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Michel E. Safar

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Systolic Hypertension in Elderly Patients

Michel E. Safar, PhD

Pulsatile arterial hemodynamics in cardiovascular diseases indicate that the aortic blood pressure curve may be represented by 2 different phenotypes: one in patients 64 years old and younger and the other in subjects older than 65 years. The 2 blood pressure curves may have exactly the same mean arterial pressure (ie, the same cross-sectional area under the curve)

but quite different shapes. In older subjects, systolic blood pressure and pulse pressure are higher, whereas diastolic blood pressure is lower than in younger subjects.

Keywords: systolic hypertension; elderly patients; arterial wall mechanics

Two typical alterations occur in elderly hypertensive patients: (1) independently of mean arterial pressure, aortic stiffness is increased in association with age-related structural alterations and calcifications of central large arteries, and (2) during the blood pressure propagation along the arterial tree, pressure wave reflections return earlier from arteriolar sites toward the heart, causing a supplementary increase of systolic blood pressure (SBP), called increased *augmentation index*.¹ The pathophysiology of aging, which is responsible for enhanced arterial stiffness and altered augmentation index, can explain the hemodynamic profile of systolic hypertension in elderly subjects.

Hypertension in older subjects means that SBP exceeds 140 mm Hg, regardless the diastolic blood pressure (DBP), which is either below or above 90 mm Hg. This blood pressure profile is very common in westernized societies and is observed either *de novo* in such individuals or after a long period of systolic–diastolic hypertension with or without anti-hypertensive drug therapy.

Current drug treatment of hypertension frequently reduces cardiovascular risk in elderly patients² but leads to a hemodynamic pattern associated with

normalization of DBP (<90 mm Hg), while SBP more frequently remains elevated (>140 mm Hg).³ Finally, the structural alterations of the large arteries observed in systolic hypertension are very similar to those observed during the aging process but differ markedly from the atherosclerotic plaques described in dyslipidemic humans.¹

Increased sodium sensitivity and nitric oxide deficiency (NO) are the 2 dominant features that are essential to understanding the mechanisms of systolic hypertension in elderly patients. Alterations of the renin-angiotensin-aldosterone system are also contributive in older subjects.

Several epidemiologic studies⁴ indicate that a positive correlation is widely observed between urinary sodium excretion and an estimate of sodium consumption of various communities around the world and the upward slope of SBP of their inhabitants with aging. No such relationship exists between sodium consumption and DBP. Sodium intake may thus be a predictor of systolic but not diastolic hypertension. Conversely, dietary sodium restriction lowers SBP and pulse pressure, especially in elderly subjects with isolated or predominantly systolic hypertension,⁵ but has only a modest effect on DBP.

It is now widely accepted in vascular biology that increased sodium intake may act on the arterial wall independently of blood pressure, mainly through changes of shear stress and endothelial function.⁶ This process involves the coordinated expression of several biologic compounds such as transforming growth factor- β (TGF- β) and endothelial NO synthase

From the Diagnosis Center, Hôtel-Dieu Hospital, Paris, France.

Address correspondence to: Michel Safar, PhD, Diagnosis Center, Hôpital Hôtel-Dieu, 1, place du Parvis Notre-Dame, 75181 Paris Cedex 04, France; e-mail: michel.safar@htd.ap-hop-paris.fr

(NOS 3).⁶ A high-salt diet mostly induces phenotypic changes of vascular smooth muscle cells, involving mainly secretory properties and resulting in collagen accumulation within the large artery wall.⁷

Regarding NO, aged rats exhibit elevated plasma nitrite and nitrate levels. In addition, NO-dependent mechanical and agonist-mediated endothelial vasodilation is attenuated in older rats versus younger rats, with resulting oxidative stress.⁷ Finally, increased sodium intake and/or endothelium-dependent NO deficiency have, together with intimal alterations, 2 major consequences: (1) they favor the development of vascular hypertrophy and extracellular matrix, mainly through increased medial aortic collagen accumulation, and (2) they lead to unopposed effects of vasoconstrictive agents. Aortic angiotensin-converting enzyme (ACE) activity increases in an age-dependent manner in rats and nonhuman primates.⁸ Aortic angiotensin II is also elevated and co-localizes with both increased ACE and metalloproteinase type 2.⁷ Both fibronectin and TGF- β expression are involved in this process.⁷ An important observation in rats is that many of the age-associated intimal and extracellular matrix changes can be markedly delayed by long-term administration of ACE inhibitors. In older hypertensive subjects, only ACE inhibitors in association with small doses of diuretics have been shown to lower SBP and pulse pressure more than the β -blocking agent atenolol for the same DBP and mean blood pressure reduction.⁹

The prediction of cardiovascular risk in subjects with hypertension is traditionally based on the height of a single point on the cyclic blood pressure curve: SBP or DBP.¹⁰ Cardiovascular risk is mainly considered to be a linear function of SBP.¹⁰ A few years ago, however, a statistical principal component analysis found that pulse pressure in the elderly was a stronger cardiovascular risk factor than SBP itself.¹¹ This finding suggested that more than the height of the mechanical signal (SBP or DBP levels), the propagation of this signal (ie, the propagation of the cyclic blood pressure curve) along the arterial tree is a major element to be considered in cardiovascular risk. Thus, arterial stiffness, determined from pulse wave velocity, timing of wave reflections, calculated from augmentation index and, finally, increase of central pulse pressure,¹² were shown to provide the most relevant information on cardiovascular risk, particularly in hypertensive elderly subjects. Recently, elevated pulse pressure was even shown to be the exclusive factor, in

association with structural arteriolar changes, predicting cardiovascular risk in hypertensive subjects.¹³

The traditional basis of antihypertensive drug therapy is to decrease vascular resistance, thus reducing mean arterial pressure through change in the structure and function of small arteries and arterioles.^{10,13} This drug treatment is known to have powerful effects on cardiovascular risk, with 2 particularities: treatment is much more beneficial for the prevention of stroke than that of myocardial infarction; drugs lower DBP (<90 mm Hg) much more readily than SBP (<140 mm Hg), resulting in a substantial increase of pulse pressure with age under long-term therapy.³ These observations suggest that the design and development of drugs acting specifically on SBP, pulse pressure, arterial stiffness, and wave reflections may be important to develop in order to further reduce cardiovascular risk.

Conclusion

As a result of recent reviews,^{14,15} 3 classes of drugs have emerged as acting on large artery walls. First, exogenous nitrates selectively lower SBP, but not DBP, in elderly subjects with isolated systolic hypertension and also in acute situations such as cardiovascular surgery. Second, retrospective analyses in elderly populations show that diuretics are the main agents used to lower more selectively SBP and pulse pressure. Finally, like the diuretics, ACE inhibitors reduce cardiovascular risk and have been shown, by comparison with various antihypertensive agents, to decrease more selectively SBP and pulse pressure in parallel with arterial stiffening and wave reflections under 2 different conditions: end-stage renal disease and sustained essential hypertension of the middle-aged and elderly.^{9,15} Both situations require sodium and water depletion and/or the combination with low doses of diuretics. Antifibrotic agents, like selective Aldo antagonists, might be useful in the treatment of systolic hypertension.¹⁵ Finally, the use of collagen cross-linking breakers could also be an interesting approach in the treatment of hypertension in the elderly.

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