

STATE-OF-THE-ART-PAPER

Mechanical Factors in Arterial Aging

A Clinical Perspective

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The human arterial system in youth is beautifully designed for its role of receiving spurts of blood from the left ventricle and distributing this as steady flow through peripheral capillaries. Central to such design is “tuning” of the heart to arterial tree; this minimizes aortic pressure fluctuations and confines flow pulsations to the larger arteries. With aging, repetitive pulsations (some 30 million/year) cause fatigue and fracture of elastin lamellae of central arteries, causing them to stiffen (and dilate), so that reflections return earlier to the heart; in consequence, aortic systolic pressure rises, diastolic pressure falls, and pulsations of flow extend further into smaller vessels of vasodilated organs (notably the brain and kidney). Stiffening leads to increased left ventricular (LV) load with hypertrophy, decreased capacity for myocardial perfusion, and increased stresses on small arterial vessels, particularly of brain and kidney. Clinical manifestations are a result of diastolic LV dysfunction with dyspnea, predisposition to angina, and heart failure, and small vessel degeneration in brain and kidney with intellectual deterioration and renal failure. While aortic stiffening is the principal cause of cardiovascular disease with age in persons who escape atherosclerotic complications, it is not a specific target for therapy. The principal target is the smooth muscle in distributing arteries, whose relaxation has little effect on peripheral resistance but causes substantial reduction in the magnitude of wave reflection. Such relaxation is achieved through regular exercise and with the vasodilating drugs that are used in modern treatment of hypertension and cardiac failure. (J Am Coll Cardiol 2007;50:1-13) © 2007 by the American College of Cardiology Foundation

William Osler's axiom that “*man is as old as his arteries*” referred to arterial stiffening, with only 1 form of this (nodular arteriosclerosis, now called atherosclerosis) causing arterial narrowing or obstruction (1). Contemporaries had similar views (2), and saw heart failure with aging as a consequence of progressive large arterial stiffening. At this time, no cuff sphygmomanometer was available, and monitoring was undertaken (if at all) with radial pulse wave sphygmograms (2-4).

This review revisits the original basic physiological concepts applied by pioneers, shows how they have been improved by new techniques, and can now be applied to understand, monitor, and treat the aging process and its sequelae (4,5). The review complements the reviews whose emphasis was on molecular, genetic, and biochemical mechanisms (5,6). Such approach enables better understanding of cardiac and renal failure, and of vascular dementia, and of how these conditions may be prevented, delayed, or treated.

While we can separate atherosclerosis as a separate disease from arteriosclerosis of aging, we cannot separate

“hypertension” by which name most of the aging changes are usually discussed (3,5). But blood pressure is a biomarker of arteriosclerosis (7). Hypertension is a condition arbitrarily defined by blood pressure limits that are achieved by the vast majority of the population who reach 90 years of age (8), and is better described by underlying structural change. However, separation of disease from aging becomes arbitrary in the elderly. It is man's destiny to die (colloquially from “natural causes”), and rarely over age 100 years. Though specific causes are written on a death certificate, these are usually an inevitable consequence of the aging process and include cardiac and renal failure, cardiac and cerebral ischemia.

Normal Arterial Function: Basic Physiology

The arterial tree has 2 functions—first, to deliver blood from the left ventricle (LV) to capillaries of bodily organs and tissues according to their need, and second, to cushion the pulsations generated by the heart so that capillary blood flow is continuous or almost so. The first function is that of a conduit, the second of a cushion (4,5).

The arterial system is a very effective conduit and a very efficient cushion. Integration of functions leads to pressure wave travel and reflection (4) (Fig. 1). Wave reflection occurs predominantly at the origin of the myriad of terminations of low resistance arteries into high-resistance arte-

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**Abbreviations
and Acronyms****ACEI** = angiotensin-converting enzyme inhibitor**AIx** = augmentation index**ARB** = angiotensin receptor blocker**CCB** = calcium-channel blocker**C-F** = carotid-femoral**LV** = left ventricle/ventricular**LVH** = left ventricular hypertrophy**PWV** = pulse wave velocity

rioles. Despite physical dispersion of such sites at different distances from the heart, and consequent interaction of reflected waves, one can usually discern a functionally discrete reflected wave in the arterial pulse (Fig. 1). While the ejection (flow) wave from the heart has a single impulse, the pressure wave has 2 impulses (4) (Fig. 1). The beginning of the reflected wave in the ascending aorta in youth corresponds (during exercise if not at rest) to the incisura or high-frequency notch created by aortic valve closure (4).

Correspondence of a vascular event (return of the reflected wave) to a cardiac event (aortic valve closure with beginning of diastole) bespeaks another aspect of cardiovascular efficiency. Pressure is increased during diastole only, when the myocardial microvasculature can be perfused. The design of the arterial tree with conduit and cushion functions combined exploits wave reflection to enhance coronary flow (4,9). The heart and vascular tree are, thus, normally "tuned" for optimal efficiency. This is further illustrated in the frequency domain where the minimal value of impedance modulus (pulsatile pressure \div pulsatile flow) in the

ascending aorta is seen to correspond to the maximal values of the LV ejection (flow) wave (4,9).

Factors determining optimal efficiency of vascular/ventricular interaction include greater distensibility of the proximal than distal aorta, dispersion of peripheral reflecting sites, the location of the heart in the upper thorax, and the inverse relationship between heart rate and body length (4,10). Such efficiency in man, however, is fragile. As the aorta ages and stiffens, aortic pulse wave velocity (PWV) increases, wave reflection returns earlier, and favorable "tuning" between LV and arterial tree is progressively lost (4,11) (Fig. 1). It is, however, maintained from the time full body length is achieved (about 17 years) through the time of peak procreative capacity (about 30 years) and must have been a survival advantage for humans from an evolutionary viewpoint. Arterial aging is the story of what happens beyond age 30 years!

How Does Aging Affect Arterial Properties?

Many studies of aging focus on factors that affect the intima, rather than the load-bearing media. Studies on intima-media thickness show progressive thickening with age (12). Autopsy studies of perfusion-fixed human arteries have shown that thickening is mostly confined to the nonload-bearing intima, and is principally due to intimal hyperplasia (13). While the media may not appreciably thicken with age, individual elastin lamellae actually thin and become separated by increasing amounts of nonload-bearing material (14) (Fig. 2).

Elastic arteries show 2 major physical changes with age (4,5). They dilate, and they stiffen (Figs. 2 and 3). Changes are most marked in the aorta, and its major proximal branches are less marked in the peripheral muscular arteries (4,15-20). The proximal elastic arteries and aorta dilate by approximately 10% with each beat of the heart in youth, while the muscular arteries dilate by only 2% to 3% with each beat (21) (Fig. 4). Such difference in degree of stretch can explain differences in aging change between proximal and distal arteries, on the basis of material fatigue (4,22). There is no reason to believe that principles of fatigue and fracture do not apply to the nonliving material in the body (23), especially elastin, which is the most inert substance in the body and has a half-life of decades (4). For 10% extension of natural rubber (24), fracture is calculated to occur at 8×10^8 cycles (corresponding to 30 years at heart rate of 70 beats/min). Fracture of elastic lamellae is seen in the aorta with aging (13) (Fig. 2), and can account both for dilation (after fracture of load-bearing material) and for stiffening (through transfer of stresses to the more rigid collagenous components of the arterial wall). For peripheral arteries with 3% extension, and the same number of cycles, fracture is not expected to occur till over 3×10^9 cycles, which corresponds to well over 100 years of life. While histological studies show gross damage to the medial elastin

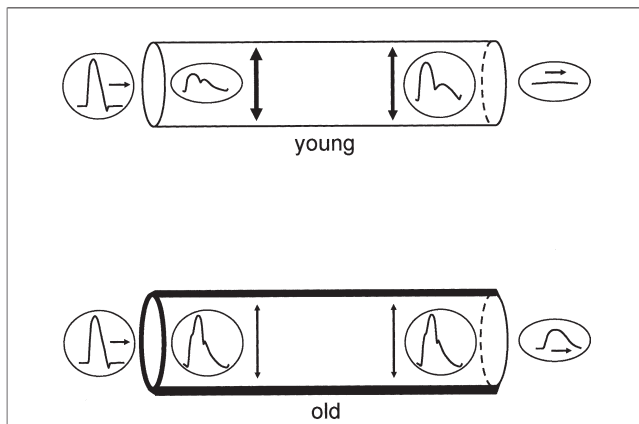


Figure 1 Distributed Models of the Arterial Tree

Simple tubular models of the arterial system, connecting the heart (left) to the peripheral circulation (right) in a young (top) and old (bottom) subject. In the young subject, the tube is distensible, whereas in the old subject it is stiff. The distal end of the tube constitutes a reflection site where the pressure wave travelling down the tube is reflected back to the heart. The wave travels slowly in the young distensible tube so that the reflected wave boosts pressure in diastole when it returns to the proximal end. The wave travels faster in the old stiffer tube, returns earlier, and boosts pressure in late systole. Flow input from the heart is intermittent in both young and old subjects. In the young subject, pulsations are absorbed in the distensible tube so that outflow is steady or almost so. In the old subject with stiff tube, pulsations cannot be absorbed, and so output from tube into peripheral microvessels is pulsatile.

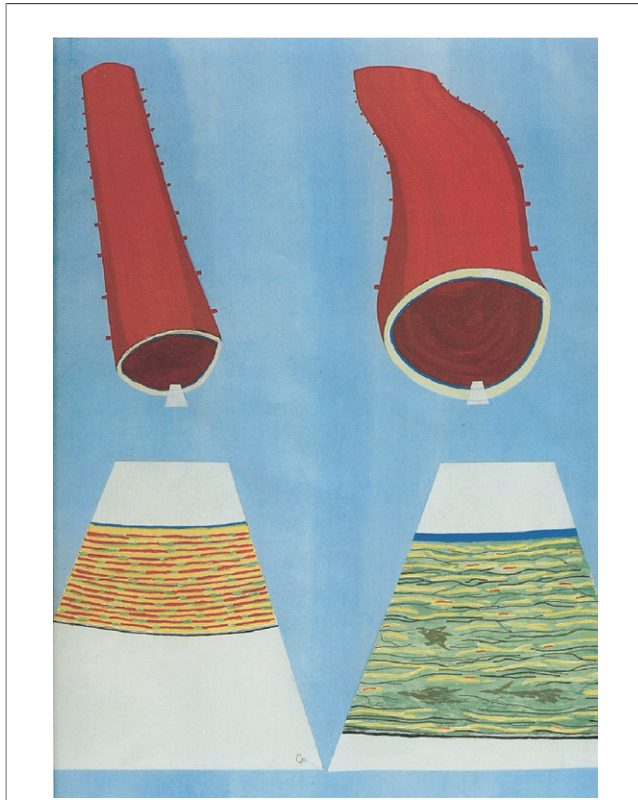


Figure 2 Cartoon of Young and Old Human Aorta

Schematic diagram of the aorta section in a young (**left**) and old (**right**) human, with inset (**below each**) the components of the aortic wall. The wall of the older human is disorganized as a consequence of fraying and fracture of the elastic lamellae (**yellow**) and loss of muscle attachments (**red**), together with increase in collagen fibers (**black**) and mucoid material (**green**), and with foci of "medionecrosis." Drawn by O'Rourke CM, after Glasgow S. Personal communication, 1994.

of the proximal aorta they show little change in distal muscular arteries (4,13,21).

These physical engineering principles extend the classic views, account for the difference between central and peripheral arteries, and the increased stiffening and dilation of proximal arteries, and explain the histological changes.

How Does Aging Affect Arterial Function?

Pathophysiology. Since aging causes arterial dilation, and of proximal elastic arteries, it does not affect conduit function of the arterial tree. But it has a marked and progressive effect on cushioning function (4,5) and ultimately a devastating effect on the heart, and the microcirculation, especially in brain and kidney. Increased arterial stiffening with age is apparent as increase in PWV (4,15,16) (Fig. 3). This is greatest in the aorta, and least in muscular arteries such as those of the upper limb.

"Aortic" PWV is estimated noninvasively from the delay of pressure wave foot at the femoral site compared to the

carotid site, and from the distance traveled by the pulse. A typical value in a 20-year-old is 5 m/s and in an 80-year-old is 12 m/s (i.e., a 2.4-fold increase over 60 years) (4,15,16). Similar values have been determined for characteristic impedance (pulsatile pressure ÷ pulsatile flow in the absence of wave reflection) in the ascending and proximal aorta (25,26). These values imply a >4-fold increase in aortic elastic modulus, since PWV depends on the square root of elastic modulus (4).

Ascending aortic impedance at heart rate frequency increases approximately 4-fold between 20 and 80 years (4) (Fig. 5). This is a consequence of early wave reflection adding to increased characteristic impedance. Implications are apparent from increase in aortic pulse pressure with age. The approximately 2-fold increase in aortic PWV between 20 and >80 years is not apparent in brachial pulse pressure. While this increases with age (4,6), the extent of change is hidden since the brachial pulse in youth is markedly amplified, whereas amplification is far less at 80 years of age (Fig. 4).

It is clear that effects of aging on arterial function have been underestimated in the past, on account of reliance on the brachial cuff systolic pressure. This increases with age from about 120 to 145 mm Hg (i.e., by around 20% between age 20 and 80 years) (4,27,28). With fall in diastolic pressure from, say, 80 to 75 mm Hg, brachial pulse pressure increases more — from some 35 to 60 mm Hg (i.e., by 70%) (6,28), while aortic pulse pressure increases far more—from some 22 to 65 mm Hg (i.e., by 200%) (4) (Fig. 6). Reliance on cuff sphygmomanometric values results in underappreciation of aging change. So does the present concept of hypertension, dependent as it is entirely on brachial cuff pressures (4,5).

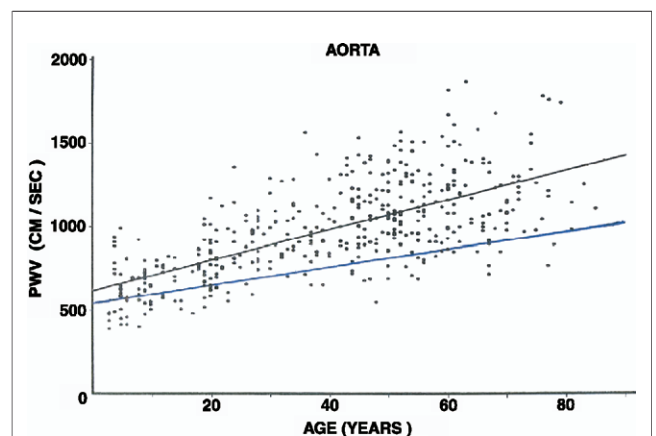


Figure 3 Change in Aortic PWV With Age

Change in aortic pulse wave velocity (PWV) with age in a group of 480 normal subjects in a northern urban Chinese community with low prevalence of atherosclerosis (15). The regression line for this group (**top**) was significantly different from that of another normal Chinese community in Guangdong (**bottom**) with similarly low prevalence of atherosclerosis but low salt intake and lower prevalence of hypertension (16).

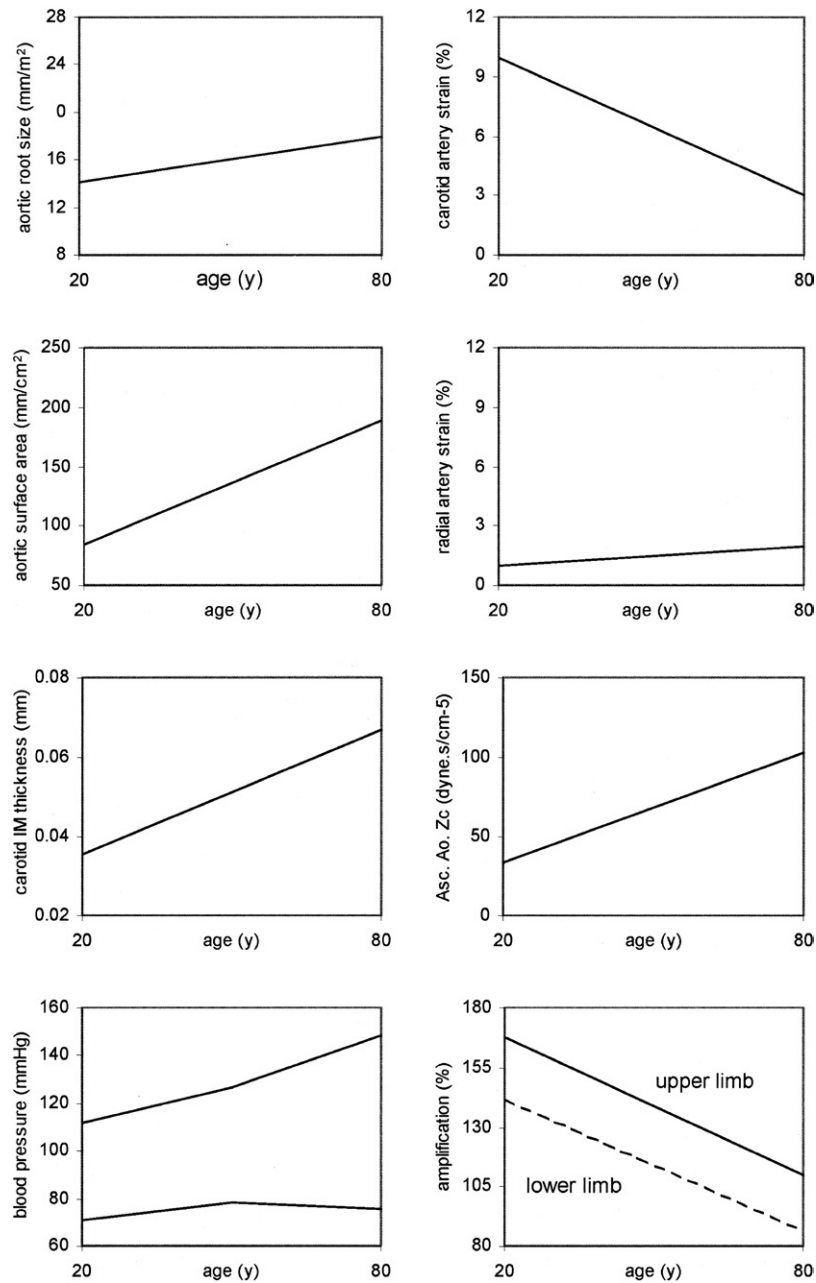


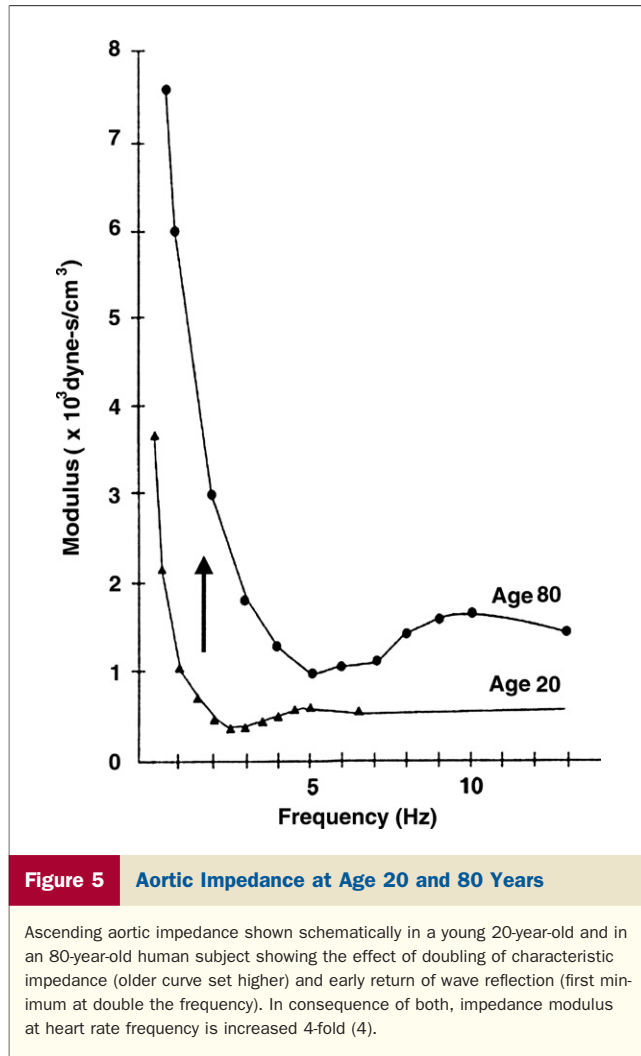
Figure 4 Changes With Age in Structural and Functional Properties of the Human Proximal Aorta and Large Muscular Arteries From 20 to 80 Years

(Left from top and down) Diameter of the ascending aorta (17), surface area of the aorta (18), carotid intima-media (IM) thickness (12), and systolic and diastolic brachial cuff pressure (27). (Right from top and down) pulsatile expansion (%) of the carotid artery and radial artery (21), ascending aortic characteristic impedance Zc (Asc. Ao. Zc) (25), and amplification of the pressure pulse between ascending aorta and radial artery (solid line [19]); and femoral artery (dashed line [20]).

Effect of Aging Process on the Heart

Aortic stiffening with age leads to increase in pressure throughout systole (both from stiffening of the proximal aorta and early return of wave reflection), and to decrease in aortic pressure throughout diastole (4-6). Increase in pressure throughout systole increases LV load. Increased ventricular load leads to LV hypertrophy (LVH), and to

increase in LV oxygen requirements (29). All predispose to development of LV failure (8). The hypertrophied heart contracts (and relaxes) more slowly, so that duration of systole is increased and of diastole reduced at any given heart rate (4,5). When duration of systole is lengthened, wave reflection causes further augmentation of late systolic pressure; thus, tension-time index and myocardial oxygen



needs are boosted by increases in both tension and time (4–6) (Fig. 7).

These increased coronary blood flow requirements are, however, associated with decreased ability to supply such blood on account of: 1) decreased aortic pressure throughout diastole; and 2) reduced period of diastole as systolic ejection duration, and slowed relaxation, impinge on duration of the cardiac cycle (4–6,30). Impaired capacity for coronary flow develops quite independently of coronary narrowing, but is worsened by any degree of atherosclerosis (31) (Fig. 7).

The combination of increased blood need and decreased capacity for coronary perfusion predisposes to ischemia (31). Any degree of ischemia worsens the situation by causing further impairment of ventricular relaxation and prolongation of ejection period (4–6) (Fig. 6) — all tending to decrease ventricular perfusion throughout diastole.

Figure 8 illustrates the mechanism that predisposes the LV to ischemia and to dysfunction from impaired relaxation with increasing age.

This mechanism links LVH with ischemia and so, with predisposition to angina even with what ordinarily might be considered hemodynamically insignificant coronary stenosis (31) or with no coronary stenosis (4,30). A vicious cycle becomes relevant in the development of “diastolic” LV failure, probably the most common form of heart failure in the elderly (32).

Effects of Age on the Microcirculation

The microcirculation is generally taken as comprising small arteries <400 μm , arterioles <100 μm diameter, and the capillaries beyond (4,5,33). These vessels usually present the greatest resistance to blood flow, and complete the change of pulsatile flow to steady flow in capillaries by repelling (reflecting) the pulsations that enter from the larger arteries. The transition from pulsatile to steady flow is complete in most organs and tissues. However, in those with high resting flow, notably the brain and kidneys, pulsations may extend more deeply towards the capillaries (4,5,33,34). In the pulmonary circulation, resistance is normally so low and arteriolar vessels so short that pulsations extend into the capillaries, and even through into pulmonary veins (35).

In contrast to the large elastic arteries, studies of aging have not found specific structural changes in the microcirculation of the skin and subcutaneous tissues (33,36). Functional changes appear to be relatively minor and comprise impaired endothelial-dependent, and endothelial-independent vasodilation (33). Even these have often been attributed to coexistent hypertension. Changes in microcirculation of the vital organs such as brain and kidney of older persons are marked, but there are usually, though not always (37), attributed to hypertension or intercurrent disease such as diabetes, renal insufficiency, or congenital defects of connective tissue (38,39).

Studies of large arteries and their changes with age, as described already, have inevitably led to the microcirculation, as apparent from flow waves depicted in Figure 1. If flow pulsations created by LV ejection cannot be cushioned in the arterial system in older persons, then where are they absorbed? If pulsatile energy loss in the circulation is more than doubled by stiffening of the aorta (40), what ill effects might this have, and where? If pulsations of the aortic wall over the first 30 years of life can induce elastin fiber fatigue and fracture (4) (Fig. 2), what might pulsation in the microcirculation do in the subsequent 50 years? The most vulnerable circulations would be those in the brain and kidneys, since the blood vessels leading down to the capillary circulation are more dilated than elsewhere and would transmit pulsations more readily into the smallest vessels (4,41,42) (Fig. 9). It is in the microcirculation of the brain and kidney that one sees the most severe lesions in older persons (39,43,44), and these are similar to the pulmonary microvascular lesions that develop over years in congenital

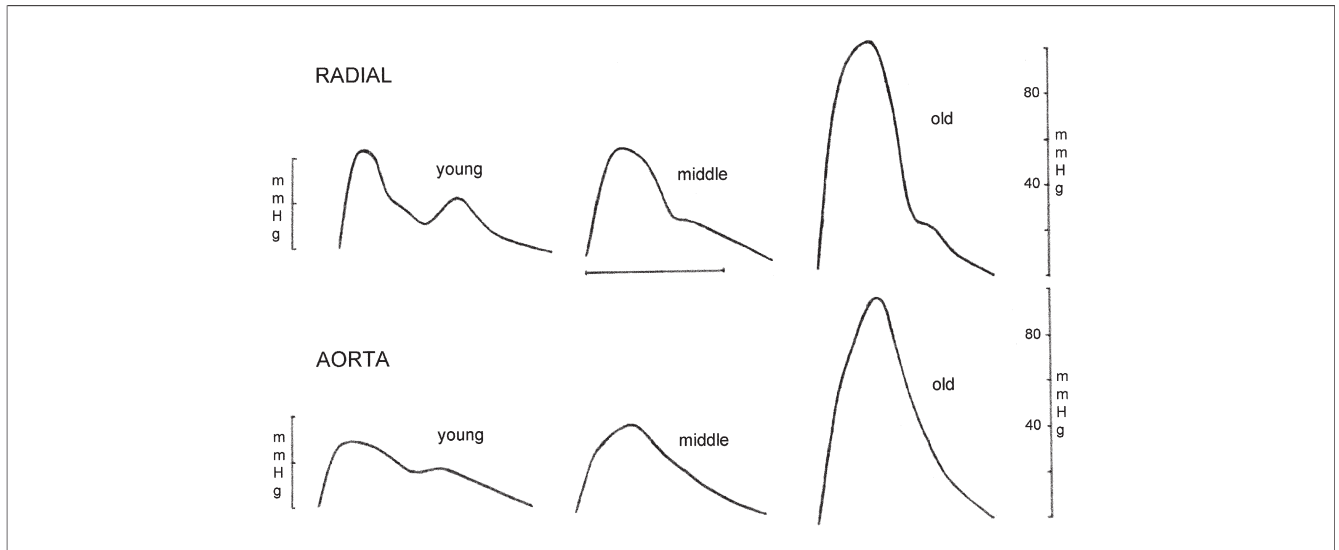


Figure 6 Pressure Waveforms in Arm and Aorta of Young, Middle-Aged, and Old Subjects

Pressure waveforms measured in the radial artery (**top**) and synthesized for the ascending aorta (**bottom**) in 3 women of the same family—an 18-year-old at **left**, a 48-year-old at **center**, and a 97-year-old at **right**. Pulse pressure is increased almost 4-fold in the ascending aorta and 2-fold in the upper limb (4). Time calibration = 0.5 s.

heart disease with left-right shunt causing high pulmonary flow pulsations, even in the absence (initially) of pulmonary hypertension (45). The lesions include damage to endothelium with thrombosis, and to the media with edema, hemorrhage, and inflammation (39,43,44) (i.e., features of medionecrosis caused by physical damage) (46,47).

This is a new evolving area that links neurology, nephrology, cardiology, and geriatrics with magnetic resonance

imaging and other imaging techniques (42,48-50). A full discussion is not possible here, but links between large artery stiffening and microvascular disease in brain and kidney, and damage to and dysfunction of these organs (42,51-53), are consistent with the strong and causative association that had been described (41,42) on the basis of pathophysiological mechanisms. Carotid flow pulsation increases with age, in association with arterial stiffening and greater pressure wave

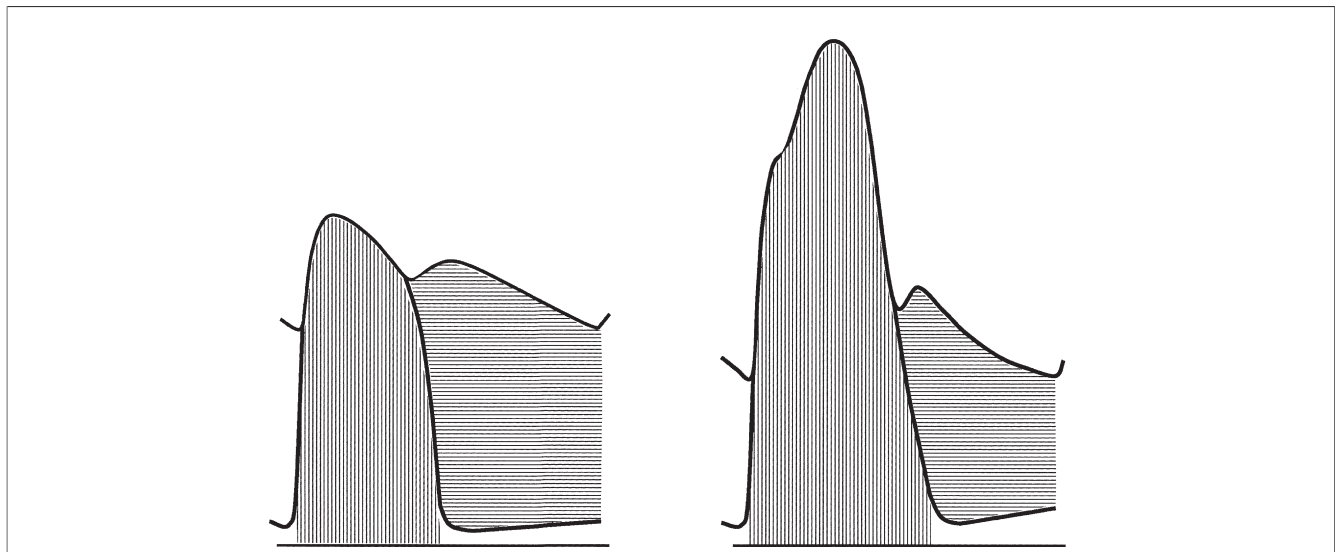


Figure 7 Aortic and LV Pressure Waves in Young and Old Subjects

Ascending aortic and left ventricular (LV) pressure waves shown schematically in a young subject at **left** and older subject with LV hypertrophy and diastolic LV dysfunction at **right**. In the older person, myocardial oxygen demands (**vertically hatched area**) are increased by the increase in LV and aortic systolic pressure and by the increased duration of systole. Ability for myocardial oxygen supply is reduced by shorter duration of diastole, lower aortic pressure during diastole, and increased LV pressure during diastole caused by LV dysfunction.

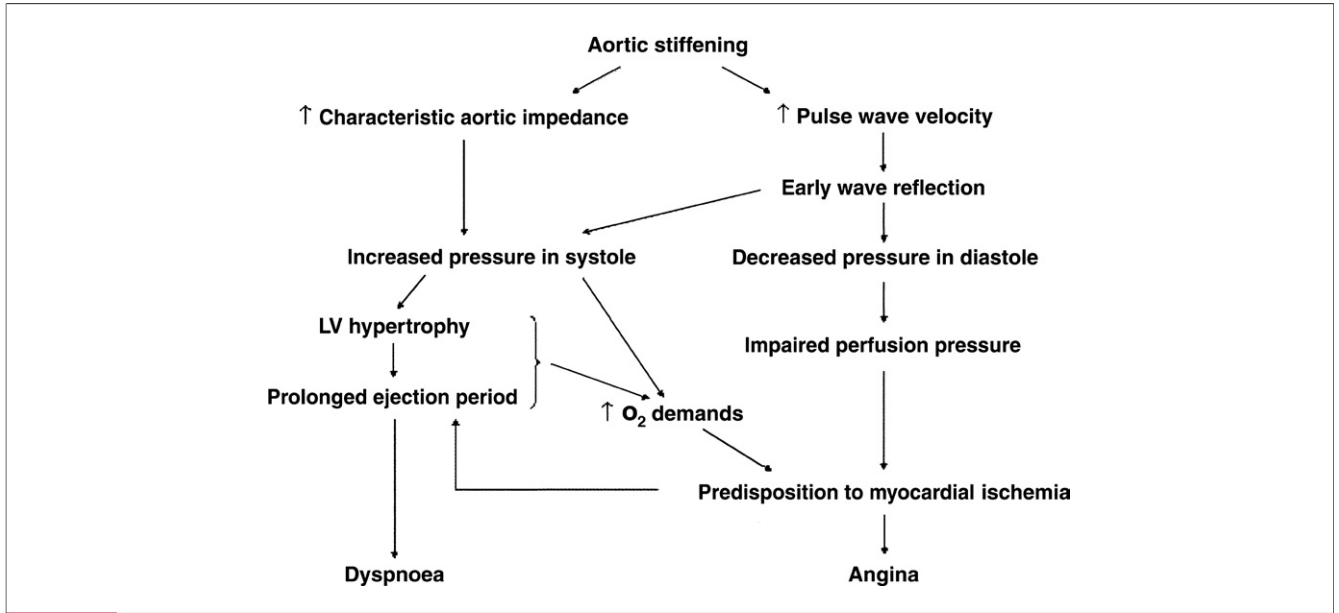


Figure 8 III Effects of Aging

LV = left ventricular.

augmentation (54) (Fig. 10). Superior sagittal sinus flow pulsations also increase with age and are most prominent in patients with “pulse wave encephalopathy” and dementia (48,50). From a therapeutic and monitoring viewpoint, interventions that reduce arterial stiffness, early wave reflection, or aortic pressure fluctuations are likely to improve the small as well as large arteries of vital organs and thereby delay, prevent, or improve cerebral and renal dysfunction in the elderly (54–58).

Monitoring of Aging Change

A variety of methods have been proposed for determination of aging change, and to supplement routine measurement of cuff systolic and pulse pressure (4–7). The simplest is the finger photoplethysmograph, whose pulsatile volume change is similar to the carotid pressure waveform (59) and whose change with age can be described as augmentation or in terms of derivatives (60). The most sophisticated involve

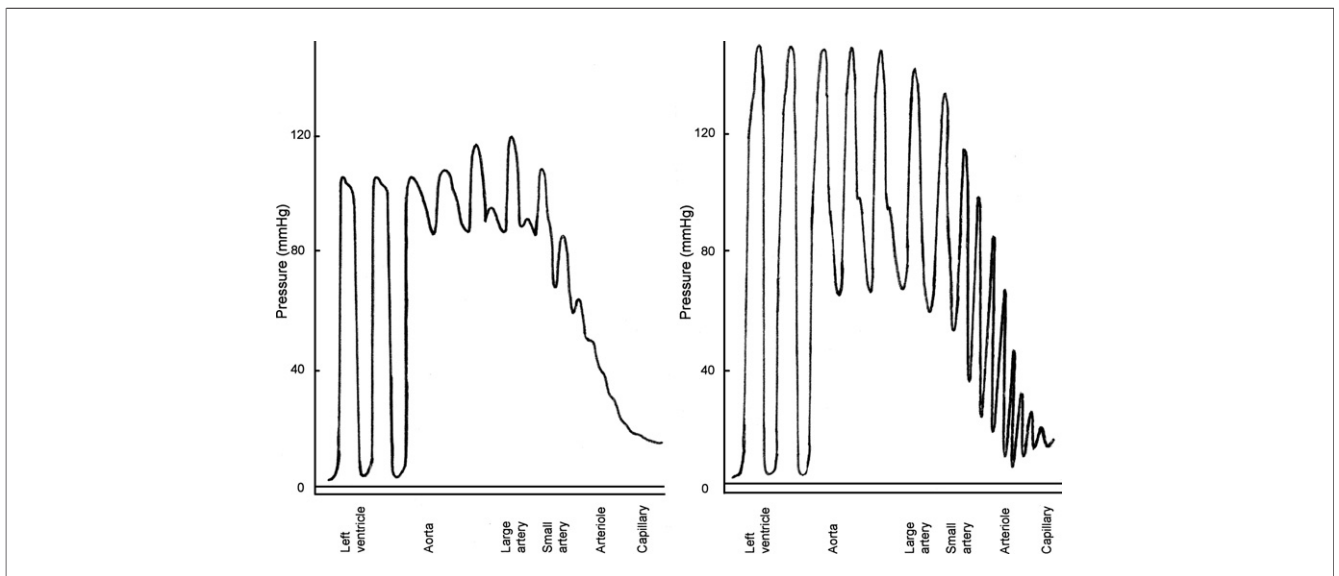
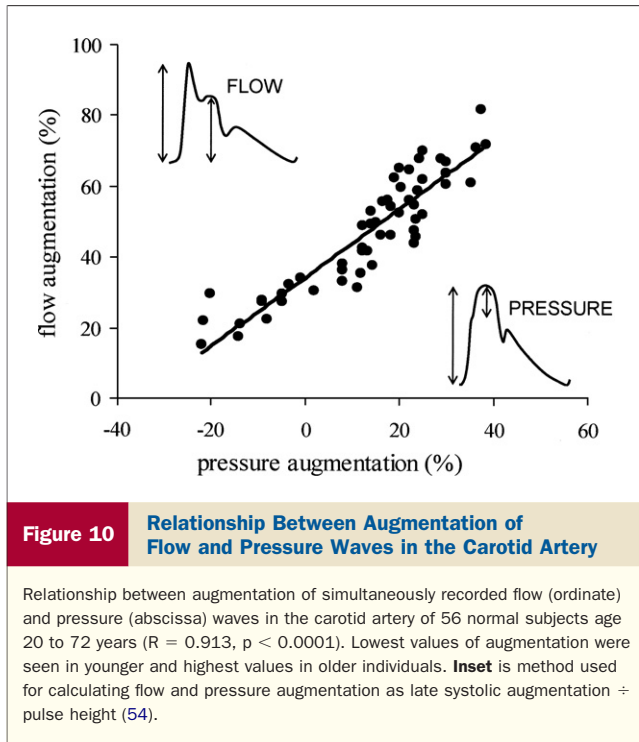


Figure 9 Pulsatile Pressure Changes in the Vascular Tree

Schematic representation of pulsatile pressure change between left ventricle and capillaries of a young subject (left) and an older human with arterial stiffening (right). In the older person, pulsations are not absorbed in the large arteries and so extend down into the microcirculation.



measurement of aortic or carotid diameter with a phase locked echo tracking device (61), central pulse pressure by different means (4,5,62), and aortic flow by ultrasound (63,64); from these central measures, aging change can be described in terms of elastic modulus or aortic impedance. All methods depend on measurement of pulsatile phenomena and, directly or indirectly, arterial stiffness. All are described in recent books and reviews (4,5,62). All have advantages and disadvantages. The 2 most popular considered in guidelines (65), and recommended by a European consensus group for clinical and epidemiological studies (62), are determination of carotid-femoral (C-F) PWV and pulse waveform analysis.

C-F PWV. Carotid-femoral PWV can be measured simply and quickly, and with good reproducibility (4–6,62). This measure is incorporated in Framingham and National Institute of Aging studies (7). Diseases such as diabetes mellitus and end-stage renal failure are characterized by high C-F PWV; in a recent study (66), a difference of 1.6 M/s in diabetics can reasonably be interpreted as equivalent to greater functional arterial age of approximately 15 years (4). Carotid-femoral PWV as a measure of aortic stiffness is associated with cardiovascular events, independently of conventional risk factors, in patients with hypertension, end-stage renal failure, diabetes, the elderly, and in normal populations (62,66–73).

Pulse waveform analysis: radial and carotid pressure tonometry. Over a century ago, clinicians described aging change as progressive rise in the late systolic component of the radial artery pulse (2–5). This was also applied in life insurance examinations to exclude applicants with prema-

ture arterial senility (3). The modern approach (4,11,62) uses high-fidelity tonometers to record noninvasively details of the radial and/or carotid pressure waveforms and mathematical processing to identify features of the wave, including the late systolic augmentation described by pioneers. One (SphygmoCor, AtCor Medical, West Ryde, Australia) goes further to generate the aortic from the radial pressure pulse using a generalized transfer function to correct distortion in the upper limb (4,5,61,62); the Food and Drug Administration has accepted this as substantially equivalent to aortic pressure measured by catheterization.

Radial, carotid, or aortic pressure waveforms can be compared against normal pressure waves at different ages (11) or the most prominent aging feature, the augmentation index (AIx) (74,75) (Fig. 11), can be compared against normal data at different ages. The AIx increases progressively with age in all arteries, up to age 60 whereafter it flattens off (74,75). At any age, AIx is higher in women than men. Arterial age may be estimated in an apparently healthy subject from comparison of an individual's AIx against normal data, at least up to 60 years of age. Precision may be improved by applying a correction for heart rate (4,5,74). Augmentation of pressure in the carotid artery is closely associated with augmentation of flow; this is an illustration of the link between large artery stiffness and increased cerebral flow pulsations with age (54) (Fig. 10). Pulse waveform analysis permits measurement of central (aortic or carotid) systolic and pulse pressure as well as duration of systole and diastole. Diastolic period is characteristically reduced in older persons, especially those who develop “diastolic” heart failure (32).

Carotid AIx is independently associated with cardiovascular outcomes in patients with end-stage renal failure (76) and coronary disease (77). The flattening of AIx with age over 60 years (Fig. 11) and in diabetic patients over 45 years (66) has been attributed to change in the LV ejection (flow) wave (4), in consequence of impaired contractility (4,78) and contrasts with progressive increase in C-F PWV (Fig. 3). The dissociation between PWV and AIx is seen under age 60 in diabetic patients (66) and may be a sign of premature impairment of LV contractility in the face of increased aortic stiffness (4,70,78).

Potential value of waveform analysis for individual assessment can be seen when a 68-year-old individual and his 37-year-old son are compared at identical brachial cuff pressures (Fig. 12). The older man's AIx was consistent with his age while the younger man's was even more youthful than expected for age but consistent with his regular exercise habit. While systolic peak pressure was similar, aortic systolic pressure in the younger man was 17 mm Hg less than his father.

Prevention, Treatment

In this review, we approach aging as a mechanical “wear and tear” issue that affects nonliving components of the body, as it likewise affects the components and fate of an old tree.

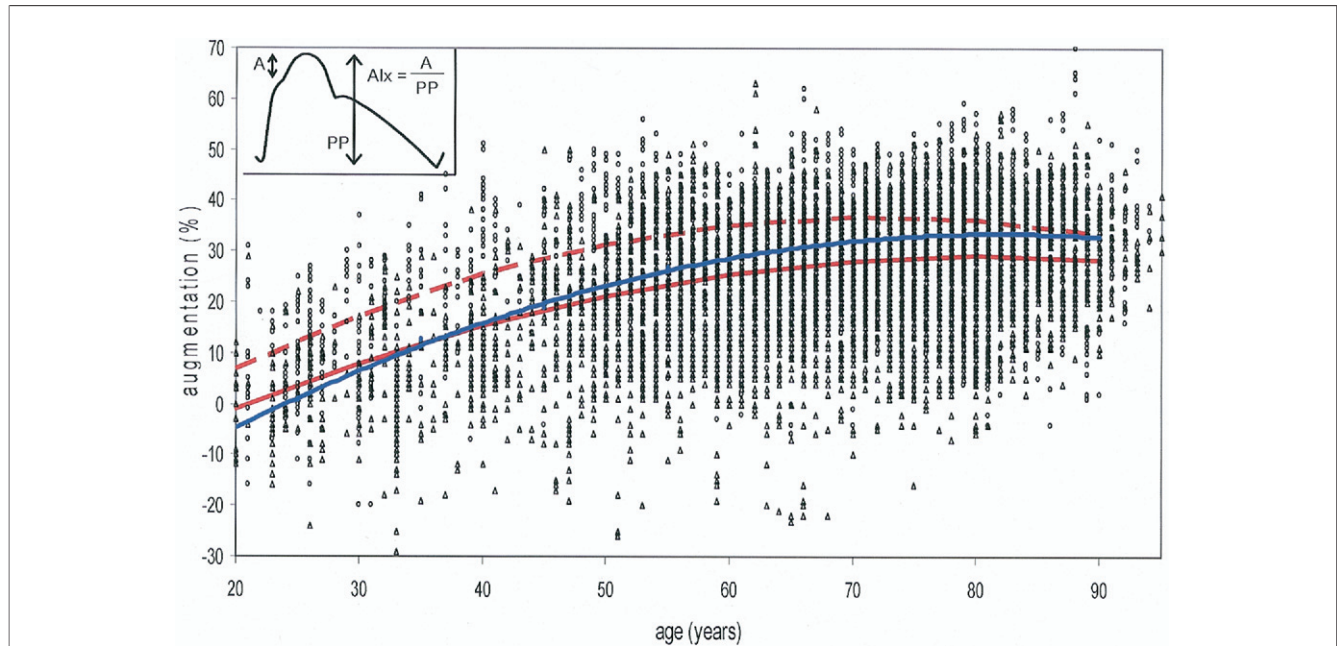


Figure 11 Relationship Between Age and Ascending Aortic Pressure Wave Augmentation

Relationship between age and ascending aortic pressure wave augmentation (A) calculated with SphygmoCor from radial artery tracings in 1,600 patients attending a cardiovascular outpatient clinic, together with values for a group of 4,001 normal U.K. men (red thin line) and women (red dashed line) from McEniery et al. (74) and 534 normal European subjects (men and women combined, thick line) from Wojciechowska et al. (75). (Inset, upper left) Method of calculating aortic pressure augmentation. Alx = augmentation index; PP = pulse pressure.

The sperm of the old man and the acorn of the tree can recreate the cycle of life, but man and the tree are doomed by the structure in which the cells exist. While we cannot be as optimistic as those who look to a genetic, molecular, or chemical solution, we can suggest how principles described here can be applied to slow the process of arterial aging and offset its inevitable ill effects and the diseases, such as atherosclerosis, which it promotes.

The key to prevention and treatment is to minimize arterial pulsations, since these are the basic cause of large artery degeneration from elastin fiber fatigue and fracture, then of microvascular damage as pulsations are funneled into smaller vessels. Yet the heart has to beat, and so the arteries to throb, as long as the body lives. Possible targets for therapy are the proximal elastic and distal muscular arteries.

Central arteries. Attention has been directed at the structural matrix proteins, collagen and elastin in the arterial wall, and the advanced glycation end products (AGE) that accumulate on the proteins, alter their physical properties, and cause the fibers to stiffen. Drugs such as ALT711 (alagebrium) can break established AGE cross-links between proteins, and can decrease arterial stiffening in experimental animals (79). While studies on animals, including aged primates, have been encouraging, results to date in humans have been less so with little or no change in aortic stiffness (80,81). When one considers the gross damage to the elastin fibers in the aorta in older human

subjects with disruption of muscular attachments (Fig. 2), it is hard to envisage benefit from any drug at this site. It is entirely possible, however, that the drug does have beneficial effects on lesser degrees of damage in more peripheral human arteries or in central arteries of (relatively) younger animals. There may be a place for this drug at an earlier stage of human aging.

There is some evidence that angiotensin-converting enzyme inhibitor (ACEI) drugs may delay progression of aortic stiffening in patients with renal failure (82) and angiotensin receptor blockers (ARBs), aortic dilation in Marfan syndrome (83). In some patients with renal failure on dialysis, an ACEI was able to prevent progressive increase in aortic PWV, and these patients had fewer subsequent events than those who did not respond to the drug (82).

In trials of antihypertensive agents, aortic PWV decreased passively in line with reduction in arterial pressure, and to a similar degree with different drugs (84,85).

Muscular conduit arteries. In contrast to central elastic arteries, there is strong evidence that arterial vasodilator drugs and exercise can markedly reduce wave reflection, and thereby decrease the augmentation of both the central pressure pulse, which in older humans impairs cardiac function, and of the augmented flow pulse, which damages the microcirculation. Studies of nitrates at cardiac catheterization have shown marked reduction in wave reflection and in aortic and LV systolic pressure with no significant change

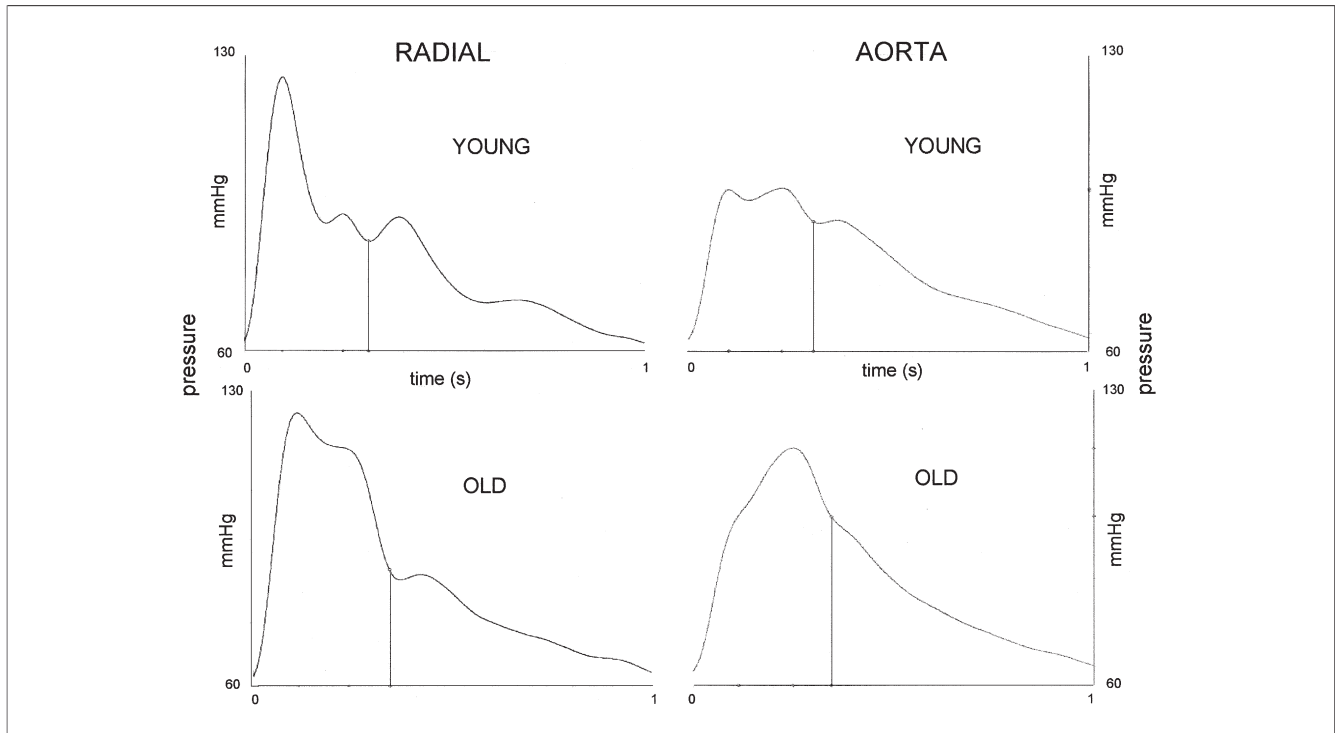


Figure 12 Arm and Aortic Pressure Waves in Young and Old Subjects

Radial (**left**) and aortic (**right**) pressure waves in a 36-year-old man (**top**) and his 68-year-old father (**bottom**) calibrated to the same brachial cuff values of systolic and diastolic pressure. For the same brachial systolic value, difference in waveform was responsible for a 17-mm Hg lesser value of aortic pressure. Millar tonometer used for recording radial wave, SphygmoCor for analysis.

in aortic stiffness (measured as characteristic impedance or PWV) (4,86), and no or far less change in peripheral systolic pressure (87,88). Such beneficial effects were also seen at cardiac catheterization with an ACEI (89) and calcium-channel blockers (CCBs) (90) as well as with nitrates, and in chronic studies (where effect was determined by carotid or radial tonometry), with ACEIs, CCBs, and vasodilating beta-blockers (91,92), but not atenolol (Fig. 13). Reduction in wave reflection and central systolic pressure explained benefits of ACEIs, ARBs, and CCBs over atenolol and placebo with respect to cardiovascular events in major trials such as HOPE (the Heart Outcomes Prevention Evaluation study), LIFE (Losartan Intervention For Endpoint reduction in hypertension study), and ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) (4) and led on to the REASON (Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patient: a comparison with atenolol) (84) and CAFÉ (Conduit Artery Function Evaluation) (85) studies. The REASON and CAFÉ studies showed that, in older hypertensive patients, wave reflection could be reduced substantially by an ACE or CCB, and that this could decrease central aortic systolic pressure and could account for reduction in cardiovascular events and in LV mass. The same explanation can be offered to explain benefits of ACEI, ARB, and CCB therapy in

decreasing cerebral and renal deterioration, which is attributable to microvascular damage (54–58).

The mechanism whereby arterial vasodilators—ACEIs, ARBs, CCBs, and nitrates reduce wave reflection—was studied by Yaginuma et al. (86) and Bank et al. (93) with nitrates. The arterial smooth muscle acts as though in parallel with elastin components of the wall but in series with collagen, such that with muscle relaxation, stresses are transferred to elastin so that the dilated artery is less rather than more stiff (4). The combination of dilation and decreased stiffness of the conduit vessels causes reduction in wave reflection (86). It is possible that newer drugs will be found that are more effective in conduit artery dilation and that can have a greater beneficial effect on reducing wave reflection and, so, the ill effects of arterial aging in the circulation.

Multiple studies attest to the benefits of physical exercise, and to the improvement in oxygen extraction from blood and in cardiovascular function that occurs with exercise training (94,95). While exercise training does not show any consistent improvement in stiffness of large elastic arteries (96,97), exercise is associated with improvement in endothelial function of muscular arteries (94) with reduction in wave reflection from peripheral sites (98,99). Such benefits come on after several weeks and persist for 1 month or more after discontinuation. Persons who exercise usually refrain from other adverse lifestyle habits—smoking, coffee drink-

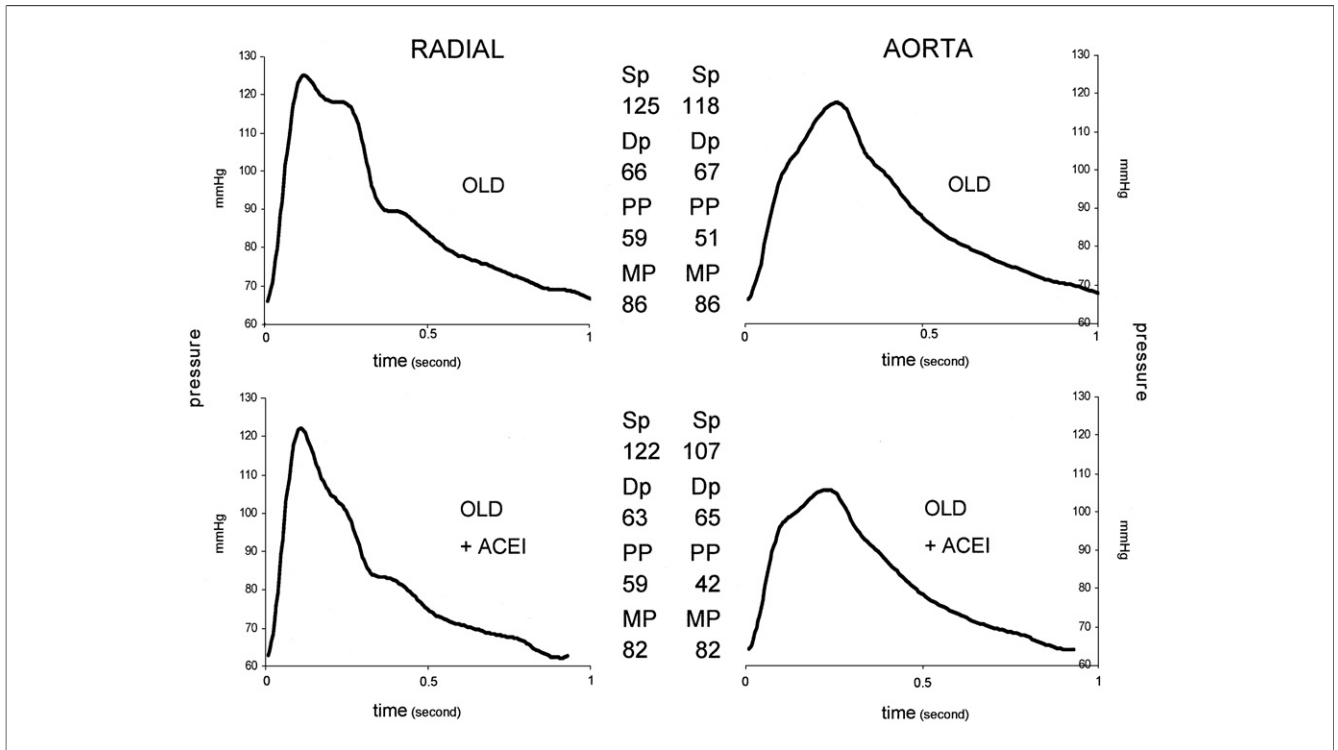


Figure 13 Arm and Aortic Pressure Waves in Old Subject Before and After Administration of Ramipril

Radial (**left**) and aortic (**right**) pressure waves in a 68-year-old man under control conditions (**top**) and 2 h after administration of ramipril 10 mg orally. Ramipril caused greater (8 mm Hg) reduction of aortic than brachial systolic pressure. ACEI = angiotensin-converting enzyme inhibitor; DP = diastolic pressure; MP = mean pressure; PP = pulse pressure; SP = systolic pressure.

ing—that increase wave reflection (100). Healthy habits, including exercise, become more important as age advances.

Regular exercise leads to reduction of arterial pressure and heart rate (95) and, hence, to both the extent of arterial strain at each cycle and the number of cycles. There is logic for using a beta-blocker to reduce elevated heart rate in a person with hypertension already receiving an effective dose of ACEI, ARB, or CCB to reduce wave reflection. Beta-blocker therapy can slow progressive dilation of the ascending aorta in Marfan syndrome (101). However, potential ill effects of beta-blockers as monotherapy for hypertension are becoming increasingly apparent (102).

As presented in this review, arterial aging is progressive from adolescence and causes problems at an accelerating pace as age advances. At what stage is drug intervention warranted? To date, we have depended on the sphygmomanometric figure of 140 mm Hg for systolic pressure before initiating drug therapy. A lower figure of 130 mm Hg is suggested by Julius et al. (103), and is already implemented in patients with diabetes mellitus or renal insufficiency (4,5). It makes more sense to consider central systolic pressure and a value of perhaps 120 to 125 mm Hg. Future trials will determine this. In the interim the old advice stands. Exercise regularly; watch the calories, the coffee, and the salt. No cigarettes. Enjoy yourself, and take advantage of your heart's beat before it wears you out!

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