Arterial Stiffness: Clinical Relevance, Measurement, and Treatment

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Hardening of the pulse, first described thousands of years ago by Chinese healers, was known even then to be an adverse prognostic sign. In Western medicine, the association of aging, increased large-arterial stiffness, and systolic hypertension has been recognized for more than a century. Yet the adverse consequences of age-related arterial stiffening still receive little attention in everyday clinical practice, perhaps because clinicians assume that nothing can be done about the process. Recent developments, however, suggest that improved clinical recognition of age-related vascular stiffening will lead to better therapy and improved outcomes for patients with hypertension. [Rev Cardiovasc Med. *2001;2(1):29-40*]

Key words: Arteries • Atherosclerosis • Blood pressure • Coronary disease • Hemodynamics • Hypertension • Vascular resistance

It is now apparent that widened pulse pressure and systolic hypertension are important indicators of morbidity and that systolic hypertension is the predominant risk factor for adverse outcomes in older hypertensive patients.[1] Clinical trials have clearly demonstrated that treatment of patients with systolic hypertension at any age benefits the heart and target organs.[2,3] In fact, a complete "paradigm shift" emphasizing the value of managing systolic hypertension in older people has been recommended by the Coordinating Committee of the National High Blood Pressure Education Program, the parent organization of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).[4]

These important changes in our approach to hypertension management strongly suggest that earlier identification of those at risk for premature arterial stiffening may allow us to improve our treatment of this high-risk group. Because wide pulse pressure and systolic hypertension are late manifestations of arteriosclerosis, they are only crude indicators of arterial wall disease. To identify the earlier stages of this age-related vascular disorder and provide greater diagnostic precision, newer, more sensitive techniques to measure arterial stiffness are under development. These new diagnostic techniques may lead to better health outcomes, but no single measure of arterial compliance or stiffness can fully describe all clinically relevant properties of arterial wall function and none of the new techniques have been

fully validated. An understanding of vascular stiffness is no longer an arcane academic exercise, because the results of early clinical studies suggest that angiotensin-converting enzyme (ACE) inhibitors and aldosterone antagonists may be superior to other drugs in ameliorating the processes that lead to premature or pathologic arterial stiffening.

Basic Principles of Arterial Function

A brief review of arterial physiology provides a background for evaluation of new techniques and interpretation of the results of clinical studies.

Pressure-volume relationships, compliance, and elastic properties. To meet the continuous needs of peripheral tissues for oxygen and substrate delivery, the arterial tree must convert cardiac pulsations into a more constant flow pattern in the distal circulation. This conversion is performed in the proximal vessels by the retention, during systole, of a portion of each cardiac stroke volume for release during diastole (Figure 1).[5] Blood vessels with high compliance (ie, low stiffness) experience only a small systolic pressure increase with a relatively large increase in volume. Individuals with compliant central arteries, therefore, exhibit relatively narrow pulse pressure (systolic minus diastolic pressure), which reflects low aortic wall tension and, usually, low left ventricular workload. Conversely, overly stiff central vessels (with a reduced capacity to be distended) cannot absorb more than a small fraction of each cardiac stroke volume without a substantial increase in pressure. As a result, individuals with stiff central arteries exhibit relatively high systolic and pulse pressures and a low diastolic pressure.

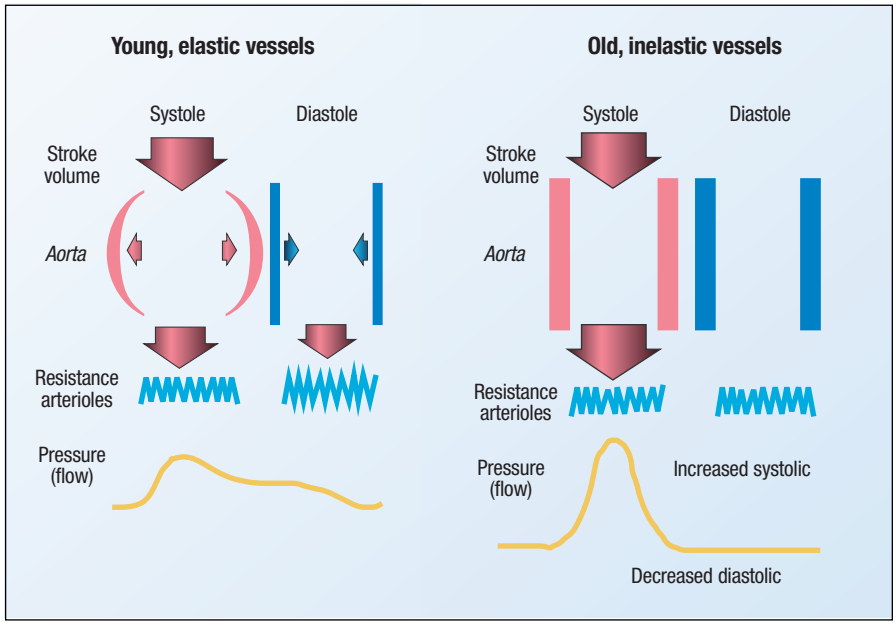

Figure 1. Aging and arterial stiffness. Systolic hypertension and wide pulse pressure are markers of diffuse arteriosclerosis, which is also characterized by decreased vascular compliance or by its inverse: increased vascular stiffness. Increased large-arterial stiffness contributes directly to the observed age-related increase in systolic pressure and to the corresponding age-related decrease in diastolic pressure. As a result of these changes, pulse pressure (systolic minus diastolic) also increases with age. If there is a concomitant increase in cardiac output or in systemic vascular resistance, there is systolic hypertension. The hemodynamic explanation of how stiff vessels lead to wide pulse pressure relates directly to the loss of elastic recoil function of the aorta and its first branches. In a normally elastic, young aorta, a fraction of each cardiac stroke volume is retained in the proximal arteries during systole. Subsequent elastic recoil delivers that stroke volume "remnant" to the periphery during diastole, resulting in a relatively smooth flow profile and a narrow pulse pressure (left panel). In a rigid aorta (right panel), the absence of elastic recoil causes the full stroke volume to be delivered through the resistance arterioles during systole. There is minimal or no diastolic flow, resulting in increased systolic pressure, decreased diastolic pressure, and increased pulse pressure, all of which characterize the hypertension of old age.

The elastic properties of the local arterial wall material can be described by E_{inc}, the ratio of elongation or length change to the force required to produce the elongation. Despite initial appearance, E_{inc} is not fully pressure-independent because the degree of arterial elongation produced depends on the dynamic loading conditions of the artery, which, in turn, depend on the relative loads attributable to the individual load-bearing components (muscle, elastin, and collagen). Each component is stretched or loaded differently at different initial pressure levels.

From a combined structure-function perspective, stiffness, compliance, and distensibility (see "Terms: What They Really Mean," page 31) depend on the behavior of specific structural elements within the arterial wall, especially muscle, elastin, and collagen, which bear the pressure on the wall at different levels of distention.

Pressure-flow relationships, pulse wave, and wave reflection. Impedance is the relationship between time-varying pressure and the flow it generates. It includes the resistance to flow, the energy used to accelerate the blood

column, and the energy stored during elastic distention. Throughout the cardiovascular system, there are many sites at which changes in impedance occur, including arterial branch points, areas of turbulence or stagnation of flow, and areas where the lumen diameter changes abruptly. Changes in impedance are important by virtue of their effects on the transmission of pressure and velocity waves within the peripheral circulation.

Arterial pulse waves are compression waves generated by the force of each cardiac contraction. These compression waves—both the pressure (or pulse) wave and the associated velocity wave that can be detected by Doppler analysis—travel at a rate somewhat greater than the velocity of the column of blood. Pressure and velocity waves fluctuate between a minimum and a maximum, each with distinct waveforms. For the purposes of this discussion, we will ignore the changes in the more complex velocity waves.

When a pressure wave traveling downstream reaches a zone of increased impedance, a fraction of that wave is reflected backward toward the heart, with the magnitude of the reflection proportional to the magnitude of the local impedance (Figure 2). Upstream changes caused by a zone of increased impedance include the appearance of a new reflected pressure wave or an increase in the magnitude of an existing reflected pressure wave. Downstream changes include increased pressure wave amplitude and increased blood flow velocity. If a pressure wave traveling downstream encounters a zone of decreased impedance, such as an aneurysmal dilatation, the pattern of change in pressure waves generated is the opposite of that described for a zone of increased impedance. Different pulse wave morphologies in different arteries are the result of local summation of incident and of reflected pressure waves at different distances from the heart (Figure 3).

Terms: What They Really Mean

Description of the diverse functions and physical characteristics of large arteries requires the use of a variety of terms, none of which, when used alone, can fully define the elastic properties of arterial walls.

Compliance. In a distensible tube (or artery), compliance is the ratio of any volume change caused by a given pressure change. Compliance increases can be misleading because, whether stiff or elastic, a larger artery, with its greater cross-sectional area and volume, will tend to accommodate more volume for a given pressure increase than will a smaller artery. Pressure and compliance exhibit a nonlinear relationship.

Distensibility. This is the relationship between the fractional change in compliance and the corresponding change in cross-sectional area or volume (volume change/volume × pressure change, or compliance per unit volume). The property of distensibility is useful in comparing arteries of different sizes.

Incremental elastic modulus (E_{inc}). The elastic properties of the local arterial wall material can be described by E_{inc}, the ratio of elongation or length change to the force required to produce the elongation. Although less sensitive to pressure fluctuations than is compliance or distensibility, the differential loading of collagen, elastin, and muscle in the atrial wall at different degrees of wall tension contributes to the nonlinearity of the relationship between distending pressure and elastic modulus.

Stiffness. There is no specific parameter that denotes stiffness, but the term is sometimes used to signify the inverse of compliance, thereby avoiding the behavioral connotations of the term "compliance."

Clinical Estimation of Arterial Stiffness

Although the properties of large arteries have been studied for several decades, the field of clinical arterial biomechanics remains in its infancy. The clinical value of any of the available techniques has yet to be proved convincingly, and no single parameter of compliance or stiffness can ever be expected to describe all clinically relevant arterial wall properties.

General limitations of compliance parameters. The context and initial conditions in which arterial stiffness–related terms are used, and the comparisons they afford, must be carefully scrutinized to avoid inappropriate data interpretation. Most important is the understanding that as arterial walls are stretched, compliance and distensibility decrease and the incremental elastic modulus shifts from muscle and elastin loading to elastin and collagen loading. In other words, *all arterial compliance variables depend on the distending pressure in the vessel*. In several clinical studies, this fundamental requirement for equivalent distending pressures during all observations has been ignored. The result is the inappropriate conclusion that a particular agent can "improve arterial compliance" when the improvement is simply the result of the lower blood pressure (BP).

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Also problematic is the concept of whole-body compliance as a physiologic variable. The heterogeneity among large and small arteries, including their relative compliances, distensibility, and elastic properties, is significant. The arterial circulation can be viewed as a complex matrix with diverse properties of the parallel circuits and of the proximal and distal vessels within each circuit. The regional arterial circulations are arranged as parallel circuits that operate individually in response to differing physiologic stimuli. These regional functional differences in the physiologic responses of the major parallel circuits (cerebral, splanchnic, muscular, renal, and cutaneous) to various vasoactive stimuli are further modified by different functions of the proximal and distal vessels within each circuit. This complex matrix arrangement casts significant doubt on the biologic relevance of indices of lumped or whole-body compliance.

Main Points

- In older patients with hypertension, systolic hypertension is the predominant risk factor for adverse outcomes.
- Systolic hypertension interacts with age to promote arteriosclerosis.
- A substantial increase in blood pressure results when overly stiff central blood vessels cannot absorb more than a small fraction of each cardiac stroke volume.
- Arterial compliance variables depend on the distending pressure in the vessel.
- Central systolic pressure augmentation from reflected waves contributes significantly to cardiac afterload and ventricular hypertrophy.
- Catecholamines and angiotensin II contribute both directly and indirectly to target organ damage.
- Agents that inhibit the renin-angiotensin-aldosterone system ameliorate the several processes that lead to pathologic arterial stiffening.

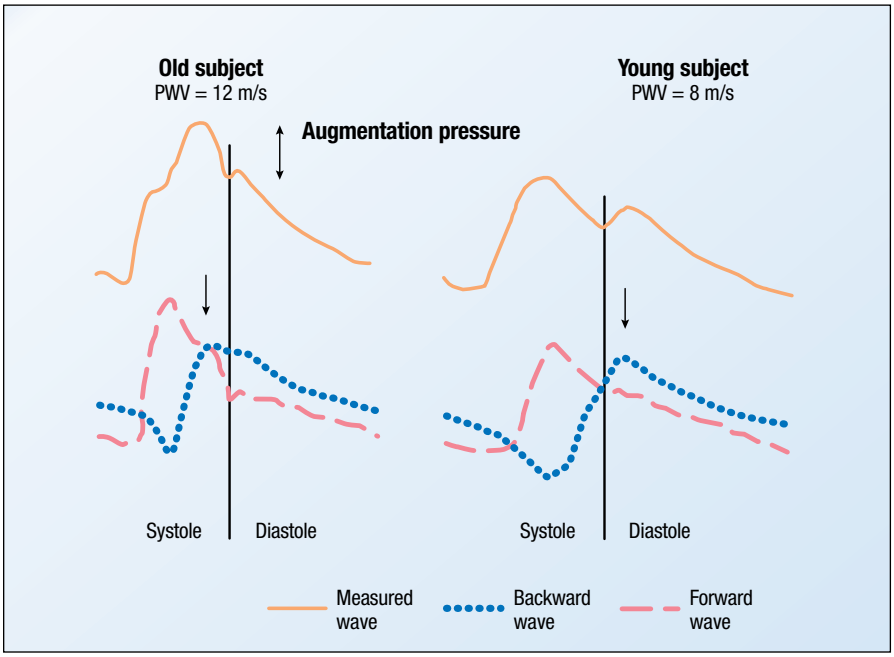

Figure 2. Central pressure contours and aging. The observed central pressure contours (upper tracings) are the sum (lower tracings) of the incident or forward-traveling wave (broken lines) and the reflected or backward-traveling wave (dotted lines). In younger subjects (right panel), the reflected wave (arrow) returns to the aortic root during diastole. As vessels get stiffer during the aging process (left panel), pulse wave velocity (PWV) increases and the reflected wave returns during late systole (arrow), where it summates with the forward systolic wave to augment central systolic pressure and increase ventricular afterload. (Adapted from Asmar R. *Arterial Stiffness.* 1999.[36])

Pulse wave velocity. Perhaps the best and most widely used technique to estimate the distensibility and stiffness of the aorta and proximal vessels is pulse wave velocity (PWV), which is related to the stiffness of the large arteries (and is inversely related to their compliance).[6] PWV has been found to increase with aging, hypertension, and renal failure.[7] PWV has been used to evaluate the vascular effects of both vasoactive substances[8] and antihypertensive drug therapy.[9,10] A longitudinal follow-up study in a selected cohort of hypertensive patients demonstrated a correlation between carotid-femoral PWV and cardiovascular morbidity and mortality.[11]

Despite these studies, there remain several concerns that may limit the interpretation of available data and the general applicability of this technique. Measurement error can be substantial, including problems related to the measurement of both transit time and distance traveled by the pulse wave. Timing is primarily affected by difficulties in identification of the "foot" of each pulse

wave, whereas interindividual differences in vascular anatomy can lead to imprecision in determining the actual distance of the measurement site from the aortic root. In addition, the most commonly used PWV parameter is carotid-femoral PWV, an admixture of data from 2 circulatory branches (aortic-carotid and aortic-femoral). The assumption that these 2 arterial circulations share similar properties under all conditions is not correct, especially when there are different degrees of constriction in the different circulations.

Systolic augmentation index. Reflected waves are very important in determining the morphology of the systolic pulse contour, peak aortic systolic pressure, and cardiac afterload. The systolic pulse contour can be decomposed into an incident wave and an augmentation (reflected) wave (Figure 2) that when summated represent the pulse contour at the aortic root. To obviate the need for central catheterization when measuring this central pulse contour, O'Rourke and associates[12] developed a proprietary transfer function that reconstructs central waveforms from their corresponding peripheral waveforms. The most relevant parameter obtained from this technique is the systolic augmentation index, which relates the magnitude of the reflected peak to the magnitude of the incident systolic pressure surge caused by ventricular contraction. The augmentation index is increased by aging and hypertension.[13]

The augmentation index is useful in the understanding of cardiac afterload, but it does not offer detailed information about arterial compliance and is highly variable. In preliminary studies, our laboratory has found that both reflected pressure waves and the augmentation index vary widely during infusion of vasoactive substances and under different physiologic conditions, such as mental stress.[14] Thus, there are both functional and structural components to the systolic augmentation index, which has uncertain value in assessing arterial wall properties.

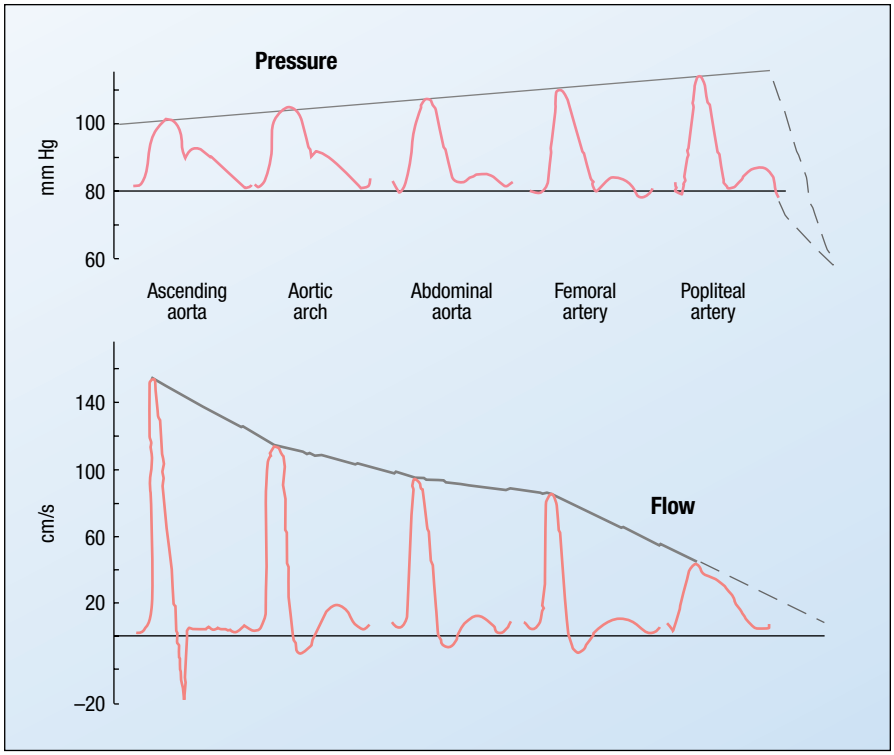

Figure 3. Pressure and flow waves in different arteries. As compression waves travel downstream, their morphologies change as a result of the summation of forward- and backward-traveling waves at each location. In general, the area under the curve is preserved, but the moment-to-moment transmural arterial pressures are widely different. (Adapted from Nicholls WW, O'Rourke M. *McDonald's Blood Flow in Arteries: Theoretical, Experimental, and Clinical Principles.* 1998.[37])

The modified Windkessel model. The idea that arterial circulation can be represented as a single capacitance (Windkessel) model first gained popularity in the early and mid-20th century. A Windkessel is a tank (capacitance reservoir) pressurized with a pump and connected to a stiff hose and nozzle (resistor) that was once used in firefighting. As in the Windkessel, energy and volume storage in the central blood vessels are dependent on an input pressure (stroke volume) and on the maintenance of system pressure by downstream resistance (the resistance arterioles). When this model was first applied to the circulation, it was assumed that cardiac stroke volume could be determined by integrating the area under a given pulse contour. It is now known that stroke volume cannot be derived reliably from arterial pulse contours, principally because of the distortions caused by reflected pulse waves.

Transferring the simple Windkessel analogy to the peripheral circulatory system was also found to be problematic, in that it did not reproduce the morphology of the peripheral pulse contour. This shortcoming was remedied by altering the model to include a second capacitance circuit and an iner-

tance component to create the modified Windkessel model.[15,16] This model offers a more faithful reproduction of the dicrotic notch and the morphology of the diastolic decay characteristics of the pulse contour than does the simple Windkessel. The modified model has been used to calculate a first-order decay component (C1, thought to be related to the compliance of the large-arterial system) and a second-order "oscillatory" term (C2, thought to represent the compliance of the distal, or smaller, vessels). The modified Windkessel model describes the diastolic decay function of the pressure waveform but does not describe any features of the corresponding velocity waveforms.

Substantial difficulties occur in applying this model to the whole cardiovascular system. The most prominent difficulty is the assumption that the Windkessel components represent discrete anatomic and physiologic entities. Ultimately, the assertions that C1 represents "proximal," or large-vessel, compliance and that C2 represents distal, or small-vessel, compliance are based entirely on a model construct that has not been experimentally validated. Both parameters are calculated from the diastolic pressure waveform, and each can be significantly affected by reflected waves. Most important, C2 is heavily dependent on systemic vascular resistance and, therefore, may not offer much additional information beyond an indication of systemic vasoconstriction. Since both C1 and C2 calculations are based on the stroke volume derived from pulse contour integration, the reliabilities of these measurements are further called into question.

Brachial arterial plethysmography. It is possible to estimate the compliance and the cross-sectional area of the brachial artery using a specially modified cuff technique with oscillometric analysis or Korotkoff sounds.[17] This new method is inexpensive but has not been used in any large-scale trials. The most obvious drawback is that it measures only local brachial arterial wall characteristics, which may be different from the properties exhibited by other arteries. Early data regarding hypertension suggest that changes in muscular arteries are not necessarily reflective of the chronic changes seen in the aorta or in the distal microvasculature.

Ultrasound tracking. Direct measurement of compliance requires the simultaneous measurement of arterial volume or cross-sectional area and the associated pressure. New high-resolution echo methods have been used to track wall position changes from diastole to systole.[9,18,19] When wall thickness is measured simultaneously, the incremental elastic modulus can be calculated, which may be useful in the differentiation of arteriosclerosis and atheromatosis. Obtaining corresponding pressure measurements can be problematic, however. Most techniques employ applanation tonometry to estimate pressure in distal superficial arteries. The assumption that the distal arterial pressures accurately reflect aortic pressures is often untrue because of the intrinsic property of distal pulse wave amplification. Recent studies of the carotid artery suggest the potential to use this technique for risk stratification.[19]

Cardiovascular Implications of Arterial Stiffness

Arterial wall pathology: arteriosclerosis versus atheromatosis. The biologic diversity of the processes affecting the arterial wall is masked by the use of the nonspecific term "atherosclerosis." At best, this term is an amalgamation of 2 major processes that tend to occur with aging in industrialized societies: arteriosclerosis, a generalized thickening and stiffening of the arterial media related primarily to hypertension; and atheromatosis, an inflammatory arterial occlusive disorder related primarily to endothelial dysfunction and excessive deposition of oxidized lipids. The 2 processes often coexist, and end-stage atheromatosis can lead to nonuniform arterial fibrosis that is consistent with the original meaning of atherosclerosis. Arteriosclerosis also exists in a "pure" form that leads to aortic uncoiling and calcification in older individuals with systolic hypertension but without atheromatosis. The pathogenetic differences in the processes of arteriosclerosis and atheromatosis suggest that the 2 processes are best considered separately.

Atheromatosis. Formation of atheromatous lesions in large arteries can be conceptualized as an "inside-out" process of patchy, low-grade vascular inflammation that is triggered by endothelial cell dysfunction and the infiltration of macrophages and leukocytes into the arterial wall. This occurs in response to local oxidation of excessive amounts of low-density lipoproteins.[20] Endothelial dysfunction, which itself is reversible, appears to involve an imbalance between vasoconstrictive growth promoters, such as angiotensin II, and vasodilatory growth inhibitors, such as nitric oxide. Over time, the chronic inflammatory vascular changes become irreversible; the accompanying structural alterations become more complex, with prominent calcification and scarring. Lumen diameter is maintained until the final stages of this process, but wall thickness and the outer di-

ameter of the artery increase. The lesions remain clinically silent while repair processes stabilize or allow regression of atheromatous plaques. At the end stage of the disease, rupture of plaques releases calcium, collagen, oxidized lipids, and other highly thrombogenic substances into the blood, promoting local occlusion, embolization, ischemia, organ dysfunction, and sudden death.[20] Atherosclerotic changes in the arterial wall cause complex effects on arterial stiffness that are, at present, poorly investigated.

Arteriosclerosis. The term "arteriosclerosis" is less commonly used today than it was at the beginning of this century. It may be useful to repopularize this word, however, because it defines a ubiquitous, age-related, diffuse, nonocclusive, noninflammatory, outside-in process that leads eventually to stiffening, dilatation, and lengthening of the aorta and its first-order branches.[13,21]

The pathologic hallmark of arteriosclerosis is a nonatheromatous, uniform thickening of the adventitia and media of the arterial wall, with roughly equal increases in extracellular matrix and vascular smooth muscle cell volume (ie, hypertrophy) without significant hyperplasia. Arteriosclerosis also includes fragmentation and loss of elastin fibers with increased deposition of collagen and other structural proteins. The breakdown of the elastin network has been attributed to the repeated mechanical strain from each stroke volume but may have other hormonal etiologies as well; there appear to be direct stimulatory effects of angiotensin II[22] and aldosterone[23,24] on extracellular matrix synthesis that are independent of their effects on BP. The net result is fibrosis and thickening of the arterial media, which increases stiffness of the arterial wall and leads to widened pulse pressure and systolic hypertension. This contributes to a wide variety of cardiovascular and metabolic problems, such as cardiac and vascular hypertrophy and target organ dysfunction. A more sensitive and reliable measure of arterial compliance may aid in prevention by identifying at-risk individuals in whom early, aggressive therapy may be particularly advantageous.

Aging, systolic hypertension, and pulse pressure. Systolic BP increases steadily with age in industrialized Western societies, whereas diastolic BP increases until about age 55 and then declines when increased large-vessel stiffness alters the flow contours such that systolic pressure is increased and diastolic pressure is decreased (Figure 4).[25] This widening of the pulse pressure occurs if the storage or capacitance function of the larger blood vessels fails.[21] Arteriosclerosis almost inevitably accompanies aging in Western societies. Systolic hypertension interacts with age to promote arteriosclerosis; pulse pressure widens at a later age in those with the lowest initial BPs (systolic below 120 mm Hg), and the rate of increase of pulse pressure is lowest in normotensives.[1,26]

Under the physiologic conditions

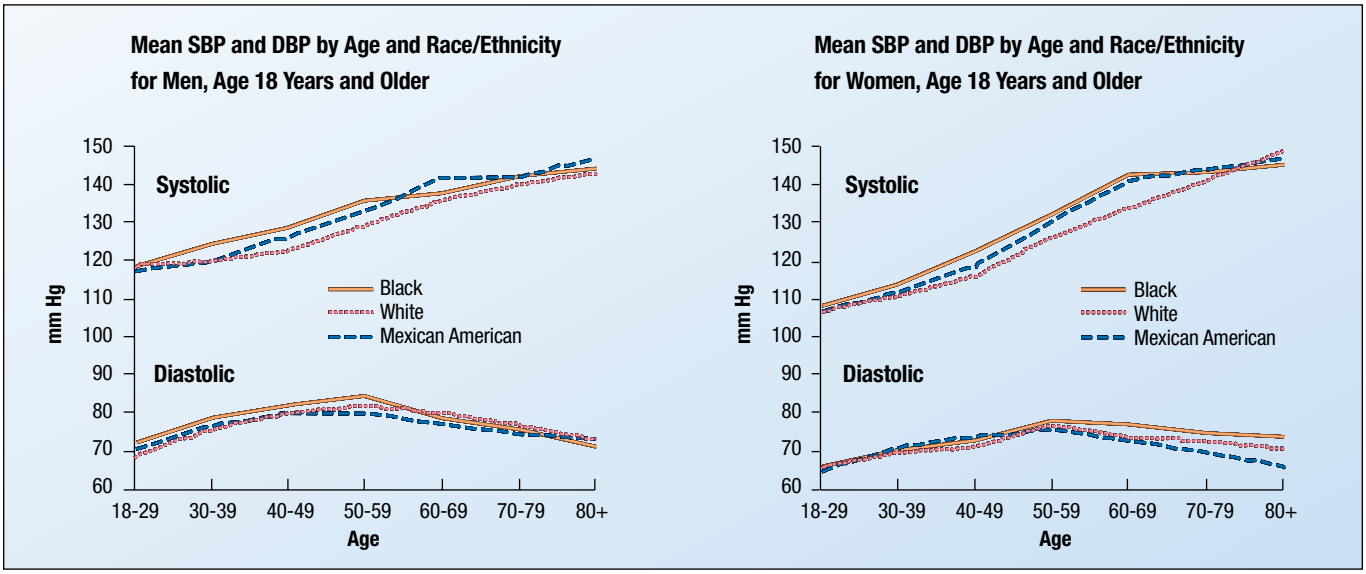

Figure 4. Blood pressure and age. In men and women, and in all ethnic subgroups, systolic blood pressure (SBP) increases almost linearly with age. Diastolic blood pressure (DBP) increases until the sixth decade and then declines. The resultant widening of pulse pressure after age 50 is reflective of increased arterial stiffness. (Adapted from Burt VL et al. *Hypertension.* 1995.[25])

that exist in young, healthy individuals, there is no major impedance mismatch in the proximal blood vessels; thus, there is no early wave reflection. PWV is sufficiently slow in young, healthy vessels that the distally reflected waves return to the heart during diastole, where they augment coronary arterial filling pressure and coronary blood flow. When arteries stiffen and PWV increases, however, the reflected pulse waves return to the heart much earlier, eventually summating with the systolic pulse itself (Figure 2).

Systolic pressure, afterload, and ventricular hypertrophy. Cardiac load can be considered the "product" of heart rate, contractility, and afterload, the last of which is influenced by systemic vascular resistance and, as discussed above, by vascular stiffness. Clinically, the double product (heart rate multiplied by systolic pressure) is often used to estimate cardiac load or myocardial oxygen consumption, with systolic pressure the more important of the 2 components. Systolic pressure (or pulse pressure) measured at the brachial artery misrepresents the central systolic pressure, because it does not reveal the magnitude of the reflected waves arriving at the heart; if the systolic pressure were measured at the aortic root, it would be a fairly good estimate of total afterload.

One of the most important cardiac effects of large-arterial stiffness is that it causes a 2-pronged increase in cardiac load. Stiff vessels generate larger systolic and pulse pressures, because the cardiac stroke volume cannot be accommodated by aortic stretch. Furthermore, as the large vessels stiffen, reflected waves return earlier to the aortic root, eventually summating with the incident systolic pressure waves. Large pulse pressures generate proportionally large reflections, and reflected waves account for an ever-greater proportion of the total cardiac afterload.[27] In addition, noncompliant vessels cannot sustain diastolic pressure by release of stored volume, and distal vasoconstriction must increase to maintain peripheral pressure during diastole. The increased vasoconstriction of chronic hypertension contributes to a further increase in reflection magnitude and elevates systolic pressure even further. Systolic hypertension is the single most important etiologic factor in left ventricular hypertrophy, which, in turn, is the single most important etiologic factor in heart failure.[28] The combined effects of stiff vessels and distal vasoconstriction lead to cardiac pressure overload and concentric ventricular hypertrophy.[27]

Sparing of muscular arteries in aging and hypertension. Aging and hypertension have relatively little effect on the walls of the large muscular arteries (brachial, radial, or femoral arteries), in contrast to their effects on the aorta and its first branches.[29] Different changes in the mechanical properties of these arteries have been reported in individuals with hypertension, with some studies showing differential responses of the radial and carotid circulations to antihypertensive therapy.[30] Why muscular arteries are not equally affected by arterial hypertension is not clear, but their apparently "normal" function may be misleading. Abrupt changes in arterial wall characteristics at any level of the circulation may be the source of altered reflection, waveforms, and changes in both proximal and distal flow and pressure, which, in turn, may contribute to circulatory pathology.

Sympathetic nervous control of vasoconstriction and arteriolosclerosis. Systemic vascular resistance is generated by contraction of the smooth muscle in the walls of small arterioles with diameters in the range of 100 to 300 mm. One of the hallmark hemodynamic abnormalities in hypertension is an inappropriate degree of systemic vasoconstriction for any given level of flow. Because BP tends to remain relatively constant despite wide fluctuations in flow, the degree of vasoconstriction is continuously adjusted. This hemodynamic abnormality is not simply a fixed increase in vascular resistance as some seem to believe but, rather, is an example of dynamic cardiovascular dysregulation. In the presence of arteriolosclerosis, hypertrophy of vascular smooth muscle cells causes further luminal narrowing, thereby amplifying the effects of any degree of physiologic vasoconstriction and sustaining increased systemic BP.

Because flow-resistance adjustments are often nearly instantaneous, it seems to be an inescapable conclusion that the syndrome of hypertension involves inappropriate activity of the only system capable of mediating both instantaneous and long-term cardiovascular adjustments: the sympathetic nervous system.[31] In turn, the intimate, mutually stimulatory effects of the sympathetic nervous and renin-angiotensin systems interact to promote both acute and chronic vascular changes. Because catecholamines and angiotensin II not only raise BP but are also important promoters of growth in vascular smooth muscle,[32] these hormones ultimately contribute both directly and indirectly to target organ damage (Figure 5). These interacting neurohormonal systems are further modified by the aging process. Aging is not only associated with

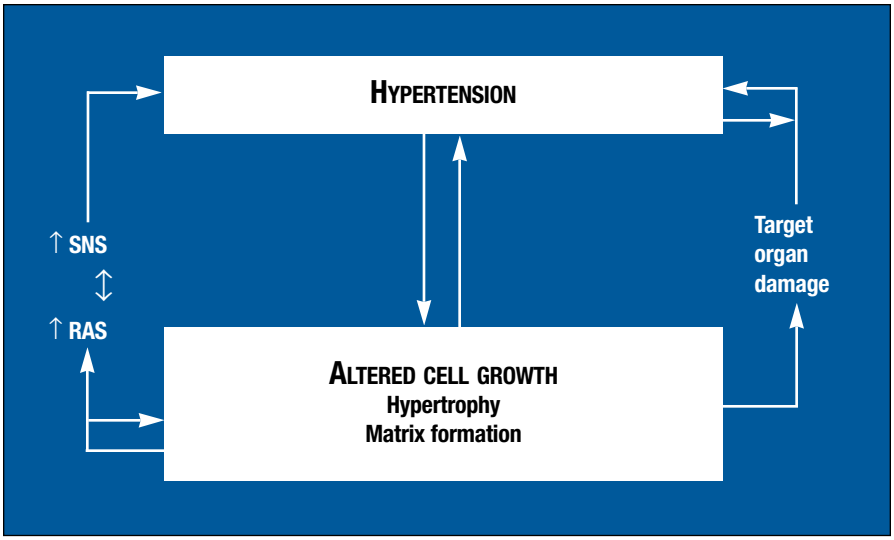

Figure 5. Mechanisms of chronic hypertension. The sympathetic nervous system (SNS) and renin-angiotensin system (RAS) continue to exert chronic pressor effects on the heart and vasculature. In addition, continued overactivity of the SNS-RAS axis induces further functional and structural change in the cardiovascular system. Cardiac and vascular hypertrophies, which result from mechanical and direct neurohumoral actions, tend to blunt arterial and cardiopulmonary baroreflexes, thus sustaining chronic increases in SNS-RAS outflow, which continue to promote high blood pressure and further degeneration. (Adapted from Izzo JL Jr. *Hypertension: A Companion to Brenner and Rector's The Kidney.* 2000.[38])

increased sympathetic nervous system activity[33] but also with accompanying increases in arteriolar and venous constriction and wall thickness, thus completing the vicious circle.

Therapy for Patients with Arteriosclerosis

The traditional belief that arteriosclerosis is an irreversible process is being challenged. The aorta and large arteries are not static structures but, rather, are structures that undergo very slow turnover of both cells and matrix proteins. In such a dynamic system, the anatomic status at any time can be described by the equilibrium between the forces of growth (hypertrophy or hyperplasia) and those of involution (atrophy and apoptosis). The net sum of these processes can be loosely termed "renewal" or "remodeling." When there is increased arterial wall thickness or hypertrophy, the forces of growth are greater than the forces of involution.

In the setting of arteriosclerosis, the progrowth forces of angiotensin II can be considered pathologic, especially because excess angiotensin II promotes the accumulation of excess matrix proteins, such as collagen, and the hypertrophy of vascular smooth muscle cells. In this dynamic environment, it seems most plausible that it is the *continuing* presence of excess angiotensin II that is required for the maintenance of hypertrophy. Logically, it also follows that removal of this ongoing pathologic input of angiotensin II would lead to a rebalancing of the forces of growth and involution and, therefore, to a decrease in arterial wall thickness that is partially independent of the BP-lowering effects of drugs that block the renin-angiotensin-aldosterone system.

Consistent with the role of angiotensin II in abnormal remodeling, ACE inhibitors have consistently favorable effects on arterial walls. Long-term ACE inhibitor therapy has been shown to be superior to diuretics or ß-blockers in improving carotid, femoral, or radial arterial compliance and is marginally superior to calcium antagonist therapy as well.[34,18] In tissue culture, angiotensin II favors collagen synthesis and vascular smooth muscle hypertrophy. In the aortas of spontaneously hypertensive rats, ACE inhibitors block the deposition of excess collagen, whereas hydralazine does not.[35] Because aldosterone has been shown to promote the deposition of extracellular matrix proteins in the heart,[23] aldosterone antagonists may be able to allow regression of these excess matrix proteins.

Thus, the process of arteriosclerosis may be at least partially reversible. Many more clinical trials will be necessary to document the clinical significance of these observations, however. For the present, attention to vigilant, lifelong BP control is the best preventive policy. As has been discussed, all measures of arterial stiffness are dependent on the distending pressure and wall tension of the arteries being investigated. *The first principle in the treatment of arterial stiffness is, therefore, the sustained reduction in systemic arterial pressure.* Beyond that important principle, there is considerable promise that drugs which reduce the acute and chronic vascular impact of the sympathetic nervous and renin-angiotensin systems may offer better long-term preservation—or perhaps even restoration—of normal arterial function. ■

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