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

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 afterload4-6 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 disease14 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 al19 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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Atherosclerotic plaques located in the carotid artery are a significant source of cerebrovascular embolism. Interestingly, a recent study by Selwaness et al\textsuperscript{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\textsuperscript{22} and, in addition, is associated with incident albuminuria and worsening of glomerular filtration in type 2 diabetes mellitus patients.\textsuperscript{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,\textsuperscript{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.\textsuperscript{25} Complementing these findings, research by Zhang et al\textsuperscript{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.\textsuperscript{27} In those patients, higher aortic stiffness is associated with higher rates of aortic dilatation and an increased requirement for surgical intervention.\textsuperscript{27} Mechanistically, recent data published by Crosas-Molist et al\textsuperscript{28} indicate that in Marfan syndrome, chronic transforming growth factor (TGF)-\textbeta\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 vasa, 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. 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. 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. 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 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. The quantification of arterial stiffness and is used by most studies in the field. PWV is considered the clinical gold standard measurement of arterial stiffness; therefore, local assessment of arterial stiffness is usually achieved via ultrasound devices. Additionally, aortic PWV may be measured locally using magnetic resonance imaging, allowing for spatially differentiated evaluation of stiffening. 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 through Doppler measurements or mag-
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, 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 and that Zucker fatty rats have greater stiffness. 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.

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. 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). Tissue inhibitors of MMPs, or TIMPs, counter this response and are critical for balancing MMP–MMP interactions, and by plasmin, thrombin, and reactive oxygen species (ROS). 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, 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. A study by Li et al tested the role of α7 nicotinic acetylcholine receptor (α7nAChR) as a subtype of nAChR and is reported to be involved in hypertension end-organ damage. A study by Gardner et al in ATVB suggested that senescence 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. Although this was established in a model of atherosclerosis, whether this VSMC phenotype plays a direct role in arterial stiffness remains to be investigated.

**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. However, recent evidence suggests that vascular remodeling in the presence of increased stiffness may contribute to medial and intimal calcification. 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.

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. Numerous studies that focused on understanding the mechanisms by which Ang II affects aging have shown that Ang II accelerates VSMC senescence in vitro and in vivo, 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. A study by Li et al tested the role of α7 nicotinic acetylcholine receptor (α7nAChR) as a subtype of nAChR and is reported to be involved in hypertension end-organ damage. A study by Gardner et al in ATVB suggested that senescence 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. Although this was established in a model of atherosclerosis, whether this VSMC phenotype plays a direct role in arterial stiffness remains to be investigated.
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 stiffening44; 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 al44 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 increases SMC apoptosis in aged mice. Furthermore, 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.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 rodents92,93 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 elastocalcinosi.63 The presence of calcium deposits in the media of large arteries increases significantly with age.101,102 Further, in animal models of medial elastocalcinosi, 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 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.49,56,108,109,122,123 Additionally, aged vessels exhibit chronic oxidative stress because of increased ROS production (eg, via leakage 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
collagen production\textsuperscript{42,124} and augmented medial elastin frag-
mentation, partly because of increased expression of MMP-2 and
MMP-9\textsuperscript{4,58,128}.

In addition to chronological aging, preterm birth also rep-
resents a risk factor for cardiovascular disorders and mortality
in adult life. In this respect, a recent study by Odri Komazec et
al\textsuperscript{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.

\textbf{Metabolic Disease}

Accelerated arterial stiffening—or rapid arterial biological
aging—is a major complication of diabetes mellitus\textsuperscript{130,131}.
Importantly, arterial stiffness predicts the development of
CVD and mortality in the patients with type 2 diabetes mel-
litus.\textsuperscript{132} Similar to age-related arterial stiffening, the process
of diabetes-accelerated arterial stiffening includes enhanced
levels of oxidative stress,\textsuperscript{133} eliciting profibrotic mechanisms
and MMP-mediated elastin fragmentation.\textsuperscript{49,134} Additionally,
medial arterial calcification is frequently found in diabetic
patients,\textsuperscript{105} and MMP-induced elastin degradation may pro-
mote calcification.\textsuperscript{135} Underlining the significance of MMPs
for diabetic arterial remodeling, a recent study published in
\textit{ATVB} by Goncalves et al\textsuperscript{136} found plasmatic levels of MMP-12
(macrophage elastase) to be elevated in type 2 diabetes mel-
litus patients and positively correlated with arterial stiffness,
indeed, 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 immedi-
ate cardiovascular damage, well in advance of adulthood.\textsuperscript{137}
Investigating the role of arterial biomechanics as a potential
mechanistic link, a recent meta-analysis of 15 studies by Cote
et al\textsuperscript{138} revealed that child/adolescent obesity is associated with
greater arterial stiffness. Moreover, according to a study con-
ducted by Rider et al\textsuperscript{139} in obese children and adults, an elevated
hepatic fat content (as assessed by \textit{H}-magnetic resonance spec-
troscopy) correlated with increased arterial stiffness, partly via
increasing serum triglyceride levels (suggesting a liver fat—tri-
glycerides—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, includ-
ing increased arterial stiffness, as recently reported by Long
et al\textsuperscript{140}. Pointing toward therapeutic opportunities, a meta-analysis
of 3 randomized controlled trials by Petersen et al\textsuperscript{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 associ-
ated 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.\textsuperscript{142} However, a longitudinal analysis of 2580 MESA
(Multiethnic Study of Atherosclerosis) participants by Gepner
et al\textsuperscript{142} revealed that neither baseline parathormone nor vita-
mion 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.\textsuperscript{142}

Pseudoxanthoma elasticum is an inherited metabolic
disorder resulting from mutations in the ATP-binding cas-
sette subfamily C member 6 (\textit{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 \textit{Abcc6}\textsuperscript{−/−} mice, Kauffenstein et al\textsuperscript{147} demonstrated
increased expression of osteogenic and chondrogenic differ-
entiation markers accompany increased arterial stiffness, as
well as enhanced myogenic tone in resistance arteries.

\textbf{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.\textsuperscript{143}
Moreover, aberrations to circadian rhythm may meet with pathologi-
consequences. For example, shift work significantly elevates
the incidence of CVD.\textsuperscript{144} In these conditions, arterial stiffness
again may, in part, confer the deleterious cardiovascular effects.
Indeed, it was shown by Kim et al\textsuperscript{145} that extreme (short and
long) sleep duration, as well as poor sleep quality, is associ-
ated with increased arterial stiffness in young and apparently
healthy participants. Mechanistically, in a study by Anea et al,\textsuperscript{43}
arterial stiffening in circadian clock-mutant mice was linked to
increased vascular expression of MMP-2 and MMP-9.

\textbf{Smoking}

Smoking, a major reversible cardiovascular risk factor, has
been linked to increased arterial stiffness.\textsuperscript{146} However, while
demonstrating an association between smoking status and
inflammatory biomarkers, as well as subclinical atheroscle-
rosis, a recent analysis of the MESA cohort (that enrolled
6814 participants without evident CVD) by McEvoy et al\textsuperscript{147}
did not find a consistent association between smoking and
local carotid and aortic distensibility. This finding is some-
what 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.

\textbf{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, epide-
miological data suggest that the CVH score is inversely associ-
ated with the incidence of CVD. A recent study conducted by
Gaye et al\textsuperscript{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 observa-
tional community-based study, the authors observed that ideal
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 (e.g., 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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**References**


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42. Lyck Hansen M, Beck HC, Irumukhedav A, Jensen PS, Olsen MH, Rasmussen LM. Proteome analysis of human arterial tissue discloses associations between the vascular content of small leucine-rich repeat proteins.
Lyle and Raaz

Causes and Mechanisms of Arterial Stiffness e9


Calcification of vascular bone morphogenetic protein signaling in diabetes mellitus. 

10.1161/01.HYP.0000111829.46090.92.

Aging Cell

Diabetic cardiovascular disease induced by oxidative stress.

J Biol Chem

Aortic pulse wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function?

Circulation
2002;106:2085–2090.

Hypertension in preschool children born preterm.

Arterioscler Thromb Vasc Biol

Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease.

Diabetologia

Aortic pulse wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function?

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