

Brief Review

Arterial Stiffness, Systolic Blood Pressure, and Logical Treatment of Arterial Hypertension

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Arterial stiffening is the principal cause of increasing systolic pressure with advancing years and in patients with arterial hypertension. It is associated with progressive arterial dilation and is due to degeneration of the arterial wall, probably as a consequence of repetitive cyclic stress; it increases systolic pressure directly by increasing amplitude of the pressure wave generated by a given flow impulse from the heart and indirectly by increasing wave velocity so that wave reflection from the periphery occurs earlier, augmenting pressure in late systole. The first mechanism affects pressure in both the central and peripheral arteries, the second predominantly in the central arteries. Change in brachial systolic pressure with age underestimates the rise in systolic pressure in the aorta and left ventricle. Arterial stiffness is reduced passively with reduction in arterial pressure. Drugs have little or no direct effect on arterial stiffness but can markedly reduce wave reflection. In patients with stiffened arteries, reduction in wave reflection decreases aortic systolic pressure augmentation. The decreased systolic pressure in central arteries brought about by this mechanism is not detected when systolic pressure is measured in a peripheral (brachial or radial) artery but can be inferred from change in contour of the pressure wave recorded in peripheral arteries. (*Hypertension* 1990;15:339–347)

Recent prospective epidemiology studies have directed attention to systolic pressure as a better guide to all-cause mortality,¹ cardiac failure,^{2,3} and stroke⁴ than diastolic pressure. These studies have in turn thrown the focus of attention in human hypertension research onto arterial stiffness and on the way that this and other factors determine the level of systolic pressure that stresses central arteries, that is faced by the left ventricle, and which can be measured in the brachial artery.^{5,6}

An appropriate approach to this subject requires consideration of a number of factors that are generally unfamiliar to clinicians. These include pressure wave reflection, pressure wave transmission, and vascular impedance, the latter a complete description of pressure/flow relations in arteries. Though complex, these and other concepts can be simplified and their essentials grasped by a thoughtful physician. They cannot be ignored if one is to understand the new advances and their implications with respect to pressure monitoring, vascular-ventricular interaction, and a logical approach to therapy.

The major recent advances that need to be considered include: 1) studies of arterial stiffness and of

vascular impedance in hypertension^{7–10} and with aging,^{11,12} 2) studies in the differential effects of drugs on the caliber of arteries and arterioles,^{13–18} 3) studies in the effects of drugs on stiffness of large and small arteries,^{15–21} 4) studies on the effects of wave reflection and its alteration by drugs in humans,^{14,22–25} and 5) studies on differences between systolic pressure in central and peripheral arteries.^{22,26,27}

Historical Perspective

Until quite recently,⁵ modern clinicians tended to ignore arterial stiffness and systolic blood pressure, concentrating their attention on the diastolic pressure of their patients and on the possibility of reducing this, if elevated, through the use of drugs that decrease peripheral resistance. Concern with individual patients and in all the large clinical trials was with diastolic pressure and with peripheral resistance. The logic of such an approach is difficult to understand because it flies in the face of pathophysiological principles underlying the complications of hypertension and of actuarial statistics available before the results of recent epidemiological studies were disseminated.^{28,29} The approach appears to reflect the simplistic interpretation of systolic and diastolic pressures recorded with a sphygmomanometer as put forth by Mackenzie³⁰ in 1926 that “As regards the relative importance of systolic and diastolic pres-

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ures, it may be said that the systolic pressure represents the maximum force of the heart while the diastolic pressure measures the resistance the heart has to overcome." The notion that systolic pressure represents cardiac strength and diastolic pressure measures arteriolar tone is repeated in modern physiological textbooks.^{28,31}

It is possible that the sphygmomanometer has led to overinterpretation of systolic and diastolic pressures as representing physiological phenomena rather than simply the top and bottom of the pressure wave in the brachial artery. Before clinical acceptance of the sphygmomanometer, there was more attention given to arterial stiffness and to peak arterial pressure. With respect to human aging, Roy³² in 1880 noted "Only in the case of young children do we find that the elasticity of arteries is so perfectly adapted to the requirements of the organism as it is in the case of the lower animals." J.C. Bramwell with the Nobel Laureate A.V. Hill stated³³ in 1922 "The amount of energy expended by the heart . . . is . . . proportional to the pressure developed; hence the amount of energy which the heart has to expend per beat, other things being equal, varies inversely with the elasticity of the arterial system." Before introduction of the sphygmomanometer, clinicians diagnosed high arterial pressure on the basis of peak pressure (the force required to extinguish the pulse), and Mahomed in 1874 charted the clinical course of renal and essential hypertension on the basis of systolic pressure and of the pulse contour.^{34,35} Earlier still, Thomas Young³⁶ conducted experiments on arterial segments and established the relation between elastic modulus and pulse wave velocity. The earliest studies on elastic theory were conducted by Young, Hooke, and others during the eighteenth and early nineteenth centuries with use of biological materials including arteries. Even in more modern times, the classical studies of Goldblatt et al³⁷ in 1934 defined hypertension on the basis of persistent elevation of systolic pressure.

Preoccupation with diastolic pressure appears to be a "sphygmomanometric phenomenon" and to have gained prominence only after the 1920s. Reconsideration of systolic pressure as of prime importance represents a return to the more physiologically based concepts that prevailed before the advent of the sphygmomanometer.

Terminology and Physical Principles

Much of the confusion in this field arises from words and their use.^{22,29} The terms "compliance" and "distensibility" mean ease of distention while "stiffness" is the inverse. A stiff artery requires high distending pressure for a given diameter increase. "Elasticity" is used by many to describe distensibility, as by Bramwell and Hill,³³ but strictly speaking it is analogous to stiffness.³⁶ In this review, I will use the term stiffness exclusively in preference to the other three. In part, this is done because the measures of arterial elasticity used regularly (i.e., incremental

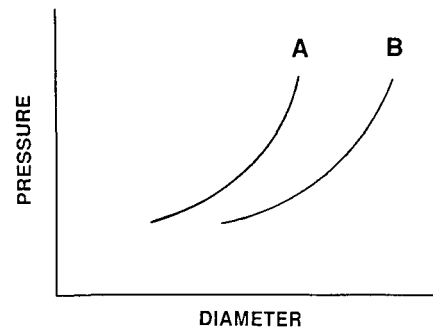


FIGURE 1. Diagrammatic representation of relation between distending pressure and arterial diameter under control conditions (A) and with arterial dilation induced by a nitrate, angiotensin converting enzyme inhibitor, or calcium antagonist (B).

Young's modulus, Peterson's E_p , pulse wave velocity, and characteristic impedance^{22,29,38-41}) all increase with rise in stiffness and decrease with its fall. A higher value denotes a stiffer artery.

This field is surprisingly complex. For details, refer to recent reviews by Dobrin,³⁸ Gow,³⁹ Nichols and O'Rourke.²² Complexities arise⁴⁰ because of nonlinear elastic behavior of the arterial wall, nonuniform elastic properties of different arteries, difficulties in accurate measurement of arterial diameter and wall thickness, relaxation or contraction of muscle in excised arteries, retraction of excised arteries, the differing effects of smooth muscle on arterial stiffness and diameter, and viscosity of the arterial wall; reciprocal changes between wall thickness and diameter with changes in caliber further complicate the relation between wall tension and distending pressure. A simplified but reasonably precise account follows.

The media of an artery is responsible for its physical properties.^{22,38-40} This is regarded as a "two-phase" structure with tension at low distending pressure borne by the elastin fibers and at high pressure predominantly by less extensible collagen fibers.⁴¹ Smooth muscle is largely responsible for viscosity of the arterial wall but contributes also to its stiffness by transfer of tension from one type of fiber to the other. The two-phase arterial composition is responsible for the nonlinear behavior of arterial wall stiffness (Figure 1).

Stiffness is determined from the tangent of the curve at any given distending pressure (or diameter) and may be expressed as E_p (wall tension for 100% diameter increase) or as Young's modulus (wall tension/cm thickness for 100% diameter increase).^{22,40} These indexes, Young's modulus (E) or E_p , can be determined in vitro or in vivo from the measured diameter change induced by a given pressure change at any given pressure or diameter as

$$E_p = \frac{\Delta P}{\Delta D} \times D$$

$$\text{and } E = \frac{\Delta P}{\Delta D} \times \frac{D}{h}$$

where ΔP and ΔD are the changes of pressure and diameter about a mean diameter D in an artery with wall thickness h . These are measures of stiffness. Compliance or distensibility is the inverse of stiffness.

Under normal circumstances, with constant vasomotor tone, an artery becomes stiffer as it is dilated^{22,38,39} because tension is progressively transferred to the less extensible collagenous elements in the wall.⁴¹ It has been shown, however, that vasodilator agents including nitrates, calcium antagonists, and angiotensin converting enzyme (ACE) inhibitors can dilate medium-sized (brachial and carotid) arteries and at the same time reduce their stiffness.^{15–20,42} Such an action is shown diagrammatically in Figure 1. Such paradoxical decrease in arterial stiffness with increase in diameter can be explained on the basis of alignment of smooth muscle in the arterial wall⁴³ such that the muscle is in series with the collagenous elements of the wall but in parallel with elastic fibers. Contraction of muscle would transfer stress from the more extensible elastic fibers to the less extensible collagen fibers and make the artery stiffer while relaxation of muscle would transfer stresses to the elastin fibers and have the opposite effect. This action was demonstrated in medium-sized arteries such as the brachial and carotid^{15–18} but appeared even more marked in the smallest arteries,^{19,20} the diameter of which can almost double and stiffness halve in humans with a tiny (0.15 mg) sublingual dose of nitroglycerin.¹⁹ Similar effects were not demonstrated in the large predominantly elastic central arteries and the aorta itself.^{14,24} These vessels appear to be little altered by vasoactive agents. This arterial dilator action is independent of any effect on arteriolar tone.^{15–18}

Pulse wave velocity is a well-accepted index of arterial stiffness.^{22,36} This is measured from the foot of pressure waves recorded at two points along the path of the pulse wave as $L/\Delta t$, where L is the distance between the two measuring sites and Δt is the time delay. In humans, pulse wave velocity is usually in the range 500–2,000 cm/sec. Pulse wave velocity (PWV) is related to Young's modulus (E), determined as described above, by the Moens Kortewig equation.^{22,40}

$$PWV = \sqrt{\frac{E \cdot h}{2r \cdot \rho}}$$

where h is arterial wall thickness, r is internal radius, and ρ is density of blood.

Another commonly used measure of arterial stiffness is the aortic characteristic impedance (Z_c), which can be determined from pressure and flow waves recorded simultaneously in the ascending aorta.^{7–9} When expressed in terms of linear flow velocity (dyne·sec·cm⁻³, not volume flow) this is numerically very similar to pulse wave velocity according to the Waterhammer formula^{22,40}

$$Z_c = PWV \times \text{blood density}$$

and blood density is usually close to unity (normally approximately 1.05 g/ml).

Like E and E_p , PWV and Z_c are dependent on distending pressure. Their values are usually given for a specified mean arterial pressure (and diameter). A new dimensionless index of arterial stiffness was recently described and is currently being evaluated.⁴⁴ This index is independent of mean arterial pressure.

The approach given here differs from that of "Windkessel" theory in which distensibility is considered to be lumped at one point and in which wave reflection cannot be considered. Windkessel theory overlooks the fundamental features of finite wave velocity and definite wave reflection in arteries.^{22,40}

Changes in the Arterial Wall With Age and Hypertension

With aging, arteries progressively stiffen,^{32,33,45,46} dilate,^{40,47,48} and lengthen.^{40,48} The arterial wall thickens.^{40,47,48} These changes are accelerated by hypertension.^{40,45,49} They are apparent as higher systolic pressure, palpability of the radial artery wall at the wrist, increased prominence of the aortic knob in the chest x-ray, and sometimes as obvious tortuosity of the axillary and brachial arteries. In children and in youth and in virtually all experimental animals that have been studied, the arterial wall comprises an orderly arrangement of elastic laminae separated by interconnecting elastic fibers, smooth muscle, collagen fibers, and connective tissue.^{47,50,51} In older humans, this orderly structure becomes deranged, with thinning, splitting, fraying, and fracture of the elastic laminae and with increase in connective tissue and collagen fibers.^{40,47,49} The total number of laminae, however, remains constant.⁴⁷ In extreme cases, however, elastic laminae are lost, and the wall undergoes "mucoid" or "cystic" medial degeneration,⁴⁸ a condition that in elderly and hypertensive persons predisposes to dissecting aneurysm. These changes with aging appear to be unique to humans. They have not been described in other species. They are not due to concomitant atherosclerosis and are seen as frequently in populations without high prevalence of this as in those with such prevalence.⁴⁵ Structural changes in the arterial wall are associated with chemical changes (i.e., a decrease in elastin, an increase in collagen, and an increase in glycosaminoglycans).⁵²

We have attributed these changes to the fatiguing effects of cyclic stress, acting over many decades on the inert nonliving elastic fibers and resulting in their fracture and separation, with subsequent stretching of the wall and remodeling.^{7,40,53} Such a theory could explain both the dilation and the stiffening (as tension is transferred to collagenous components of the wall) that are seen with age, and why such changes are accelerated in hypertension and why they are not seen in "older" animals whose life span in years (and in pulsatile "cycles") is far less than in humans. The theory⁵⁴ conforms to the principles of "stress fatigue."

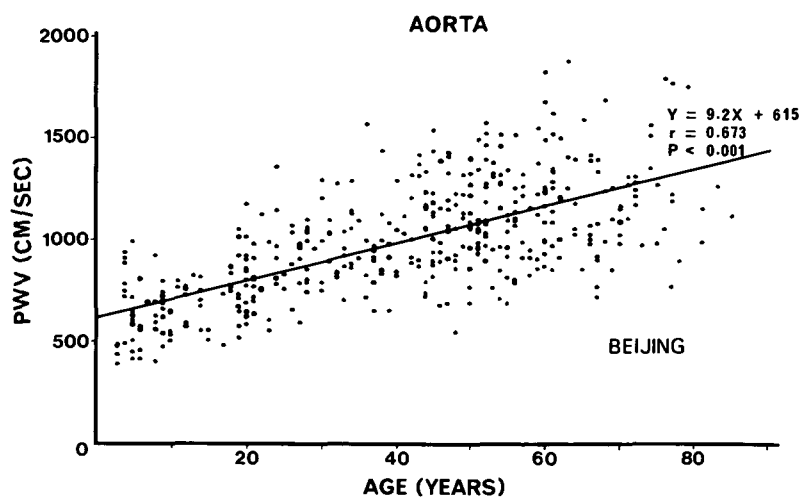


FIGURE 2. Plot showing relation between aortic pulse wave velocity and age in a group of 480 normal subjects from a community with low prevalence of atherosclerosis. From Avolio et al⁵⁵ with permission, American Heart Association.

Changes in arterial stiffness with age are apparent as an increase in pulse wave velocity^{33,45} (Figure 2) and increase in aortic characteristic impedance.²² The increase in pulse wave velocity with age is less apparent in populations with low prevalence of hypertension.⁴⁵ Studies in normotensive subjects and in hypertensive patients have shown a close relation between left ventricular hypertrophy and characteristic impedance⁵⁶ and with other measures of arterial stiffness.⁵⁷ Progressive arterial stiffening with age is considered responsible for the progressive left ventricular hypertrophy seen in aging human subjects.⁵⁸

Ascending Aortic Impedance With Age and Hypertension

Changes in ascending aortic impedance with aging¹¹ and in hypertension^{8,9} are similar and are illustrated schematically in Figure 3.⁷ In elderly and in hypertensive subjects, peripheral resistance (impedance modulus at zero frequency) is increased; in the elderly, peripheral resistance increases principally from a decrease in vascularity of tissues and so in the number of arterioles and, in hypertensive subjects, principally from decreased caliber of individual arterioles.^{29,40} The major changes, however, are due to increase in arterial stiffness²⁹ and are manifest in two features of the impedance curves. The first is the general elevation of impedance modulus at high frequencies where the individual effects of wave reflection are cancelled out; this is the characteristic impedance. Characteristic impedance is a measure of stiffness of the proximal thoracic aorta and, when expressed in terms of flow velocity, is linearly related to its pulse wave velocity through the Waterhammer formula,⁴⁰ as previously described. The second feature is the "shift to the right" of impedance curves so that the minimum of modulus and phase occur at higher frequencies. This is due to earlier return of wave reflection and is caused by increase in pulse wave velocity between the heart and peripheral reflecting sites. The first feature is thus a manifestation of increased stiffness of the proximal

aorta while the second indicates increased stiffness of the whole arterial tree.

In hypertensive patients, these changes are largely due to the increased arterial stiffness caused by high arterial pressure. Merillon et al⁸ showed that the changes revert almost to normal with reduction of mean arterial pressure while similar changes can be induced in normal subjects by increase in mean arterial pressure.

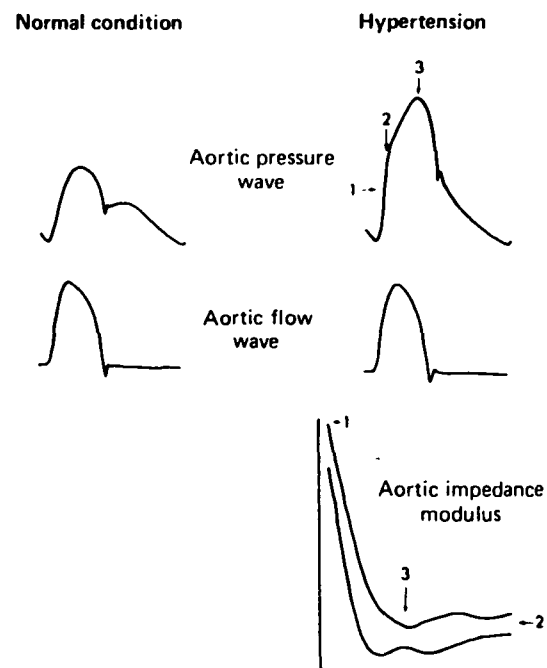


FIGURE 3. Diagrams showing effects of hypertension on ascending aortic impedance (bottom panel) and on the ascending aortic pressure wave (top panels) as generated by the same ventricular ejection wave (center panels), and as explained on the basis of 1) increased peripheral resistance, 2) decreased aortic distensibility, and 3) early return of wave reflection from peripheral sites. For explanation see text. From O'Rourke.²⁹

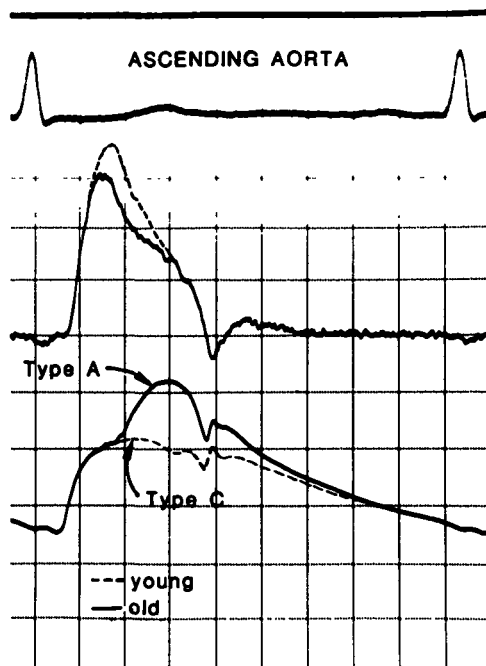


FIGURE 4. Representative tracings showing ascending aortic flow velocity and pressure waves recorded in a young (type C pressure wave) and an old (type A pressure wave) subject. From Nichols et al.¹¹

Effects of Increased Arterial Stiffness on the Ascending Aortic Pressure Wave

Figure 3 shows diagrammatically the effects of altered ascending aortic impedance on the amplitude and contour of the aortic pressure wave. With hypertension, mean arterial pressure is high; this is explicable on the basis of increased peripheral resistance. At the peak of ventricular ejection, pressure rises farther and to a greater level than normal; this is explicable on the basis of increased characteristic impedance and is predictable from the Waterhammer formula.⁴⁰ Beyond this level, however, pressure continues to rise to a late systolic peak where it falls almost exponentially though late systole and early diastole without interruption by any diastolic wave. This is attributable to early wave reflection; the reflected wave, usually apparent in early diastole, moves into systole as a result of increased pulse wave velocity.⁷ Figure 4 shows pressure and flow waves actually recorded in the ascending aorta of a young and an old human subject.¹¹ The older subject shows similar features to the hypertensive. These are explicable on the same basis, with increased amplitude to an early systolic shoulder attributable to high stiffness of the proximal aorta and with appearance of the late systolic wave and disappearance of the diastolic wave attributable to increased stiffness of the whole arterial tree and consequent early return of wave reflection from peripheral sites.^{40,53}

These features of the arterial pressure wave were first described by Mahomed in 1874³⁴ as aids to the diagnosis of high blood pressure. He noted that in

such patients: "The percussion wave is usually well marked and distinctly separated from the tidal" and "The tidal wave is prolonged and too much sustained" and "The dicrotic wave is very small and often scarcely perceptible." With regard to aging, he further noted that "A similar appearance is produced by degeneration of the arteries, but if due to this cause, a very slight pressure is sufficient to extinguish the pulse, while a pulse of high tension generally requires a more considerable one."

These changes in the arterial pressure wave have an adverse effect on cardiac function^{7,11,40} through boosting pressure in systole, thus increasing myocardial oxygen demand and hindering ventricular ejection while at the same time causing a relative reduction in pressure throughout diastole, which compromises coronary perfusion.⁵⁹ These effects can be viewed as the very opposite to those achieved by arterial counterpulsation.⁴⁰

Changes in the arterial pressure wave appear to have a deleterious effect on the arteries themselves and predispose to their further degeneration.^{7,40,53} There is a higher peak pressure, a higher pulse pressure, and a higher rate of change of pressure. All these factors might be expected, on the basis of principles of material fatigue,⁵⁴ to lead inextricably on to fatigue and fracture of elastic fibers, and thence to dilation, thinning, and ultimately rupture of the arterial wall.

Arterial Pulse in Central and Peripheral Arteries

In experimental animals and in young human subjects, the arterial pressure pulse wave is substantially greater and systolic pressure substantially higher in peripheral than in central arteries.^{22,40} This is a consequence of wave reflection, which augments the peak of the pressure wave in peripheral arteries close to the reflection sites.^{22,40} As arteries stiffen with increasing age or with hypertension, pulse wave velocity increases so that pressure wave augmentation is seen in central as well as in peripheral arteries.^{40,60} There is less amplification of the pulse wave and less increase in systolic pressure between central and peripheral arteries in the presence of arterial stiffening.⁶⁰ The increase in systolic pressure of central arteries with age is therefore considerably greater than that noted from recordings in peripheral arteries. In youth, peripheral systolic pressure is greater than central systolic pressure, whereas in later life the two are very similar.^{40,60}

Noninvasive studies of the central (carotid) and peripheral (radial) pressure pulse in humans clarified this subject. Kelly et al²⁶ measured pressure pulse waves noninvasively in over 1,000 normal subjects (3–93 years old) and showed that the 68% increase in radial artery pressure between age 10 and 70 years is almost exclusively due directly to arterial stiffening, whereas the larger 91% or 38 mm Hg increase in amplitude of the carotid pressure wave is almost equally due to the direct effect on arterial stiffness and to early wave reflection from the lower part of the body. In the carotid and the central arteries, wave

reflection from the lower part of the body can be seen to augment the systolic peak of the wave after age 30, whereas such augmentation is usually not seen in the radial or brachial artery until approximately age 80.²⁶ Because of the unusual wave transmission in the brachial system of humans, wave reflection from the lower body is seen earlier on the carotid and ascending aortic pressure pulse where it augments systolic pressure but is seen later on the brachial or radial pulse where it generates a secondary wave on the falling limb of the systolic pressure wave.^{26,61}

Implications of these points are of singular importance in selection and monitoring of therapy and are discussed further below. They may be stated in essence here. It may be possible through reduction of wave reflection to decrease systolic pressure in central arteries of mature human adults by 20 mm Hg; however, such a reduction might be accomplished without any alteration in peripheral systolic pressure.²⁷

Effect of Drugs on Stiffened Arteries

Direct Effects

Considerations of arterial wall behavior (Figure 1) suggest that vasoactive drugs may have an important effect on arterial stiffness. Data on this subject are somewhat conflicting, but definite patterns are only now starting to emerge.^{6,18,42} It appears that vasodilator drugs do reduce arterial stiffness but only in association with increase in arterial diameter.^{15-20,62} Change in caliber is minimal in the aorta and central elastic arteries but more marked in the muscular arteries such as the brachial or carotid and quite pronounced in the tiny prearteriolar arteries whose pulsation can be measured in finger or forearm plethysmography.

Studies on this subject have drawn attention to the separate arterial and arteriolar dilator properties of vasodilator drugs. Nitroglycerin in low doses is usually regarded as a venodilator only.⁶³ Certainly this drug does not dilate arterioles in such doses, but it has a marked effect on caliber of the brachial or carotid arteries^{15-18,57} and apparently an even greater effect on the caliber of smaller arteries.^{14,19,20,62} Feldman et al¹³ demonstrated this effect on coronary arteries; here nitroglycerin had progressively greater dilator effects on the higher order branches. It appears that these effects occur throughout the systemic arterial tree.¹⁴ Dihydralazine is the opposite of nitroglycerin^{15,57}; it appears to have no direct effect on caliber of arteries but has strong vasodilator actions on arterioles. This drug reduces peripheral resistance through arteriolar dilation, but the associated fall in arterial pressure is associated with passive reduction in caliber of the brachial artery. Safar and colleagues^{15-18,57,64} studied a wide variety of drugs and showed that nitroprusside, calcium antagonists, and ACE inhibitors dilate both conduit arteries and arterioles. They reduce arterial pressure through peripheral arteriolar dilation, but this is associated with an increase in brachial arterial caliber, not a

passive decrease as seen with hydralazine. This important work from Safar, London, Simon, and associates in Paris points to the need for a new classification of vasodilator agents with respect to the ability to dilate either arterioles or arteries (as well as veins).

Arterial dilators such as nitroglycerin have little effect on the ascending, the thoracic, or abdominal aorta.²⁴ Fitchett et al²³ and Yaginuma et al¹⁴ were unable to demonstrate any direct effect of this drug on aortic pulse wave velocity or on the timing of wave reflection from peripheral sites. By using more sophisticated techniques in experimental animals, Latson et al²⁴ showed a small (10%) decrease in aortic wave velocity with nitroglycerin. In humans, no drug study has shown any definite reduction in aortic pulse wave velocity that could be attributed directly to the drug. Differences between central and peripheral arteries may be related to the difference in muscle content.

Studies of drug effects on characteristic impedance in the ascending aorta have been equally inconclusive.^{22,25} As with studies of wave velocity, these are bedeviled with difficulties in allowing for the independent effects of change in mean distending pressure; further problems have arisen from expression and interpretation of impedance in terms of flow velocity or flow volume.^{22,40}

Present evidence suggests that drugs have little or no direct effect on the stiffness of the aorta or its major branches.

In contrast to the aorta, however, most studies of peripheral arteries such as the brachial or carotid have shown that drugs that dilate their vessels reduce arterial stiffness appreciably.^{6,15-19,57} Studies of the smallest arteries indicate that stiffness of these can be almost halved by a tiny dose of nitroglycerin.^{20,21,62} Calcium antagonists and ACE inhibitors probably have a similar effect on these small (prearteriolar) arteries, but they dilate the arterioles as well.

The functional significance of these findings remains to be determined. Our recent work suggests that changes of stiffness in peripheral conduit arteries has little effect on timing of wave reflection or on central hemodynamics.¹⁴

Indirect Effects

Although drugs appear to have little direct effect on stiffness of major arteries and on arterial pressure through this mechanism, they can have quite profound effects on the intensity of wave reflection and so on the augmentation of systolic pressure caused by early wave reflection. Recent clinical studies have addressed this topic.^{14,23,25,27,65-67} Intensity of wave reflection was inferred from modulus and phase of impedance in the ascending aorta^{14,29} and from apparent phase velocity.²³ These studies permitted separation of pressure waves into anterograde and retrograde (reflected) components. They showed that small doses of nitroglycerin can almost abolish peripheral wave reflection and so markedly reduce

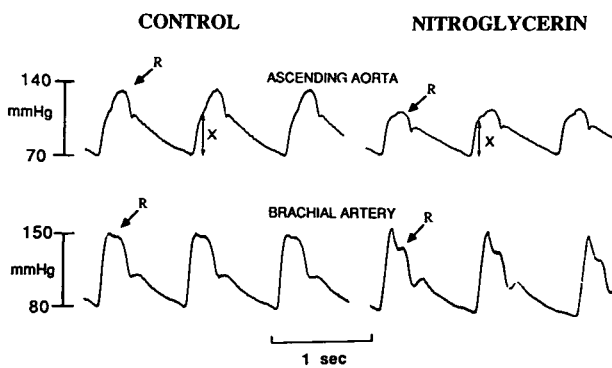


FIGURE 5. Representative tracings showing pressure waves recorded directly with a Millar micromanometer catheter in the ascending aorta (top panels) and brachial artery (bottom panels) before (left panels) and after (right panels) administration of 0.3 mg nitroglycerin sublingually. From O'Rourke et al.⁶⁷

systolic pressure in the ascending aorta, without any change in peripheral resistance.^{14,23} Similar reductions in wave reflection were demonstrated with nitroprusside,²⁵ which persisted during exercise. These changes in wave reflection have been attributed to dilation of small peripheral arteries with nitroglycerin (and nitroprusside)^{14,23–25} and have been simulated in a model of the systemic arterial system.¹⁴

Recent studies on arterial stiffening with age and hypertension showed that the distorted (inappropriately early) wave reflection that boosts pressure in the ascending aorta and central arteries^{7–12} can be reduced or almost abolished through use of drugs that reduce peripheral wave reflection.^{14,25,27,65} Clearly this is a useful strategy in management of hypertension and in the treatment of angina pectoris and cardiac failure, but the most recent studies, not yet published in full,²⁷ indicate that beneficial effects may not be apparent from conventional monitoring of the pressure in a peripheral artery such as the brachial or radial.

Differences Between Central Aortic and Brachial Pressure Waves During Vasodilator Therapy

Figure 5 shows the effects of nitroglycerin on the amplitude and contour of the pressure wave in the ascending aorta and brachial artery of a patient studied during the course of cardiac catheterization. In this patient, there was little change in venous return or in mean arterial pressure. Similar changes have been seen in a group of 14 patients, though they are often modified by effects of venodilation with reduction in venous return and mean arterial pressure.²⁷ Through reduction in lower body reflection, nitroglycerin causes substantial reduction in the secondary reflected wave in the ascending aorta and brachial artery. In the ascending aorta, this led to a substantial fall in systolic pressure of approximately 20 mm Hg, whereas in the brachial artery there was no fall in systolic pressure. This differential effect on

aortic and brachial systolic pressure is clearly a consequence of the timing of wave reflection and so of wave transmission in the upper limb.^{22,61} In this case, measurement of brachial systolic pressure failed to show a fall in ascending aortic systolic pressure of 20 mm Hg. In the whole series of 14 patients, measurement of brachial systolic pressure underestimated the fall in aortic systolic pressure by an average of 10 mm Hg.

This phenomena has been investigated through noninvasive measurement of the carotid and radial pressure waves, and similar effects have been demonstrated with nitroglycerin (i.e., reduction or disappearance of the late systolic augmentation in the central artery without corresponding change in the peripheral artery).⁶⁸ Other drugs have been investigated and similar acute effects seen with agents known to cause dilation of peripheral arteries (i.e., isosorbide dinitrate, nifedipine and nicardipine, captopril and enalapril, and dilevalol,⁶⁵ a β -blocking agent with arterial dilator properties. The effect has not been observed with other antihypertensive agents without vasodilating effects. In a long-term, double-blind crossover comparison of dilevalol and atenolol, it was estimated that dilevalol probably reduced systolic pressure in the ascending aorta and central arteries by 5–8 mm Hg more than atenolol for a similar reduction in brachial systolic pressure.⁶⁵

This differential effect of vasodilator agents on central and peripheral pressure waves is a consequence of arterial stiffening, of early return of wave reflection, and of systolic pressure augmentation in central arteries.^{27,61,68} One would not expect to see it in young subjects where wave reflection returns to the heart predominantly in late systole and early diastole (Figure 4). However, it would be expected to be operative in normotensive subjects over the age of 30 and hypertensive patients under this age. The subject is thus relevant to the vast majority of patients who require treatment for hypertension, angina pectoris, and cardiac failure.

The phenomenon illustrated in Figure 5 explains reduction in left ventricular afterload and myocardial blood requirements with nitroglycerin; it explains relief of angina pectoris and of left ventricular failure with sustained brachial artery pressure. The phenomenon may well explain the greater efficacy of ACE inhibitors in regression of hypertensive left ventricular hypertrophy,⁶⁴ and the beneficial effects of ACE inhibitors and of nitrates in prolonging life expectancy in patients with cardiac failure. In the past such benefits have not been attributed to reduction in ventricular afterload, probably because this was considered identical to systolic pressure in the brachial artery.

Implications to Arterial Pressure Measurement

Sphygmomanometric arterial pressure measurement has come to be accepted almost uncritically after a period of almost 100 years. Diastolic pressure is now challenged as an index of arteriolar tone and of the hypertensive state and as a guide to the

presence of left ventricular hypertrophy.^{28,57} Systolic pressure in the brachial artery is now accepted as a better guide to left ventricular hypertrophy and index of cardiovascular risk.¹ In an effort to improve precision in diagnosis and therapy, other indexes of left ventricular hypertrophy have been sought including characteristic aortic impedance and aortic pulse wave velocity. In a further attempt to improve precision in diagnosis and therapy, efforts are now being made to determine central systolic pressure and its augmentation either from noninvasive measurement of the carotid pressure pulse wave⁶⁵ or from noninvasive measurement of the radial pressure wave.^{65,69} We are presently seeking methods to determine aortic systolic pressure from the amplitude and contour of the radial pressure pulse, recorded noninvasively. This might be expected to improve substantially on the present methods as applied to patients with stiffened arteries.

In conclusion, arterial stiffness is a major determinant of systolic blood pressure in central vessels and so of left ventricular load and oxygen requirements and of the damaging stresses on arterial walls. Increased arterial stiffness increases systolic pressure in two ways: first, by increasing amplitude of the initial pressure wave generated by ventricular ejection and second, by causing reflected waves from the periphery to return during systole and so augment the initial wave. Both mechanisms contribute almost equally to the increased systolic pressure in central arteries and the left ventricle, which is seen with aging and in hypertension. Arterial stiffness decreases with lowered distending pressure, as when blood pressure is reduced, but is little altered by drugs. Vasodilator drugs, however, reduce wave reflection through their effects on the small peripheral arteries and arterioles and can markedly reduce the augmentation of systolic pressure that in central arteries is a consequence of early wave reflection. Because of differential timing of wave reflection, such beneficial effects on pressure in central arteries may not be seen when pressure is measured in the brachial or radial arteries.

Arterial stiffness increases with aging and is a major factor in progressive myocardial hypertrophy with age, and in arterial degeneration and cardiac failure. Drug therapy does not significantly reduce arterial stiffness but can reduce its ill effects by lowering arterial pressure and decreasing peripheral reflection, thus delaying and reducing amplitude of the reflected wave in central arteries. This is a desired strategy in management of hypertension, angina pectoris, and cardiac failure.

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KEY WORDS • blood pressure • vascular impedance • arteries • vascular dilation • aging