Killing Me Unsoftly

Causes and Mechanisms of Arterial Stiffness

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Abstract—The aorta is a blood vessel that provides a low-resistance path for blood flow directed from the heart to peripheral organs and tissues. However, the aorta has another central hemodynamic function, whereby the elastic nature of the aortic wall provides a significant biomechanical buffering capacity complementing the pulsatile cardiac blood flow, and this is often referred to as Windkessel function. Stiffening of the arterial wall leads to fundamental alterations in central hemodynamics, with widespread detrimental implications for organ function. In this Recent Highlights article, we describe recent contributions in *ATVB* that have highlighted the novel mechanisms and consequences of arterial stiffness and the clinical conditions in which arterial stiffness occurs, with a focus on advancements in the field. **(*Arterioscler Thromb Vasc Biol*. 2017;37:e1-e11. DOI: 10.1161/ATVBAHA.116.308563.)**

Key Words: aging ■ aortic compliance ■ arterial stiffness ■ pathophysiology ■ wall stress

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The aorta, as the major conduit artery of the human body, is primarily thought of as a blood vessel that provides a low-resistance path for blood flow directed from the heart to peripheral organs and tissues. However, the aorta has another central hemodynamic function, whereby the elastic nature of the aortic wall provides a significant biomechanical buffering capacity complementing the pulsatile cardiac blood flow, and this is often referred to as Windkessel function. In systole, the compliant aortic wall stretches to accommodate the bolus of blood ejected by the left ventricle, thereby dampening an increase in systolic arterial pressure (SAP). In diastole, the aortic wall's elastic recoil enables continued aortic blood flow and limits the diastolic drop in arterial pressure.

As a consequence, stiffening of the arterial wall—that is, the loss of Windkessel properties—leads to fundamental alterations in central hemodynamics, with widespread detrimental implications for organ function. In this Recent Highlights article, we describe recent contributions in *ATVB* that have highlighted the novel mechanisms and consequences of arterial stiffness, the relevance to clinical conditions, and recent advancements in the field (Figure).

Clinical Significance of Arterial Stiffness

A major functional manifestation of arterial stiffening is a progressive incapacity to dampen the cyclic arterial pressure changes generated by pulsatile cardiac contractions. Arterial stiffness ultimately leads to increased SAP, as well as decreased diastolic arterial pressure, both of which contribute to an increase in pulse pressure (=systolic arterial pressure–diastolic arterial pressure). Thus, isolated systolic hypertension, the most common form of hypertension among the elderly, is typically because of age-associated increases in aortic stiffness that result in excess morbidity and mortality.[1–3]

Elevated SAP as a result of aortic stiffening increases left ventricular afterload[4–6] and is associated with left ventricular hypertrophy.[7] Additionally, aortic stiffness reduces diastolic blood pressure and leads to impaired coronary perfusion.[8,9] Hence, the coronary perfusion to myocardial demand equilibrium is unbalanced. Clinical studies have demonstrated that aortic stiffness is a strong risk factor and contributor to incident heart failure (HF), including both HF with reduced ejection fraction and HF with preserved ejection fraction.[10,11] Moreover, increased aortic stiffness may also contribute to severe exercise intolerance in older patients with isolated HF with preserved ejection fraction.[12]

Increased, or undamped, pulsatile forces also extend to the vulnerable microcirculation of unprotected organs with low vascular resistance, such as the brain and kidneys.[13] As such, increased arterial stiffness is associated with cerebral small vessel disease[14] and impaired cognitive function in the elderly,[15–17] as well as in young to middle-aged adults.[18] Recently, an analysis of the prospective, population-based AGES-Reykjavik study (Age, Gene/Environment Susceptibility-Reykjavik) by Ding et al[19] demonstrated that increased carotid arterial stiffness in patients aged >65 years is an independent risk factor for incident cerebral microbleeds, which frequently occur in older populations and are associated with an increased risk of recurrent stroke, cognitive impairment, and dementia in the deep or infratentorial brain regions. In addition, arterial stiffness was found to be an independent predictor of stroke, in addition to coronary heart disease, in apparently healthy subjects.[20] Unstable

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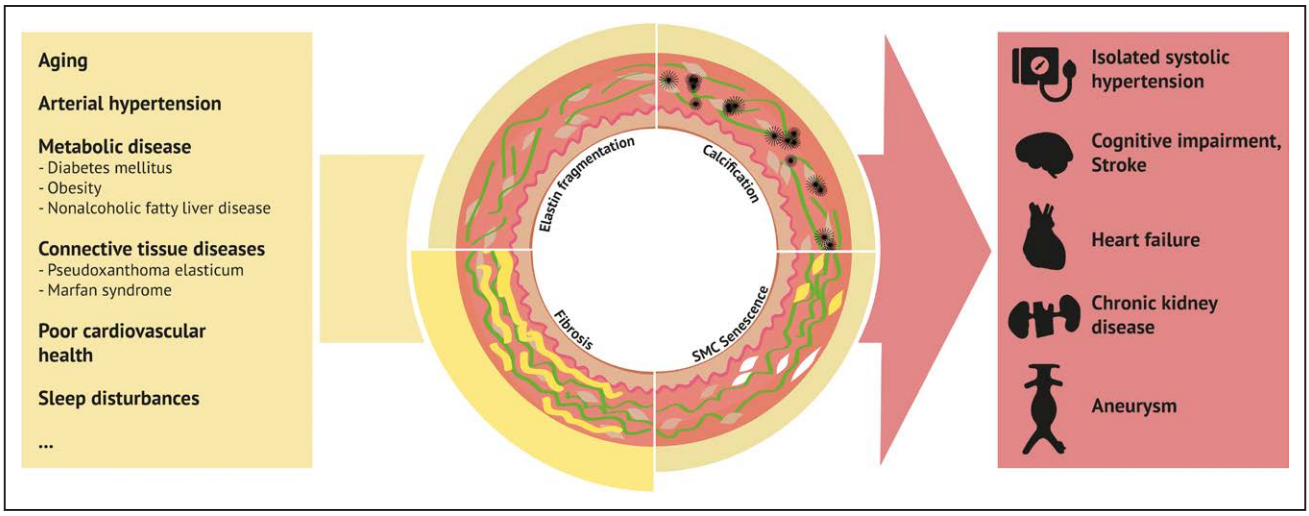

Figure. Arterial stiffness: contributing factors. Clinical conditions, mechanisms, and effects associated with increased arterial stiffness. Green lines represent elastic lamellae, yellow areas indicate fibrosis, black spots mark medial calcium depositions, and fusiform structures indicate vascular smooth muscle cell (VSMCs).

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atherosclerotic plaques located in the carotid artery are a significant source of cerebrovascular embolism. Interestingly, a recent study by Selwaness et al[21] found that increased aortic stiffness is linked not only to a higher prevalence of carotid atherosclerosis but also to increased intraplaque hemorrhage as a marker of plaque instability. With respect to renal function, increased arterial stiffness has been shown to accelerate renal impairment in preexisting chronic kidney disease[22] and, in addition, is associated with incident albuminuria and worsening of glomerular filtration in type 2 diabetes mellitus patients.[23]

Finally, arterial stiffening may not only augment pulsatile hemodynamic stress leading to end-organ injury, but may also directly promote arterial pathologies. Although it remains controversial as to whether increased arterial stiffness precedes or is a consequence of pathologies, such as atherosclerosis,[24] a recent study demonstrated that segmental aortic stiffening, and the resultant aortic stiffness gradients, may trigger aortic remodeling, leading to abdominal aortic aneurysm formation.[25] Complementing these findings, research by Zhang et al[26] conducted in nonhuman primates indicates that the abdominal segment of aged aortae exhibits the highest regional stiffness, thus, making the abdominal aorta a predilection site for aneurysm formation. Furthermore, aortic stiffness is elevated in various connective tissue diseases, including Marfan syndrome, that predispose patients to progressive aortic dilatation, potentially resulting in fatal aortic dissection and death.[27] In those patients, higher aortic stiffness is associated with higher rates of aortic dilatation and an increased requirement for surgical intervention.[27] Mechanistically, recent data published by Crosas-Molist et al[28] indicate that in Marfan syndrome, chronic transforming growth factor (TGF)-β signaling is associated with increased expression of vascular smooth muscle cell (VSMC) contractile markers and actin stress fiber formation, as well as collagen I secretion, ultimately leading to increased VSMC and extracellular matrix (ECM) stiffness. On the other hand, active VSMC contraction may serve as a crucial protective mechanism against aortic dissection, as recently suggested by Ferruzzi et al[29] after elegant ex vivo experiments in dissection-prone murine aortas.

In the light of these extensive pathomechanistic implications, it is not surprising that arterial stiffness has emerged as a strong independent predictor of cardiovascular events and all-cause mortality.[30] Thus, sufficiently monitoring and effectively targeting arterial stiffening holds great promise to universally address a wide range of cardiovascular complications that lead to increased morbidity and mortality.

Physiological Arterial Compliance and Assessment of Arterial Stiffness

To better understand what influences arterial stiffness, one must understand the physiological parameters that contribute to arterial compliance. Arteries are conduits comprising 3 key layers: the intima, media, and adventitia. These layers function together to sense and respond to acute changes in blood pressure via dilation or constriction and respond to chronic changes by undergoing growth and remodeling. The intima is the innermost layer of an artery and is primarily made up of a single layer of endothelial cells on the luminal side of the vessel. The endothelium functions to present an antithrombotic surface to flowing blood.[31] The media consists of concentric layers of elastin, which form the elastic lamellae, fibrillar collagen, and VSMCs, and it is this layer that provides blood vessels with most of their compliance and the ability to contract and dilate. The outermost layer of the artery is the adventitia, and it is primarily composed of fibroblasts and collagen and functions to give the vessel support and a surface with which to tether onto other tissues. In the case of larger vessels, such as the aorta, the vessel layers also include a network of small blood vessels, called vasa vasorum, that help supply oxygen and nutrients to the larger vessel wall. Between each of the 3 layers in humans is an elastic lamina, comprising a fenestrated tube of elastin fibers, that further adds to the vessel's compliance

and separates the different layers of the vessel.[32] Numerous cell types in the vessel wall, including endothelial cells, VSMCs, and fibroblasts, sense mechanical changes and respond by producing vasoactive molecules, ECM, and ECM-degrading proteases. Several mechanisms that contribute to increases in arterial stiffening and the pathophysiologic conditions linked to increased arterial stiffness are discussed further.

In vivo, arteries are under constant multiaxial mechanical loading, where pulsatile blood pressure distends the vessel and induces a cyclic circumferential stress, whereas blood flow through the vessel lumen induces shear stress along the endothelial cell layer of the vessel wall. Vessels in vivo also exist under an axial load, as demonstrated by their retraction on excision and removal.[33] Vessels remodel in response to changes in loading conditions. Besides changing geometric parameters, such as the inner vessel diameter or vessel wall thickness, vascular remodeling can occur through artery calcification, increased intima–media thickness, and impaired flow-mediated dilation.[34] This vascular wall remodeling alters the stiffness or compliance of the vessel, and these changes occur to restore mean and local stresses. For example, Matsumoto and Hayashi[35] showed that the different layers of blood vessels thicken to different degrees in response to supraphysiological loading, with the inner layers increasing the most because of the highest stress in that layer.

In the clinical setting, arterial stiffness can be assessed by numerous noninvasive modalities, and there are several excellent reviews that focus on this specific topic.[36–38] Regional quantification of carotid–femoral pulse wave velocity (PWV) is considered the clinical gold standard measurement of arterial stiffness and is used by most studies in the field.[39] PWV represents the speed of a pressure wave propagating down a blood vessel and is directly correlated with the vessel's elastic modulus. Increased PWV as a result of arterial stiffening is the basis for further indices of aortic stiffness, such as augmentation index.[39] Arterial pulse waves traveling from the heart to the periphery are typically reflected at sites of impedance mismatch, such as peripheral branch points or small arterioles. When arteries are compliant, PWV is slow and reflected waves return in diastole, augmenting central diastolic arterial pressure. In contrast, when arteries are stiffer and PWV is higher, reflected waves arrive earlier and augment central SAP. This augmentation of central SAP can be visualized through central pulse contour analysis as the pressure difference between the first and the second (augmented) systolic pressure peak. Of note, a recent study by Schultz et al[40] found that central blood pressure waveform (and, therefore, augmentation index) is mainly influenced by aortic compliance (reservoir function) rather than by timing of pulse wave reflections.

Stiffening processes may not uniformly affect the arterial tree,[41] and segmental arterial stiffening may be critical for arterial pathologies, such as abdominal aortic aneurysm formation[42]; therefore, local assessment of arterial stiffness is desirable. This can be achieved by quantification of the fractional change in arterial diameter produced by cyclic systolic–diastolic pressure change. Arterial wall displacement is usually achieved via ultrasound devices. Additionally, aortic PWV may be measured locally using magnetic resonance imaging, allowing for spatially differentiated evaluation of stiffening.[41]

Given the popularity of mouse models to study various pathologies of cardiovascular disease (CVD), including arterial stiffness, reliable methods to quantify arterial biomechanics are essential. As such, the aforementioned in vivo metrics of arterial stiffness, such as PWV (either determined though Doppler measurements,[43,44] applanation tonometry,[45] or magnetic resonance imaging[46]) or local arterial compliance and distensibility[25,47,48] have been established for use in murine studies. Those methods are indispensable for longitudinal in vivo studies measuring arterial stiffness but only allow indirect assessment of biomechanical properties. In contrast, ex vivo tests allow for comprehensive biomechanical testing using a variety of loading protocols. At the macroscale, the mechanical stress–strain relationship may be obtained via tensile testing using simple uniaxial strip or ring tests or more complex planar biaxial tests. However, planar tensile testing does not use physiologically relevant mechanical loading conditions for arterial vessels. In this regard, pressure myography systems may be better suited to obtain vascular pressure–diameter or force–length relations as a direct measure of vascular circumferential or axial stiffness.[47,49] For dissection of vascular mechanical properties at the cellular or even subcellular level, established methods, such as atomic force microscopy,[28] nanoindentation, or micropipette aspiration, are available. Although these have proven to be powerful tools to assess individual cell stiffness, it remains to be determined whether changes in cell stiffness in vitro directly correlate with changes in vessel stiffness in vivo.

Underlying Mechanisms of Arterial Stiffening

Mechanical factors, such as hemodynamic forces, and humoral factors, including hormones like angiotensin II (Ang II), salt, and glucose, all function to influence vessel remodeling. The changes that ultimately result in artery stiffening can occur in ways that are both common and different in common diseases, such as hypertension, diabetes mellitus, and aging. Herein, we highlight the most common mechanisms that contribute to changes in arterial stiffness, with a focus on mechanistic insights recently identified by studies published in *ATVB*.

Changes in ECM

The vessel wall comprises ECM proteins, including collagen, elastin, glycoproteins, and proteoglycans. Collagen and elastin function to provide structural integrity and elasticity. ECM stability is assured by the intra- and intermolecular covalent cross-linking of elastin and collagen, initiated by lysyl oxidase (LOX), a copper-dependent amine oxidase. Conversely, matrix metalloproteases (MMPs), through their proteolytic effects, function to degrade the ECM by creating uncoiled collagen and broken/frayed elastin. Therefore, an appropriate balance of LOX and MMP activity is necessary to maintain vascular compliance. Indeed, the importance of collagen/elastin ratios and collagen and elastin disarray was recently demonstrated in monkeys. The study by Zhang et al[26] published in *ATVB* clearly

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demonstrated that aortic stiffness increases with age; however, the most severe increases in aortic stiffness were observed in the abdominal aorta, where values in young monkeys equaled or exceeded values of thoracic aortic stiffness in old monkeys. Altogether, these results suggest that regional differences exist between the abdominal and thoracic regions of the aorta that ultimately differentially impact arterial stiffness.

LOX deficiency in mice is associated with aortic aneurysm, tortuosity, and rupture,[50] suggesting that LOX activity is essential to maintain the elastic features of blood vessels. Although obesity and aortic stiffness have been linked, clear mechanistic insight was lacking. Recent studies demonstrated that *ob/ob* and *db/db* mice exhibit higher aortic PWVs and lower aortic compliance[51–53] and that Zucker fatty rats have greater stiffness.[54] Mechanistically, a recent study in *ATVB* demonstrated that obesity results in aortic stiffening in both humans and mice and that this is, in part, mediated through LOX downregulation, leading to elastin fragmentation and a significant increase in PWV.[55]

Vascular cells, as well as inflammatory cells, produce ECM proteins, as well as the various MMPs capable of degrading collagen and elastin. Further degradation of the basement membrane ECM occurs through the activation of MMP-2 and MMP-9, which have gelatinase activity.[56] Increases in MMP enzymatic activity are regulated by increases in gene expression, activation by cleavage of pro-MMP protein, through MMP–MMP interactions, and by plasmin, thrombin, and reactive oxygen species (ROS).[57,58] Tissue inhibitors of MMPs, or TIMPs, counter this response and are critical for balancing the vessel remodeling process.[56] Furthermore, the deposition of proteoglycans also contributes to thickening of the vessel wall ECM and, thus, vessel wall stiffness. Using a proteomics approach, a group recently examined the protein extracts of well-defined, homogenous, nonatherosclerotic left mammary artery samples from 10 patients with high PWV and 9 with low PWV by quantitative proteome analysis. Interestingly, the study demonstrated that changes in the amounts of small leucine-rich proteoglycans, known to be involved in collagen fibrillogenesis, and of some nonfibrillar collagens, in addition to alterations in proteins related to human arterial smooth muscle, are associated with increased arterial stiffness.[59]

Data from patients previously demonstrated that mutations of the gene (*TGFBR2*) that codes the TGF-β type II receptor predispose patients to thoracic aortic aneurysms and dissections[60,61] and that these mutations also lead to decreased expression of contractile proteins in medial smooth muscle cells (SMCs) in response to TGF-β.[62] Jay Humphrey's group published a study in *ATVB* earlier this year, demonstrating that postnatal disruption of TGF-β type II receptor *Tgfbr2* in SMCs compromises both active (contractile) and passive (structural) biaxial biomechanical properties in the murine thoracic aorta.[29] Furthermore, they found that daily in vivo treatment with rapamycin largely preserves or restores biaxial contractile properties, but not passive structural properties.

Vascular Calcification and VSMC Senescence

Arterial calcification is associated with CVD events and mortality, independent of vessel type, and early studies noted that older patients typically exhibit both greater arterial stiffness and arterial calcification, suggesting an association. Arterial stiffening is known to involve ECM changes, such as those described in the previous section, and it is thought that these changes may be exacerbated by increases in arterial calcification.[63] However, recent evidence suggests that vascular remodeling in the presence of increased stiffness may contribute to medial and intimal calcification.[64] A recent study in individuals without prevalent CVD showed in a multivariable-adjusted model that both higher carotid–femoral PWV and central pulse pressure are associated with greater thoracic aorta calcification and abdominal aorta calcification, whereas higher augmentation index was associated with abdominal aortic calcification.[65]

Circulating hormones like Ang II influence vessel remodeling and modulate vascular stiffness. Ang II, for example, stimulates collagen formation, triggers matrix remodeling and vascular hypertrophy, depresses nitric oxide (NO)–dependent signaling, increases ROS production, and reduces elastin synthesis.[66] Numerous studies that focused on understanding the molecular mechanisms by which Ang II affects aging have shown that Ang II accelerates VSMC senescence in vitro and in vivo,[67,68] suggesting a detrimental prosenescent role of Ang II in vascular aging. Furthermore, it has been shown previously that Sirtuin 1, a nicotinamide adenine dinucleotide–dependent deacetylase, inhibits Ang II–induced cell hypertrophy and senescence.[69,70] α7 nicotinic acetylcholine receptor (α7nAChR) is a subtype of nAChR and is reported to be involved in hypertension end-organ damage. A study by Li et al tested the role of α7nAChR in Ang II–induced senescence of VSMCs and found that activation of α7nAChR alleviates Ang II–induced VSMC senescence through promoting NAD^+–Sirtuin 1 pathway, suggesting that α7nAChR may be a potential therapeutic target for the treatment of Ang II–associated vascular aging disorders.[71] Interestingly, another publication by Gardner et al in *ATVB* suggested that senescent VSMCs may be active participants in CVD processes and assume a proinflammatory state and secrete factors that promote chemotaxis of mononuclear cells in vitro and in vivo and that release active MMP-9 and secrete less collagen and prime endothelial cells and VSMCs to a proinflammatory state.[72] Although this was established in a model of atherosclerosis, whether this VSMC phenotype plays a direct role in arterial stiffness remains to be investigated.

Increased Oxidative Stress

In addition to alterations in ECM composition and organization, arterial stiffness is strongly affected by VSMC tone and endothelial cell signaling. Endothelial cell–derived NO is a key modulator of VSMC tone, which is also modified by mechanostimulation, in part, because of cell stretch and changes in calcium signaling. The bioavailability of NO can be reduced by increased production of ROS caused by increased stress and hormones, such as Ang II. Indeed, it has been well described that Ang II stimulation of VSMCs leads to increased ROS (superoxide) production via NADPH oxidase enzymes and that this increased superoxide can, in turn, react with NO to form peroxynitrite and other highly reactive

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species that promote abnormal vascular tone. For more comprehensive reviews on NADPH oxidase–derived ROS and their effects on vascular signaling, see the following references: Brown and Griendling,[73] Lyle and Griendling,[74] and Lassegue and Griendling.[75] The melanocortin 1 receptor is expressed by vascular endothelial cells and has been shown to enhance NO bioavailability and vasodilator function on pharmacological stimulation. Interestingly, a recent study demonstrated that deficiency in melanocortin 1 receptor signaling is associated with increased arterial stiffness and impairment in endothelium-dependent vasodilatation, suggesting a physiological role for melanocortin 1 receptor in the regulation of arterial tone. In addition to increases in ROS in response to humoral factors, mechanotransduction can also lead to increases in ROS production, and this has been reviewed previously.[76–78] Furthermore, changes in blood flow from laminar to more turbulent flow have also been shown to increase ROS production.[79,80] Interestingly, a recent study published in the *ATVB* showed in patients with flow reversal during diastole (present in one third of study participants) that flow reversal in peripheral arteries is accompanied by vascular dysfunction and aortic stiffening[81]; however, whether this is because of increased ROS production remains to be investigated.

In addition, recent studies suggest that mitochondrial dysfunction plays an important role in aging and impairing vascular function.[82,83] A comprehensive study by Zhou et al[44] presented data to support that prolonged exposure to increased mitochondrial oxidative stress decreases aortic compliance and induces cardiac dysfunction. Indeed, they provided evidence that superoxide dismutase (SOD) 2 deficiency over a lifetime is sufficient to induce aortic stiffening, decrease aortic compliance, and cause cardiac dysfunction. Additionally, they showed that aortic stiffening with aging in $SOD2^{+/-}$ mice is associated with structural changes in the aortic wall in vivo, with increased collagen content and ruptures in elastin laminae. Moreover, they find that SOD2 deficiency also increases collagen I expression, decreases elastin expression, and increases MMP-2 expression and activity in aged SMCs. Furthermore, they demonstrated that SOD2 deficiency over a lifetime increases SMC apoptosis in aged mice and sensitizes SMCs to staurosporine-induced increases in cleaved caspase-3 and cleaved Poly ADP ribose polymerase, or PARP, levels.[44] This prolonged SOD2 deficiency impairs cell survival, increases inflammatory signaling responses, and increases aortic stiffness with aging.[44]

Conditions Linked to Arterial Stiffness

Aging

Epidemiological studies clearly indicate that age is the dominant risk factor for CVD.[84] One critical mechanism linking age to increased cardiovascular risk may be age-related stiffening of conduit arteries, such as the aorta. In fact, a reduction of elastic properties (stiffening) is the main manifestation of arterial aging in conduit arteries, and vice versa, aging is the main factor leading to arterial stiffening.[38,85,86] Thus, the concept that vascular (biological) age is better related to prognosis than chronological age is rapidly evolving. Therefore, understanding the mechanisms how chronological aging interferes with arterial elasticity offers the exciting opportunity to uncouple chronological from vascular aging. Arterial aging comes along with a wide spectrum of vascular alterations, including ECM remodeling and calcification, VSMC senescence and apoptosis, and inflammation and oxidative stress (see above). Those phenomena synergistically result in age-related medial degeneration and sclerosis,[87] the substrate for age-related arterial stiffening.

As conduit arteries age, there is an increase in vascular wall stiffness mainly because of alterations of the ECM structure, leading to an imbalance between collagen and elastin.[85,88,89]

Because of thinning and fracture of the elastic laminae, mechanical load is transferred to collagen fibers, which are 100 to 1000 times stiffer than elastic fibers.[90] Elastin fragmentation may result from age-related material fatigue and fracture,[91] as well as increased MMP-mediated proteolysis. Indeed, increased expression of MMP-2 is evident in the medial layer of aged rodents[92,93] and is localized to sites of fragmented elastin.[94] Moreover, high serum MMP levels (MMP-2 and MMP-9) were associated with increased arterial stiffness, as measured by PWV, in healthy individuals and patients with isolated systolic hypertension.[95] Notably, aortic stiffness and elastase activity are influenced by MMP-9 gene polymorphisms.[96] Furthermore, there is an increase in arterial collagen synthesis and deposition with age. Collagen isoforms found in the aorta are mainly (80%–90%) of type I and III, with some type IV,[97–99] and their concentration gradually increases after the age of 50 years.[98,100]

The arterial wall may also stiffen because of calcification of the elastic lamellae, termed medial elastocalcinosis.[63] The presence of calcium deposits in the media of large arteries increases significantly with age.[101,102] Further, in animal models of medial elastocalcinosis, there is a strong correlation between aortic calcium content and arterial stiffness.[103,104] Interestingly, medial calcification is associated with local expression of mineralization-regulating proteins that are normally expressed in osteogenesis.[105] This observation gave rise to the now widely accepted concept that vascular calcification is an active cell–driven process characterized by osteogenic differentiation of vascular cells. Indeed, VSMCs may acquire an osteogenic phenotype, expressing bone/mineralization-associated proteins (eg, Runx2, Sox9, and Msx2)[106,107] that actively regulate arterial calcification.[108–110] Additionally, recent data indicate that the osteogenic transcription factor Runx2, independently of its known role as a regulator of vascular calcification, may induce arterial fibrosis and stiffness.[49]

Another age-related alteration to arteries is the development of chronic, low-grade inflammation in both rodents[111–113] and humans (ie, inflammaging).[100,114,115] There is ample evidence that vascular and systemic inflammation is associated with (or precedes) conduit arterial stiffening.[116–121] Mechanisms of inflammatory vascular stiffening include the induction of MMPs, calcification, and fibrosis by inflammatory stimuli and cells.[49,56,105,108,122,123] Additionally, aged vessels exhibit chronic oxidative stress because of increased ROS production (eg, via leakiness of the mitochondrial respiratory chain or increased NADPH oxidase activity), as well as defective antioxidant mechanisms (eg, age-dependent downregulation of SOD2).[124–127] Mechanistically, oxidative stress may increase vascular

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collagen production[44,124] and augmented medial elastin fragmentation, partly because of increased expression of MMP-2 and MMP-9.[44,58,128]

In addition to chronological aging, preterm birth also represents a risk factor for cardiovascular disorders and mortality in adult life. In this respect, a recent study by Odri Komazec et al[129] in this journal demonstrated significantly increased aortic stiffness in 5- to 7-year-old children born at a gestational age <32 weeks, possibly because of inadequate elastin synthesis. Thus, one could argue that those children are already born with significantly progressed arterial biological age.

Metabolic Disease

Accelerated arterial stiffening—or rapid arterial biological aging—is a major complication of diabetes mellitus.[130,131] Importantly, arterial stiffness predicts the development of CVD and mortality in the patients with type 2 diabetes mellitus.[132] Similar to age-related arterial stiffening, the process of diabetes-accelerated arterial stiffening includes enhanced levels of oxidative stress,[133] eliciting profibrotic mechanisms and MMP-mediated elastin fragmentation.[49,134] Additionally, medial arterial calcification is frequently found in diabetic patients,[105] and MMP-induced elastin degradation may promote calcification.[135] Underlining the significance of MMPs for diabetic arterial remodeling, a recent study published in *ATVB* by Goncalves et al[136] found plasmatic levels of MMP-12 (macrophage elastase) to be elevated in type 2 diabetes mellitus patients and positively correlated with arterial stiffness, hence, indicating a potential of MMP-12 as a biomarker and possibly as a therapeutic target of diabetic arterial stiffness.

As another increasingly prevalent and clinically relevant metabolic disorder, childhood obesity promotes immediate cardiovascular damage, well in advance of adulthood.[137] Investigating the role of arterial biomechanics as a potential mechanistic link, a recent meta-analysis of 15 studies by Cote et al[138] revealed that child/adolescent obesity is associated with greater arterial stiffness. Moreover, according to a study conducted by Rider et al[139] in obese children and adults, an elevated hepatic fat content (as assessed by ^{1}H-magnetic resonance spectroscopy) correlated with increased arterial stiffness, partly via increasing serum triglyceride levels (suggesting a liver fat—triglycerides—arterial stiffness pathway). Additionally, a cross-sectional study of 2284 Framingham Heart Study participants revealed that nonalcoholic fatty liver disease without overt CVD exhibit a broad spectrum of vascular dysfunction, including increased arterial stiffness, as recently reported by Long et al.[140] Pointing toward therapeutic opportunities, a meta-analysis of 3 randomized controlled trials by Petersen et al[141] (involving 1259 participants) recently indicated that modest weight loss (mean 8% of total body weight) achieved with diet and lifestyle changes seems to improve arterial stiffness.

Vitamin D deficiency and hyperparathyroidism are associated with increased cardiovascular risk. Through interference with the renin–angiotensin system, modulation of VSMC proliferation, calcification, and vascular wall inflammation, a deregulated vitamin D/parathormone system may affect arterial stiffness as a mechanism to increase cardiovascular risk.[142] However, a longitudinal analysis of 2580 MESA (Multiethnic Study of Atherosclerosis) participants by Gepner et al[142] revealed that neither baseline parathormone nor vitamin D concentrations were associated with changes in arterial stiffening during nearly a decade of follow-up. Yet, the study demonstrated a cross-sectional association between arterial stiffness and high parathormone.[142]

Pseudoxanthoma elasticum is an inherited metabolic disorder resulting from mutations in the ATP-binding cassette subfamily C member 6 (*ABCC6*) gene. The vascular phenotype is characterized by progressive calcification and fragmentation of elastic fibers. However, until recently, the consequences for arterial function remained obscure. In a model of *Abcc6*$^{-/-}$ mice, Kauffenstein et al[47] demonstrated increased expression of osteogenic and chondrogenic differentiation markers accompany increased arterial stiffness, as well as enhanced myogenic tone in resistance arteries.

Sleep Disturbances

Although adequate sleep is critical for cardiovascular health (CVH), epidemiological studies have demonstrated an increased risk for CVD for both short and long sleep duration.[143] Moreover, aberrations to circadian rhythm meet with pathological consequences. For example, shift work significantly elevates the incidence of CVD.[144] In these conditions, arterial stiffness again may, in part, confer the deleterious cardiovascular effects. Indeed, it was shown by Kim et al[145] that extreme (short and long) sleep duration, as well as poor sleep quality, is associated with increased arterial stiffness in young and apparently healthy participants. Mechanistically, in a study by Anea et al,[43] arterial stiffening in carcadian clock-mutant mice was linked to increased vascular expression of MMP-2 and MMP-9.

Smoking

Smoking, a major reversible cardiovascular risk factor, has been linked to increased arterial stiffness.[146] However, while demonstrating an association between smoking status and inflammatory biomarkers, as well as subclinical atherosclerosis, a recent analysis of the MESA cohort (that enrolled 6814 participants without evident CVD) by McEvoy et al[147] did not find a consistent association between smoking and local carotid and aortic distensibility. This finding is somewhat surprising, and interpretations are rather speculative. For instance, smoking may differentially affect specific arterial segments. As such, studies using carotid–femoral PWV as the clinical gold standard to assess arterial stiffness on a regional scale might be helpful to further evaluate this discrepancy.

Poor Cardiovascular Health

The assessment of CVH as proposed by the American Heart Association CVH score enables an integrated approach to evaluate the combinatorial effects of smoking, physical activity, body mass index, diet, blood glucose, total cholesterol, and blood pressure on cardiovascular end points. As such, epidemiological data suggest that the CVH score is inversely associated with the incidence of CVD. A recent study conducted by Gaye et al[148] now sheds light on potential mechanisms that may promote the protective or adverse effects of ideal or poor CVH on CVD. Analyzing data from 9155 participants of an observational community-based study, the authors observed that ideal

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CVH was associated with substantially less arterial stiffness and thickness. Strikingly, the difference in carotid arterial stiffness between ideal and poor CVH corresponds on average to 15 years difference in chronological age, thus, identifying poor CVH as a dramatic accelerator for arterial biological aging.[148]

Conclusions

Arterial stiffening is a feature of physiological vascular aging that is accelerated in a variety of pathological conditions associated with increased cardiovascular risk, such as type 2 diabetes mellitus. Of note, arterial stiffness by itself is a strong risk factor for a broad spectrum of CVDs, including arterial hypertension, HF, myocardial infarction, and stroke. Moreover, arterial stiffening seems to precede the onset of overt end-organ disease. Thus, increased arterial stiffness may represent a critical causal link between cardiovascular risk and eventual disease and might, therefore, qualify as a universal target for therapeutic intervention.

To test this intriguing hypothesis, it is essential to demonstrate that reducing arterial stiffness is effective in reducing cardiovascular morbidity and mortality. As a first step, a variety of prognostically relevant cardiovascular drugs, such as angiotensin-converting enzyme inhibitors, Ang II receptor blockers, β-receptor blockers, aldosterone antagonists, or statins, were shown to reduce arterial stiffness.[149] However, using those agents, it is difficult to discern whether modulation of arterial stiffness is of any additional benefit unrelated to the drugs' primary effects (eg, antihypertensive or cholesterol lowering). Moreover, many antihypertensive interventions will lower the arterial distending pressure and unload the arterial wall mechanically - therefore functionally reducing arterial stiffness to some extent. However, to achieve a more effective impact on arterial stiffness beyond mere blood pressure control it may be important to therapeutically address the intrinsic biomechanical properties of the arterial wall. To this end, the increasing recognition of epigenetic regulators (such as microRNAs) in the vascular system may yield a variety of novel therapeutic targets to counteract structural arterial remodeling that underlies arterial stiffening.[150] Furthermore, the recent mechanistic insights into the pathophysiologic mechanisms behind arterial stiffening, such as those recently reported in *ATVB* and highlighted here, may uncover new therapeutic targets for this disorder and its consequences.

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Disclosures

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