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Summary

In the elderly, as in the middle-aged, hypertension is a major risk factor for cardiovascular (CV) morbidity and mortality. Hypertension has an increased prevalence in the elderly and has a specific haemodynamic pattern involving four main particularities: increased pulse pressure (PP), resulting from an increase of systolic blood pressure (SBP) and a decrease of diastolic (DBP); disappearance of PP amplification; early wave reflections; and increased arterial rigidity. All these alterations taken together largely explain why PP, aortic stiffness and wave reflections are nowadays recognised as significant independent predictors of CV risk.

Beneficial effects on arterial stiffness and wave reflections have been shown with nitrates, drugs affecting the renin-angiotensin system (RAS), spironolactone and aminoguanidine. The main therapeutic trial demonstrating the role of arterial stiffness in the control of SBP and PP in hypertensive subjects was performed in patients with end-stage renal disease undergoing haemodialysis. Optimisation of antihypertensive therapy in the elderly would need a combination of using standard hypertensive drugs at adapted dosages, development of new antihypertensive agents and individualisation of therapy.

Introduction

In the elderly, as in the middle-aged, hypertension is a major risk factor for CV morbidity and mortality (CV and all-cause).[1] The prevalence of hypertension increases with age. In elderly populations, over 65 years of age, the majority of subjects are hypertensives. Furthermore, in industrialised countries, the majority of hypertensives are over 65. Thus, quantitatively, hypertension in the elderly is the major problem of hypertension.[2-5]

Some aspects of hypertension are not specific to the elderly. In particular, the proven drug-related CV benefits also exist in the elderly,[6] although therapeutic trials have only recently included elderly hypertensives.[7-11] Furthermore, it seems that the magnitude of the relative drug-related CV benefit is not related to age.[12]

On the other hand, some aspects are obviously specific to the elderly, such as pathophysiological aspects, namely large artery stiffness, wave reflections and decreased renal function, the consideration of DBP as inclusion and titration criteria in therapeutic trials, the increased CV risk and the increased drug-related absolute CV benefit, or the effect of different drugs on arterial structural and functional parameters. The goal of this review is to focus on these specific aspects of hypertension in the elderly.

From diastolic to systolic and from systolic to pulse pressure, in terms of assessment of cardiovascular risk in hypertension in the elderly

Hypertension in the elderly has a very specific feature: SBP is predominantly elevated and its elevation is disproportionate to the level of DBP. From this general framework, two different haemodynamic patterns have been described: first, isolated systolic hypertension (ISH) with SBP >140 mmHg but normal or low (<90 mmHg) DBP; second, systolic–diastolic hypertension in which the increase of SBP is disproportionately higher than the increase (>90 mmHg) in DBP. Because of these particularities, it is important to recall the historical development of antihypertensive drug therapy in the elderly.

In the early therapeutic trials, only subjects with systolic-diastolic hypertension were recruited. Thus, the exclusive choice of DBP as the main inclusion criterion at entry had, by definition, influenced greatly the baseline characteristics of the hypertensive population.[13] The subjects with ISH, i.e. with a selective increase of PP, which is the difference between SBP and DBP, were completely excluded from the trials and, therefore, not analysed in the primary results or in the first meta-analysis.[13,14] This bias, which had by definition affected the older section of the population, was introduced, not only in selecting the subjects, but also at the end of the follow-up. Those with elevated SBP (>140 mmHg) were considered as 'adequately' treated, although only their DBP was controlled (<90 mmHg).[14] However, many epidemiological investigations have consistently shown that SBP is a significantly better predictor of CV risk than DBP, particularly over 50 years of age, the period during which the majority of CV events occur[15,16] These observations suggested that more attention should be paid to SBP and PP, both independent predictors of CV risk to a much larger degree than DBP. Hence, in 1991, the SHEP study[8] was published and largely responded to this question since, in old subjects with isolated systolic hypertension, it was clearly shown that antihypertensive drug therapy markedly reduced CV risk through a selective decrease of SBP and PP. However, this change was associated with a

Table 1 Some aspects of hypertension are specific to the elderly.

- Systolic blood pressure (SBP) elevation is disproportionate to the level of diastolic blood pressure (DBP).
- With increasing age, there is a shift from DBP to SBP then to pulse pressure as a predictor of coronary heart disease.
- Both small and large arteries contribute independently to the pathophysiology of high blood pressure. However, it is the large arteries, which are mainly modified in the elderly.

further decrease of DBP, which was previously normal or low at inclusion and became significantly lower than before treatment.

In the more recent therapeutic trials, which were mainly conducted in the elderly, either with isolated systolic or with systolic–diastolic hypertension, it has been consistently shown that an adequate control of DBP (<90 mmHg) by drug treatment was consistently obtained in large populations of hypertensive subjects. By contrast, a satisfactory control of SBP (<140 mmHg) was observed to a much lesser extent.[17] In parallel, it was shown that, over 55–60 years of age, PP was the most powerful mechanical factor available to characterise those hypertensive subjects at greatest risk for subsequent myocardial infarction, stroke or CV death.[18-25] This predictive value of PP was noted even in successfully treated hypertensive subjects, whose blood pressure (BP) was very close to normal values.[26]

Finally, the study of the different BP components in relation to CV risk assessment at different ages can be summarised by the findings of Franklin SS *et al.*,[25] based on the Framingham Heart Study participants: with increasing age, there is a gradual shift from DBP to SBP and then to PP as predictors of coronary heart disease risk. In patients <50 years of age, DBP was the strongest predictor. The age of 50–59 years was a transition period, in which all three BP indices were comparable predictors, and from 60 years of age on, DBP was negatively related to coronary heart disease risk, so that PP became a superior predictor to SBP (Table 1).

Why is pulse pressure more closely related to cardiovascular risk than the other blood pressure components in hypertension in the elderly? From pathophysiology to epidemiology and clinic

It is logical nowadays to consider hypertension as a powerful risk factor, acting mechanically on the arterial wall, and being potentially responsible for CV events, mainly of cardiac, cerebral and renal origin.[1] Since the goal of drug treatment of hypertension is to prevent such CV complications, it seems likely that the totality of the BP curve, mainly composed of mean BP (MBP) and PP, and not only of the two arbitrary points of the curve, SBP and DBP, should be considered to adequately define and quantify the disease in the elderly.

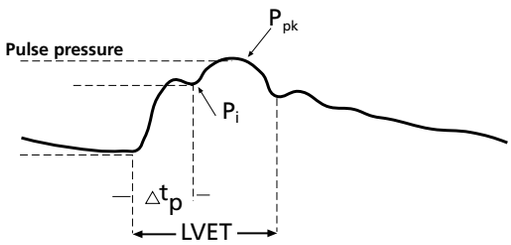
In fact the BP curve is built up of the summation of two different components, a steady component, MBP, and a pulsatile component, PP.[27] MBP, the product of cardiac output and total peripheral resistance, is the pressure required for the steady flow of blood to adequately deliver oxygen to peripheral tissues and organs. MBP and total peripheral resistance relate to the wall/lumen ratio of small arteries and arterioles and increase physiologically with age, but in a relatively small extent.[27,28] The pulsatile component, PP, is the consequence of the intermittent ventricular ejection from the heart. It is the role of large conduit arteries, in particular the aorta, to minimise the pulsatility. In addition to the pattern of left ventricular ejection, the determinants of PP (and SBP) are the cushioning capacity of arteries, and the timing and intensity of arterial wave reflections.[27] Each of these mechanical factors are substantially worsened with age.[27,28] Finally, in this concept, for a given cardiac activity, both small and large arteries contribute independently to the pathophysiology of hypertension. However, it is the large arteries which are mainly modified in hypertensive subjects over 65 years of age since increased PP, due both to an increase of SBP and to a decrease of DBP with age, is the dominant characteristic of this population and increases exponentially with age.[29,30]

At all ages, the arteries have two distinct but inter-related functions: to deliver an adequate supply of blood to peripheral tissues (the conduit function) and to smooth out pressure oscillations due to intermittent ventricular ejection (cushioning function).[27,28] The former, which relates to the control of mean blood flow and MBP, has been extensively studied for many years and will not be detailed in this chapter. The latter points to oscillatory flow and pressure and relates to arterial wall stiffening with deleterious consequences on the heart upstream. This picture is specifically observed in the elderly.

The principal cushioning role of arteries is to dampen the pressure oscillations resulting from intermittent ventricular ejection ('Windkessel' effect). Physiologically, 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, thereby ensuring continuous perfusion of organs and tissues. The cushioning function is very efficient in young and healthy humans and the extra energy lost on account of the intermittent ventricular ejection is only 10–15% greater than if the heart's output was continuous.[27,28] The efficiency of Windkessel function, which depends on the visco-elastic properties of the arterial wall and the 'geometric' characteristic of the arteries, including their diameter and length, are substantially and independently modified by age and high BP. All indices of arterial stiffness (compliance, distensibility etc.) are greatly influenced by the level of MBP, decreasing with increased pressure.

This cushioning function is specifically altered

Figure 1 Carotid pressure waveform recorded at a speed of 100 mm/s. The height of the late systolic peak (P_{pk}) above the inflection (p_i) is the effect of arterial wave reflection on blood pressure. $\triangle t_p$ represents the travel time (milliseconds) of the pulse wave to peripheral reflecting sites and back. LVET = left ventricular ejection time.



during the ageing process,[31,32] a condition associated with 'sclerotic' remodelling of arterial walls, increased collagen content and changes in extracellular matrix (arteriosclerosis). Arteriosclerosis is primarily a medial degenerative condition that is generalised throughout the thoracic aorta and central arteries, causing dilatation, diffuse hypertrophy and stiffening of arteries. Arteriosclerosis is sometimes considered as a 'physiological' ageing phenomenon[27,31,32] and results in diffuse fibroelastic intimal thickening, increase in medial ground substance and collagen, and fragmentation of elastic lamellae, with secondary fibrosis and calcification of the media. These changes are substantially more pronounced in the aorta and central arteries than in the limb arteries.[32] Changes that are in some aspects similar to the ageing process are observed in essential hypertension.[31,32] Nevertheless, substantial differences characterise these two conditions. In hypertension, the arterial dilation is not constantly observed. While ageing is principally characterised by alterations and decreased content of elastin in the arterial wall, hypertension is principally characterised by increased collagen content.[32]

In the elderly, the principal consequences of the stiffening of the arterial wall are a selective or predominant increase in SBP and PP, together with a decrease in DBP. For the understanding of this process, two different mechanisms should be distinguished.[27] The first, direct mechanism, involves the generation of a higher forward pressure wave by the left ventricle ejecting into a stiff arterial tree, resulting in an increase in SBP. The second mechanism is indirect, via the influence of increased arterial stiffness on the pulse wave velocity (PWV) and the timing of the incident (forward) and reflected (backward) pressure waves (Figure 1). Indeed, the ejection of blood into the aorta generates a pressure wave that is propagated at a given PWV to other arteries throughout the body. This forward travelling pressure wave is reflected at any points of structural and functional discontinuity of the arterial tree (which so define a reflection coefficient), generating a reflected ('echo') wave travelling backward towards the ascending aorta. Incident and reflected pressure waves are in constant interaction and are summated in a measured pressure wave. The final amplitude and shape of the measured aortic pressure wave are determined by the phase relationship (the timing) between the two component waves. In physiological conditions, this timing means that the peripheral (brachial) PP is significantly higher than the central (aortic) PP for the same MBP. This important physiological phenomenon is called PP amplification. The timing of incident and reflected pressure waves depends on the PWV, the travelling distance of pressure waves, and the duration of ventricular ejection, which are all greatly influenced by age. The desirable timing may be disrupted by increased PWV due to arterial stiffening. With increased PWV, the reflecting sites appear 'closer' to the ascending aorta and the reflected waves occur earlier, thus becoming more closely in phase with incident waves in this region. Thus, ageing results in a disappearance of PP amplification, as a consequence of a more important increase of SBP and PP in central than in peripheral arteries. Furthermore, the earlier return of the background pressure wave in old people means that the reflected wave impacts on the central arteries during systole and reduces aortic pressure during diastole. Hence the viscoelastic properties of the arterial system influence PP, both through the levels of SBP (which is increased) and of DBP (which is decreased). This process leads to an increase of peripheral and mostly central (aortic) PP in aged people.

Finally, the haemodynamic pattern of hypertension in the elderly involves four main particularities: increase in PP due to an increase of SBP and a decrease of DBP; disappearance of PP amplification; early wave reflections; and increased arterial rigidity. The latter involves MBP-independent intrinsic modifications of the arterial wall of central (but not peripheral) arteries. As shown earlier, such modifications are structurally mediated, although a role of vasomotor tone, probably originating from the endothelium, cannot be excluded.[33,34]

Taken together, the described changes in arterial stiffness and wave reflections, which develop particularly in old subjects,[31] have deleterious consequences on left ventricular function. Through provoking an increase in pressure wave amplitude and early wave reflections, arterial stiffening increases peak- and end-SBP in the ascending aorta, contributing to increased myocardial oxygen consumption. Thus, increased aortic SBP induces myocardial hypertrophy, impairs diastolic myocardial function and ventricular ejection. In addition, increased SBP and PP accelerates arterial damage, increasing the fatigue of biomaterials, causing degenerative changes and further arterial stiffening. Finally, the stiffness-induced reduction of DBP alters the driving pressure of the coronary circulation, favouring myocardial ischaemia. All these alterations taken together largely explain why PP[18-24,26] (Figure 2), aortic stiffness[35-41] and wave reflections[42] are nowadays recognised as significant independent predictors of CV risk (Table 2).

Figure 2 Risk associated with increasing systolic blood pressure at fixed levels of diastolic blood pressure. The two-year probability of a cardiovascular endpoint was adjusted for active treatment, sex, age, and previous cardiovascular complications, and smoking by Cox multiple regression with stratification for trial. (European Working Party on High Blood Pressure in the Elderly Trial; Systolic Hypertension in Europe Trial; Systolic Hypertension in China Trial). Reproduced with permission from Blacher J, Staessen JA, Girerd X *et al*.[23]

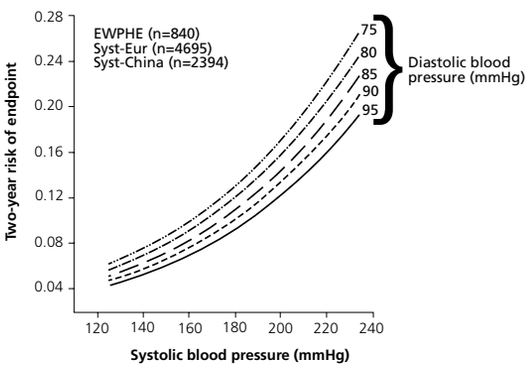


Table 2 The changes in arterial stiffness and consequently in velocity of the pulse wave have deleterious effects.

- Increase in systolic blood pressure (SBP) induces left ventricular hypertrophy, impairs myocardial diastolic function and ventricular ejection.
- Increases in SBP and pulse pressure accelerate arterial damages causing further stiffening.
- The stiffness-induced reduction of diastolic blood pressure alters the driving pressure of the coronary circulation, favouring myocardial ischaemia.

The target trials on pulse pressure, arterial stiffness and wave reflections

To demonstrate the independent predictive role of arterial stiffness and wave reflections on CV risk, a few specific interventional studies focussing on hypertensive subjects have been recently performed. They show that:

1. drugs may act on large artery structure and function independently of MBP changes, particularly in the elderly, and
2. prolongation of survival in hypertensive subjects not only requires BP reduction, but also a significant decrease of arterial stiffness.

The main therapeutic trial demonstrating the role of arterial stiffness in the control of SBP and PP in hypertensive subjects was performed in patients with end-stage renal disease undergoing haemodialysis.[43] Many studies have previously shown that the clinical and haemodynamic profile of these patients is very close to those described in hypertension in the elderly[31,32] and even constitute a caricature of this hypertensive population. The objective of the trial was to reduce CV morbidity and mortality through a therapeutic regimen involving salt and water depletion by dialysis; then, after randomisation, angiotensin-converting-enzyme (ACE) inhibition or calcium-entry blockade, and finally the combination of the two agents and/or their association with a β-blocker. Using this procedure, it was possible to evaluate over a long-term follow-up period (51 months) whether the drug-induced MBP reduction was associated with a parallel decrease of arterial stiffness with resulting effects on CV risk. During the follow-up, it was clearly shown that MBP, PP and aortic PWV were reduced in parallel in survivors. In contrast, in subjects who died from CV events, MBP was lowered to the same extent as in survivors, but neither PP nor PWV were significantly modified by drug treatment.

Finally, it seems likely from the results of this trial that the lack of aortic PWV attenuation, despite the significant drug-induced reduction in MBP, was a significant predictor of CV death in subjects with advanced renal failure.[43]

This result raises the hypothesis of a need, in hypertensive subjects and particularly in the elderly, to develop drugs acting specifically on the large artery wall, i.e. either on arterial stiffness or on wave reflections or on a combination of both, with a resulting potential lowering of CV risk.[44]

Pulse pressure, arterial stiffness, wave reflections and pharmacological agents

Since elderly hypertensives are at greater CV risk than middle-aged hypertensives, for the same relative risk reduction, pharmacological agents will have a greater absolute benefit, i.e. the number of subjects needed to be treated to avoid a single CV event will be smaller in the elderly.[12]

From the data discussed above, an antihypertensive drug reducing MBP may also decrease SBP through a decrease in MBP and DBP and a resulting passive reduction of arterial stiffness. This kind of intervention is able to substantially reduce CV risk in hypertension, particularly in the elderly.[6] Nevertheless, in the case of subjects with an isolated or disproportionate increase of SBP over DBP, i.e. with a selective increase of PP, as observed in older hypertensive subjects, the goal of treatment should be to substantially decrease SBP with maintenance or even increase of DBP. Thus, the target mechanism for this procedure is mainly to obtain an active decrease in arterial stiffness and/or an improvement in wave reflections.

Beneficial effects on arterial stiffness and wave reflections have been shown with nitrates, drugs affecting the RAS, spironolactone and aminoguanidine.

Nitrates are known to dilate larger rather than smaller arteries, whether or not the endothelium is intact.[27,28,45] Earlier studies showed that nitrates cause an acute selective decrease in SBP over DBP in healthy volunteers, as well as in subjects with borderline or sustained essential hypertension.[45] Since the baroreflex response following nitrates is

attenuated with age, an acute and selective reduction in SBP is constantly observed in older subjects with systolic hypertension.[45] Taylor[46] previously reported that an increase in the arterial cross-sectional area at peripheral bifurcations could theoretically cause a delay of wave reflections, with subsequent selective decreases of SBP and PP through changes of peripheral reflection patterns. In clinical situations, such changes of SBP and PP have been widely demonstrated in randomised studies[27,45] but, in some cases, are difficult to detect. Indeed, under nitrates, the PP amplification is modified from the central aorta to the brachial artery, making that the SBP changes are more pronounced at the aorta than at the brachial artery site.[27] Finally, for a therapeutic approach a major point to consider is that a selective decrease in aortic SBP may be constantly obtained using nitrates, as a consequence of changes of muscular artery geometry and subsequent modifications of the reflection coefficients within the distal compartment of the arterial tree.

Indeed, since angiotensin II (Ang II) stimulates the production of various types of collagen fibres,[47] ACE inhibition and Ang II AT_1-receptor blockade have been used as pharmacological tools to demonstrate that *in vivo*, chronic inhibition of the effects of Ang II prevents the aortic accumulation of collagen in spontaneously hypertensive rats (SHR).[48] In SHRs, antihypertensive doses of ACE inhibitors (ACE-I) were shown to prevent the chronic accumulation of aortic collagen, whereas this result was not observed with the non-specific vasodilator, hydralazine, for the same BP reduction. The collagen reduction was noted even with non-antihypertensive doses of ACE-I and paralleled the decrease of ACE measured in the aortic tissue, but not in the plasma.[48] Further experiments clearly indicated that the collagen effect was not due to bradykinin, but specifically involved the blockade of Ang II AT_1-receptors.[49] Thus, it is important nowadays to re-evaluate the possible links between sodium, diuretics, RAS inhibitors and the changes of extracellular matrix of arterial vessels in humans and in rat models of hypertension.

- In recent years, experimental studies in rats have shown that aldosterone might affect the mechanical properties of large arterial vessels, as well as myocardial stiffness.[50] In hypertensive humans, studies of two weeks' duration do not produce any change in brachial artery stiffness following spironolactone.[31] Long-term studies are needed in subjects with hypertension, particularly in the elderly, to demonstrate a reduction of arterial stiffness with this compound. Interestingly, in untreated hypertensive subjects, increased aortic stiffness and increased plasma aldosterone have been shown to be significantly associated.[51]
- Mechanical properties of large arteries may be modified independently of BP, not only through structural modifications of elastin and collagen content, but also through specific effects on the interstitial macromolecules implicated in the cell-cell and cell-matrix attachments and in the resulting mechanotransduction changes.[52] In subjects with systolic hypertension, a double-blind trial has demonstrated that aminoguanidine decreases PP and arterial stiffness independently of MBP.[53] Finally, numerous substances such as, for example, anti-integrins and even oestrogens, may be proposed in the future to improve the mechanical properties of hypertensive large arteries independently of MBP.

Prospective views and conclusions

Nowadays, the standard treatment of hypertension in the middle-aged patient aims to decrease SBP, DBP and MBP and therefore to shift the age-BP curve towards lower values of SBP, DBP and MBP. Taken together, the material discussed in this review clearly indicates that, over 50–60 years of age, a novel objective of treatment should be to reduce the physiological increase of SBP and decrease of DBP with age, thereby reducing the slope of the age-PP curve. This goal may be achieved only through a specific action on large and not small arteries, thus modifying arterial stiffness and wave reflections, and normalising not only SBP, DBP and MBP, but also PP.

A first approach is to use standard antihypertensive drugs, since some of them have noticeable effects on the mechanical properties of large arteries. However, the most effective dosages commonly used for the lowering of SBP and DBP may not be adequate for PP. Moreover, the level of brachial PP reduction may differ from that of aortic PP reduction.[27] Further investigations are needed to resolve these important new aspects of clinical CV pharmacology.

The second approach consists to develop new antihypertensive agents acting on conduit arteries with specific effects not only on vasomotor tone, but also on the composition of the arterial wall. The goal is to act more on the secretory phenotype than on the contractile phenotype of vascular smooth muscle cells. These new agents might operate specifically via mechanotransduction mechanisms acting on cell-cell and cell-matrix attachments of the vessel wall.[52,53] Thus, new therapeutic trials to further evaluate the attenuation of the CV morbidity and mortality resulting from changes in arterial stiffness and wave reflections are needed.

Finally, a third approach should be considered. There is extreme inter-individual variability in the increase of SBP and PP and the observed decrease of DBP with age. Thus, a selection of hypertensive subjects at risk, based on the screening of the associated environmental and/or genetic factors responsible for this variability, should be taken into account when choosing antihypertensive drug treatment.

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