Antihypertensive drugs and arterial stiffness

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Arterial stiffness is recognized as an important determinant of outcome in the hypertensive population. Although pulse pressure is an indirect index more recently relatively simple non-invasive techniques to measure pulse wave velocity, particularly in the aorta and arterial wave analysis have been developed and applied to clinical trials. There are clear differences in the effects of antihypertensive drugs on these parameters and stiffness is becoming a therapeutic target in its own right.

Expert Rev. Cardiovas. Ther. 1(1), 65–78 (2003)

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> ‘*When you can measure what you are speaking about and can express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind*’. Lord Kelvin, 1891.

While referring to the sphygmomanometric measurement of blood pressure, the same comments are very pertinent to the measurement of arterial stiffness.

For thousands of years, the arterial pulse as a diagnostic tool has attracted Chinese, Egyptian, Arabic and European physicians, who appreciated that the stiffness of the palpated pulse was of some prognostic significance. The development of sphygmography in the 19th century allowed a physical tracing of the arterial pressure waveform [1]. In 1874, Mahomed described the changes in the arterial pulse in a hypertensive patient as being distinct from those in the pulse tracing of a normotensive subject (FIGURE 1). That drug therapy could alter the arterial pressure waveform was also demonstrated around this time when the effect of nitrates was demonstrated (FIGURE 2). However, how to measure these changes numerically still eluded scientists. The development of devices that permitted numerical expression of such abnormalities and our ability to quantify drug effects was not available until late into the 20th century. The recent development of noninvasive methods such as Doppler ultrasound, pressure-sensitive transducers, applanation tonometry and photoplethysmography to record arterial flow or pressure waves, together with new techniques of analysis with automatic and computerized calculations has opened up new horizons. The application of the measurement of arterial stiffness in epidemiological and therapeutic studies has been firmly established and has become both an important measure of cardiovascular risk and a therapeutic target in its own right.

Hypertension is characterized by a reduction in the caliber or number of small arteries or arterioles with an increase in mean arterial pressure (MAP), which is a product of cardiac output and peripheral vascular resistance, considering pressure and flow to be constant over time. However, the heart is a pump and generates pulsatile flow, thus the blood pressure (BP) curve may be considered as the summation of a steady component, MAP, and a pulsatile component, the pulse pressure (PP). The large arteries are not just conduits but also act as cushions, converting pulsatile flow from the heart into steady flow by expanding during systole and propelling blood to the periphery by their elastic recoil during diastole – the Windkessel effect. Besides the pattern of left ventricular ejection, the determinants of PP are the cushioning function of large arteries and the timing and intensity of wave reflection [1]. The cardiac ejection generates a primary wave, which travels with a finite speed, the pulse wave velocity

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KEYWORDS:
β-blockers, ACE inhibitors, aldosterone antagonists, angiotensin II receptor antagonists, antihypertensive drugs, arterial stiffness, calcium-channel blockers, diuretics

ISSN 1478-7210

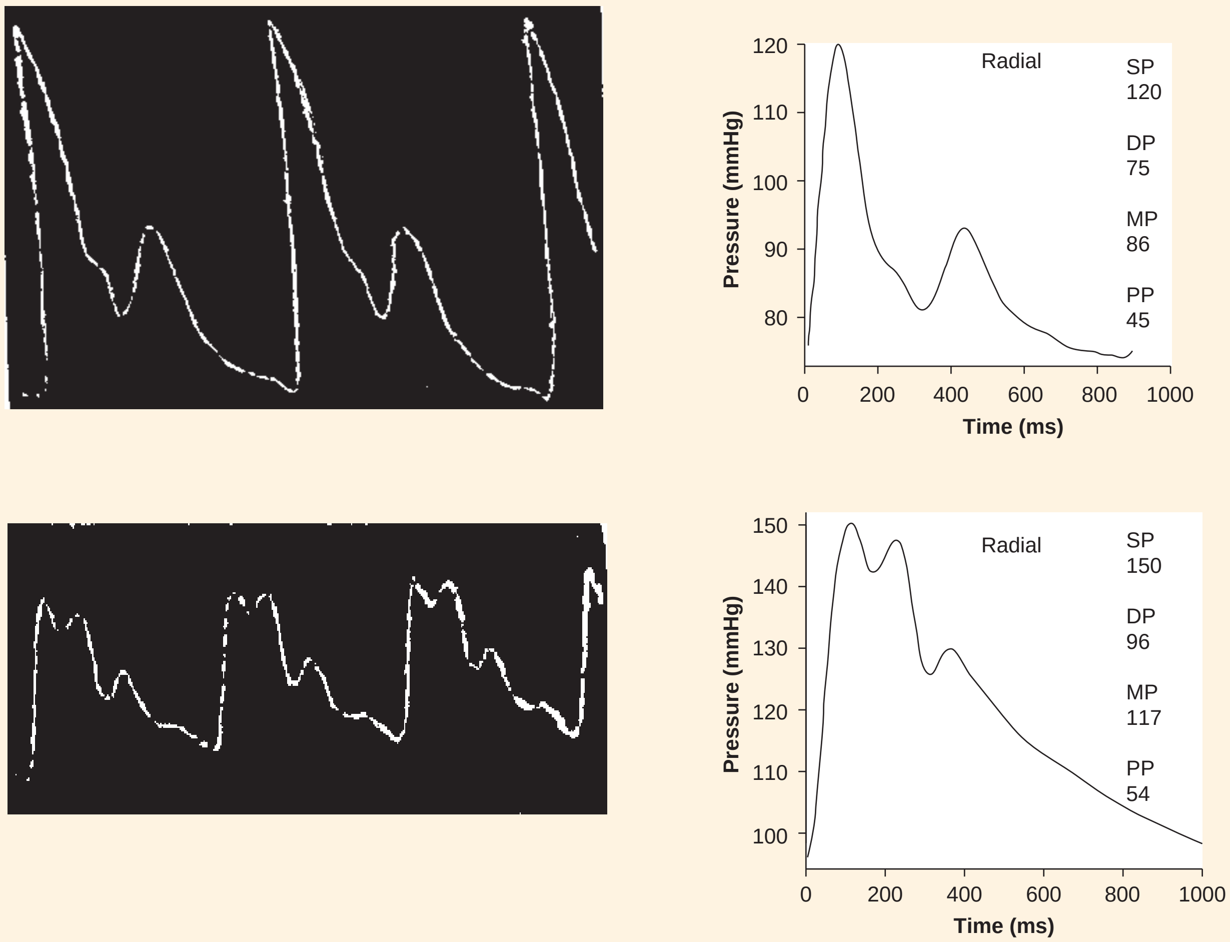

Figure 1. Radial sphygmograph in normal and hypertensive subjects. A. Left panel as recorded in 1874. B. Right panel as recorded in 2003, which includes blood pressure measures.
DP: Diastolic pressure; MP: Mean pressure; PP: Pulse pressure; SP: Systolic pressure.

(PWV), and is reflected back from any point of geometric discontinuity in the arterial tree. In youth, the reflection takes place in diastole but in patients with stiffer central arteries, as in the elderly or hypertensive individuals, the reflected wave would augment left ventricular and systolic blood pressure (SBP) and reduce aortic pressure during diastole. This alteration of SBP and diastolic blood pressure (DBP) with a resultant increase in PP is seen in both essential hypertension and isolated systolic hypertension (ISH) in the elderly but there are important differences between the two clinical situations. In the younger hypertensive population, increased peripheral resistance plays a primary role together with an increase in stiffness of the central arteries and persistence of the PP gradient along the arterial tree, causing PP to remain higher in peripheral than in central arteries, the MAP is reset to a higher value.

A different scenario is seen in ISH, where there is a disappearance of the PP gradient along the arterial tree due to more pronounced stiffening of the central rather than peripheral arteries. There are also differences in structural alteration in the arterial wall between the young and old hypertensive patients. In the young hypertensive, much of the medial hypertrophy is due to the increased blood pressure itself as it may disappear under isobaric conditions in the carotid circulation [2]. However, increased stiffness in the aorta has been observed even under isobaric conditions [3]. In the elderly hypertensive, the medial hypertrophy involves a large increase in extracellular matrix and adventitia and is associated with decreased arterial compliance and distensibility independent of blood pressure [4].

In addition to arterial stiffness, which is determined by central arteries, there are other factors that influence the different arterial behavior in hypertension and the aging process, and most of these are combined in patients with ISH. The reflection coefficients of the pressure wave located at the origin of resistance vessels are modified with aging and hypertension due to changes in the endothelium and neurohumoral control. The location of the reflection sites may also change with age and hypertension due to an increase in the caliber and length of vessels, the production of reflection sites closer to the heart and important alterations in the microvasculature [1]. These factors indicate that both increased arterial stiffness from the central

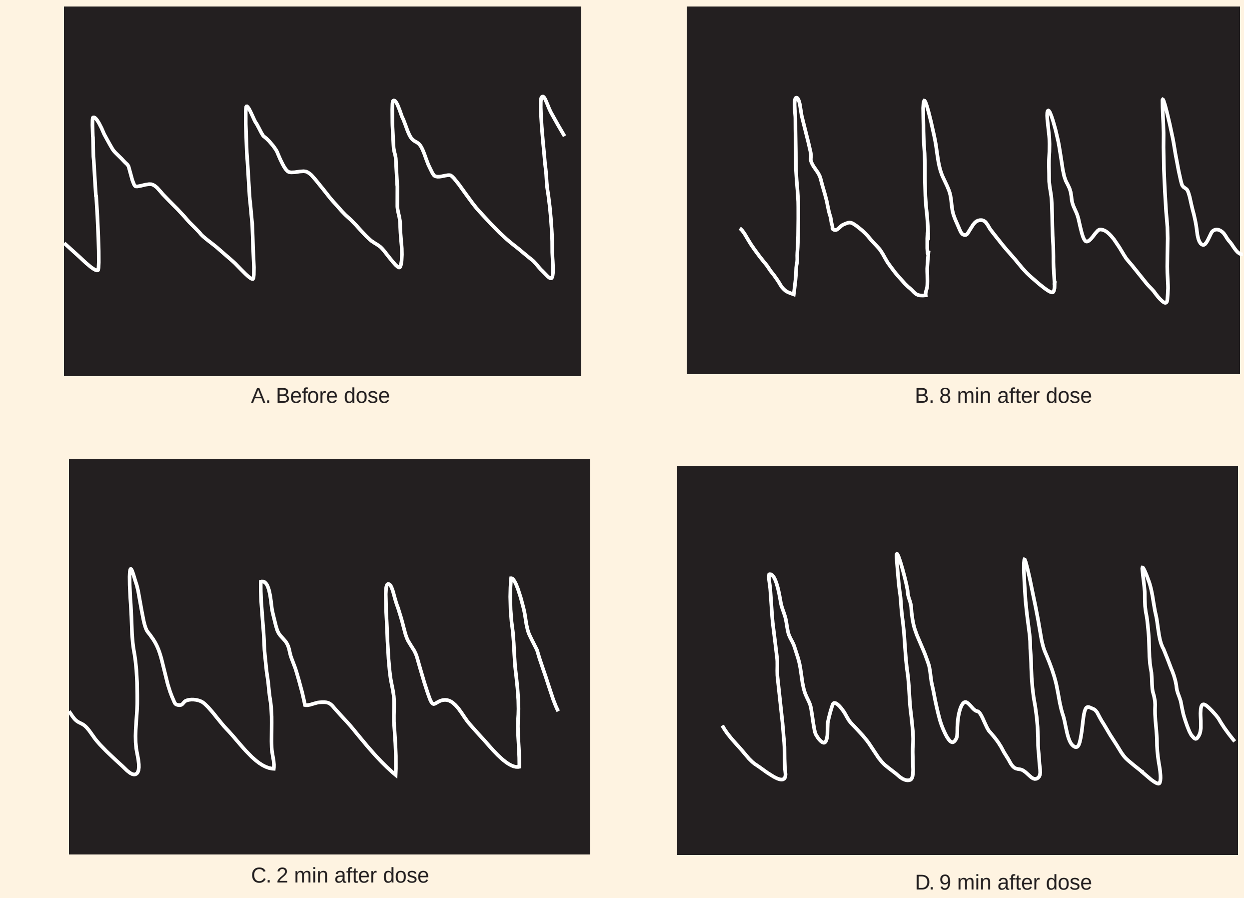

Figure 2. Radial artery sphygmographs showing the effects of nitroglycerin in causing a reduction in the late systolic shoulder of the pulse.

arteries and alteration of wave reflection generated at peripheral large and small arteries contribute to the predominant increase in PP in both hypertension and ISH.

Models for the measurement of arterial stiffness

The oldest proposed model of the arterial system is a Windkessel model, which considers the whole arterial system as one common chamber. Though conceptually useful, it is unrealistic, as the elastic properties of arteries are distributed throughout the vasculature and differ according to site; also the arterial pulse wave has a finite velocity and exhibits wave reflection from the periphery, which imparts a different amplitude and contour to the arterial pressure waveform in central and peripheral arteries. Moreover, arteries respond differently to disease conditions, such as aging and hypertension, and also to drug therapy depending on the arterial site that is being evaluated. Some methods of assessment of arterial stiffness currently being used are based on this model.

The more realistic model of the arterial system is the single elastic tube, that is, the artery. A wave generated by myocardial contraction travels along the arteries towards the periphery with a finite PWV and is reflected back. This finite PWV is evidence against the arterial tree acting as a Windkessel. The pressure wave at any point is the result of an incident and a reflected wave. In youth, when the arteries are distensible and PWV is low, the reflected wave returns to the ascending aorta during diastole. With arterial stiffening, PWV is high and the reflected wave merges with the systolic part of the incident wave, causing a high pressure in systole and low pressure in diastole throughout the vasculature, increasing myocardial load and decreasing diastolic coronary perfusion pressure. The timing of the reflected wave is determined by the PWV; reflection occurs in diastole with low PWV and in systole when the PWV is high. The amplitude of the reflected wave, however, depends upon the sites of wave reflection. A wave traveling along an artery will be reflected at any point of discontinuity where there is a mismatch of impedance and in the periphery where the low-resistance arteries terminate in high-resistance arterioles. The arterial–arteriolar junction is now well-established as the predominant site of wave reflection in the circulation [1].

Assessment of arterial stiffness

Different methods are currently being used and even with a host of indices available, none has proved superior and all have shown problems in either measurement or interpretation. For instance,

Box 1. Cardiovascular conditions and risk factors associated with arterial stiffness.

- Aging [5]
- Hypertension [3,6,7]
- Coronary artery disease [8,9]
- Diabetes [10,11]
- Smoking: acute and chronic [12,13]
- End-stage renal disease [14]
- Hypercholesterolemia [15]

using an inappropriate model may make a method unreliable. Also, methods that use cardiac output measurements that are not validated are also prone to error. Some techniques measure arterial diameter in a central artery but use pressure values from a peripheral artery, thus ignoring PP amplification. Finally, heart rate and cardiac contractility could potentially confound certain indices, such as the augmentation index (AIx; height of the late systolic peak in the aortic pressure waveform divided by aortic PP), which is inversely related to heart rate.

There are also fundamental problems in the application of physical terms to arterial stiffness. The arterial wall consists of both elastin and collagen in the media, thus giving a nonlinear relationship between pressure and diameter. Hence stiffness may only be quantified at a given level of MAP. Also, collagen and elastin are lined by smooth muscle cells, whose activity may change the contribution of each to arterial stiffness, thus arterial stiffness varies with smooth muscle tone and is affected by neuro-humoral control, local metabolic factors and vasoactive drugs.

With all other factors being equal, methods that are noninvasive, validated, simple, quick and reproducible are obviously more desirable in clinical practice, large epidemiological studies and therapeutic trials. A number of methods are in common use.

Direct measurements

Direct measurement of arterial stiffness relates measurement of change in arterial diameter and pressure at the same site. Following on from the earlier work by Milnor [16] and O'Rourke [17], Stefanadis and coworkers [18] have intensively studied the local pressure–diameter relationship invasively with the ultrasound/ catheter tip method. Such measures can also be performed noninvasively at any site quite accurately using the ultrasound technique [19,20]. However, the usefulness of this method is limited by the need to estimate the pressure change at the same site reliably, as PP amplification precludes the use of brachial BP measurements for estimating diameter change at the carotid artery. In common with many ultrasound techniques it relies heavily on the ability of the operator to image the vessel wall but has limited resolution to detect very small changes in vessel diameter. Magnetic resonance imaging has also been used to measure the aortic distensibility [21], but costs and limited availability will preclude its widespread application.

Measurements based on PWV

PWV is a simple, noninvasive method of estimating arterial stiffness and is described by the Bramwell–Hill formula:

$$\mathrm{PWV}^2 = \Delta P \cdot V/\Delta V \cdot \rho$$

Where ΔP and ΔV are the changes in pressure and volume, V is the baseline volume and ρ is the density of blood.

PWV can be measured with Complior™ (Colson, Paris, France) and SphygmoCor™ (Atcor Medical, Sydney, Australia) and by other customized devices. All devices can measure PWV in different arterial segments. PWV is calculated by the formula:

$$\mathrm{PWV} = \text{distance (m)/transit time (s)}$$

The distance is measured on the surface of the body by a tape measure between the two recording sites. Transit time is measured as the time delay between the feet of the recorded proximal and distal waves. The Complior is an automated device that measures the time delay between the two ends of the arterial segment, beat-to-beat, using pressure transducers and has been found to be quite accurate and reproducible [22]. With the SphygmoCor device, transit time between arterial sites is determined in relation to the R wave of the electrocardiogram. A proximal and distal wave are recorded sequentially a short time apart. The transit time is obtained by subtraction from the delays between the ECG and both pulses. To select a fiducial point on the pulse wave as the reference point, the system allows the user a choice of four different algorithms [23] and is quite reproducible [24] but has not to date been compared extensively to the Complior technique. Other methods used for measuring PWV include the Wall Tack System [25], Doppler Ultrasound [26] and the Qkd System [27].

Carotid–femoral PWV is most commonly measured as it is considered a surrogate marker of aortic PWV [28], although PWV in the arm and leg circulations has also been measured in different studies. PWV increases markedly with age in the central elastic arteries such as the aorta but not in the upper limb muscular arteries [29]. A highly elastic aorta will transmit the wave relatively slowly (6 m/s) whereas an older individual with hypertension will have a faster transit time (e.g., 14 m/s). PWV increases markedly with age [29] and SBP [30].

Since all values of arterial stiffness are pressure-dependent, comparisons have to be related to the same BP. Thus, isobaric indices [31] or complex statistical modelling to adjust for the nonlinear relationship between arterial stiffness and BP have been used. Heart rate may introduce some small error but it is not significant for PWV measurements.

Methods based on analysis of the arterial pulse

Instead of directly measuring arterial stiffness, the effects of stiffness on the arterial pressure or flow wave can also be quantified. In the past, the arterial waveform could only be recorded intra-arterially, which limited its use. However, noninvasive devices have made such measurements possible in the clinical setting.

Applanation tonometry

The SphygmoCor device performs pulse wave analysis by applanation tonometry using a pressure manometer lightly compressing an artery (radial or carotid usually) against a bony surface. FIGURE 1B shows a typical radial artery waveform in a normotensive and a hypertensive subject. The aortic AIx may be derived from peripheral arterial pressure wave, most commonly the carotid or the radial pressure wave, by means of a transfer function that has been validated against intra-arterial measurements [32–36] and has been found to be quite reproducible [24,37]. The AIx is significantly correlated to PWV in both normotensive and hypertensive patients [38].

The relationship between arterial stiffness and AIx is complex, and there has been considerable debate as to whether the AIx is a valid measure of arterial stiffness. By consensus, the AIx is thought to represent a global surrogate index of arterial behavior, reflecting the influence of arterial function, including vessel wall properties, arterial wave reflection, body height and ventricular vascular coupling with a significant effect of changes in heart rate [39].

Arterial stiffening is responsible for the characteristic changes seen in the arterial pressure waveform with aging [5]. AIx varies from less than zero at age 18 to as high as 50% by 70 years of age and in hypertensive patients [40]. The increase in AIx is seen at a much earlier age in hypertensive patients.

The pulse transit time can be estimated from the initial wave foot to the reflected wave foot in the aortic pressure waveform. It is related to aortic PWV [15,41] and has been used as an index of aortic PWV by some investigators. However, how well the pulse transit time relates to aortic PWV remains to be established.

Proximal & distal compliance from a modified Windkessel model

This technique is based on the arterial pulse recording at the level of the radial artery (CR-2000™, Research Cardiovascular Profiling System, Eagan, MN, USA) [42] based on the modified windkessel model [43] validated by Cohn and coworkers [42] allowing determination of proximal ‘capacitative’ compliance (C^1) and distal ‘oscillatory’ compliance (C^2). A tonometer sensor is strapped on the wrist and calibrated with an oscillometric brachial BP and after obtaining an appropriate hold down pressure, the PP is obtained without the aid of the operator. There is an age-dependent decline in both C^1 and C^2 [44]. Changes have also been described in isolated systolic hypertension [45] and in diabetes mellitus using this technique [46]. C^2 was significantly and inversely related to AIx [47] but the authors found C^2 to have a variability of 33% compared with a variability of 6.7% for AIx and suggest that this may make the C^2 measurements of lesser diagnostic precision than that of AIx. There has been criticism of this study [48] suggesting that the error resides in the AIx measurements than in that of C^2.

Second derivative of the finger plethysmograph

The amplitude ratios of the second derivative of the peripheral BP pulse waveform obtained by finger plethysmography allows the study of the effects of aging and vasoactive agents [49,50]. The parameter |b/a| designates the ratio of the amplitudes of the second (b) and first (a) inflection of the second derivative of the plethysmograph obtained from a photoplethysmographic device (Fukuda Co, Tokyo, Japan). This technique is undergoing further validation at present.

Other systems looking at the arterial PP include subclavian pulse tracing and Doppler-echocardiography methods.

Recommendations for use or procedures and reference values for the different modalities, such as distensibility, compliance, PWV, aortic impedance, capacitive compliance and oscillatory compliance, have been published both for normotensive healthy individuals and in disease states, particularly hypertension and heart failure [51,52].

Arterial stiffness in the population: prognostic implications

A number of indices have been used in epidemiological studies as indices of arterial stiffness. An indirect measure has been the use of PP, which is primarily determined by left ventricular ejection and the stiffness of the aorta and the larger central arteries. Although earlier reports suggested that PP was no better than SBP and DBP, in particular in coronary heart disease, more recent data, particularly from the trials in hypertension (MRC, EWPHE, Syst-Eur and Syst-China) have shown that brachial PP is a stronger predictor than SBP for myocardial infarction in hypertensive populations [53]. In contrast, a meta-analysis of 1 million people with no evidence of vascular disease, screened for inclusion in large-scale studies with a single BP measurement, PP was of lesser prognostic value than SBP or DBP alone [54]. In large epidemiological studies, such as the Framingham study [55] (in the US), and a study on a French population [56] of normotensive and hypertensive subjects, PP was a strong determinant of myocardial infarction beyond the age of 50 years. As left ventricular ejection is relatively stable with age, arterial stiffness is the principal factor responsible for an increased PP with aging and was found to play an important role in the development of hypertension in the Atherosclerosis Risk in Communities (ARIC) study [57].

Carotid–femoral PWV, a marker of aortic stiffness has been shown to be a strong independent predictor of cardiovascular and all-cause mortality in patients with end-stage renal disease [58]. This finding has been confirmed following adjustment for all other risk factors in diabetic patients with renal disease [59]. Again, using aortic PWV, the follow-up study of patients with essential hypertension confirmed that a higher PWV was also associated with cardiovascular morbidity and mortality [60]. In the prospective ARIC study, the cumulative incidence of hypertension in normotensive people aged 45–64 years was related to higher arterial stiffness as assessed by carotid ultrasound [57]. There is also evidence that increased wave reflection and central arterial pressure are independent factors associated with poor survival in end-stage renal disease [61]. In end-stage renal disease patients on hemodialysis, the disappearance of PP amplification was a significant predictor of all-cause mortality, independent of age; carotid PP was more powerful than brachial PP in the

Table 2. Summary of effect of major antihypertensive drug groups on arterial stiffness (see text for details) as assessed by pulse wave velocity (PWV) and other methods.

	PWV	Wave reflection	Carotid dist.
Diuretics			
Hydrochlorthiazide	NC		NC
Indapamide	NC		
Bendrofluazide	NC	NC	
β-blockers			
Propranolol	↓		NC
Bisoprolol	↓		
Dilevalol	↓		
Atenolol	↓	NC/↓	
Metoprolol	NC		NC
Nebivolol	↓	↓	
Calcium-channel blockers			
Dihydropyridine			
Nitrendipine, isradapine	↓		
Lacidipine, nifedipine, felodipine	↓		
Verapamil	↓		
Aldosterone antagonists			
Canreonate	NC		
Spironolactone	NC/↓	↓	
Eplernone	↓		
ACE inhibitors			
Captopril	↓	↓	
Ramipril, lisinopril, cilazapril	↓		
Trandolopril	↓	↓	↑
Quinapril	↓	↓	↑
Fosinapril		↓	
Angiotensin II receptor antagonists			
Losartan	↓	↓	
Telmisartan	↓		
Valsartan	↓	↓	

↑: Increased; ↓: Decreased; dist: Distensibility; NC: No change.

prediction of all-cause mortality [62]. Aortic PWV has emerged as an independent predictor of mortality in both Type 2 diabetes [63] and of stroke in the hypertensive population [64].

Time is also required for a fuller evaluation of the prognostic value of measures of stiffness. At present, there are a number of outcome studies to determine whether arterial stiffness measurements are predictive of future cardiovascular events in patients being treated for hypertension (ASCOT) hypercholesterolemia (SEARCH) and non-insulin-dependent diabetes (FIELD).

There is also some evidence that the effect of drug therapy on arterial stiffness, independent of its effect on BP, may have an important bearing on outcome. For patients with end-stage renal disease, the improvement in aortic distensibility in response to antihypertensive therapy was associated with decreased mortality and survival [65]. Thus, a lack of an effect on aortic PWV, despite significant drug-induced reduction in MAP, was not associated with a significant reduction in cardiovascular death. It has also been suggested that an important factor in the superiority of the angiotensin II (ATII) receptor antagonist, losartan, over atenolol in reducing cardiovascular risks in the hypertensive population in the LIFE study may be, in part, related to the fact that the former reduced arterial stiffness significantly whereas the latter did not [66]. There is now considerable information on the effect of antihypertensive therapy on arterial stiffness.

Antihypertensive drugs & arterial stiffness

The effects of antihypertensive drugs on arterial stiffness are complex and vary with time, the arterial territory being studied and the distending pressure in the arteries. Antihypertensive drugs could have both short-term functional and long-term structural effects on the arterial wall. The functional effects are both direct and indirect. Direct vascular effects occur due to vascular smooth muscle relaxation, particularly in the medium-sized muscular arteries. The drug could also decrease arterial stiffness by indirect mechanisms; attenuation of wave reflections by dilatation of muscular arteries and also secondary to the reduction in MAP due to decreased arteriolar tone. The structural effects may include vascular remodelling as well as changes in the distribution of elastin and collagen in the vessel wall.

In patients with essential hypertension, numerous studies have shown a decrease in arterial stiffness with the various classes of antihypertensive agents, either acutely or during long-term studies. Long-term studies are much more desirable as the acute effects of a particular drug may not reflect its long-term effect on stiffness, which may be attenuated with counter-regulatory mechanisms. However, short-term studies do have an important role in hypotheses testing and provide important ground-work for long-term studies.

There is a large body of literature on the effect of these agents on arterial stiffness in animal models of hypertension particularly the spontaneously hypertensive rat. By and large, animal models have been generally predictive of what is seen in man. It is important also to consider the type of study, and emphasis will be placed on randomized, controlled studies. In addition, many of the studies referred to below are of a relatively short duration, around 1 month, and where longer-term studies are available this shall be emphasized. TABLE 2 summarizes the effect of the major antihypertensive drug groups on arterial stiffness as measured by PWV and arterial wave reflection.

Nitrates

Nitrates were shown as far back as the 1800s to have a pronounced effect on the arterial pressure waveform (FIGURE 2). The antihypertensive effect of nitrates has been demonstrated in earlier studies, which showed that nitrates cause a selective decrease in SBP over DBP in both healthy volunteers and patients with essential hypertension [67]. Nitrates increase arterial compliance of elastic and muscular arteries in normotensive and hypertensive subjects [68], which is due to an increase in arterial diameter and not an effect on the distensibility or PWV of both the carotid artery and the aorta. The most remarkable effect of nitrates is on the peripheral muscular arteries, decreasing arterial wave reflections and thus have a preferential effect on aortic SBP. This change in aortic SBP may be missed if only the brachial BP is measured. The effect of nitrates is also dependent upon the dose, showing muscular artery dilatation and reduced wave reflection with the lowest dose, arteriolar dilatation and decreased peripheral resistance with the highest dose and venodilatation with the intermediate dose [69]. There may be promise in the use of nitrates in the treatment of hypertension, especially ISH, which is primarily characterized by increased arterial stiffness and very high arterial wave reflection. In a double-blind randomized controlled trial, isosorbide mononitrate 60 mg was compared with captopril 25 mg, eprosartan 600 mg and placebo, all given separately in random order on different days to patients with ISH. All of the drugs were shown to decrease brachial and aortic SBP and PP but only isosorbide mononitrate significantly decreased arterial wave reflection in these patients [70]. All these findings indicate that the major sites of the action of nitrates are muscular arteries (from the medium-sized arteries to the origin of arterioles). Sinotridil, a NO donor, has been shown to be mores selective for large artery compliance than isosorbide dinitrate [67]. Such drugs may be of interest for the treatment of patients with ISH.

Diuretics

As hypertensive complications mainly affect the conduit arteries and sodium contributes to arterial stiffness [1], it is suggested that diuretics may have blood-pressure-independent effects on the large arteries. However, the reality has been the converse; the effects of diuretic compounds on the vascular wall in hypertensive subjects have been disappointing.

Safar and colleagues demonstrated in an open placebo-controlled study that indapamide 2.5 mg once daily for 3 months had no effect on brachial–radial PWV in hypertensive subjects [71]. Similarly, neither indapamide 2.5 mg or to canreonate 50 mg once daily in a 6-week open study had an effect on brachial–radial PWV despite adequate BP reduction [72]. The effect of hydrochlorthaizde 25–50 mg once daily was compared to a calcium channel blocker, felodipine 5–10 mg once daily for 6 weeks. Only felodipine markedly improved arterial distensibility in the aortic and limb circulations though it also had a significantly greater effect on SBP than hydrochlorthiazide [73]. Kool and coworkers compared the angiotensin converting enzyme inhibitor (ACEI) perindopril with the combination of hydrochlorthaizide and amiloride in mild-to-moderate hypertension for 6 months [74]. For the same BP reduction, hydrochlorthiazide had no effect on carotid and femoral distensiblity but decreased brachial artery stiffness only, whereas perindopril decreased stiffness in all three arteries. More recently we showed, in a randomized controlled trial comparing losartan 50 mg once daily with hydrochlorthiazide 25 mg in mild-to-moderate hypertension, that the latter had no effect on PWV or arterial wave reflection [75].

This lack of effect of diuretics on arterial stiffness in these studies is difficult to explain in the light of undoubted efficacy in reducing events in the hypertensive population, albeit in studies of 3–8 years duration. The modification of plasma potassium does not seem to be involved, as both indapamide and canreonate, two drugs with often opposite effects on potassium levels, had no effect on arterial stiffness [76]. Two other possible explanations have been put forward. First, the antihypertensive effect of diuretics in younger hypertensives is quite modest, which may result only in small passive changes in arterial stiffness. Second, the salt and water depletion induced by diuretics is known to activate both the renin–angiotensin and sympathetic nervous system, thus favouring arterial constriction and increased arterial stiffness [76]. This was tested by Benetos and colleagues, who compared, in a randomized double-blind trial of hypertensive patients, the arterial changes produced by hydrochlorthiazide 50 mg plus amiloride 5 mg once daily to hydrochlothiazide 25 mg in combination with captopril 50 mg [77]. Both groups produced the same reduction in BP but the diuretic combination only had an effect on carotid diastolic diameter, whereas only the ACEI-diuretic combination decreased arterial wave reflection. However, in elderly patients with isolated systolic hypertension, a diuretic combination of hydrochlorthiazide and amiloride has been shown to have a similar beneficial effect on arterial stiffness as assessed by ultrasound, reducing radial artery hypertrophy and improving carotid artery compliance, as the ACE inhibitor perindopril. A lack of counter-regulatory mechanisms may have contributed as the reactivation of the renin–angiotensin and sympathetic nervous system is blunted in elderly patients [78]. Of note, diuretics are particularly efficacious and significantly reduce events in this population.

It would therefore appear that despite significant reductions in BP, the thiazide group of diuretics is not associated with any change in either PWV or arterial wave reflection. This is of particular interest in that diuretics may therefore be used in comparative studies with other agents in essential hypertension. However, most of the studies done so far with diuretics on arterial stiffness have been both short-term and under-powered to detect small changes in PWV and arterial wave reflection.

β-blockers

In general the data suggests that most but not all β-blockers may have a favourable effect on arterial stiffness. Four-week treatment with bisoprolol 10 mg once daily in hypertensive subjects showed a reduction in carotid–femoral and brachial–radial but not in femoral–tibial PWV [79]. Also in a double-blind study propranolol 40 mg acutely reduced PWV in healthy volunteers [80]. In a double-blind 12-week study, both atenolol 50–150 mg and dilevalol 200–400 mg once daily reduced aortic, arm and leg PWV compared with placebo in hypertensive subjects but the authors believed that this was secondary to BP reduction. [81]. Barenbrock and coworkers showed an improvement in carotid distensibility with lisinopril 5–20 mg once daily but not with metoprolol 50–200 mg once daily in a double-blind trial of hypertensive patients [82]. Atenolol 100 mg was compared to cilazapril 5 mg once daily for 6 months in hypertensive patients in a double-blind study. There was an improvement in the elastic modulus of the ascending aorta using MRI with both drugs [83]. However, De-Cesaris and colleagues [84] in an open study in hypertensive patients compared atenolol 100 mg once daily with the calcium channel blocker nitrendipine 20 mg once daily. After 8 months treatment, only nitrendipine reduced brachial–radial PWV. Metoprolol 200 mg once daily was compared with the ACE inhibitor lisinopril 20 mg once daily in a 10 months open study in hypertensive subjects. For the same BP reduction, metoprolol had no effect on brachial–radial PWV compared with lisinopril [85]. Ting and colleagues measured aortic impedance, resistance, wave reflections and compliance in normotensive and hypertensive individuals using invasive methods and studied the acute effects of propranolol followed by phentolamine, nitroprusside, captopril and nifedipine in doses enough to normalize BP in the hypertensive patients [68]. Propranolol had an adverse effect on all these parameters, which was only partially offset by phentolamine. In a long-term, double-blind, randomized study comparing atenolol to fosinopril in 79 normotensive and 79 hypertensive subjects, both the drugs lowered BP equally but fosinopril had a significantly greater effect on carotid wave reflection than atenolol [86].

Atenolol 50 mg once daily was compared with a low dose combination of indapamide 0.625 mg and perindopril 2 mg once daily for 12 months in the REASON project [87,88]; both the drugs reduced DBP to the same extent, however, the indapamide/perindopril combination caused a significantly greater reduction in SBP both at the brachial and carotid artery. Both treatments reduced PWV to the same extent, however, only the indapamide/perindopril combination attenuated carotid wave reflections. However, the authors did not take into account the difference in heart rate on the two treatments, as heart rate is a significant confounding factor when studying wave reflection. A recent study has shown that atenolol and nebivalol both decrease PWV and also decrease the AIx when an allowance is made for the reduced heart rate [89].

Calcium-channel blockers

Numerous studies have looked at the effect of calcium channel blockers on arterial stiffness and in general all dihydropyrides have a positive effect reducing PWV. Nitrendipine 20 mg was compared to cadralazine 20 mg acutely in hypertensive patients. Both drugs reduced BP and carotid–femoral PWV [90]. Similar results were seen with 6-month treatment with lacidipine 4 mg once daily or nifedipine 20 mg twice daily, showing a reduction in brachial–radial PWV in hypertensive patients [91]. However, an acute study looking at the effect of lacidpine 2 mg showed no effect on carotid–femoral PWV compared with placebo despite adequate BP reduction [92]. Asmar showed a reduction in carotid–femoral PWV but not in brachial–radial or femoral–tibial PWV with nitrendipine 20 mg once daily for 4 weeks in hypertensive patients [93]. Nitrendipine 40 mg twice daily compared with atenolol 100 mg once daily for 8 months reduced PWV [85] and the same results were replicated by Tedeschi and colleagues [94]. Felodipine 5–10 mg once daily for 10 months produced a greater reduction in SBP with active reduction in PWV in the aorta, arm and leg when compared to a hydrochlorthaizde 25–50 mg/day [73]. Simon and colleagues in a double-blind study in hypertensive patients showed that isradapine 2.5–5 mg once daily but not metoprolol 50–100 mg daily reduced brachial–radial PWV [95]. A few studies have also looked at the effect of nondihydropyridine calcium-channel blockers on PWV, one study compared verapamil 240 mg once daily to the ace inhibitor trandolopril 2 mg and the combination of trandolopril 2mg/verapamil 180 mg for 6 months and showed similar reduction in PWV with the three different treatments [96]. Nifedipine also acutely reduces arterial wave reflection in hypertensive patients [68].

Although the most commonly used calcium-channel blocker, amlodipine, has not been formally studied, it would appear that as a member of the dihydropyridine group of antihypertensive calcium-channel blockers, it should reduce aortic PWV.

Drugs acting on the renin–angiotensin–aldosterone axis

Since angiotensin II stimulates the production of various types of collagen fibers [97] together with a number of growth factors [98], ACE inhibition and ATII receptor antagonism have been used as pharmacological models demonstrating *in vivo*, the effect of chronic inhibition of ATII on arterial stiffness [99–101].

ACE inhibitors

There is now an extensive body of literature on the effect of ACE inhibitors on arterial stiffness in both normotensive and hypertensive subjects (TABLE 2).

In an invasive study using intra-arterial captopril in hypertensive patients, large artery compliance was increased significantly [102]. In a placebo-controlled crossover study in patients with essential hypertension, acute administration of quinapril increased carotid artery distensibility and decreased PWV and arterial wave reflections, effects in part independent of BP reduction [103]. Perindopril accutely [104] and chronically improved aortic compliance, mainly by increasing distensibilty [74]. Both perindopril and nitrendipine decreased arterial stiffness in patients with end-stage renal disease [14]. Lisinopril and metoprolol reduced BP equally in hypertensive subjects but only lisinopril decreased arterial stiffness, an effect that persisted for at least 4 weeks after drug withdrawal [84]. While ramipril reduced PWV in hypertensive subjects treated for

42 days, there was no relationship between the changes in PWV and the reduction in BP [105]. Trandolopril increased brachial artery compliance, reversed left ventricular hypertrophy and decreased arterial wall thickness in hypertensive patients treated for 1 year, the benefit persisting 1 month after discontinuation of treatment [106]. In a double-blind comparison of fosinopril and atenolol in hypertensive patients over a 8-week period, the ACEI was significantly more effective than the β-blocker in decreasing arterial wave reflections despite the same BP reduction with the two treatments [86]. Compared with hydrochlorthaizide, cliazapril improved aortic stiffness in hypertensive subjects treated for 3 months as measured by PWV during hand-grip [107]. Quinapril decreased PWV, regressed left ventricular hypertrophy and iliac intima–media thickness independently of BP reduction in a 6-month study of hypertensive subjects [108]. Antihypertensive doses of perindopril but not hydralazine were shown to prevent the chronic accumulation of aortic collagen. The collagen reduction was noticed with nonhypertensive doses of perindopril and paralleled the decrease in converting enzyme measured in the aortic tissue but not in the plasma [100]. Mostly, the effects of ACEI on arterial stiffness are more pronounced in the presence of certain gene polymorphisms, such as the AT1 receptor gene polymorphism [109].

The Complior Study, which involved over 2000 hypertensive patients, showed significant reductions in PWV at 6 months with perindopril [110]. In a comparative study (the REASON project [87]), the combination of perindopril with inadapamide and atenolol both significantly decreased PWV [88]. However, only the perindopril/indapamide combination attenuated carotid wave reflections with a preferential reduction in aortic systolic and PP. There is now a large body of acute and long-term double-blind clinical studies in a hypertensive population which have shown ACE inhibitors consistently to have a favourable effect on arterial stiffness, when compared with other antihypertensive agents. This benefit is a class effect and appears to be independent of BP reduction. The decrease in arterial intima–media thickness, aortic collagen and persistence of these effects after discontinuation of therapy suggest that ACEI not only have functional effects on the vessel wall but may also promote vascular remodelling and structural changes.

Angiotensin II receptor antagonists

Given the favourable effects of ACE inhibition, it was not unexpected that ATII antagonists had similar effects. The ATII receptor antagonist valsartan was added to therapy for 2 weeks in poorly controlled hypertensives who were on at least three antihypertensive drugs including an ACE inhibitor and arterial wave reflections measured by the AIx significantly reduced [111]. In a 4-week, cross-over study with the AT_1 receptor antagonist losartan compared to hydrochlorthiazide in patients with essential hypertension, for the same BP, only losartan decreased PWV and the aortic AIx and enhanced PP amplification [75]. Similar results have been seen with valsartan [112]. The decrease in PWV and arterial wave reflection appeared to be independent of BP reduction. Schriffrin and colleagues treated hypertensive patients with either losartan or atenolol for 1 year [113]. BP was reduced comparably in both groups but only in the losartan-treated patients was there a decrease in media:lumen ratio of microvasculature obtained from subcutaneous gluteal biopsy specimens and an improvement in acetylcholine-induced endothelial-dependent relaxation. In a clinical study of hypertensive Type 2 diabetic patients, telmisartan significantly reduced PWV compared to placebo [114]. In a randomized cross-over study in hypertensive patients comparing valsartan 160 mg/day with captopril 100 mg/day, both therapies produced a similar reduction in PWV and AIx which remained significant when corrected for BP reduction. Of note, when both therapies were combined, the reduction in arterial stiffness was significantly greater compared with monotherapy even when corrected for the greater BP reduction with the combined regimen [115]. The study raises the possibility that agents that independently reduce arterial stiffness may in combination have an additive effect [115]. Using finger plethysmography, losartan increased arterial compliance after 4 weeks of treatment [116]. There was no correlation between the reduction in BP and the effect on arterial compliance suggesting a BP independent effect. Omipatrilat, which is a dual ACE and neutral endopepdidase inhibitor-vasopepdidase inhibitor, in a 12 week double-blind study in hypertensive patients, when compared to enalapril, was significantly more effective in reducing BP and also produced a greater reduction in carotid–femoral PWV, although the difference did not achieve statistical significance [117].

Aldosterone antagonism

In recent years, several *in vitro* investigations have indicated that aldosterone may act directly on large arterial vessels. Immunohistochemical studies have shown that the mineralocorticoid receptors predominate in the aorta and their distribution decreases with the size of the arteries [118]. In hypertensive subjects, increased aortic stiffness and plasma aldosterone levels are statistically associated [119]. In contrast, in hypertensive patients, studies of 2-week duration did not identify a change in brachial artery stiffness after administration of spironolactone [4]. Six-week treatment in an open study with the aldosterone antagonist, canreonate 50 mg daily, did not alter PWV in a hypertensive population [72]. More recently, however, in a randomized, controlled, 1-month study in a hypertensive population, comparing spironolactone 50 mg with bendrofluazide 2.5 mg, only spironolactone reduced PWV and AIx and following adjustment for change in BP, the reductions remain significant [120].

A preliminary study suggests that the more selective aldosterone antagonist eplerenone may also reduce aortic PWV in hypertensive patients [121].

Expert opinion & five-year view

A large number of antihypertensive drugs have been shown to reduce arterial stiffness. The greatest evidence is in relation to their effect on decreasing PWV but there is increasing evidence that they also reduce arterial wave reflection. Since these techniques examine stiffness in regional areas and are affected by somewhat different factors, a selective effect on only one variable is not unexpected. Further comparative studies on commonly employed techniques are required and until consensus emerges studies should incorporate these two measures to ensure selective or regional effects on stiffness are not overlooked.

Most evidence relates to ACEI, in both acute and long-term therapy, but it appears that ATII antagonists show a similar effect. Longer-term studies are required to see whether the effects are associated with vascular remodelling but preliminary studies looking at the microvasculature are encouraging. New therapies influencing elastin and collagen function or turnover may result in drugs devoid of antihypertensive effect that can reduce stiffness. Experimentally aminoguanidine, which reduces accumulation of advanced glycation end products on the extracellular matrix, reduced the age-related increase in collagen cross-linking and aortic PWV [122,123]. An exploration of the molecular basis of stiffness and the role of genetic polymorphisms in these systems will enhance targeting of therapy. The finding that decreasing PWV may be independently associated with decreased cardiovascular events has now made arterial

Key issues

- Arterial stiffness is now an established cardiovascular risk factor and is probably the single best prognostic index for future events in the hypertensive population
- Reliable noninvasive techniques, aortic pulse wave velocity (PWV) and arterial pulse wave analysis, are now routinely used in many hypertension clinics and are incorporated into ongoing large clinical trials.
- Not all antihypertensive agents reduce stiffness. The strongest evidence is for angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and calcium channel blockers, which have been shown to reduce PWV and arterial wave reflection. Evidence for β-blockers is less clear-cut, although most studies show a reduction in PWV, and diuretics have no effect in essential hypertension. Nitrates reduce arterial wave reflection, in particular and may have a role in isolates systolic hypertension but they have no effect on aortic PWV.
- Therapy targeted at reducing stiffness independently of antihypertensive effect is under study.

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