

Frontiers in Research Review: Arterial Function

AGE, HYPERTENSION AND ARTERIAL FUNCTION

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SUMMARY

1. Ageing exerts a marked effect on the cardiovascular system and, in particular, the large arteries. Using a variety of techniques to assess arterial stiffness, many cross-sectional studies have demonstrated a significant relationship between age and aortic stiffness, although the age-related changes observed in peripheral arteries appear to be less marked.

2. The relationship between arterial stiffness and hypertension is more complex. The distending, or mean arterial, pressure is an important confounder of measurements of arterial stiffness and, therefore, must be taken into consideration when assessing arterial stiffness in hypertensive subjects or investigating the effect of antihypertensive agents. Current methods for correcting for differences in distending pressure involve pharmacological manipulation, statistical correction or mathematical manipulation of stiffness indices.

3. Many studies have provided evidence that both peripheral (muscular) and central (elastic) arteries are stiffer in subjects with mixed (systolic/diastolic) hypertension compared with normotensive subjects. However, it is unclear to what extent differences in mean arterial pressure explain the observed differences in hypertensive subjects. In contrast, isolated systolic hypertension is associated with increased aortic, but not peripheral artery, stiffness, although the underlying mechanisms are somewhat unclear.

4. Traditional antihypertensive agents appear to reduce arterial stiffness, but mostly via an indirect effect of lowering mean pressure. Therefore, therapies that target the large arteries to reduce stiffness directly are urgently required. Agents such as nitric oxide donors and phosphodiesterase inhibitors may be useful in reducing stiffness via functional mechanisms. In addition, inhibitors or breakers of advanced glycation end-product cross-links between proteins, such as collagen and elastin, hold substantial promise.

Key words: ageing, arterial stiffness, augmentation index, drug therapy, hypertension, pulse wave velocity.

INTRODUCTION

Large arteries were once considered as inert conduits, but are now recognized to play an important physiological role in buffering the oscillatory changes in blood pressure resulting from intermittent ventricular ejection. This action reduces pulse pressure, smoothes peripheral blood flow and improves the efficiency of the cardiovascular system as a whole. Stiffening of large arteries leads to a number of adverse haemodynamic consequences, including a widening of pulse pressure and, ultimately, the development of isolated systolic hypertension. This is now the most common form of hypertension in the UK and US and carries a threefold increase in the risk of stroke and a doubling in the risk of heart disease.¹ Aortic stiffness is now recognized as an important, independent determinant of cardiovascular risk in a variety of patient groups. Aortic pulse wave velocity (PWV) is an independent predictor of cardiovascular mortality in subjects with end-stage renal failure,² hypertension,³ diabetes mellitus⁴ and in those aged over 70 years.^{5,6} More recently, three publications have demonstrated that aortic PWV independently predicts outcome in unselected, middle-aged and older adults.^{6–8}

In addition to acting as a 'risk marker', arterial stiffening may also promote disease by a number of different mechanisms.^{9,10} Elevated systolic pressure promotes left ventricular hypertrophy and ventricular stiffening, ultimately leading to diastolic dysfunction and heart failure.¹⁰ Low diastolic pressure reduces coronary blood flow, exacerbating the situation and predisposing to ischaemia. A wide pulse pressure is also transmitted to other arteries, such as the carotid, which undergo a process of remodelling to reduce wall stress, leading to intima-media thickening.¹¹ Shear stress rate also falls as arteries stiffen,¹² reducing endothelial nitric oxide (NO) production, a key event in atheroma formation. The increased pulse pressure due to stiffening of central large arteries has also been implicated in possible microvascular abnormalities in the brain and kidney.¹³ Finally, arterial stiffening increases cyclical stresses within the wall, accelerating elastic fibre fatigue–fracture, further stiffening the vessel and creating a vicious circle. The present review will focus on the effects of age and hypertension on the mechanical properties of the large arteries and explore the therapeutic potential of the large arteries.

ASSESSING ARTERIAL STIFFNESS

Arterial stiffness can be assessed using a variety of different techniques. These broadly fall into measures of stiffness at one discrete location (e.g. ultrasound-derived distensibility and compliance), more regional measures (such as PWV) and measures of systemic compliance

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and wave reflection.¹⁴ Pulse wave velocity is often considered as the current 'gold standard' measure of stiffness. It is a measure of the speed with which the pressure waveform propagates along a segment of the arterial tree; the stiffer the vessel, the faster the wave travels. Pulse wave velocity is inversely related to distensibility according to the 1922 Bramwell-Hill equation:

$$PWV = \sqrt{1/D\rho}$$

where D is distensibility ($D = (\Delta V/V)/\Delta P$, where V is the volume or diameter and P is the pressure) and ρ is the density of blood.

Although not the focus of the present review, it is important to recognize that each technique yields subtly different information concerning vessel structure and function and the various indices quoted in publications are not always interchangeable. More detailed information about the biomechanical properties of arteries and the various stiffness indices are available from a variety of sources.^{12,15,17}

AGEING AND ARTERIAL STIFFNESS

Ageing is associated with a number of profound changes in the cardiovascular system. One of the most consistent and well-studied changes is the gradual dilatation and hardening of the large arteries, the process of arteriosclerosis. Although this was well recognized centuries ago:

'In extreme old age, the arteries themselves, the grand instrument of the circulation, by the continual apposition of earth, become hard and as if it were bony, till, having lost the power of contracting themselves they can no longer propel the blood, even through the largest channels, in consequence of which death naturally ensues.' (John Wesley, 1703–1791)¹⁶

only more recently have we been able to quantify such changes and begin to understand the underlying mechanisms.

In their landmark 1922 paper, Bramwell and Hill were among the first to demonstrate a significant correlation between aortic PWV and age.¹⁸ Subsequently, their observation has been confirmed in a number of different populations,^{19–25} including in both urban and rural locations and in areas with a low incidence of atherosclerosis.^{26,27} It has also been demonstrated using a variety of different techniques and indices of stiffness, including analysis of impedance spectra,^{28,29} determination of aortic compliance/distensibility using both ultrasound^{23,30,31} and magnetic resonance imaging,³² pressure waveform analysis^{22,33,34} and *ex vivo* post-mortem analysis of aortae.³⁵ Most of these cross-sectional studies suggest a linear relationship between aortic stiffening and age. However, closer analyses of data and one small ($n = 60$) longitudinal study with 20 years follow-up data³⁶ suggest a non-linear effect, with acceleration of age-related aortic stiffening after the 5th decade of life. We have recently examined this important question in a cohort of 4001 healthy individuals from the Anglo-Cardiff Collaborative Trial (ACCT).²²

As hypothesized, there was a curvilinear relationship between age and aortic PWV, which was best represented by a second-order polynomial (Fig. 1). Age-related changes in aortic PWV were less marked in younger subjects and became increasingly prominent after the age of 50 years, such that between the ages of 20 and 30 years PWV would be expected to increase by approximately 0.4 m/s, but by approximately 1.8 m/s between the age of 70 and 80 years. This rapid rise in aortic PWV after the 5th decade of life mirrors the age-related widening in brachial pulse pressure, which has previously

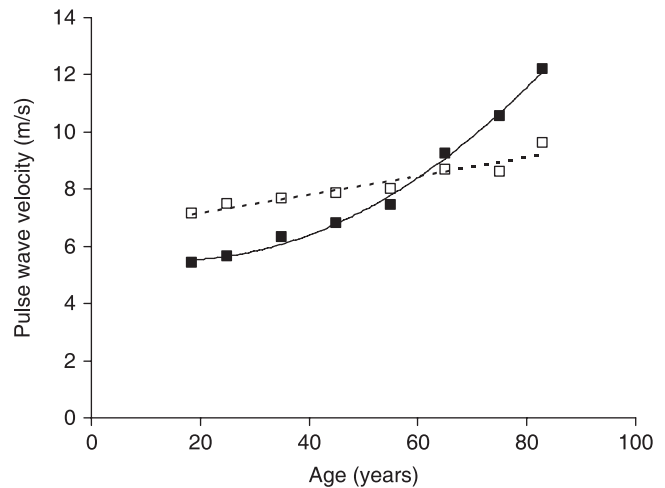


Fig. 1 Age and aortic and brachial pulse wave velocity (PWV) in healthy subjects. Data from the Anglo-Cardiff Collaborative Trial (ACCT) study population.²² Note the relatively linear relationship for brachial PWV (—□—) compared with the curved relationship for aortic PWV (—■—).

been described in nearly all populations world-wide.³⁷ This effect would also explain the marked rise in the prevalence of isolated systolic hypertension in later life, given that this form of hypertension results primarily from stiffening of the large arteries.

The relationship between gender and aortic stiffening is controversial. A greater increase in aortic stiffness with age among women, particularly after the menopause, has been reported and attributed to changes in hormonal status.³⁸ Such an effect would provide one possible explanation for the greater prevalence of isolated systolic hypertension among women. Indeed, a steeper age-related rise in pulse pressure among women has been reported previously.³⁹ However, most studies have not found any difference in age-related aortic stiffening between men and women.^{25,39–41} Indeed, in the ACCT cohort, although aortic PWV was on average approximately 2% lower in women than men, there was no difference in the rate of stiffening between genders.²² Thus, most available data suggest that factors other than accelerated aortic stiffening must be responsible for the greater widening of pulse pressure among women with age. Clearly this question deserves more intensive investigation, in large cohorts, using a variety of different indices, including regional stiffness measurements, before a definitive answer can be provided.

In contrast with the marked age-related changes in stiffness that occur in the human aorta, peripheral muscular arteries are much less affected. Brachial PWV rises much more gradually with age,^{21,22,26} as does femoral PWV.²⁶ Elastic modulus and compliance of the radial and brachial arteries also changes very little with advancing age.^{25,41,42} Perhaps, unsurprisingly, given its structure, the carotid artery would appear to have a somewhat intermediate phenotype and does display a degree of age-related stiffening.^{41–44} The relative immunity of the peripheral arteries to stiffening with age is usually attributed to a much lower ratio of elastin to smooth muscle and collagen and lower cyclical stress, but may also reflect other biological processes, such as the ability of arteries to remodel and the mechanisms by which they achieve this.

The augmentation index provides a composite measure of wave reflection and systemic arterial stiffness. Several studies have consistently reported a gradual rise in augmentation index with age.^{22,33,34}

Interestingly, data from the ACCT study suggest that this is, again, non-linear and that greater changes are seen with age in younger individuals and that after the age of 55 years the augmentation index changes relatively little.²² This increase in wave reflection with age means that central (aortic) systolic pressure rises more steeply than in the brachial artery. Therefore, the normal amplification of pulse pressure from central to peripheral arteries actually declines with age and, in the oldest individuals, central and peripheral pulse pressures are not markedly different. There is also a marked gender difference in augmentation index, with higher values among women at all ages.^{22,34} The lower average height among women compared with men accounts for most, but not all, of this difference.

Unfortunately, most data concerning age-related arterial stiffening come from cross-sectional observations. Longitudinal data concerning aortic PWV are only available from two relatively small studies. Monnier followed 60 healthy subjects over 20 years and reported accelerated aortic stiffening after the age of 45 and noted that there was considerable variation in the rate of stiffening among the cohort.³⁶ Benetos *et al.* studied a mixed cohort of approximately 500 hypertensive and normotensive individuals for 6 years.⁴⁵ Blood pressure at baseline, creatinine and age were the most important determinants of aortic stiffening over the follow-up period. However, there were fewer than 300 normotensive individuals and data concerning potential risk factors for accelerated age-related stiffening, such as inflammation, insulin resistance, body fat distribution or exercise levels, were not reported.

Mechanisms responsible for arteriosclerosis

Arteriosclerosis is often considered to be the result of simple 'wear-and-tear' in the large arteries, a consequence of fatigue fracture of the elastic elements within the media. Indeed, by the age of 60 years the average individual will have experienced over 2 billion stress cycles of the aorta (average heart rate \times age). However, we now recognize that arteriosclerosis is actually pathological and is neither inevitable nor irreversible.⁹ Several indigenous human populations do not show any age-related rise in pulse pressure with age.^{46,47} Moreover, in animal models, inhibiting angiotensin receptor signalling markedly delays vascular ageing⁴⁸ and breaking non-enzymatic collagen cross-links reduces arterial stiffness in aged animals⁴⁹ and humans.⁵⁰ Furthermore, within populations, arterial stiffness and the rate of stiffening varies considerably.⁴⁵ Conditions such as diabetes and renal dysfunction are also associated with accelerated arteriosclerosis, leading to so-called 'premature vascular ageing'. This makes arterial stiffening an attractive therapeutic target but, in order to fully exploit this novel target organ, a better understanding of the factors responsible for arterial stiffening is required.

Unfortunately, in contrast with atherosclerosis, the pathophysiological processes underlying arteriosclerosis have attracted much less attention. Nevertheless, over the last century a number of age-related structural changes within the arterial wall have been described, including deposition of collagen, loss of elastin, medial calcification and formation of non-enzymatic cross-links between microfibrils;^{9,10} Each of these changes is likely to contribute to the arteriosclerotic process, but their relative importance is unclear, as is the variation between individuals. The aortic media also contains sheets of smooth muscle cells, which are tangentially attached to the elastic lamellae; by varying the distribution of force between the elastic and collagenous fibres, changes in smooth muscle tone provide dynamic, or functional,

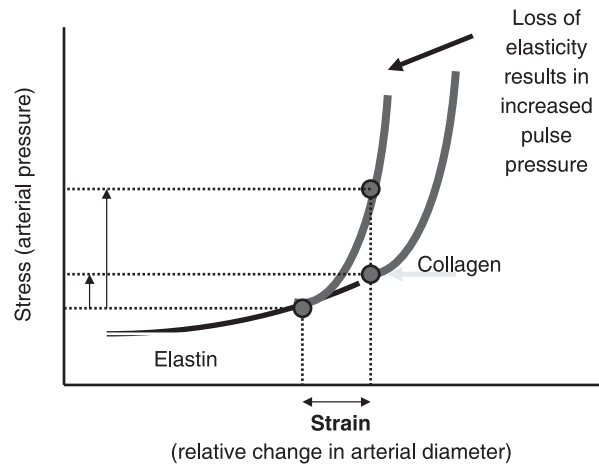


Fig. 2 Stress–strain relationship of the human aorta. Non-linear relationship between arterial stress (pressure) and strain (change in relative diameter). At lower strains, the stress is taken up predominantly by the elastin fibres. At higher strains, the stress is taken up by the stiffer collagen fibres. The effects of age or loss of arterial elasticity are generally to engage the collagen fibres at lower strain, hence effectively increasing pulse pressure for the same strain (as indicated by the arrows).

regulation of stiffness.⁵¹ Interestingly, we⁵² and others⁵³ have recently shown that endothelial NO regulates large artery stiffness *in vivo* and, therefore, the reported decline in endothelial NO production with age may underlie some of the age-related arterial stiffening.

HYPERTENSION AND ARTERIAL STIFFNESS

The relationship between arterial stiffness and hypertension is complex and often misunderstood. Arteries such as the aorta, by virtue of their structure, are elastic. Thus, when a force is applied to them they extend; the less they extend, the 'stiffer' the vessel. However, in the case of arteries this is not a linear relationship: at higher applied forces vessels become stiffer (i.e. they are more resistant to extension). One way in which this behaviour can be quantified is by examining the stress–strain relationship, where stress is the force per unit area applied (mean arterial pressure) and strain is the fractional increase in tissue dimension relative to the unloaded tissue (relative change in arterial diameter). The ratio of stress over strain is called Young's elastic modulus. As shown in Fig. 2, arteries have a non-linear stress–strain relationship; thus, the elastic modulus depends on the stress at which it is measured. This is the same for other indices of arterial stiffness, such as distensibility or PWV. Therefore, when making an *in vivo* assessment of arterial stiffness, the measured value will depend on the distending pressure (i.e. the mean pressure). Because blood pressure varies considerably both within and between individuals, this introduces an important confounding variable that must be taken into consideration. It is of particular importance when making measurements in hypertensive subjects or investigating the effect of antihypertensive agents.

Many ways of correcting for differences in distending pressure have been developed, including altering the pressure around the artery (which really is only applicable to limb vessels), changing mean pressure pharmacologically (which introduces the confounding influence of the direct action of drugs on the large arteries), statistical correction or mathematical manipulation of stiffness indices. Each

approach has its own advantages and disadvantages. Two widely used methods are calculation of the stiffness index β ⁵⁴ and isobaric compliance.⁵⁵ Although these indices make use of the relationship between diameter and pressure (exponential for the β index), comparison between different arteries or with treatment that alters blood pressure can become difficult to interpret. The β index is non-dimensional and has been used to compare normal and hypertensive subjects⁵⁶ and specific abnormalities, such as Marfan's syndrome.⁵⁷ Isobaric compliance can be difficult to interpret because a specific pressure value is required for comparisons⁵⁸ and adaptive changes (such as wall dimensions) to different normal operating pressures can give different values for similar intrinsic wall properties. A further complication is introduced in both indices when the diameter is measured at one location (e.g. carotid artery) and the pressure used to determine the index at another (e.g. brachial artery). Although comparisons at the same mean pressure may be justified, calculations involving pulse pressure can give different results, especially with similar peripheral pulse pressure values but markedly different pulse wave shape.⁵⁴

Statistical correction is widely used, but it is important to ensure that the observed relationship between mean pressure and stiffness is linear within the study group before simply adopting standard multiple linear regression. It is also important to appreciate that correction should be made for mean and not systolic arterial pressure. As is perhaps apparent from the basic physiology underlying arterial haemodynamics, there is a much higher degree of correlation between stiffness indices and systolic pressure⁵⁹ because systolic pressure is, to some extent, physiologically dependent on stiffness. Conversely, there is less correlation between mean pressure and stiffness, because mean pressure is little influenced by stiffness. Therefore, correction of stiffness indices for systolic pressure may lead to erroneous results.

In contrast with the confounding influence of mean pressure, pulse pressure provides an indirect index of the stiffness of the large arteries because it depends largely on stroke volume, the compliance of the large arteries and the influence of reflected pressure waves. This is important because it suggests that essential hypertension should not be considered as a single phenotype; rather, that the underlying physiological cause of 'widened pulse pressure hypertension' (i.e. isolated systolic hypertension) may be different from 'high mean pressure hypertension' (i.e. mixed (systolic/diastolic or diastolic) hypertension; Fig. 3). For this reason, we will discuss the evidence concerning large artery function in these two forms of hypertension separately.

Mixed (systolic/diastolic) hypertension

This is the 'classical' form of essential hypertension and most commonly affects young and middle-aged subjects. The main physiological abnormality in this form of hypertension, at least once established, is an increased peripheral vascular resistance. Several groups have examined muscular artery stiffness in such individuals. Gribbin *et al.* reported increased brachial artery PWV in hypertensive individuals compared with normotensive subjects, but this difference disappeared after transmural pressure was normalized using a pressure box.⁶⁰ Several other groups have confirmed this using a variety of different techniques.^{61–63} Therefore, the current consensus view is that although muscular artery stiffness is increased in hypertensive subjects, this is related directly to the higher operating pressure and stiffness is normal when pressure is reduced to the normal

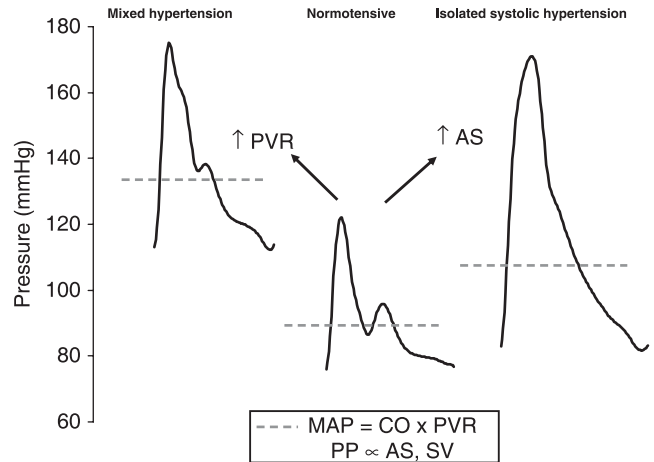


Fig. 3 Physiology of essential hypertension. Examples of arterial pressure waveforms from a normotensive subject, a patient with mixed (systolic/diastolic) hypertension and a patient with isolated systolic hypertension. MAP, mean arterial pressure (the product of cardiac output (CO) and peripheral vascular resistance (PVR)); PP, pulse pressure (proportional to stroke volume (SV) and arterial stiffness (AS)). In mixed hypertension, the primary haemodynamic abnormality is an increased PVR, whereas in isolated systolic hypertension, the primary abnormality is increased AS.

range. Interestingly, muscular arteries tend to dilate in hypertensive subjects, which may lead to paradoxical increased compliance in hypertensive subjects. Increased wave reflection^{28,64} and augmentation index¹⁵ have also been consistently reported among hypertensive subjects. However, augmentation index is also dependent on mean arterial pressure⁶⁵ and it is unclear to what extent an increased mean pressure explains the observed differences in hypertensives.

The central 'elastic' arteries are also stiffer in subjects with essential hypertension. Indeed, aortic PWV is higher in such subjects compared with normotensive controls^{66–70} across a wide spectrum of ages.^{67,69} Such effects have been confirmed using other techniques, such as assessing aortic input and characteristic impedance,^{28,64} and ultrasound-derived indices.⁷¹ The aorta varies considerably in structure along its length, suggesting that regions may be influenced differentially by conditions such as hypertension. However, few investigators have undertaken systematic measurements of regional aortic stiffness. Ting *et al.*⁶⁸ assessed regional velocity along the aorto-femoral trunk and found only iliac PWV to be elevated. However, this requires confirmation in a considerably larger number of patients. Whether increased aortic stiffness is simply due to the higher operating pressure of hypertensive arteries is less clear. It is obviously more difficult to change local pressure in the aorta physically than in the periphery, which has led some investigators to alter systemic pressure pharmacologically. Both Ting *et al.*⁶⁴ and Merillon *et al.*²⁸ found that sodium nitroprusside infusion, which reduced mean arterial pressure, normalized aortic stiffness, suggesting that isobaric stiffness was normal in hypertensives.

It is also unclear whether arterial stiffness is increased in the normotensive offspring of hypertensive versus normotensive parents. In the offspring of hypertensive parents, increased blood pressure and carotid artery stiffness have been reported,⁷² whereas in a small sample of subjects, aortic PWV was normal despite significant differences in blood pressure.⁷³ Yasmin *et al.*⁷⁴ reported that although brachial PWV was normal in the offspring of hypertensives, central

augmentation index was elevated, even after correcting for differences in blood pressure. However, in a more recent study, the observed elevations of aortic PWV and central augmentation index in the offspring of hypertensives disappeared after correcting for differences in blood pressure.⁷⁵ Nevertheless, there is a marked paucity of data in this area and many of the published studies are small, lack adequate matching and have included subjects with mixed hypertension and systolic hypertension. Therefore, whether mixed hypertension *per se* is associated with aortic stiffening remains to be proven definitively.

Isolated systolic hypertension

In contrast with mixed systolic/diastolic hypertension, isolated systolic hypertension is predominantly a disease of older individuals. It is estimated to affect between one-third and one-half of those over 60 years of age, making it the most common form of hypertension in the UK and US, and is frequently resistant to treatment, with many patients never reaching target pressures. Although once considered to be benign and a 'natural' consequence of ageing, isolated systolic hypertension is now recognized as a major risk factor for cardiovascular disease. Indeed, pulse pressure is a stronger predictor of cardiovascular risk in older adults than diastolic or mean pressure.⁷⁶

Physiologically, stroke volume and the elasticity of the large arteries are the principle determinants of pulse pressure. Early investigators recognized this fact¹⁸ and demonstrated a positive relationship between brachial pulse pressure and aortic PWV.⁶⁶ This suggests that isolated systolic hypertension, which, by definition, is associated with a widened pulse pressure, should pathophysiologically be a condition of stiff arteries.

Nichols *et al.* were among the first to investigate haemodynamics in older subjects with systolic hypertension.⁷⁷ They found an elevated aortic characteristic and input impedance in such individuals compared with age-matched normotensive controls, indicative of aortic stiffening and evidence of increased wave reflection. Two subsequent studies, using ultrasound-derived aortic distensibility, have confirmed increased aortic stiffness in systolic hypertension.^{78,79} However, once again, the confounding effect of differences in mean arterial pressure needs to be considered, although mean pressure is typically elevated to a lesser degree than in subjects with mixed systolic/diastolic hypertension.

Stella *et al.* reported reduced radial and carotid artery isobaric distensibility using ultrasound in a small group of systolic hypertensives.⁸⁰ Although Mitchell *et al.* reported an elevated aortic and brachial PWV and proximal aortic stiffness in a much larger cohort of individuals (128 subjects and 30 normotensive controls), only differences in proximal stiffness remained significant after correcting for mean pressure.⁸¹ We have recently reported increased aortic, but not brachial, isobaric PWV in 116 untreated subjects with systolic hypertension versus 114 controls.⁸² Interestingly, we were unable to find any difference in augmentation index between the groups.

The available data indicate that systolic hypertension is associated with a preferential increase in aortic, but not peripheral, artery stiffness. Moreover, this increased stiffness appears to be a real effect and not a consequence of a higher mean arterial pressure, as with the mixed systolic/diastolic form of hypertension. Given the close relationship between age, widening of pulse pressure and arterial stiffening, isolated systolic hypertension may be viewed as an extreme form of age-related aortic arteriosclerosis. The mechanisms underlying this are unclear, but degeneration of elastic wall components,

endothelial dysfunction and medial calcium deposition all probably play a role. Mitchell *et al.*⁸¹ have suggested that there is functional aortic stiffening due to narrowing of the aortic root, but this remains speculative and does not fit the classical pathological description of the condition.¹⁵

THERAPEUTIC POTENTIAL OF LARGE ARTERIES

Many studies have examined the influence of pharmacological therapies on arterial stiffness. However, most of these studies have been conducted in small numbers of subjects, without adequate controls for changes in mean arterial pressure, and have produced conflicting results (for a detailed review, see Mahmud and Feely⁸³). One problem is that many of the studies conducted thus far have concentrated on the effects of traditional antihypertensive agents to reduce arterial stiffness, which mostly act indirectly, by lowering mean arterial pressure, rather than having a direct effect on the large arteries. Indeed, this may explain why many patients with isolated systolic hypertension are resistant to treatment. Therefore, there is an urgent need for novel therapies that can selectively target the large arteries in order to reduce arterial stiffness directly.

In this respect, agents that reduce arterial stiffness via functional mechanisms, such as altering smooth muscle tone, may be useful. Glyceryl trinitrate reduces arterial stiffness in subjects with isolated systolic hypertension⁶¹ and many trials have demonstrated sustained reductions in blood pressure with nitrate preparations.⁸⁴⁻⁸⁶ In addition, specific inhibitors of phosphodiesterase, such as sildenafil, may also be helpful by upregulating endogenous NO production, whereas reducing the effects of vasoconstrictors, such as endothelin-1, using selective ET_A receptor antagonists, may also be of use. Alternatively, therapies that either promote or reduce the activities of enzymes and/or their endogenous inhibitors, involved in the breakdown of elastin and collagen, present an intriguing target for novel therapies to reduce arterial stiffening. In addition, recent data suggest that the thiazolium derivative ALT-711, which breaks down established advanced glycation end-product cross-links between proteins such as collagen and elastin, can reduce arterial stiffness in older individuals with increased arterial stiffness.⁵⁰ Even newer therapies that aim to inhibit the formation of cross-links are currently undergoing clinical development and are awaited with interest. However, further studies are required to determine whether arterial structure or function provides the most effective therapeutic target for the pharmacological treatment of increased arterial stiffness.

CONCLUSIONS

An expanding body of evidence demonstrates that arterial stiffness is an important, independent predictor of outcome and appears to promote the development of cardiovascular disease via a number of different pathways. The precise mechanisms underlying the process of arterial stiffening remain unclear. However, ageing and hypertension exert marked effects. Indeed, ageing is strongly associated with the development of isolated systolic hypertension, probably the most common clinical manifestation of arterial stiffening and a condition associated with considerable excess cardiovascular risk. Currently, there are relatively few therapeutic strategies that reduce arterial stiffness via direct effects on the large arteries. Nitrates are one such strategy and appear to be useful in treating isolated systolic

hypertension. In addition, newer, novel therapies targeted at breaking collagen cross-links or preventing their formation may be effective in reducing arterial stiffness and the associated cardiovascular risk.

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