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Abstract—Arterial stiffness is a growing epidemic associated with increased risk of cardiovascular events, dementia, and death. Decreased compliance of the central vasculature alters arterial pressure and flow dynamics and impacts cardiac performance and coronary perfusion. This article reviews the structural, cellular, and genetic contributors to arterial stiffness, including the roles of the scaffolding proteins, extracellular matrix, inflammatory molecules, endothelial cell function, and reactive oxidant species. Additional influences of atherosclerosis, glucose regulation, chronic renal disease, salt, and changes in neurohormonal regulation are discussed. A review of the hemodynamic impact of arterial stiffness follows. A number of lifestyle changes and therapies that reduce arterial stiffness are presented, including weight loss, exercise, salt reduction, alcohol consumption, and neuroendocrine-directed therapies, such as those targeting the renin-angiotensin aldosterone system, natriuretic peptides, insulin modulators, as well as novel therapies that target advanced glycation end products. (***Arterioscler Thromb Vasc Biol*. 2005;25:932-943.)**

Key Words: arterial stiffness ■ isolated systolic hypertension ■ mechanisms ■ therapeutics ■ pathophysiology

Increased central arterial stiffening is a hallmark of the aging process and the consequence of many disease states such as diabetes, atherosclerosis, and chronic renal compromise. Accordingly, there is a marked increase in the incidence and prevalence of clinical surrogate markers of vascular stiffness, such as pulse pressure and isolated systolic hypertension, with age and these associated conditions.[1–6] Arterial stiffening is also a marker for increased cardiovascular disease risk, including myocardial infarction, heart failure, and total mortality, as well as stroke, dementia, and renal disease.[7–14] This has been recently reviewed by Safar et al.[15] By altering the resting and stress-induced hemodynamics and energy expenditure, vascular stiffness not only contributes to these clinical repercussions and lowers the threshold for their symptoms but also likely contributes to more dyspnea with exertion and orthostatic hypotension in older adults. Although the structural and cellular changes that underlie arterial stiffness may predispose the vasculature to further insult by atherosclerotic disease, the mechanisms explaining this link are still undergoing investigation. Wang and Fitch provide a recent summary of the putative relationship between arterial stiffness and atherosclerosis.[16]

Earlier work on arterial properties focused on fluid mechanics and the impact of hemodynamic and reflective wave properties on the development of arterial stiffness and the arterial waveforms.[17,18] The development of methods to measure and assess specific aspects of arterial stiffness, as recently reviewed by Oliver and Webb,[19] greatly facilitated understanding of its role in cardiovascular disease. Here, we build on this earlier review to discuss more recent theories on the mechanisms contributing to arterial stiffness, its physiological impact on the cardiovascular system, and treatment strategies to confront it.

Mechanisms of Vascular Stiffness

Vascular stiffening develops from a complex interaction between stable and dynamic changes involving structural and cellular elements of the vessel wall (Figure 1). These vascular alterations are influenced by hemodynamic forces[20,21] as well as by "extrinsic factors" such as hormones, salt, and glucose regulation. Stiffness is not uniformly disseminated throughout the vascular tree but is often patchy,[22,23,24] occurring in central and conduit vessels while sparing more peripheral arteries.[25,26] Common diseases, such as hypertension and diabetes mellitus, or simply aging itself, amplify the vascular changes that result in artery stiffening and can do so in different, yet synergistic, ways.

Structural Components of Arterial Stiffening

The stability, resilience, and compliance of the vascular wall are dependent on the relative contribution of its 2 prominent scaffolding proteins: collagen and elastin. The relative content of these molecules is normally held stable by a slow, but dynamic, process of production and degradation. Dysregulation of this balance, mainly by stimulation of an inflammatory milieu, leads to overproduction of abnormal collagen and

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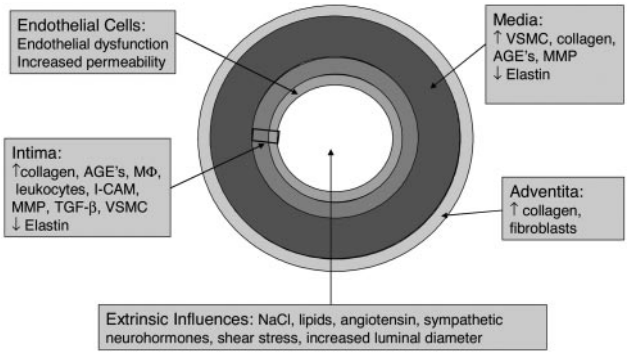

Figure 1. Summary of the multiple causes and locations of arterial stiffness.

diminished quantities of normal elastin, which contribute to vascular stiffness.[27] Increased luminal pressure, or hypertension, also stimulates excessive collagen production.[28] On gross pathologic vascular specimens, these molecular changes manifest as a doubling to tripling of intima-medial thickness between ages 20 to 90,[29,30] as well as a hypertrophied vascular smooth muscle layer.[31] Histological examination of the intima of stiffened vessels reveals abnormal and disarrayed endothelial cells, increased collagen, frayed and broken elastin molecules, infiltration of vascular smooth muscle cells, macrophages and mononuclear cells, and increased matrix metalloproteinases, transforming growth factor (TGF)-β, intracellular cell adhesion molecules, and cytokines.[32] In addition to vessel wall thickening, aging is associated with a gradual increase in central artery lumen diameter (9% per decade from 20 to 60 years in the ascending aorta),[33] although some recent studies have suggested this does not occur.[34]

The extracellular matrix (ECM) of the vessel wall is comprised of collagen, elastin, glycoproteins and proteoglycans. The first two provide structural integrity and elasticity, and are potently regulated by catabolic matrix metalloproteases (MMPs). Through their collagenolytic and elastinolytic effects, MMPs degrade the ECM by creating uncoiled, less effective collagen and broken and frayed elastin molecules, respectively (Figure 2). Vascular cells, as well as inflammatory cells such as macrophages and polymorphonuclear neutrophils, produce collagenases (MMP-1, MMP-8, MMP-13)

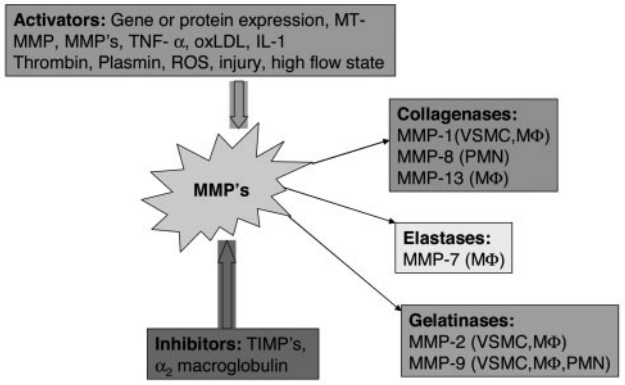

Figure 2. Matrix metalloproteinases affect collagen and elastin balance and are regulated by various activators and inhibitors.

and elastases (MMP-7 and serine proteases).[35] Further degradation of the basement membrane ECM and stimulation of chemotactic agents occur through gelatinase activation (MMP-2 and MMP-9).[22,36] Enzyme activity is regulated by augmented gene expression, post-translational activation by cleavage of pro-MMP protein, by MMP–MMP interactions, and by plasmin, thrombin, and reactive oxygen species (ROS).[37–39] Tissue inhibitors of MMPs counter this response, and MMP–tissue inhibitors of MMPs balance is central in controlling remodeling.[22] Deposition of chondroitin sulfate, heparin sulfate, proteoglycans, and fibronectin can also thicken and stiffen the ECM of vessel walls.[40]

Collagen molecules provide the tensile strength of the vessel wall and are enzymatically cross-linked soon after their formation to render them insoluble to hydrolytic enzymes.[41] Breaks in the integrity of these intermolecular bonds cause unraveling of the collagen matrix. Moreover, because of their slow hydrolytic turnover rate, collagen is particularly susceptible to nonenzymatic glycation cross-linking as described. This leads to increased collagen content, often with a more unorganized and dysfunctional fiber distribution. Elastin molecules are also stabilized by cross-linking (by LOX) to form desmosine and isodesmosine. Disruption of these cross-links contributes to weakening of the elastin array with predisposition to mineralization by calcium and phosphorous, together increasing arterial stiffness.[33,42,43] Moreover, activation of various serine and metalloproteases generate broken and frayed elastin molecules.[44] Alterations in elastin production and molecular repair mechanisms additionally contribute to the loss of vascular elasticity.[45–47]

Arterial stiffness is also caused by advanced glycation end products (AGEs), which result from nonenzymatic protein glycation to form irreversible cross-links between long-lived proteins such as collagen.[48,49] AGE-linked collagen is stiffer and less susceptible to hydrolytic turnover. This results in an accumulation of structurally inadequate collagen molecules.[50] Similarly, elastin molecules are susceptible to AGE cross-linking reducing the elastic matrix of the wall.[51,52] AGE may also affect endothelial cell function by quenching nitric oxide and increasing the generation of oxidant species such as peroxinitrite.[53] Through their immunoglobulin superfamily receptors (RAGE), AGE stimulates stress signaling and inflammatory responses, increasing the expression of p12(ras), NF-κB, oxidant radical formation, pro-inflammatory cytokines, growth factors, and vascular adhesion molecules.[54,55] Such mediators can increase vascular stiffness via MMPs,[56] contribute to endothelial dysfunction that elevates smooth muscle tone, depress endothelial flow-mediated dilation, worsen the response to vascular injury, affect angiogenesis, and promote atherosclerotic plaque formation.[57–59] A profibrotic response can be also triggered independently from a TGF-β pathway by the interaction of RAGE with AGE ligands.[60]

It remains less clear whether the deposition of lipids in the vascular wall and development of atherosclerotic lesions alone contribute to vessel stiffness. Young subjects with isolated hypercholesterolemia have normal or even increased arterial compliance.[61] With progressing age, the relationship between arterial compliance and low-density lipoprotein

(LDL) cholesterol becomes negative, as a result of more pronounced endothelial dysfunction.[62] Clearly, the pathophysiology of atherosclerosis involves many similar inflammatory, protease, and oxidase-mediated stress/remodeling cascades that can lead to vessel remodeling and altered collagen and elastin structure. However, because stiffness and atherosclerosis often coexist, causality remains uncertain.

Cellular Role in Vascular Stiffening

In addition to structural changes, arterial stiffness is strongly affected by endothelial cell signaling and vascular smooth muscle cell (VSMC) tone. VSMC tone can be modified by mechanostimulation, itself, in part because of cell stretch and changes in calcium signaling, and by paracrine mediators such as angiotensin II,[63] endothelin,[64] oxidant stress,[65] and nitric oxide. Endothelial dysfunction is evidenced clinically by an impaired vasodilatory response to acetylcholine.[66,67] This stems, in part, from an imbalance between nitric oxide and endothelial-derived hyperpolarizing factor and constricting hormones, and oxygenases (eg, cyclooxygenase, NADPH, and xanthine oxidase).[68] Nitric oxide expression may itself be reduced,[67,69] and increased expression of a natural nitric oxide synthase (NOS) inhibitor, asymmetrical dimethylarginine, has been linked to vascular stiffening.[70] Bioavailability of nitric oxide is also reduced by activation of reactive oxygen species caused by stress, hormones, and likely AGEs.[71] The formation of peroxynitrite and other highly reactive species results in abnormal vascular tone.[67,72]

Although many studies have established a role of endothelial dysfunction in vascular stiffening, recent studies have suggested the opposite holds as well—ie, that structural stiffening could alter endothelial function and thereby worsen stiffening. When endothelial cells cultured in distensible silastic tubes are exposed to realistic pulsatile perfusion, the combined phasic shear and stretch results in greatly augmented phosphorylation of the serine-threonine kinase Akt and subsequent stimulation of endothelial NOS.[72] However, neither phosphorylation nor endothelial NOS expression are stimulated in cells cultured in stiff tubes and exposed to identical pulsatile perfusion. These data suggest that the ability of the vessel wall to stretch impacts endothelial mechanotransduction far more than a pulsatile stimulus, and this lack of compliance may promote a decline in NOS activity, leading to further arterial stiffness.

Neuroendocrine Signaling and Salt

Many hormones are known to modulate vascular stiffness. Angiotensin II (AII) stimulates collagen formation, triggers matrix remodeling and vascular hypertrophy, depresses nitric oxide-dependent signaling, increases oxidant stress, and reduces elastin synthesis.[63] In addition, AII stimulates cytokines and growth factors in the matrix that contribute to an increased inflammatory response.[47,73–75] Many of these changes are transduced by AII-stimulated NADPH oxidase and NOS uncoupling.[76] Aldosterone (ALDO) synthesis is primarily controlled by the action of AII on the angiotensin type I receptor, and also promotes vascular stiffness and hypertension by stimulating VSMC hypertrophy, fibrosis, and fibronectin.[77,78] The action of ALDO is closely tied to endothelin-1; infusion of ALDO increases endothelin-1 production, which has vasoconstrictive and fibrotic effects on the vasculature itself.[79]

Dietary salt augments vascular stiffness with increasing age, and low-sodium diets consumed by older adults improve arterial compliance.[80,81] In response to NaCl, VSMC tone is stimulated and vascular wall composition altered with a marked increase in the medial layer with VSMC hypertrophy and abundant collagen and elastin production.[82–85] Salt intake interacts with genetic polymorphisms for genes such as angiotensin type I receptors, nitric oxide, and ALDO synthase.[86–88] Sodium also impairs endothelial function by reducing the production of nitric oxide by NOS, thereby diminishing nitric oxide bioavailability and by stimulating NOS inhibitor asymmetrical dimethylarginine and enhancing NADPH oxidase activity.[81] This results in enhanced ROS stimulation as a common mechanism for arterial stiffening.

Glucose, Insulin, and Vascular Stiffening

In patients with diabetes and metabolic syndrome, arterial stiffening is consistently observed across all age groups. For example, increased arterial stiffness and abnormal endothelial reactivity is already present in obese children with metabolic syndrome.[89] A core feature appears to be insulin resistance, because central arterial stiffness and insulin resistance are positively correlated.[90,91] Furthermore, the extent of metabolic changes predicts arterial stiffness in a dose-dependent fashion.[3] Chronic hyperglycemia and hyperinsulinemia increases the local activity of renin-angiotensin-aldosterone system (RAAS) and expression of angiotensin type I receptor in vascular tissue,[92] promoting development of wall hypertrophy and fibrosis.[93,94] Hyperinsulinemia itself has proliferative effects, because insulin resistance impairs PI3-kinase–dependent signaling responsible for the acute metabolic effects of insulin, yet activity of growth-promoting mitogen activated kinase pathways remains relatively preserved.[95] Impaired glucose tolerance also enhances nonenzymatic glycation of proteins with covalent cross-linking of collagen (AGEs) and alters the mechanical properties of interstitial tissue of the arterial wall.[96] Stiffness is further increased by endothelial dysfunction caused by high LDLs, free fatty acids,[97] endothelin-l, inadequate vasodilatory effects of insulin, or decreased levels of adiponectin[98] and natriuretic peptides.[99] Importantly, increased arterial stiffness in the metabolic syndrome is not the consequence of fully established diabetes, but rather caused by subtle hormonal and metabolic abnormalities present from the very beginning of an insulin-resistant state.

Chronic Renal Disease

Arterial stiffening increases in patients with chronic renal insufficiency, and aortic pulse wave velocity (PWV), a marker of stiffening, is a strong independent predictor of mortality in this population.[12] Arterial stiffening in renal disease involves several mechanisms. Intima-medial thickening occurs in response to increased wall stress from hypertension. Increased extracellular matrix collagen content and VSMC proliferation are promoted by activated systemic and local RAAS. Further, elasticity and digestibility of collagen

and other ECM proteins are reduced because of AGE formation[100] and reactions with methylglyoxal and other reactive carbonyl compounds, which are increased in uremic patients.[101] Arterial stiffening in renal disease is also driven by diffuse calcifications in the arterial media without much inflammation, producing a histological picture quite different from calcifications in complex atherosclerotic plaque.[102,103] Rather, data support a role of osteoblast-like cells that secrete bone matrix proteins.[104–106]

Genetics of Vascular Stiffening

Given the involvement of numerous proteins and hormones in vascular stiffening, it is perhaps not surprising that genetic polymorphisms have been identified that are associated with increased arterial stiffening. In a recent genome-wide scan of the Framingham Heart Study population, DeStefano et al report that having chronically increased arterial pulse pressure has moderate inheritability (0.51 to 0.52). There appears to be minimal overlap between linkage peaks of pulse pressure (PP) versus systolic or diastolic pressure,[107] suggesting that genes contributing to PP variability are separate. Several highly suggestive regions have been identified, some in concordance with genome scans in different cohorts, such as 122 cM region of 15 chromosome,[108] 164 cM region of 8 chromosome (in proximity of ALDO synthase gene),[109] and 70 cM region of 7 chromosome.[110] Gene candidates in these locations have not been identified but may ultimately disclose unexpected genes related to blood pressure traits. Interestingly, several linkage peaks for PP have been observed in regions coding multiple components of growth hormone/insulin growth factor axis (insulin-like growth factor, insulin-like growth factor binding protein 1 and 3, and growth hormone insulin-like growth factor), supporting the importance of this pathway on vascular structure.

Candidate gene analysis has also identified loci coupled to measures of arterial stiffness. For example, variations in arterial stiffness have been related to gene polymorphisms in the angiotensin-converting enzyme (ACE) or angiotensin type I receptor,[73,111] endothelin A and B receptor,[112] collagen-Iα1,[113] fibrillin-1, and IGF-1[114] Importantly, these studies have been generally limited by small and preselected study populations. None of these genes seems to have a major effect in the general population, which likely reflects the polygenic and multifactorial nature of hypertension.[115]

Vascular Stiffening Pathobiology

Vascular stiffening results in widening of the arterial pulse pressure, which can profoundly influence blood vessel and heart biology. In arteries, the impact is primarily related to changes to mechanical vascular stimulation caused by increased pulsatile shear and pressure.[116,117] Local regions near bifurcations have more turbulent flow and experience a higher amplitude of oscillatory shear stress with elevated stress, magnifying endothelial dysfunction and vascular disease.[118] In compliant arteries, increased pulsatile perfusion can augment vasodilation, a change linked to enhanced nitric oxide production as well as activation of calcium-sensitive K^+ channels linked to endothelial-derived hyperpolarizing factor.[119,120] This is further amplified when PP is enhanced in vascular beds dilated by local stimulation of ATP-sensitive K^+ channels,[121] a common mechanism regulating regional flow in the coronary arteries and peripheral vasculature. However, this augmentation of flow by pulse perfusion may require normal vascular distensibility, because reduction of wall compliance appears to block key signaling involved with this response.[72]

From the perspective of the heart, vascular stiffening influences the load imposed on the ventricles, the efficiency of cardiac ejection, and the perfusion of the heart itself. Hearts ejecting into a stiffer arterial system must generate higher end-systolic pressures for the same net stroke volume. The result is a greater energy requirement for a given level of ejected flow.[122] Chronic ejection into a stiffer vasculature induces cardiac hypertrophy even at similar levels of mean arterial pressure (MAP).[123] Vascular stiffening also changes the manner by which the heart is perfused. Normal coronary flow is predominantly diastolic, so that changes in systolic pressure have relatively little impact on mean perfusion. However, in hearts ejecting into a stiff arterial system, coronary perfusion displays far more systolic flow associated with the elevated systolic perfusion pressure.[119,124] What this means, however, is that when heart performance is diminished—for example, by an acute ischemic event—coronary flow is far more sensitive to the decline in systolic function than it otherwise would be. This was demonstrated in a canine model in which cardiac ejection was randomly directed into the normal compliant aorta or a stiffer conduit.[124] Hearts ejecting into the stiffer conduit had greater chamber dilation and cardiodepression during an acute coronary occlusion than those ejecting into the compliant aorta, despite having matched levels of basal cardiac metabolic demand.

Clinical Implications of Vascular Stiffening

Isolated systolic hypertension (defined as systolic blood pressure $>$140 and diastolic blood pressure $<$90 mm Hg) and elevated pulse pressure (PP=systolic blood pressure−diastolic blood pressure) are 2 clinical manifestations of decreased vascular distensibility.[4] The prevalence of hypertension increases with age such that $>$60% of people older than age 65 years are hypertensive with systolic blood pressure $>$140 mm Hg and/or a diastolic blood pressure $>$90 mm Hg; older blacks have a higher prevalence of hypertension than do whites in all age groups.[1,2] However, unlike younger hypertensive subjects in whom systolic blood pressure, diastolic blood pressure, and MAP are all risks for cardiovascular events,[125–127] isolated systolic hypertension, elevated PP, and increased PWV pose more significant risks for strokes, myocardial infarctions, heart failure, and overall mortality in older adults.[7,9–11,14,128–132] This difference in risk implies a different pathophysiological mechanism for hypertension in younger versus older individuals and perhaps a different therapeutic approach.[8,133,134] In fact, it is reported that every 2-mm Hg increase in systolic blood pressure increases the risk of fatal stroke by 7% and fatal coronary heart disease event by 5%.[135]

Chronic elevation of mean blood pressure also leads to thickening of arterial wall, mostly in media. Hypertension-driven remodeling represents a compensatory mechanism that

normalizes increased wall stress. In contrast to the effects of aging, intrinsic stiffness of wall material in hypertensive individuals may not differ from normotensive controls,[136,137] and hypertension-related wall hypertrophy is least partly reversible after adequate reduction of mean pressure.[138] Elevation of peripheral vascular resistance combined with increased arterial stiffness in older subjects leads to development of isolated systolic hypertension. There is growing evidence that response of PP to therapy may also be relevant to outcomes. In post-hoc analysis of Systolic Hypertension in the Elderly Program (SHEP) trial data, widening of PP (>10 mm Hg) on active drug therapy was associated with increased risk of stroke.[10] Another analysis of the same study showed that the risk stemming from excessive diastolic blood pressure reduction is dose-dependent, with a threshold at ≈60 mm Hg.[139]

It is important to underscore that a reduction in blood pressure and/or an increase in vascular compliance are associated with a reduction in cardiovascular risk. However, it is often difficult to separate the effects of pharmacological and lifestyle interventions on blood pressure reduction alone from their direct effects on the vascular wall properties. Changes in MAP tend to correlate better with changes in arterial compliance than do changes in systolic blood pressure. As highlighted in these clinical and observational trials, interventions that lower blood pressure and that are associated with reduction in cardiovascular risk are associated with a decrease in measures of arterial stiffness (PWV, augmentation index, compliance); however, they may not necessarily have any direct effect on structural components of the vessel wall that contribute to stiffness.

Can We Intervene? Reducing Vascular Stiffening

There are a number of strategies to reduce vascular stiffening. Several factors involve *lifestyle* issues, such as reducing body weight, exercise, lowering salt intake, and moderate alcohol consumption. Other strategies are pharmacological in nature, focusing on nitric oxide-dependent pathways, antioxidants, RAAS inhibitors, TGF-β inhibition, 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibition, and AGE cross-link breakers. We briefly review the current evidence of such *destiffening* approaches.

Although reduction of body weight alone in uncomplicated obesity significantly reduces blood pressure, the isobaric compliance of the carotid artery appears unaltered.[140] However, obesity is often accompanied by the metabolic syndrome, and substantial improvement of the latter also occurs with weight loss. Interestingly, clinical evidence linking improvement in the metabolic syndrome state and vascular *destiffening* remains lacking. Whereas many weight-reduction diets have been proposed, there are no data directly supporting one method or another as a means for arterial destiffening. In contrast, several dietary supplements appear to influence compliance. For example, supplementation of n-3 polyunsaturated fatty acids (eicosapentaenoic acid and docosahexaenoic acid) increases systemic arterial compliance in dyslipidemic subjects, presumably by lowering of triglycerides and very LDL.[141] A high dietary intake of isoflavones, nonsteroidal plant-derived compounds abundant in soy beans, is associated with a lower PWV,[142] and administration of red clover isoflavones for 6 weeks reduces PWV in healthy volunteers;[143] an effect that may relate to the affinity of isoflavones to bind to human estrogen receptors.

Stiffness of large arteries increases with age, even in healthy individuals without any cardiovascular disease,[144] but is less pronounced in those who engage in regular endurance exercise.[144,145] Even once established, large artery stiffening can be diminished by a program of physical exercise.[146] In middle-aged sedentary men, 3 months of aerobic training (walking or jogging 40 minutes per day at 70% to 75% of maximum heart rate) enhanced carotid artery compliance to levels observed in similarly aged endurance-trained men.[145] Whether low-to-moderate exercise imparts similar effects is less clear.[147,148] In one randomized, crossover study of individuals with systolic hypertension, moderate aerobic exercise had no impact on large artery compliance.[149] Intensive exercise has limited effects on aerobic capacity and may not alter arterial stiffness in very old subjects.[148] The vascular benefits of exercise are indirectly related to a decline in the release of neurohumoral vasoconstrictors and reduced efferent sympathetic tone, and to endothelial mechanical-signaling associated with increased pulsatile flow and stretch and consequent enhanced nitric oxide stimulation.[150] These changes appear to persist after exercise training.[151] In contrast to aerobic training, resistance training (weight lifting) increases proximal aortic stiffness[152] and is associated with higher incidence of left ventricular hypertrophy than in sedentary controls.[153]

Moderate alcohol consumption has been associated with significantly lower PWV in both genders, even after adjusting for mean blood pressure and other variables.[154,155] There is a J-shaped relationship between alcohol intake and PWV, but this weakens after adjusting for high-density lipoprotein cholesterol,[154]suggesting that an important part of protective effects of alcohol are related to increased cellular cholesterol efflux and reverse cholesterol transport stimulated by chronic ethanol exposure.[156]

Among diet-related factors, salt intake probably has the most potent effects on vascular stiffness. The salt ingestion of our human ancestors was probably >10-times less than it is normally consumed in a Western diet today.[157] Salt supplementation to such current dietary levels induces dose-dependent increases in blood pressure in nonhuman primates,[158] whereas even short-term salt restriction in hypertensive patients substantially lowers blood pressure.[159] High salt intake accelerates age-related changes in vasculature,[160] and both short-term[80] and longer-term[161] sodium restriction increases arterial compliance, relatively independently from the effect on mean blood pressure. Besides altering mean pressure, salt exposure triggers structural and functional pressure-independent changes in the vascular wall. Salt-sensitive rats raised on a high-salt diet display increased vascular stiffness and altered arterial wall composition that precedes blood pressure increases by weeks.[162] These pressure-independent changes are caused by abnormal endothelial function, increased smooth muscle tone, intimal-medial thickening, and increased collagen, fibronectin, hyal-

uronic acid, and collagen cross-link formation.[163,164] Vascular RAAS is also activated with a local increase in AT2 synthesis,[165] whereas nitric oxide production decreases.[166] Smooth muscle tone also increases because of endogenous Na pump ligands such as marinobufagenin or ouabain-like substances that increase with high-salt intake.[81]

Among the pharmacological approaches for reducing vascular stiffness and/or its cardiac effects, diuretics, nitrates, and RAAS inhibitors are most commonly used. Although providing some usefulness, these agents have not solved the problem, and there remains a serious lack of effective therapies that directly target the structural abnormalities and changes in vascular signaling that underlie stiffening. Diuretics[167] together with calcium channel antagonists have long been the first line of treatment,[168,169] whereas β-blocking agents are less valuable.[170] The latter slow heart rate, leading to an increase in PP and central pressure augmentation, and also increase the reactive load on the heart.[171,172]

Nitrates do not substantially affect stiffness of the proximal aorta, yet they reduce PP more selectively than other vasoactive drugs by inducing only minimal changes in diastolic or mean pressure.[173,174] This may occur by a more selective effect on venodilation[175,176] and attenuation of peripheral wave reflections during systole.[176,177] Long-term effects have been limited by development of nitrate tolerance, among other potential mechanisms.

Atrial natriuretic peptide (ANP) and brain natriuretic peptide elevate intracellular cGMP by activation of a receptor-coupled guanylate cyclase.[178] Administration of ANP or brain natriuretic peptide acutely decreases ovine iliac artery stiffness in vivo, whereas infusion of a selective antagonist of natriuretic peptide receptor type A ($NPR\text{-}_A$) increases stiffness, suggesting that baseline distensibility is under active control of circulating natriuretic peptides.[179] Natriuretic peptides also exert antiproliferative and antifibrotic activities in the cardiovascular system, and long-term ANP infusion enhances carotid compliance and decreases wall thickness in spontaneously hypertensive rats.[180] The bioavailibility of natriuretic peptides can be enhanced by inhibiting neutral endopeptidase 24.11 (NEP 24.11), a catabolic enzyme for natriuretic peptides and other vasoactive peptides such as bradykinin and adrenomedullin. The combined ACE and neutral endopeptidase inhibitor (omapatrilat) has been tested in several clinical trials[181,182] and was found to lower proximal aortic impedance (characteristic impedance) more than a similar dose of enalapril.[183] The incidence of angioedema with the medication proved limiting, however.

Nitrates and natriuretic peptides enhance vascular cGMP synthesis, and this can also be accomplished by blocking cGMP catabolism using phosphodiesterase 5 inhibitors.[184] Phosphodiesterase 5 inhibition by sildenafil can also reduce wave reflections and lower PP,[185] and may accomplish this without the tolerance from long-term nitrate exposure. Chronic phosphodiesterase 5 inhibition might also potentiate antiproliferative effects from circulating ANP and brain natriuretic peptides— but such speculations remain to be tested.

The RAAS system plays a central role in short-term and chronic blood pressure control and adaptive responses. Activation of RAAS by suprarenal aortic banding,[186] administration of AII or ALDO, or salt feeding in salt-sensitive rat strains[162] alters the ECM composition of cardiovascular tissues—expanding the matrix and increasing fibrosis. Initially, RAAS-driven fibrosis is characterized by increased inflammatory cells in the tissue and activation of redox-sensitive NF-κB pathway. Inhibition of monocyte chemoattractant peptide (MCP-1) by a monoclonal antibody prevents macrophage accumulation, induction of TGF-β1, and fibroblast-mediated fibrosis in myocardium and vessels in rat model of aortic constriction.[187] AII-driven ROS production activates redox-sensitive transcription factor NF-κB, which stimulates a wide array of genes involved in growth-specific and tissue-specific "response-to-injury" programs. AII-mediated ROS generation is also implicated in reduced nitric oxide-synthesis by NOS caused by enzyme uncoupling.[188] Clinical evidence supporting pressure-independent benefits of angiotensin type I receptor blockade on arterial stiffness remains lacking, although some data hint at a benefit.[189]

ALDO-responsive mineralocorticoid receptors are also present in the heart and large arteries.[190] In parallel with AII, ALDO is produced directly in vascular wall.[191] ALDO upregulates and increases the sensitivity of angiotensin type I receptors,[192] and therefore mediates and exacerbates AII-induced cardiovascular damage, particularly in the setting of a high-sodium diet. Pharmacological inhibition of RAAS by low-dose angiotensin type I receptor antagonists[193] or ALDO receptor antagonists[194] prevents development of fibrosis in animals without altering blood pressure.[194–196] In experimental models, ALDO antagonists can prevent age-related collagen accumulation in the absence of hypertension.[197] Lastly, local RAAS activity can be modified by inhibition of ACE, which blocks AII-mediated and bradykinin-mediated effects, but favors the former.[198] ACE inhibition effectively lowers blood pressure but appears less effective in preventing vascular fibrosis and stiffening over angiotensin type I receptor or ALDO-receptor antagonists.[186]

TGF-β1 is a central player in the development of fibrosis in chronic inflammatory conditions.[199] Fibroblasts and smooth muscle cells respond to TGF-β1 by expansion of extracellular matrix, upregulation of proteoglycans, fibronectin, and collagen synthesis paralleled by downregulation of gelatinases (MMP-2 and MMP-9) and upregulation of their tissue inhibitors (TIMP-1). TGF-β1 plays a substantial role in mediating AII effects on ECM remodeling and vascular fibrosis. Activation of TGF-β1 by AII is mediated by ROS created by NADP(H) oxidase, and is coupled to several signal transduction pathways, including MAP kinase, and notably the Smad pathway. Pharmacological modification of TGF-β–Smad pathway are therefore prospective targets for antifibrotic therapy.[200,201]

Arterial stiffness is improved by therapy with 3-hydroxy-3-methylglutaryl–coenzyme A inhibitors. The effects of statins on arterial compliance are more pronounced in muscular arteries than in the aorta or carotid artery, and are detectable after several weeks of therapy.[62,202] Statin efficacy is in part attributable to reduction of circulating LDL cholesterol, but they also can improve stiffness of arteries in the absence of hyperlipidemia. This may relate to their enhance-

ment of Akt kinase and consequent activation of NOS and angiogenesis,[203] effects on endothelial progenitor cells, and inhibition of GTP-binding proteins Rac1 and RhoA, that are involved in regulation of VSMC growth and proliferation, and in regulation of vascular NADPH oxidase activity.[204]

Arterial stiffening related to insulin resistance and diabetes can be modified by pharmacological ligands of peroxisome proliferator activated receptor (PPAR)-γ receptors. PPAR-γ are ligand-activated nuclear transcription factors that regulate intermediate metabolism. Activation of PPAR-γ by thiazolidinediones (pioglitazone, rosiglitazone, troglitazone) increases insulin sensitivity and improves glycemic control, and these drugs are now widely used in the management of type II diabetes. PPAR receptors are also expressed in vascular tissue and contribute to vascular homeostasis. Activation of PPAR- γ prevents vascular remodeling and inhibits wall inflammation in AII-stimulated rats.[205] In type 2 diabetics, 3 months of pioglitazone treatment reduced aortic PWV while increasing adiponectin[206] and lowering C-reactive protein. Interestingly, the decrease of PWV and C-reactive protein levels occurred irrespective of improved diabetic control, suggesting that vascular and antidiabetic effects of glitazones may be partially independent.

Whereas most antihypertensive agents are directed at the dynamic vasoconstrictive component of arterial stiffness, newer therapeutics are targeting structural causes in the vessel wall such as AGE cross-linking of collagen, which were previously thought irreversible. Drugs that block the formation of AGEs (aminoguanidine, pyridoxamine, and OPB-9195), those that nonenzymatically cleave existing AGE cross-links (alagebrium [ALT-711]), and drugs that either serve as sham RAGEs or block RAGE are undergoing development. Although aminoguanidine improves vascular distensibility, reduces PWV, and reduces diabetic nephropathy, clinical trials demonstrate glomerulonephritis at high doses.[207–209] Pyridoxamine and OPB-9195 remain in preclinical testing; the latter reduces blood pressure in genetically hypertensive rats and decreases the intimal hypertrophic response to balloon vessel injury in diabetic rats.[210,211] In animal models, administration of an AGE cross-link breaker, (3-phenylacyl-4,5-dimethylthiazolium chloride, or alagebrium chloride) reduces arterial stiffening, slows PWV, enhances cardiac output, and improves left ventricular diastolic distensibility.[212–214] In a randomized, placebo-controlled trial in 93 humans older than age 50 years with increased arterial stiffness (PP >60 mm Hg and systolic blood pressure >140 mm Hg), ALT-711 was associated with a significant reduction in PP and PWV and improvement in compliance compared with placebo.[215] The effect of this agent in older adults with isolated systolic hypertension and diastolic heart failure are undergoing investigation. Soluble RAGE molecules, which act as a false AGE ligands, suppress atherosclerotic development in apolipoprotein E knockout mice and decrease VSMC proliferation to balloon injury in diabetic rats.[216–218] Soluble RAGE molecules decrease expression of MMPs, vascular cell adhesion molecule-1, macrophage chemotactic factor, and tissue factor, all key factors in vascular inflammation and arterial stiffness.[219] These agents currently remain in preclinical testing.

Summary

The growing prevalence and associated risk of arterial stiffness provide a major thrust to better understand the underlying molecular, cellular, and genetic causes and the resultant physiological impact of this condition. Elucidation of these mechanisms will aid in more specifically targeted therapeutic interventions because currently available antihypertensive medications fall short at increasing the compliance of the central arterial vessels. Reduction of arterial stiffness of these larger vessels will likely have a significant impact on morbidity and mortality of older adults, as well as diabetic subjects and those with chronic renal disease, and will likely improve quality of life in these populations.

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