Large artery stiffness in hypertension

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Effects of hypertension on large arteries **The mechanical properties of large arteries make a major contribution to cardiovascular haemodynamics through the buffering of stroke volume and by propagation of the pressure pulse. A sustained increase in blood pressure often leads to stiffness of the large arteries, especially when other risk factors are present. The increased stiffness, in turn, aggravates hypertension by increasing systolic blood pressure and can induce cardiac hypertrophy and arterial lesions. Epidemiological studies strongly suggest that subjects with stiffer arteries have a high pulse pressure, and that stiffening of large arteries is associated with excess morbidity and mortality independently of other cardiovascular risk factors.**

Environmental and genetic factors **Apart from high blood pressure and ageing, various environmental and genetic factors that influence the composition of the extracellular matrix of the arterial wall can increase arterial stiffness. Clinical studies suggest that the presence of some genotypes may be a particularly important risk marker for arterial stiffness, and may modulate the effects of hypertension, ageing and lipids on large arteries.**

Effects of antihypertensive drugs **The development of accurate, non-invasive methods has now made it possible to detect alterations of the large arteries. Among antihypertensive drugs, angiotensin converting enzyme inhibitors and calcium channel blockers have proved to be highly effective in improving large artery compliance, and have shown no adverse effects on metabolic factors that can alter arterial structure and function such as lipids, plasma glucose and insulin tolerance. Therefore these drugs may be particularly suitable for treating patients with increased arterial stiffness. Finally, a determination of genotypes may be helpful in the future in choosing antihypertensive therapy.**

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Physiological role of the large arteries

The arterial system has two distinct and interrelated functions: first, to deliver an adequate supply of blood to the different tissues (conduit function) and second, to transform the discontinued (systolic) ventricular ejection to a continuous (systolodiastolic) peripheral flow (cushioning function).

The conduit function of large arteries

For the conduit function, large arteries must deliver an adequate quantity of blood from the heart to peripheral organs and tissues as required for metabolic activity. To allow efficient metabolic exchange, a continuous, steady and constant arteriolar and capillary blood flow is required. To maintain such a steady flow, a steady pressure head must be applied to the blood in order to overcome energy losses through blood viscosity and friction (resistance to flow). From the haemodynamic point of view, the function of arteries as conduits is exclusively related to steady (mean) blood pressure and blood flow, and the relationship between these two parameters which defines vascular resistance. Mean blood pressure, defined by measuring the area under the blood pressure curve and dividing this area by the time interval involved, is entirely determined by cardiac output and vascular resistance. The efficiency of the conduit function depends on the calibre of the arteries and the constancy of mean blood pressure, with an almost imperceptible mean pressure gradient between ascending aorta and peripheral distributing arteries.

The cushioning function of large arteries

The principal role of arteries as cushions is to dampen the pressure oscillations resulting from intermittent ventricular ejection [1,2]. Large arteries can instantaneously accommodate the volume of blood ejected from the heart, storing part of the stroke volume during systolic ejection and draining this volume during diastole, permitting continuous perfusion of organs and tissues (Windkessel effect).

During systole, the rise in pressure up to the time of peak velocity depends on left ventricular performance and the distensibility of the ascending aorta. Peak systolic pressure will be greater if the arterial wall is stiffer. However, after the closure of aortic valves, arterial pressure gradually falls as blood is drained to the peripheral vascular network. The minimum diastolic blood pressure is determined by the duration of the diastolic interval and the rate at which the pressure falls. The rate of pressure fall is influenced by the rate of outflow (i.e. peripheral resistance), and by viscoelastic arterial properties. At a given vascular resistance, the fall in diastolic blood pressure will be greater if the rigidity of large arteries is increased.

The viscoelastic properties of arterial walls are also a determinant of the speed of propagation of the arterial pressure wave (pulse wave velocity) and of the timing of wave reflections.

Thus stiffening of the arteries increases the pulse wave velocity and may be responsible for an earlier return of the reflected waves, which can be superimposed on the incident pressure wave, thus contributing further to the increase in pulse pressure and systolic blood pressure.

Atherosclerosis versus stiffness (arteriosclerosis): two distinct but associated alterations in large arteries

The terms atherosclerosis and arteriosclerosis are often used indiscriminately to refer to alterations and lesions in large arteries. From the etymological point of view the term arteriosclerosis identifies arterial stiffness. Atheromatosis should be used to identify the segmentary lesions leading to thrombostenotic plaques. Since advanced atheromatic lesions are very often calcified, the term atherosclerosis can be used instead of atheromatosis.

In hypertension and in the ageing process, structural and functional changes in blood vessels involve the total arterial system, but principally the aorta and its major branches. Both ageing and hypertension have strong effects on the level of arterial stiffness (arteriosclerosis). In contrast, atherosclerosis is a more parcellar disease and predominates in particular arteries, such as the coronary arteries, and more specifically at arterial bifurcations. In these vessels, there is little possibility that non-fibrous and non-calcified plaques can increase arterial rigidity to any great extent. However, the atherosclerosis process makes a sizeable contribution to the increase in collagen content and in calcification of the vessels and, in the presence of advanced age and/or hypertension, may increase arterial rigidity.

In clinical practice, atherosclerosis of the lower limbs is an important marker of disease [3]. Increased systolic and pulse pressures are commonly observed in these patients, due to increased arterial rigidity and wave reflections. Even though ventricular ejection and vascular resistance may be within the normal range, systemic and forearm arterial compliance may be reduced. In subjects with atherosclerosis of the lower limbs, increased pulse pressure and increased systolic pressure are significantly and independently associated with the reduction in the vasodilating properties of the diseased limbs, whereas no comparable association is observed with mean arterial pressure.

Coronary ischaemic disease is substantially associated with reduced aortic compliance [4,5]. This haemodynamic pattern may decrease aortic diastolic blood pressure irrespective of mean arterial pressure, thus reducing coronary perfusion. The pathophysiological mechanisms of the association between coronary lesions and arterial stiffness remain unclear. One hypothesis is that the aorta and coronary arteries are altered by the same factors and therefore increased aortic stiffness is an indirect index of generalized atherosclerosis. Another possible mechanism is that increased aortic stiffness tends to decrease diastolic blood pressure, and consequently coronary perfusion, and to increase systolic blood pressure, thus increasing cardiac wall tension and myocardial oxygen consumption. Experimentally, decreased aortic compliance exacerbates myocardial ischaemia in the presence of stenosis of the coronary artery [6]. Whether this mechanism contributes to the incidence of coronary heart disease following antihypertensive drug therapy is an unresolved question.

Epidemiological aspects of arterial stiffness

So far, no epidemiological studies have been directed towards assessing arterial stiffness as an independent cardiovascular risk factor, largely because of practical difficulties in measuring arterial stiffness in the large populations required to determine cardiovascular morbidity and mortality rates. However, increasing interest in the clinical consequences of arterial stiffness has led several groups to approach this question indirectly by studying two risk factors, mean blood pressure (which depends mainly on the tone and structure of small arterioles) and pulse pressure (which depends mainly on the stiffness of large arteries).

Mean versus pulse pressure

Epidemiological studies have widely revealed a close correlation between blood pressure and the incidence of cardiovascular disease [7]. The respective roles of systolic and diastolic blood pressure have also been investigated [7–9]. The results have shown that diastolic blood pressure is more strongly related to cardiovascular risk before the age of 45 years, whereas systolic pressure is more strongly related to risk after the age of 45 years [8]. However, in these studies the level of systolic, diastolic or mean blood pressure was considered on an exclusive basis. The concept that the pulsatile component of blood pressure could influence cardiovascular morbidity and mortality independently of mean arterial pressure was not evaluated in these older studies.

The relationship between the two components of blood pressure, mean arterial pressure and pulse pressure, and cardiovascular risk was investigated in 18 336 men and 9351 women, aged 40–69 years and living in Paris [10]. Since mean arterial pressure and pulse pressure are now known to be tightly interrelated, the statistical evaluation used a principal component analysis in order to define two independent parameters, independently reflecting the steady component and the pulsatile component of blood pressure. With cross-sectional analysis, the findings related to the steady component index were quite similar to those previously reported for diastolic or mean blood pressure in most published epidemiological studies, in that mean pressure and diastolic pressure are strong determinants of the overall cardiovascular risk, involving the brain, the heart and the kidney [7,8]. In contrast, the pulsatile component index was exclusively related to cardiac changes, as judged from the degree of cardiac hypertrophy evaluated from electrocardiography. The specific role of the pulsatile component index as an independent cardiac risk factor was confirmed by a 10-year survival analysis [10]. In particular, in women older than 55 years, the pulsatile component index

was independently correlated with coronary disease mortality.

The J-shaped curve relating cardiovascular risk to blood pressure levels

In most epidemiological studies a linear relationship between cardiovascular risk and blood pressure has been reported, the higher the blood pressure, the higher the risk of cardiovascular disease. This hypothesis is often assumed in therapeutic trials on hypertension and seems to be especially true from life insurance actuarial data. However, although it seems likely that the curve relating cardiovascular risk to blood pressure is linear for a diastolic pressure of >85–90 mmHg, linearity cannot be completely assumed for diastolic pressures below this level. Several studies have suggested that heart attack mortality is related to diastolic pressure in a curvilinear relationship (J- or U-shaped curve) [11,12]. Under this hypothesis the risk decreases as blood pressure falls, but an increased risk is expected below an optimum value of blood pressure. This finding has been observed in untreated as well as treated patients, and a similar phenomenon has been found in large population studies. Whereas most patients show a positive relationship between diastolic blood pressure and heart attack mortality (the lower the pressure, the lower the incidence), in the subgroup of patients with pre-existing ischaemic heart disease, the curve was J-shaped, with an increase in mortality when diastolic blood pressure fell below 85 mmHg [11,12]. Interestingly, the relationship relating systolic pressure to heart attacks is linear: the lower the systolic pressure, the lower the risk, even for very low systolic pressures. These results strongly suggest that an excessive drop in diastolic but not systolic blood pressure may be dangerous, especially in patients with a history of atherosclerotic lesions.

In accordance with this concept, Madhavan *et al.* [13] prospectively assessed the influence of pulse pressure in more than 2000 patients with cardiovascular disease. The results showed that a high pulse pressure (>63 mmHg) was associated with a roughly threefold increased incidence of cardiovascular events during treatment. Interestingly, it was only among patients with a high pretreatment pulse pressure (i.e. increased arterial stiffness) that the J-shaped relationship between diastolic blood pressure and myocardial infarction was found. In other words, pretreatment pulse pressure not only provides valuable prognostic information in itself, but is also useful in identifying those patients in whom an excessive fall in diastolic pressure following treatment is likely to be associated with an increased risk of myocardial infarction. A decrease in diastolic pressure as a consequence of stiffening of the large arteries has been discussed by several authors [14].

We suggest that in subjects with high aortic stiffness, a decrease in vascular resistance following antihypertensive treatment may cause an excessive decrease in diastolic blood pressure if large artery compliance is not improved (i.e. pulse pressure is not reduced). We propose that at least part of the J-shaped relationship between diastolic pressure and cardiovascular mortality can be attributed to a decline in diastolic pressure as a direct consequence of stiffening of the large arteries. Therefore, decreased aortic compliance may be the mechanism by which a specific fall in diastolic blood pressure leads to a decrease in coronary flow. This concept has not been fully evaluated in the various therapeutic trials of hypertension.

However, although pulse pressure evaluated at the site of the brachial artery roughly reflects large artery elasticity, it remains an indirect and not always accurate parameter for the evaluation of arterial stiffness. Therefore more accurate, non-invasive methods are preferable for evaluating the elastic properties of large arteries. Recent progress in the development of simple, reliable and highly reproducible automatic devices have now made it possible to design new epidemiological studies in which the influence of arterial stiffness on cardiovascular morbidity and mortality can be better assessed.

Factors increasing arterial stiffness

In terms of vascular mechanics, it is generally accepted that the composition of blood vessels influences the distensibility of the vessel wall [15,16]. This concept takes account of the relationship between structure and the mechanics of the vessel wall in terms of the elastic moduli of individual wall components, mainly vascular smooth muscle, collagen and elastin proteins [15]. Moreover, arterial mechanical properties are dependent on the level of interaction between arterial wall components (cells and extracellular matrix). These interactions are mediated by adhesion proteins such as fibronectin and laminin and their receptors the integrins [17,18]. Stimulation of these receptors promotes cell adhesion and migration and influences the phenotype of the smooth muscle cell (contractile versus synthetic state). Recent results indicate that fibronectin influences mechanical properties through the occurrence of new collagen cross-linking within the arterial wall. Therefore, adhesion proteins and their receptors are candidate proteins for controlling vascular tone and regulating arterial stiffness. These functional and structural modifications to the arterial wall have important effects on the cardiovascular system, increasing the incidence of fracture, rupture and aneurysm formation in arteries and, potentially, the development of atherosclerosis.

Ageing and hypertension are the most common factors leading to arterial stiffness (Fig. 1). Other genetic and environmental factors can increase arterial stiffening and accelerate the effects of age and hypertension.

Ageing

In elderly patients a potential risk factor for increased cardiovascular morbidity and mortality is stiffening of the aorta and other large arteries. From the macroscopic standpoint, age changes in the larger arteries are associated with increases in the aortic diameter and wall thickness, in elastin fragmentation and calcification, and in the collagen content [19]. These findings are predominantly responsible for the increase in

pulse wave velocity with age [1]. These alterations are more pronounced in central (thoracic aorta, carotid) than in peripheral (femoral or radial) arteries [20].

Although age and hypertension both alter the arterial wall and increase stiffness, the predominant anatomical and functional changes are not the same, and must be distinguished. The diameter enlargement and the elastin degradation are the main age-related changes, due essentially to tissue fatigue [1,19], whereas hypertrophy and collagen accumulation are the principal hypertensive alterations and can be attributed to the increased mechanical stress (defensive mechanism) and/or the increased activity of trophic humoral factors [15,21].

Despite these differences, age-related structural changes in the aortic and carotid wall are strongly accelerated in the presence of hypertension.

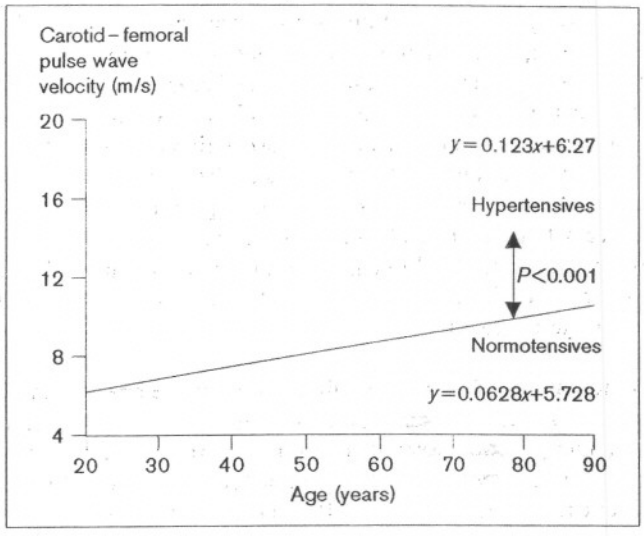
Arterial stiffening with ageing is accompanied by an elevation in systolic blood pressure which averages 25–35 mmHg between the third and the eighth decades of life in healthy subjects. In the past, vascular stiffening and increases in systolic blood pressure and pulse pressure have been considered a part of normal ageing and no treatment for these alterations has been proposed. However, older subjects with increased systolic blood pressure and pulse pressure are now known to have higher cardiovascular morbidity and mortality [7,8]. In addition, it is clear that a decrease in systolic pressure and in pulse pressure following antihypertensive treatment can reduce the incidence of cardiovascular events; this benefit is highly significant for both cerebrovascular and coronary events, even in very aged patients [22,23].

Therefore, large artery stiffening must be seen as a common but not normal ageing related process, and should be considered a major risk factor for cardiovascular events.

Arterial hypertension

It is generally accepted that hypertension increases stiffness of the large arteries by inducing several structural alterations in the arterial wall including hypertrophy, and changes in the extracellular matrix, mainly an increase in collagen. In addition, an increase in blood pressure is a major determinant of arterial wall stiffness in hypertension [1,15,24,25]. Local hormonal changes in hypertensive subjects may have pressure-independent effects on the arterial wall, mainly by modifying cell growth or synthesizing extracellular matrix [26,27]. Nevertheless, it is difficult to know whether the changes in arterial stiffness are pressure-related or due to intrinsic changes in the arterial wall or to a combination of both factors. Experiments on rings or strips of arterial segments studied *in vitro* and, in some cases, *in vivo* [28–30] are controversial; carotid and aortic elastic properties in hypertensive animals were shown to be decreased or unchanged according to different experimental models and procedures. Moreover, recent *in vivo* studies have shown that the relationships between structural changes and distensibility during hypertension are more complex.

Fig. 1



For any given age, carotid–femoral pulse wave velocity is higher in hypertensives compared with normotensive controls, indicating increased aortic stiffness in the hypertensives.

First, if at the site of the central aorta and the carotid artery, decreased values of operating (i.e. evaluated at mean pressure level) distensibility have been observed [31–35], in more peripheral arteries, such as brachial and radial arteries, distensibility was barely or not modified [32,36], despite the development of arterial hypertrophy.

Second, at the site of the central aorta and the carotid artery, decreased values of operating distensibility have been observed compared to normotensives. However, distensibility measured at the same blood pressure level [35,37] is often similar in normotensive and hypertensive subjects, indicating that distensibility is highly proportional to blood pressure levels. These results show that arterial wall hypertrophy, which is present in a large majority of patients with chronic hypertension, is not a determinant of the development of arterial stiffness. It seems that for a given blood pressure level, arterial distensibility of the central arteries in hypertensives may be altered as a function of various environmental and/or genetic factors which affect the composition of the extracellular matrix of the arterial wall. In this respect, genetic determinants may play a key role in the response of large arteries to hypertension.

The important concept is that in those hypertensive patients who develop exaggerated stiffness of the large arteries, the hypertension will be aggravated, with increases in systolic blood pressure and pulse pressure and the clinical consequences outlined earlier in this review. It is therefore particularly important to identify patients with an increased risk of such alterations.

Genetic factors of the renin–angiotensin system

The genetic background may influence the large arteries in many ways. First, genetic disorders are responsible for some uncommon but severe monogenic cardiovascular diseases such as homozygous familial dyslipidaemia, Liddle's disease [38] and Gordon's syndrome [39]. Second, the association of several genetic and environmental factors leads to the development of many risk factors such as essential hypertension, dyslipidaemia, salt sensitivity and non-insulin-dependent diabetes [40,41]. In this case, multiple genetic and environmental factors participate in the development of risk factors responsible for arterial alterations.

Finally, genetics can influence the vulnerability of the arterial wall to risk factors such as hypertension, ageing, cholesterol and smoking. In other words, for a similar degree of risk, arterial stiffening may be more or less pronounced as a function of genetic factors. Identification of such genetic markers may be of major interest in the detection of high-risk patients. In humans, these factors can now be identified by studying variants (polymorphisms) of genes coding for proteins that are implicated in cardiovascular regulation (candidate genes) [42–46].

Research interest is now focusing on the relationship between genetic factors of the renin–angiotensin system and modulation of large artery stiffness. The renin–angiotensin system is an important regulator of blood pressure, salt and water homeostasis and large artery structure [21]. The genes associated with this system have been studied for their effects on arterial disease [42–45], and molecular biological techniques have been used to identify polymorphisms for several of these genes [42–44]. Increasing evidence from human genetic studies now indicates that the ACE genotype is an independent risk factor for cardiac [47,48] and arterial hypertrophy [49], and myocardial infarction [43,45], so that the renin–angiotensin system is directly implicated in these cardiovascular alterations. Most of the actions of this system are mediated by angiotensin II through stimulation of AT_1 receptors [50]. The recent identification of AT_1-receptor gene A/C polymorphism thus suggests that the AT_1-receptor is involved in arterial alterations [51]. This polymorphism is related to the transversion of cytosine for adenine located at the 5′ end of the 3′ untranslated region in position 1166 of the AT_1 gene. The polymorphism is probably not functional but might be in linkage disequilibrium with an unidentified functional variant. It has been shown that the frequency of the AT_1 C allele is increased in patients with severe hypertension [51] or myocardial infarction [52].

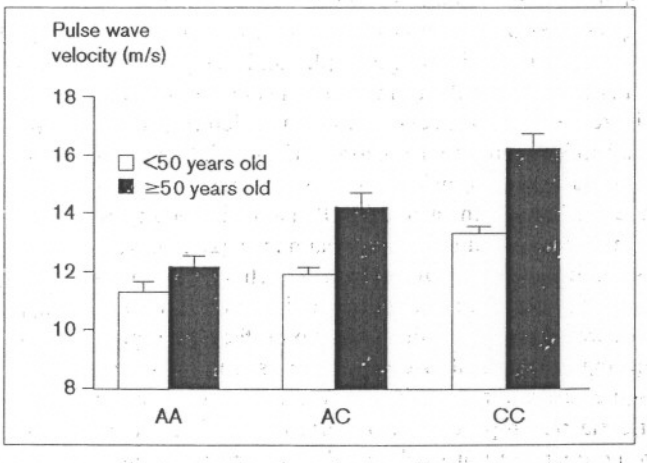
Recently, we studied polymorphisms of the renin–angiotensin system genes for their effect on the development of aortic stiffness in hypertensive and normotensive subjects [53,54]. Arterial stiffness was assessed by measuring aortic pulse wave velocity, which is a non-invasive, accurate, safe and reproducible method suited to the screening of large populations. In hypertensives the presence of the AT_1 C allele was associated with increased aortic stiffness in both sexes, independently of blood pressure levels, and this polymorphism explained 11.6% of the variance in pulse wave velocity. The effect appeared to be codominant in that mean pulse wave velocity values in AT_1 AC heterozygotes were intermediate between those of the two groups of homozygotes. The results of these studies show several interactions between this genetic polymorphism and other risk factors.

First, the fact that AT_1 polymorphism is associated with aortic stiffness in hypertensives but not in normotensives may be related to a potentiation of the arterial effects of hypertension in some genotypes of the AT_1 receptor. This result is also consistent with experimental studies [55] showing that angiotensin II-induced vascular smooth muscle proliferation *in vitro* was strongly enhanced by increased mechanical stretching, suggesting that hypertension-associated mechanical or structural alterations may be potentiated by angiotensin II receptor stimulation.

Second, the strong association between AT_1 genotype and aortic stiffness was observed in both younger and older hypertensive patients but this effect was more pronounced in the older patients (Fig. 2). In other words, older patients with the C allele (approximately 45% of the population) develop more severe vascular stiffening than patients without the C allele, suggesting that this polymorphism could modify the effects of age on arterial stiffness.

Third, in our study an interaction was found between AT_1 genotype and total cholesterol : high-density lipoprotein (HDL) ratio, affecting aortic stiffness [53]. Thus in hyperten-

Fig. 2



There is a strong association between angiotensin II AT_1-receptor genotype and aortic stiffness in both younger and older hypertensive patients but this effect is more pronounced in the older patients. Thus patients with this mutation (presence of the C allele) develop, with ageing, more severe vascular stiffening than patients without the C allele, suggesting that this polymorphism could modify the effects of age on arterial stiffness. Adapted from Benetos *et al.* [54].

sives presenting the C allele, a positive correlation was observed between this ratio and the pulse wave velocity. In contrast, in patients without the C allele (AA homozygotes) an increase in the total : HDL cholesterol ratio was not associated with increased stiffness. These intriguing results suggest that the effects of lipids on large arteries may vary as a function of the AT_1 genotype.

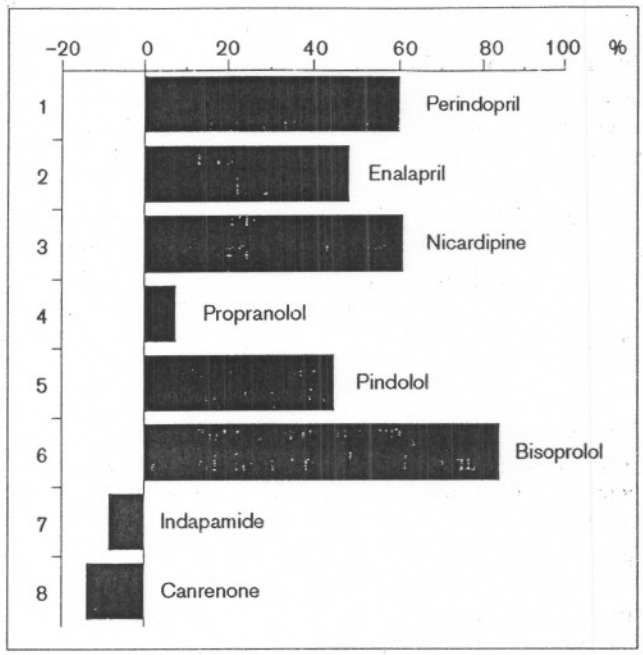
Taken together, these results suggest that the AT_1 gene polymorphism is a particularly important risk marker for arterial stiffness, and could modulate the effects of hypertension, ageing and lipids on large arteries. Studies in larger populations are needed to evaluate the role of several candidate genes as modulators of the response of the large arteries to the classical risk factors

Improvement of arterial stiffness with antihypertensive drugs

Dissociated actions of drugs on blood pressure and large artery mechanical properties

Studies of pharmacological agents clearly indicate that for the same blood pressure reduction, arterial stiffness may be modified to a greater or lesser extent depending on the antihypertensive compound (Fig. 3). A marked increase in compliance is obtained with ACE inhibitors [56–59], calcium entry blockers [60,61] and nitrates [62–64]. Inconsistent changes are obtained with blockade of the autonomic nervous system, particularly following α- and β_1-blockade [65,66]. Minor changes are observed with diuretic compounds [67,68], non-cardioselective β-blocking agents such as propranolol [69] and dihydralazine (or derivatives) [70]. Thus, vasodilating compounds may have different effects on large arteries despite similar effects on peripheral resistance and blood pressure. Experimental studies have shown that even when ACE inhibitors are administered in low, non-antihypertensive doses, these drugs are able to prevent the accumulation of collagen in the aortic media and improve arterial rigidity, whereas other vasodilators such as dihydralazine or diuretics have little or no effect on these arterial parameters [27]. The underlying mechanism for these differences is not yet completely understood but there are indications that non-pressure-related factors are involved in the development of cardiovascular alterations during hypertension. In particular, drug-induced activation or inhibition of the renin–angiotensin or the sympathetic systems seems to be able to modify arterial stiffness.

Fig. 3



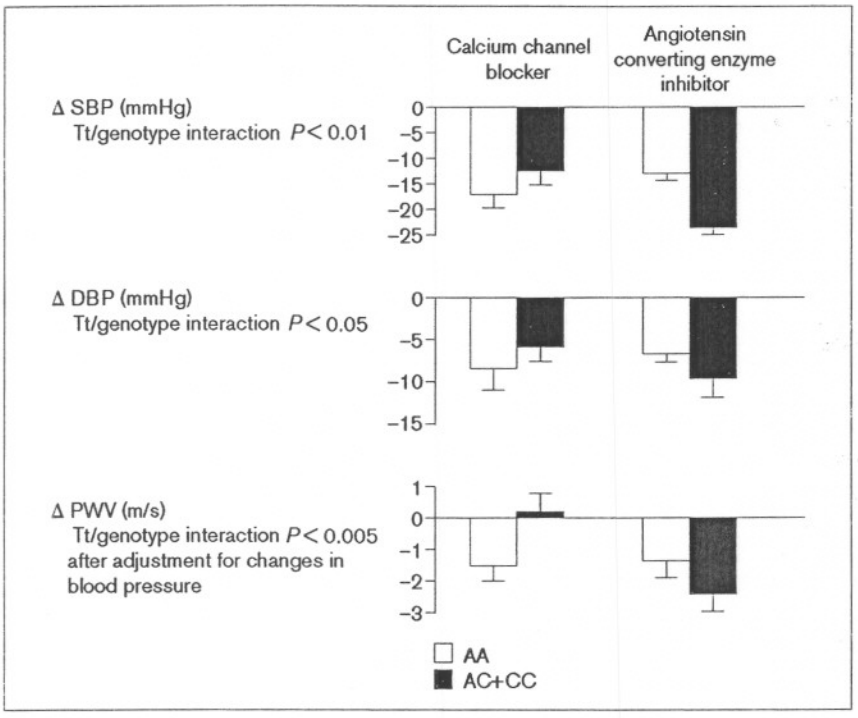
Improvement of arterial distensibility with different antihypertensive drugs. For the same blood pressure reduction, arterial distensibility may be increased to a greater or lesser extent depending on the antihypertensive compound. Data obtained from clinical studies by M. Safar's group.

Pharmacogenetics: a new pharmacological concept

Another important point is that human essential hypertension is a multifactorial and heterogeneous disease and this heterogeneity influences the response to the antihypertensive drugs. Currently, clinicians have very few markers to indicate which mechanisms are predominant in a given hypertensive patient. Such markers could have a major impact on therapeutic strategies and drug choice. It has been suggested that plasma levels of renin or ACE could be helpful in determining the best type of drug therapy for individual hypertensive patients, with ACE inhibitors and β-blockers being more effective in patients with high plasma renin activity, and diuretics and calcium channel blockers more effective in low-renin patients [71]. However, plasma renin levels may not reflect the tissue activity of the renin–angiotensin system [72]. Thus genetic polymorphisms of the renin–angiotensin system might be a more reliable indicator than renin or ACE plasma levels when assessing the activation of this system and predicting the efficacy of drugs. We have found that AT_1 A/C receptor polymorphism influences the effects of antihypertensive drugs on blood pressure and arterial stiffness (Fig. 4). In patients carrying the C allele, the increase in arterial compliance was more pronounced during treatment with ACE inhibitors than with calcium channel blockers, whereas the inverse tendency was observed in AA homozygotes [73]. These results show that identification of genetic markers could be useful in the choice of drugs for hypertension.

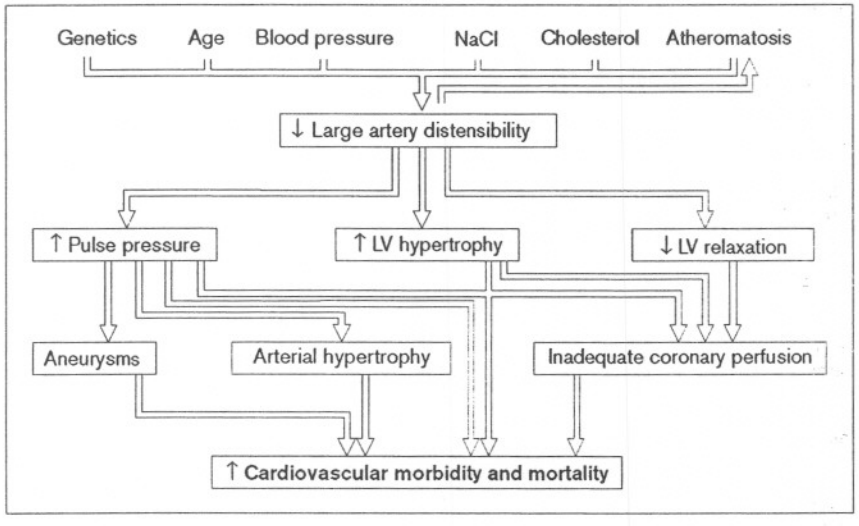
Finally, treatments based on a combination of drugs may be useful in a large spectrum of hypertensive patients. For example, a calcium channel blocker + ACE inhibitor combination could be particularly useful in patients with arterial stiffness, since both compounds have shown a high efficacy in improving large artery compliance, and provide synergistic effects when given together. Another advantage of this combination is that neither of the two compounds has adverse effects on metabolic factors that can alter arterial structure and function such as lipids, plasma glucose and insulin tolerance.

Fig. 4



Changes in systolic (SBP) and diastolic (DBP) blood pressure and pulse wave velocity (PWV) following treatment with angiotensin converting enzyme (ACE) inhibitors or calcium channel blockers according to the angiotensin II AT_1 receptor A/C genotype. In patients carrying the C allele, blood pressure decrease and increase in arterial compliance was more pronounced with ACE inhibitors than with calcium channel blockers, whereas the inverse tendency was observed in AA homozygotes. Adapted from Benetos *et al.* [73].

Fig. 5



Schematic representation of the relationships between risk factors, arterial stiffness and cardiovascular alterations. Large artery stiffening caused by the combined effects of multiple risk factors could be responsible for a large number of fatal and non-fatal cardiovascular events. LV, left ventricular.

Conclusions

Many aspects of the clinical management and the pathophysiology of hypertension may be better understood when the status of the large arteries is taken into consideration. Large arteries are not merely passive conduits: they have an important place in the genesis, evolution and the therapeutic approach to the hypertensive vascular disease. The large artery–blood pressure relationship is reinforcing in nature. An increase in blood pressure often leads to large artery stiffness, especially when other risk factors are present. In turn, the increased stiffness aggravates hypertension by increasing systolic blood pressure and can induce cardiac hypertrophy and arterial lesions (Fig. 5).

A major question for clinicians is to determine the risk profile of the individual hypertensive patient and propose a more

rational therapeutic strategy. The development of accurate, non-invasive methods has made it possible to detect alterations to the large arteries in the early stages. Determination of genetic polymorphisms may be of major importance in identifying high-risk patients and selecting appropriate antihypertensive therapy.

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