFκB expression are promising [20, 34]. For example, inhibition of NFκB in older animals improves endothelium-dependent dilation via a NO-dependent mechanism. This finding indirectly suggests NFκB contributes to age-related aortic stiffness by reducing NO bioavailability and impairing endothelial function. As such, anti-inflammatory interventions may lead to reductions in aortic stiffness.

Nitric Oxide (NO)

Impaired endothelium-dependent dilation is a key functional outcome contributing to arterial stiffness. Decreased expression and/or activity of endothelial NO synthase (eNOS)—a critical enzyme—leads to reduced NO bioavailability and endothelial dysfunction [35]. The reduced capacity for the arteries to dilate indicates VSMCs are not relaxing, which is largely due to reductions in NO bioavailability. Equally important is the influence of NO to modulate arterial inflammatory proteins and transforming growth factor Beta 1, which the latter is implicated in structural changes within arteries [36]. Thus, NO boosting interventions are quite important as both functional and structural changes within arteries are influenced by this critical signaling mechanism.

Reductions in NO bioavailability have been attributed to oxidative stress. More specifically, greater superoxide production reacts with NO to form peroxynitrite, which modifies proteins and is a common marker of oxidative stress. Additionally, the key cofactor for NO production, tetrahydrobiopterin (BH₄) becomes oxidized contributing to uncoupling of eNOS resulting in less NO bioavailability and more superoxide production [35]. The greater oxidative stress is due to both enhanced pro-oxidant and reduced antioxidant enzyme expression and/or activity. Targeting oxidative stress to improve NO bioavailability would be critical for improving both functional and structural mechanisms leading to arterial stiffness.

Transforming Growth Factor Beta 1 (TGF- β 1)

TGF- β 1 is a profibrotic cytokine involved with adventitial remodeling, and thus implicated in aortic stiffness. Adventitial TGF- β 1 expression is increased in aged rodents that, in turn induces a phenotypic change of adventitial fibroblasts into pro-secretory myofibroblasts. This phenotypic transition results in greater collagen I protein expression in myofibroblasts, which is associated with increased adventitial collagen I expression and aortic stiffness. The collagen secretory phenotype induced by TGF- β 1 also promotes superoxide production, which was shown to mediate the effects of TGF- β 1 in fibroblasts [37]. Thus, TGF- β 1 is an important profibrotic cytokine with increased age-related expression with limited in vivo evidence for its effects on arterial stiffness. Interventions focused on attenuating adventitial TGF- β 1 signaling may be of importance as the adventitia is a key load-bearing layer of arteries.

Advanced Glycation End-Products (AGEs)

As discussed previously, AGEs are responsible for cross-linking extracellular proteins that ultimately contribute to aortic stiffness. Notably, AGEs also bind the receptor of advanced glycation end-products (RAGE) which results in intracellular signaling that promotes negative biological consequences such as greater arterial stiffness seen with aging [26]. Limited experimental evidence exists for this hypothesis; however, it has been shown that ex vivo administration of biologically active AGEs to arteries from young rodents enhances aortic stiffness [38]. AGEs accumulation within the artery was not assessed, but these findings indicate AGEs signaling promotes increases in mechanical stiffness. Moreover, an AGEs enriched diet increases pro-inflammatory cytokine expressions in adipocytes, which may be the downstream signaling event leading to greater mechanical stiffness [39]. However, little is currently known about AGEs signaling and arterial stiffness.

Summary

The mechanisms underlying arterial stiffness are multifaceted, complex and inter-related. Although mechanistic insight for arterial stiffness is accumulating, the scientific community is in the beginning stages of understanding the disease's etiology. Novel therapeutics to effectively treat and manage arterial stiffness will target the functional and structural components of this emerging risk factor.

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2015, VIII, 61 p. 8 illus., 1 illus. in color., Softcover

ISBN: 978-3-319-24842-4