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New progress on the study of aortic stiffness in age-related hypertension

John O. ONUH, Hongyu QIU*

Center for Molecular and Translational Medicine, Georgia State University, Atlanta, GA, USA, 30303

Abstract

Hypertension is a worldwide known cause of morbidity and mortality in the elderly and is a major risk factor for cardiovascular complications such as stroke, myocardial infarction, renal complications and heart failure. Although the mechanisms of hypertension remain largely unknown, a recent new concept is that aortic stiffening is a cause of hypertension in middle-aged and older individuals, which highlighted the importance of aortic stiffening in the development of age-related hypertension. Understanding the pathogenesis of aortic stiffness therefore became one of the important approaches to preventing and controlling hypertension. This review discusses the recent progress of the potential causes of aortic stiffening and its implication on the pathogenesis of hypertension, in terms of aging, inflammation, metabolic syndromes, neuroendocrine and the interaction among these causes.

Condensed abstract

A recent analysis from clinical and animal studies found that aortic stiffening is a cause rather than a consequence of age-related hypertension, highlighting the importance of understanding of aortic stiffening. This review discusses the potential causes of aortic stiffening and its implication on the pathogenesis of age-related hypertension.

Keywords

Aortic stiffness; Hypertension; Aging; Vascular smooth muscle cells; Inflammation

1. Introduction

Systemic hypertension, referring to the high blood pressure (BP) in the systemic arteries, is a major cause of morbidity affecting over 30% of the adult population, leading to cardiovascular complications (stroke, myocardial infarction and heart failure) and death [1, 2]. Despite intense research, there is no consensus on the primary cause of this disorder.

*Correspondence and Request for reprints to: Hongyu Qiu, MD, PhD, Center for Molecular and Translational Medicine, Georgia State University, Atlanta, GA, USA, PSC 558, 100 Piedmont Ave SE Atlanta, GA 30303, hqiu@gsu.edu, Tel: +1 (404) 413-3371.

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It is known that hypertension is a highly age-related human disease; however, the reasons why BP increases with age are poorly understood. The long-held view has been that the major determinant of systemic hypertension is the increased total peripheral resistance (TPR) or the systemic vascular resistance (SVR), which is caused by the vasoconstriction of small arteriolar (known as resistance arterioles). Accordingly, the traditional antihypertensive therapies has been concentrated on the effects to decrease peripheral vascular resistance by using vasodilators (calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor antagonists). However, despite decades of extensive efforts, the clinical management remains mandatory, particularly in elderly patients [3–8]. In recent years, the studies from others' and our group have shown that aortic stiffening is associated with both hypertension and aging [9–12], indicating a possible mechanistic link between the two. Importantly, based on the analysis of clinical data and animal studies, a recent statement from the American Heart Association (AHA) asserts that aortic stiffness is a cause rather than a consequence of hypertension in middle-aged and older individuals [13]. This new concept highlights the importance of aortic stiffening in the development of aging-related hypertension. More so, carotid-femoral pulse wave velocity (PWV) has been shown to correlate strongly with age and BP, with reduced elasticity of the arterial walls leading to increase in stiffness[14]. The aortic PWV is inversely related to the distensibility and central augmentation index (AI_x) [15]. Aortic PWV increased non-linearly with age especially in older people (>50 year) while AI_x increased non-linearly in younger people (<50 years) [15]. This condition may eventually lead to vascular aging, especially early vascular aging (EVA) in some patients that manifest this condition prematurely [16]. Recently, arterial stiffening was associated with heritable traits as manifested by differences in the contributions of genetic and cardiovascular factors to increases in PWV and intima media thickness [17, 18]. Therefore, better understanding the mechanism of aortic stiffening is essential to develop strategies to prevent hypertension in the elderly. The objective of this review therefore is to highlight some of the causative mechanisms responsible for aortic stiffness in aging-related hypertension.

2. Aortic stiffness and systemic hypertension during aging

It is predictive of increased incident hypertension especially in elderly [19–21]. One of the main clinical signs of systemic hypertension in elderly is the divergent changes in systolic BP (SBP) and diastolic BP (DBP), resulting in an increased pulse pressure (PP), or called as “isolated systolic hypertension”. Although the studies have indicated that both peripheral and central arteries are stiffer in subjects with mixed (systolic/diastolic) hypertension compared with normotensive subjects [22–24], isolated systolic hypertension is associated with increased aortic, but not peripheral artery stiffness [13, 25]. Aortic stiffness is known to be closely associated with increased PWV and pulse pressure (PP) which are both different ways to measure pulsatile energy In the elderly, sudden changes in PP due to early arrival of arterial pressure wave reflections as well as excessive PP transmission exerts considerable burden on the vascular systems leading to CVD complications [26, 27].

Even though it is widely accepted that the increased aortic stiffness is a fundamental manifestation with hypertension and advanced aging [28–32], it is challenging to distinguish the cause-effect relationship among the hypertension- and aging- induced aortic stiffness, as

most patients with hypertension are also of advanced age. Our studies in non-human primate models have shown that aortic stiffness is increased with aging in advance of the increase of BP [9, 10]. We also found that the pharmacologic reduction of aortic stiffness preceded the reduction of BP in hypertensive rats, suggesting the recovery of aortic elasticity is likely not a secondary effect of the reduction in BP, but rather a contributing factor [11, 25]. In addition, the latest analysis in clinical researches showed that the aortic stiffening was associated with the BP progression and the incident hypertension 7 years later [20], supporting the fundamental contribution of aortic stiffening in the development of hypertension in older individuals [13]. In a longitudinal study of a large prospective cohort study, it was also reported that PWV increase is mainly determined by age and SBP and that this effect may also exist in the pre-hypertensive range [33]. This PWV increase is steeper in men than in women with advancing age and therefore suggesting a gender difference. These results together reinforce the concept that aortic stiffening is a primary pathologic alteration independent of hypertension, and, thus, to identify the mechanism of aortic stiffening may build a basis for novel preventive strategies for aging-related hypertension. In the following sections, we will summarize the recent studies on the aortic stiffness in age-related hypertension.

3. Causes of aortic stiffening

It is known that aortic stiffening is an independent risk factor for cardiovascular morbidity and mortality, and strongly associated with the aging process. [9, 20, 34, 35]. Although the exact underlying causes still remain largely unknown, several theories have been advanced to explain the possible pathophysiological mechanisms of aortic stiffness [10, 14, 36, 37], such as aging, metabolic syndromes, inflammation, neuroendocrine and other undefined factors [14, 38, 39], as summarized in Figure 1. These factors exerts great effects on the aorta, leading to the changes in structure, function and mechanical properties of the aortic walls with the consequent increase in aortic stiffness [14, 19, 39].

3.1. Aging

Aging has been defined as the “age-related decline in physiological functions essential for survival and fertility” [39]. Clinical observations in human [20] and the studies on nonhuman primate models demonstrated that aortic stiffness increase with aging in “health” conditions without BP changes [9]. These data indicate that aging itself contributes to the aortic stiffening which is independent of the BP. It is also shown that aging-induced aortic stiffening exhibits a gender difference, e.g., the increased stiffness is greater in old males than females [9]. In addition, species variances were found between the animals with short life-span (like the rodents) and long life-span (like primates and human) [9].

The increased aortic stiffness during aging has been ascribed to numerous factors that induces the alterations in gene regulations and protein expressions or degradations, which subsequently leads to the changes of vascular properties responsible for the aortic stiffening, including the extracellular matrix (ECM), endothelial cells and vascular smooth muscle cells. Despite the conflicting reports, it is widely accepted that increased aortic stiffness of aging is associated with medial thickening, increased total collagen content, and advanced

glycation end products (AGEs), the decrease and fragmentation of elastin as well as the collagen/elastin ratio [9, 19, 40, 41]. Our studies also showed that, although there were several common histological and biochemical changes in matrix proteins in aging aorta, the expression of collagen isoforms (type 1 and 3) and the decrease of elastin correlates to the gender difference in aortic stiffness [9]. In addition, a new observation from our study is the upregulation of the collagen type 8 in aging males. Since collagen type 8 is usually upregulated due to vascular injury and it functions to promote vascular smooth muscle cell migration [9, 42], the increase of collagen type 8 isoform indicates a new mechanism responsible for vascular stiffening during aging [9].

Aging-related aortic stiffness is also associated with endothelial dysfunction (measured by the reduction of endothelium dependent dilatation) [14, 43]. The endothelium is responsible for the maintenance of vascular homeostasis by regulating vascular tone through a mechanism that ensures a balanced production of vasodilators as well as vasoconstrictors, blood fluidity and coagulation and regulation of inflammation through the production of NO, cytokines and adhesion molecules [44]. However, under the aging or other pathological conditions, the delicate balance between vasodilators and vasoconstrictors produced by the endothelium is disrupted, with disturbance in the NO pathway, and resulting in inflammation and promotion of monocyte and T-cell adhesion, foam cell formation, ECM digestion and VSMC migration and proliferation [44, 45].

In addition to these traditional theories with the alterations in ECM and endothelial dysfunction, increasing evidences have shown that VSMCs also play an important role in the age-related aortic stiffness. First, our researches on a non-human primate-aging model demonstrated that the expression of multiple genes encoding proteins of the cytoskeleton and membrane receptors is up regulated in aging VSMCs [9, 10]. Second, the aortic VSMC-mediated tissue stiffness is increased in aging monkeys vs young monkeys independent of ECM [9, 10]. Third, by using an atomic force microscopy, it has been demonstrated that the intrinsic stiffness of individual VSMCs itself was significantly increased during aging [9, 10]. These data demonstrated a novel concept that increased vascular stiffness with aging is also due to intrinsic elastic properties of VSMCs. This concept, differs from the traditional theory, may open new therapeutic avenues for the treatment of vascular stiffening by targeting directly VSMC stiffness. Moreover, our recent findings demonstrated that intrinsic properties of VSMCs in large arteries, but not in distal arteries, are crucial contributors to the pathogenesis of aortic stiffening in hypertension [11]. Furthermore, VSMCs are also found to play an important role in aortic stiffness via extracellular effects by regulating ECM synthesis and degradation [10, 46].

3.2. Inflammation

Various clinical studies suggests a link between inflammation and aortic stiffness [14, 35]. The PWV is often found to be increased in patients with inflammatory diseases. The effects of inflammation on aortic stiffness also increases with age [39]. C-reactive protein (CRP), an inflammation marker, has been reported to be associated with higher aortic stiffness in a community of middle aged and elderly men [47]. On the contrast, a history of higher degree of immunodeficiency definitely was associated with aortic stiffening in immune

compromised HIV patients [48]. Lower CD4 counts and a higher sensitivity CRP in HIV patients were significantly associated with higher aortic PWV indicating a potential role of inflammation in the pathogenesis of aortic stiffness [48].

Chronic inflammation and vascular infiltration of immune inflammatory cells have been implicated as the underlying causes for vascular alterations [49]. Chronic inflammation could be triggered by the generation of reactive oxygen species (ROS) due to increased oxidative stress. The inflammatory cytokines and chemokines are the major determinants of the process involved in aortic stiffening via vascular remodeling [49–51] and endothelial dysfunction, such as interleukin, transforming growth factor- β (TGF- β), insulin-like growth factors (IGF-1) and nuclear factor kappa beta (NF- κ B) [14, 35, 39, 50, 52, 53]. Uric acid has also been reported to play a pro-inflammatory role leading to the activation of renin–angiotensin system (RAS) and the development of aortic stiffening [50, 54]. Decrease of nitric oxide (NO) caused by either inflammatory cytokines or ROS generation [51, 55] has been associated with the increase of aortic stiffness. Moreover, overactive sympathetic nervous system, aldosterone and metabolic syndromes also play important roles in stimulating inflammatory responses and T cell infiltration [39], resulting in the vascular injury, leading to the development of aortic stiffness and hypertension [35, 39].

3.3. Metabolic syndrome disorder

Metabolic syndrome, defined by the presence of three or more of abdominal adiposity (obesity), dyslipidemia, hypertension, insulin resistance and hyperglycemia, is a known risk factor for cardiovascular disease (CVD) [39]. PWV and pulse pressure (PP) have been shown to be significantly higher in the subjects with metabolic syndrome than in subjects of same age without these conditions [38]. It was also observed that PWV is frequently observed to be increased in patients with hyperlipidemia. The effects of metabolic syndrome on vascular functions are varied and extensive. For instance, hyperglycemia and dyslipidemia have been reported to induce endothelial dysfunction and oxidative stress leading to the activation of extracellular proteins of the matrix metalloproteinase (MMPs) and the resultant vascular remodeling and arterial stiffening [39, 50, 56]. Weight loss has the effect of reversing these metabolic syndrome-induced changes leading to normalization and indicating that metabolic syndrome (hyperglycemia and dyslipidemia) may be a potential target for intervention in cases of aortic stiffness [39, 57, 58]. In addition, a longitudinal study of non-Hispanicwhite hypertensionss from the Genetic Epidemiology Network of Arteriopathy (GENOA) study reported that arterial stiffness was associated with longitudinal increases in BP in hypertension [1].

Metabolic syndrome is known to induce arterial stiffening, but also accelerates vascular aging and the development of hypertension [38, 39, 50]. The effects of metabolic syndrome become more severe after middle age and increasing with age, suggesting that aging may be associated with metabolic syndrome-induced aortic stiffening [39, 59].

In addition, obesity is reported to cause an increase in aortic stiffness with age suggesting adverse association between body fat composition and aortic stiffness manifests at older age [56, 59]. Also, the effects vary between men and women. Obesity and/or diabetes

significantly predisposes women to increased CVD and aortic stiffness than men and may probably be due to steroidal hormonal differences between men and women [56].

The exact mechanisms for this observed association are not properly understood but it may be linked to insulin insensitivity, hyperglycemia, activation of RAS, sympathetic nervous system activation and modulation of smooth muscle tone [59, 60]. Aldosterone in particular and mineralocorticoid receptor (MR) signaling have been found to be associated with increased aortic stiffness in obese individuals [56, 61–63]. It was found that spironolactone, a mineralocorticoid receptor antagonist (MRA), prevented aortic stiffness induced by the consumption of western diet, with an improvement in aortic medial thickening and fibrosis and consequently, the activation of extracellular receptor kinase 1/2 (ERK1/2) pathway and a marked improvement in inflammation. These outcomes suggests that MR is involved in the development of aortic stiffness in female mice exposed to western diet induced insulin resistance and that complications arising from CVD can be prevented with low dose administration of spironolactone [56].

3.4. Sympathetic nervous system activation

The autonomic nervous system (ANS) plays a pivotal role in peripheral resistance and blood pressure control possibly through the autonomic vasomotor nerves and circulating catecholamines [39, 64]. The sympathetic nervous system (SNS) was previously considered to be a short-term regulation of blood pressure but current knowledge suggests it plays an important long-term role and may actually contribute to idiopathic hypertension [64]. The role of the autonomic nervous system in the regulation of aortic stiffness is still a contentious issue with conflicting outcomes from different in vitro and in vivo human studies [64]. It is, however, important to note that vascular smooth muscle tone is partly regulated by the sympathetic neural activity through release of noradrenaline (a potent vasoconstrictor) that may induce aortic stiffening [64].

Also, metabolic syndrome, insulin resistance, and adipokine production have been associated with increased sympathetic nervous activity leading to metabolic syndrome-induced hypertension [39, 65]. Other factors that may lead to sympathetic nervous system activation and thereby increased blood pressure and aortic stiffness are inflammation in brain stem [66], salt sensitivity [67] and vascular endothelial dysfunction arising from decreased NO availability [68].

4. New molecular mechanisms related to aortic stiffness

Previous studies on the molecular mechanisms of aortic stiffness focused on the regulation of ECM and endothelial dysfunction, which has been summarized in several reviews [12, 36]. In this section, we focus on some new mechanistic studies related to the aortic stiffness, particularly on the VSMCs. Proteins and signaling pathways that are involved in the regulation of VSMC plasticity and stiffness have also been reported in aortic stiffness in both aging and hypertensive models [11, 12, 25, 36, 69], such as the increased expression of cytoskeleton proteins, e.g., alpha-smooth muscle actin, α -SMA, SM22 and integrin β 1 [9–12, 25, 36, 70]. Our recent studies also showed that Rho/ROCK pathway-mediated activation of SRF transcription was a key signaling involved in aortic stiffening in

hypertension which is independent of the change of BP [11, 25]. Upregulation of Rho/ROCK pathway results in a shift in polymerization of G-actin into F-actin [25]. This change in actin dynamics causes the release of myocardin from G-actin, resulting in nuclear localization and accumulation of myocardin [25]. It also stimulates the nuclear translocation of myocardin related transcription factor-A/B (MRTF-A/B) from the cytoplasm, thereby increasing the transcription of SRF [36]. The upregulation of SRF/myocardin not only induced the expression of the downstream stiffness-associated proteins, but also activate integrin $\beta 1$ and BMP1/LOX signaling pathways [46], which further changes the ECM remodeling and VSMC-ECM interaction. Inhibition of these pathways ameliorates the intrinsic VSMC stiffening [11], and also reduced the aortic wall stiffness. These results highlighted the deterrent role of VSMCs mechanical property in the aortic stiffening [36, 46].

Some aging-related genes have also been also implicated to play notable roles in the pathogenesis of aortic stiffening and hypertension [34, 39, 71], such as the Klotho gene, an aging-suppressor gene that prolongs lifespan when overexpressed and reduces lifespan when disrupted [34, 39, 72]. Haplodeficiency of the Klotho gene has been reported to cause aortic stiffness and hypertension [34, 39, 71]. Mechanistically, deficiency of the Klotho gene down-regulates the activities of AMP-activated protein kinase alpha (AMPK α) and endothelial nitric oxide synthase (eNOS) in aortas [34]. Reciprocally, overexpression of this gene up-regulated IL-10, an anti-inflammatory cytokine, and down-regulated NOX2 expression, NADPH oxidase activity and the generation of superoxide in the aortas [34, 39, 73], implying the inhibition of inflammation and oxidative stress [39]. In addition, it has been reported that the circulating Klotho level, which is expressed in the kidney, decreases with age and in particular, after the age of 40 years at which point incidence of hypertension is on the increase [34, 39]. Deficiency of Klotho gene caused a significant reduction in the expression and activity of SIRT1, an NAD⁺-dependent protein in aortic endothelial and smooth muscle cells in KL^{+/-} mice as well as increased collagen expression and enhanced fragmentation of elastin [34]. These effects were stopped by treating with a SIRT1 specific activator, SIRT1720, suggesting that activation of SIRT1 may hold the key for the treatment of the aortic stiffness and hypertension [34].

Aortic stiffness and hypertension has also been reported to be influenced by some specific miRNAs that regulate smooth muscle cell phenotype and modulate inflammation in the endothelial cells [2, 74]. TGF- β signaling in VSMCs was activated following chronic down-regulation of miR-181b expression with age leading to modulation of ECM growth and function [2]. Also, activation of TGF- β increased in the aged aortas and consequently caused aortic stiffening with age [2]. In addition, myocardin has also been reported to suppress MRTF-A expression through the activation of miR-1, suggesting another way to reduce MRTF-A/B/SRF signaling by myocardin [36, 75]. The summary of these new mechanisms is presented in the Figure 2.

5. Future direction

Although efforts have been made at understanding the pathogenesis of age-related aortic stiffness in hypertension [10, 11, 25, 36, 46], therapeutic anti-aortic stiffening has not been

widely applied. Future researches should focus on the investigation of the common mechanisms that induces aortic stiffness, such as the aging, inflammatory/immune-disorder, metabolic disorder and sympathetic nervous system activation. In addition, attentions should be given to the interaction among the circulating molecules or factors and their targeted cells in the vessels (ECs and VSMCs). Furthermore, it needs to explore the regulatory network at the epigenetic, genomic and transcriptional levels of aortic stiffness. Efforts should also be geared towards treatment of hypertension by developing drugs that target mechanisms of aortic stiffness, such as anti-VSMC stiffness [11, 25, 36].

In addition, it is worthy to note that the gender difference between males and females is another important research topic since it exists in aging related aortic stiffness and hypertension. Furthermore, investigation of mechanisms that caused the regional difference of the arteries and VSMC characters may also lead to discovery of specific targets for the treatment. Finally, it should not be neglected that there are potential species variance in the rodent and non-human primate as well as human studies, particularly in aging studies, which needs to be considered and bring more attention to the selection of the animal models.

6. Conclusions

Increased evidence support that age-related aortic stiffness is a cause of hypertension [13]. Aging and aging-induced multiple disorders, such as metabolic syndromes, inflammation and neuroendocrine, cause comprehensive effects on the target cells (ECs, VSMCs and inflammatory cells) of the aorta, resulting in the aortic stiffening, subsequently increased BP in elders. A proper understanding of the pathophysiological mechanisms of aging-related aortic stiffness is therefore needed to remedy the cause of the hypertension in the elderly, and develop the therapeutic strategy by targeting the key signaling pathways involved in the aortic stiffing. This review mainly focused on the recent progress made on the potential causes of aortic stiffening and its implication on the pathogenesis of age-related hypertension as well as developing strategies to prevent hypertension in the elderly. As such, this limitation of the study implies that the outcome of this review should not be extended to other clinical settings other than age-related aortic stiffness and hypertension.

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Abbreviation definition list:

BP	blood pressure
TPR	total peripheral resistance
SVR	systemic vascular resistance
ACE	angiotensin-converting enzyme

SBP	systolic blood pressure
DBP	diastolic blood pressure
PP	pulse pressure
PWV	pulse wave velocity
ECM	extracellular matrix
AGEs	advanced glycation end products
VSMCs	vascular smooth muscle cells
ECs	Endothelial cells
NO	nitric oxide
ROS	reactive oxygen species
TGF-β	transforming growth factor- β
IGF-1	insulin-like growth factors
NF-$\kappa\beta$	nuclear factor kappa beta
RAS	renin–angiotensin system
CRP	C-reactive protein
CVD	cardiovascular disease
MRA	mineralocorticoid receptor antagonist
ANS	autonomic nervous system
SNS	sympathetic nervous system
MR	mineralocorticoid receptor
MRTF-A/B	myocardin related transcription factor-A/B
SRF	serum response factor
eNOS	endothelial nitric oxide synthase
AMPKα	AMP-activated protein kinase alpha
MMPs	matrix metalloproteinase

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Figure 1. Summary of the causes of aortic stiffness and its implication on the age-related hypertension

Figure 2. Summary of the biochemical pathways mentioned and their actions on wall components underlying stiffening.
 EC; endothelial cells, VSMC; vascular smooth muscle cells, ECM; extracellular matrix.