BLOOD PRESSURE 1995; 4 (Suppl 3): 31–37

# Arterial and Cardiac Changes in Hypertension in the Elderly

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## INTRODUCTION

Hypertension is a cardiovascular risk factor which is generally related to the reduction in the caliber or number of *small* arteries with a resulting increase in peripheral resistance and mean blood pressure (MBP) [1–3]. MBP is the product of cardiac output and peripheral resistance and refers to steady phenomena, accepting pressure and flow as constant over time. This definition, which is based on the study of the pressure-flow relationship, ignores that blood pressure and flow fluctuates over the cardiac cycle. In clinical management, pressure is determined in terms of systolic (SBP) and diastolic (DBP) blood pressure, which refer to a pulsatile (not static) phenomenon, SBP and DBP being the extremes of the extent of the blood pressure oscillation around a mean value MBP. Finally a more realistic approach consists to consider that blood pressure is composed of a steady component (MBP), and a pulsatile component, pulse pressure (PP). MBP is the pressure for the distribution of steady flow to the tissues and organs, and represents the useful component of external heart work for oxygen delivering. The pulsatile component of BP is due to the intermittence of ventricular ejection, representing the "unproductive" component of external heart work. It is the role of *large conduit arteries* to dampen the pulsatility. Besides the pattern of left ventricular ejection, the determinants of PP (and SBP) are the visco-elastic properties of arterial wall (arterial stiffness), and the timing and intensity of arterial wave reflections.

Because SBP increases more with age than DBP, and because DBP even tends to fall above 70 years of age [1] (Fig. 1), hypertension in the elderly is characterized by a predominant alteration in the pulsatile component of blood pressure and in the large conduit arteries. This review summarizes the role of large arteries and their clinical impact in term of assessment of cardiovascular damage in hypertensive subjects in the elderly. Two different aspects are generally described in this variety of hypertension: isolated systolic hypertension with diastolic blood pressure normal or low, and diastolic hypertension with a disproportionate increase in systolic blood pressure over diastolic blood pressure.

## SYSTEMIC HEMODYNAMICS

The difficulties of the non-invasive determinations of blood pressure are generally underestimated in the elderly. Since the initial description by Osler [4], it has become well accepted that elderly patients with atherosclerotic disease may have inappropriately elevated cuff pressure when compared with intra-arterial pressure [5, 6], due to excessive atheromatosis and/or medial hypertrophy of the arterial tree. Intra-arterial determinations in elderly patients [7] indicate more complex abnormalities: cuff determinations overestimate diastolic blood pressure whereas systolic pressure measurements are largely accurate. Such findings strongly suggest that the incidence of isolated systolic hypertension in the elderly has been largely underestimated by non-invasive cuff measurements.

Intra-arterial determinations of brachial artery blood pressure have been performed after 3 day's hospitalization in old subjects with hypertension and age and sex-matched normal subjects [7–11]. While diastolic pressure was mostly maintained within the normal range, a significant and sustained increase in systolic pressure was observed, resulting in a substantial elevation of pulse pressure. This finding was observed even in subjects with hypertension with the same mean arterial pressure as normal subjects. In this latter case it was even shown that not only systolic pressure was significantly increased but also that diastolic pressure was slightly reduced, contributing significantly to the elevated pulse pressure. However, it is important to note that these hemodynamic modifications were recorded at the site of the brachial artery. At this site, the pressure wave is usually of higher amplitude than in the central aorta. Although there is some reduction in amplification of the pulse with age, the age-related increase in pulse pressure in the central aorta is greater than is apparent from recording of brachial artery pressure [1]. Finally, an elevated incidence of increased values of brachial and aortic systolic and pulse pressure is a characteristic pattern of hypertension in the elderly.

The finding of an increased pulse pressure with nearly normal values of mean arterial pressure in elderly patients is important to consider because cardiac output and systemic vascular resistance

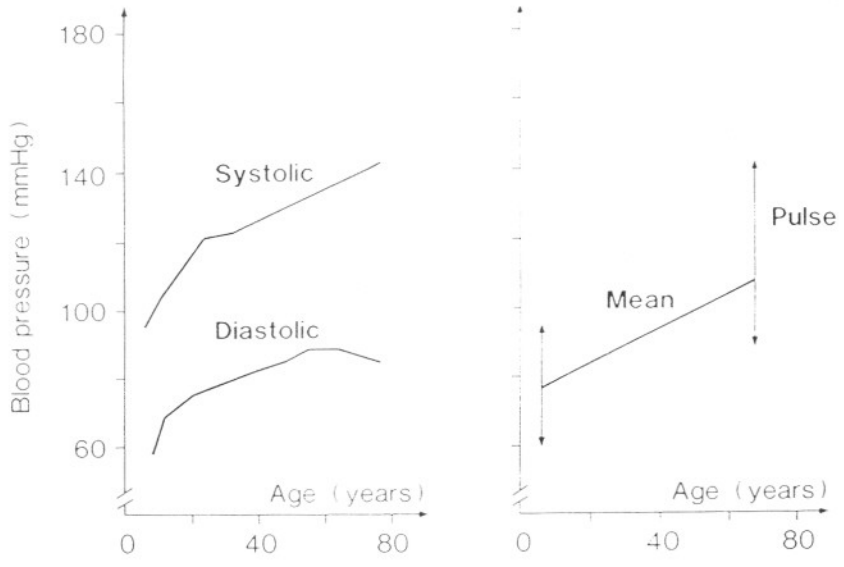


*Fig. 1.* Changes in systolic, diastolic, mean and pulse pressure with age [13].

remain largely within the normal range [7–11]. Increase in vascular resistance is observed only in elderly subjects with systolic-diastolic hypertension and a disproportionate increase in systolic blood pressure [11]. On the other hand, ventricular ejection, assessed from the ratio between stroke volume and left ventricular ejection time, is comparable to that of age-matched normal subjects. Thus, the increase in pulse pressure seems to be predominantly due to an increased arterial stiffness, or to an alteration in the timing of reflected waves, or to a combination of both factors.

## ARTERIAL STIFFNESS AND TIMING OF REFLECTED WAVES IN ELDERLY PATIENTS

Propagative and non-propagative models have been proposed in man to determine arterial stiffness [1, 12]. The latter conceives the arteries as a system of interconnected tubes with fluid storage capacity. The basic assumption is that all pressure changes within the arterial tree occur quasi-simultaneously (i.e., pulse wave velocity is infinite), an approximation which may be accepted for the systemic circulation and in particular regional systems such as the forearm. In man, propagative models, which assume a finite value of pulse wave velocity, seem to be more suitable for the evaluation of arterial stiffness and compliance. Propagative models are all derived from the Moens-Korteweg equation, applied to the case of thin-wall elastic tubes [12]. Under such conditions, arterial compliance is equal to the product of arterial volume (or cross-sectional area per unit length) and distensibility [13]. In man, the arterial cross-sectional area is deduced from the non-invasive determination of the inner diameter, using an echo-Doppler system, as previously validated in the literature [14–16]. Distensibility is derived from the determination of pulse wave velocity. Wave velocity is measured by displaying two pressures or flow pulses simultaneously. The time difference between the feet of the two pulses is measured. The distance between the two sites of measurement along the arterial system divided by the time difference gives the pulse wave velocity (PWV). According to the Bramwell and Hill formula, arterial distensibility (D) is given by the formula:

$$D = (3.75/PWV)^2$$

In patients with hypertension in the elderly, whatever the method used (propagative or non-propagative model), systemic arterial compliance is reduced [7–11, 13]. The reduction is observed even in comparison with controls matched for age, sex, and mean arterial pressure [10, 11, 13]. Thus, elderly patients with systolic hypertension exhibit intrinsic alterations of the arterial wall, unrelated to the level of mean arterial pressure. The same findings has also been recognized in patients with systolic hypertension and end stage renal disease [14] and in patients with isolated systolic hypertension and arteriosclerosis obliterans of the lower limbs [8].

For the mechanism of the predominant increase of systolic pressure in elderly patients, another factor may interfere: the change in the timing and amplitude of wave reflections. Physiologically, the blood pressure curve results from the summation of an incident pressure wave, coming from the heart, and a backward pressure wave, returning to the heart from peripheral

vessels [1, 12]. When pulse wave velocity is increased, addition of forward and backward waves leads to amplification of the pressure curve exclusively during systole and thus produces a high systolic peak. However, the reflection time is also critical in the summation of forward and backward waves. This depends on the length of the vessel. The shorter the vessel, the sooner the reflection occurs. In normal human subjects, the origin of resistant vessels acts as the principal reflection site. In elderly patients, which involves frequently arterial lesions of the lower part of the body, the terminal abdominal aorta may be a major site of reflection, the reflections occurring in the direction of heart. The pressure waves thus traverse the arterial system more quickly because of their smaller dimensions. This causes superimposition of the forward and backward waves during systole, and leads to a marked increase in aortic systolic pressure. An important argument in favour of this mechanism has been provided by the study of subjects with traumatic amputation of the lower limb. Such subjects display a high incidence of systolic hypertension over 50 years of age, resulting from the increased arterial stiffening and the shorter length of the arterial system due to traumatic amputation [17]. More recent evidence results from the noninvasive study of the change of amplitude and timing of wave reflections with age. Wave reflections are significantly altered by age, leading to a high systolic peak. Such changes are much more pronounced in subjects with reduced body height, i.e., with reduced length of the arterial system, as observed in old women with isolated systolic hypertension [18, 19].

## STRUCTURAL AND FUNCTIONAL COMPONENTS OF INCREASED ARTERIAL STIFFNESS IN HYPERTENSION IN THE ELDERLY

With aging, arteries progressively stiffen due to thickening of media and intima with accumulation of collageneous fibers, and deposition of calcium with degeneration of the elastic laminae [1]. The loss of distensibility is partly compensated by the progressive dilatation of arteries predominantly due to the fragmentation and rupture of elastin fibers, a specific aspect of the aging process independent of high blood pressure. As arteries stiffen, the pulse wave velocity, the most classical marker of arterial stiffness, progressively increases with an increase in systolic blood pressure and a tendency for diastolic blood pressure to decrease (Figs. 1 and 2). These changes, which are most marked in the aorta, are often attributed to the fatiguing effect of cyclic stress acting over many decades. Recent clinical and experimental studies have indicated that cyclic stress may effectively contribute to arterial damage [7, 20–22]. A major manifestation of these changes is the rise in SBP and PP, and the reduction or disappearance of pressure amplification between ascending aorta and peripheral arteries due to early wave reflections with an increase in pulse wave velocity.

For a long time it was believed that structural changes of the arterial wall provided the exclusive explanation for the increased systolic and pulse pressure in elderly patients. More recently, the role of functional factors has been recognized, derived from studies of the effects of: *i*) sodium intake, *ii*) administration of nitrates, and finally *iii*) abnormalities in the functioning of the sympathetic nervous system.

Isotonic saline infusion causes a higher increase in systolic pressure in patients with systolic hypertension than in age matched controls [23]. The increase in systolic pressure is mainly due to an increase in arterial stiffness following salt administration, whereas diastolic pressure is only marginally modified. The findings suggest that sodium may act on the arterial wall either directly, or through associated modifications of the autonomic nervous system, or by a combination of both factors. In the literature, the observation in dialyzed subjects of an increase in pulse wave velocity with sodium intake, and a decrease with salt restriction, is consistent with the effects of saline infusion in these patients [24].

While sodium intake acts to increase systolic pressure in elderly patients, nitrate compounds have an opposite effect on systemic hemodynamics [25–27]. Following acute administration, nitroglycerin has been shown to decrease systolic pressure selectively in patients with systolic hypertension and arteriosclerosis obliterans of the lower limbs [8]. This reduction in systolic pressure is related both to a decrease in arterial stiffness [26] and to a delay in the timing of wave reflections [1]. No significant change in ventricular ejection and vascular resistance is observed. Similar effects on systolic blood pressure reduction have been observed in elderly subjects with isolated systolic hypertension [28], and confirm that nitrate compounds considerably improve arterial stiffness in such patients.

Recent studies involving catecholamines clearance and microneurography have suggested that an activation of the autonomic nervous system is frequently observed in elderly patients [29–31]. At the site of large arteries, this finding is less evident to demonstrate. An experimental model of *in situ* isolated carotid artery has been used to evaluate the elastic properties of the arterial wall in young (3-month old) and older (18-month old) Wistar rats [32]. Pharmacological stimulation of $\alpha_1$-adrenoceptor with phenylephrine decreased

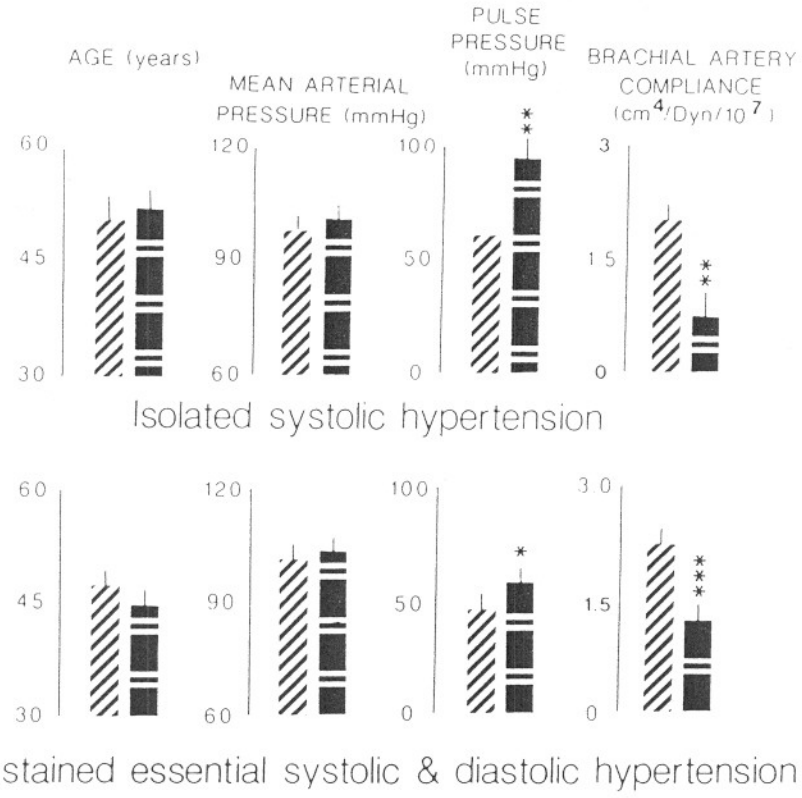


*Fig. 2.* Brachial artery parameters in hypertension in the elderly [13].

compliance in older but not in younger animals. Blockade of these receptors with prazosin, urapidil or labetolol increased compliance in younger and had less effect on older rats [32, 33]. Beta-receptor stimulation with isoproterenol or blockade with propranolol had no effect in any of the studied groups. Thus, with aging there is an increased vasoconstricting effect of $\alpha_1$-agonists and a decreased vasodilative action of $\alpha$-blockade. Such results were not associated with changes in $\alpha$-adrenoreceptor number or affinity [32] and are consistent with an increase in basal adrenergic $\alpha$ tone in old normotensive rats.

## AORTIC STIFFNESS IN THE ELDERLY AND HEART-VESSELS COUPLING

The dominant factor contributing to the development of cardiac hypertrophy is increased end-systolic stress. This parameter is influenced by the geometrical properties of the ventricle as well as by the level of systolic blood pressure. Since systolic blood pressure is largely influenced by aortic wave velocity and timing of reflected waves, this observation suggests important interactions between cardiac performance and physical properties of the arterial system, with predominant alterations in the elderly [34].

Aortic input impedance, determined by arteriolar tone, aortic distensibility and diameter, and the intensity and timing of arterial wave reflections, provides valuable information concerning the characteristics of the arterial system in accepting pulsatile flow from the heart, independently of ventricular properties [19, 34–36]. Several determinants of aortic impedance are altered in elderly hypertensive subjects. As we showed above, decreased aortic distensibility and pronounced effects of wave reflections have been observed. Increased pulse pressure, decreased aortic distensibility and increased characteristic impedance have been found to be strongly associated with the extent of cardiac hypertrophy in elderly subjects with hypertension [19, 20, 34]. Arterial wave reflections (AWR), an important determinant of cardiac afterload, are increased in elderly hypertensive subjects. Patients with higher AWR are characterized by a substantially higher cardiac mass (predominantly higher septal thickness), indicating the role of the early return of wave reflection in the mechanism of the hypertensive cardiac hypertrophy [19].

Increased arterial stiffness and alterations of wave reflections not only contributes to develop cardiac structure but also participate to modify coronary perfusion. As we mentioned earlier [2], at any given value of mean arterial pressure, increased arterial stiffness not only causes an increase in systolic blood

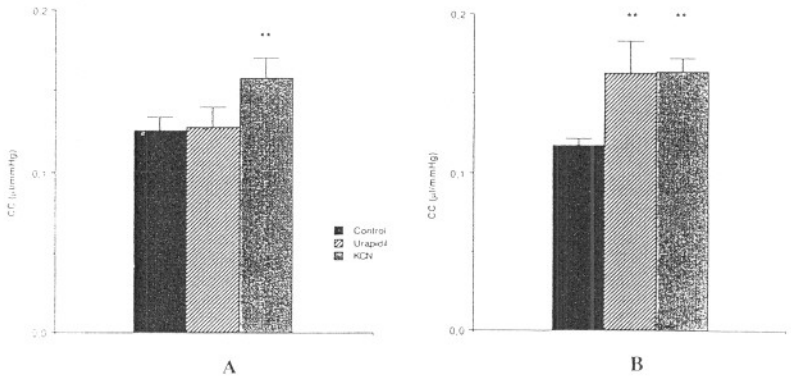


*Fig. 3.* Urapidil increases carotid compliance: Bar graphs showing carotid compliance (CC) at the 100–150 mmHg pressure level in spontaneously hypertensive rats under control conditions after incubation with urapidil with dosage corresponding to 1 mg/kg (panel A) and 2 mg/kg (panel B), and after potassium cyanide (KCN) poisoning. $^{**}p < 0.01$ vs control conditions [33].

pressure but also a decrease in diastolic blood pressure. Maximal left coronary inflow occurs in early diastole, when the ventricles have relaxed and extravascular compression of the coronary vessels is virtually absent [1]. Thus, at any given value of mean arterial pressure, coronary blood flow will tend to further fall if aortic stiffness is increased, i.e., particularly in old subjects with hypertension. Interestingly, increased aortic stiffness is frequently associated with coronary ischemic disease in populations of atherosclerotic subjects [37].

Taken together, these findings suggest that the increased arterial stiffness observed in older hypertensive patients has important consequences on both the degree of cardiac hypertrophy and the perfusion of the coronary circulation. Together with decreased cardiac compliance and rhythmic disorders, which are frequent in the elderly, these hemodynamic factors contribute greatly to precipitate congestive heart failure.

## THERAPEUTIC ASPECTS

Since increased systolic and pulse pressure may have specific deleterious effects on ventricular performance and the arterial wall, drug therapy could be useful in returning arterial wall properties and systolic pressure towards normal values in older subjects with systolic hypertension. It is obvious that any antihypertensive drug reducing arteriolar tone and, therefore, mean arterial pressure, may decrease systolic pressure through a decrease in diastolic and mean pressure and a resulting passive decrease in arterial stiffness and reduction in wave reflections [1, 38, 39]. However, in the case of an isolated or disproportionate increase in systolic pressure, the target mechanisms are rather the decrease in ventricular ejection or mostly the active increase in arterial compliance and decrease in wave reflections. A decrease in ventricular ejection is a classical way of obtaining a decrease in systolic pressure, as observed with ventricular pacing and treatment of atrioventricular blocks. An active decrease in arterial stiffness may be obtained independently of the decrease in mean arterial pressure with drugs specifically causing a reduction in smooth muscle tone in the wall of large arteries. An important mechanism involved in the decrease in systolic and pulse pressure is the reduction in (and delay of) wave reflections through peripheral vasodilatation and reduction in pulse wave velocity [1, 38, 39]. The latter possibility may functionally reverse some of the deleterious effects of arterial damage, thus restoring the normal relationship of wave reflection to ventricular ejection.

From these basic assumptions it seems logical that the decrease in arterial stiffness with delay of (and reduction in) wave reflections may be an effective strategy in the management of hypertension and left ventricular pressure overload. However, from the various conventional antihypertensive agents, nonselective $\beta$-blocking drugs induce an increase in wave reflections, and in conjunction with a decrease in heart rate, increase the duration of left ventricular ejection, i.e., the time interval for reflected waves to sum up with incident wave [38–40]. On the other hand, the classical diuretic compound, hydrochlorothiazide [41], the vasodilating drug cadralazine [42], the central antihypertensive agent clonidine [43], and several other $\beta$-blocking agents have no sizable effect on arterial rigidity, measured from pulse wave velocity [26]. These agents therefore seem to be devoid of significant arterial effects and are expected to lower aortic SBP less than brachial SBP. The best therapeutical effect on arterial rigidity and wave reflections is obtained with drugs that dilate small or medium-sized conduit arteries or which dilate both small arteries and arterioles. Such modifications are observed with $\alpha$-blocking agents [33, 44–48] (Fig. 3), calcium antagonists and angiotensin converting enzyme inhibitors [26]. These drugs not only decrease MBP and reduce pulse wave velocity but might also reduce the reflection coefficient and the

amount of reflected pressure. This may lead to a higher reduction of aortic than brachial SBP and might play a role in the regression of left ventricular hypertrophy.

## ACKNOWLEDGMENTS

This study was performed with the help of INSERM (Institut National de la Santé et de la Recherche Médicale, Paris), the Ministry of Research and Association Claude Bernard (Assistance Publique de Paris). We thank Mrs. Anne Safar for the preparation of the manuscript.

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