special medical editorial

Am J Physiol Heart Circ Physiol 285: H1363–H1369, 2003;
10.1152/ajpheart.00513.2003.

Pulse pressure and arterial stiffness in rats: comparison with humans

Michel E. Safar and Pierre Laurent
Department of Internal Medicine, Broussais Hospital, 75674 Paris, France

THE DEVELOPMENT of appropriate animal models for investigating human hypertension has been extremely valuable for studies of the natural history and the pathophysiological mechanisms of the disease (21). It has been considered that there is a strong similarity between spontaneously hypertensive rats (SHR) and patients with essential hypertension. Both have their apparent onsets of the condition very early in life, a reflection of their genetic backgrounds. The arterial hypertension involves a progressive increase of vascular resistance that initiates profound cardiac and systemic vascular adaptations and produces parallel increases of systolic (S), diastolic (D), and mean (M) arterial blood pressure (BP). Neural mechanisms seem to predominate in the early stages of both species' hypertensive diseases (especially in SHR), although in rats, multiple structural and functional disorders seem to be involved.

Partly as a consequence of antihypertensive drug therapy, the clinical aspects of human hypertension have changed considerably in recent years. In younger populations, milder and milder forms of hypertension are observed. In the elderly, more attention is accorded to isolated systolic hypertension and its treatment (7, 20, 42, 50). Systolic hypertension always involves a disproportional increase of SBP over DBP and differs markedly from the proportional increase of SBP and DBP commonly observed in SHR. In this context, relatively few studies on BP measurements and the pathophysiological mechanisms of high BP in old SHRs have been reported. Thus the purpose of this editorial is to provide some new insights into the mechanisms of systolic hypertension in humans and SHR, primarily taking into account the role on SBP, pulse pressure (PP), and PP amplification in the elderly of both populations.

SBP AND PP IN RATS AND HUMANS

Basic Concepts

Studies of pulsatile arterial hemodynamics have shown that the cyclic BP curve may be divided into two components (39, 42): a steady component mean arterial pressure (MAP) and a pulsatile component PP. Because of the propagation of the pressure wave and the summation of the incident and reflected waves at each specific point of the vascular circuit, SBP is physiologically higher, whereas DBP is slightly lower, in peripheral than central arteries. In contrast, MAP is practically constant along the totality of the arterial tree (Fig. 1).

In normotensive and hypertensive humans, studies of pressure wave transmission under basal conditions have shown that the amplification between the aortic arch and brachial PP averaged 18–31%. Nichols and O'Rourke (42, 43) found that brachial amplification was strongly dependent on the duration of ventricular systole, being decreased when it was lengthened, and increased when it was shortened. Thus, in humans, it is clear that brachial artery tracings may give a falsely high SBP value and falsely low DBP value compared with the ascending aorta and the rest of the arterial tree under basal conditions and those with a shortened duration of systole. From these findings, it is important to take into account for hypertensive subjects, not only peripheral (brachial), but also central (thoracic aorta and carotid artery) BP measurements.

In rats, the situation is more complex. Usually, tail SBP is measured. Therefore, it is assumed that tail SBP reflects central SBP and that there are no substantial SBP and PP amplifications in rats. In fact, studies in Wistar-Kyoto (WKY) rats (60, 61), either conscious or under anesthesia, have shown that significant SBP and PP amplifications are observed in these animals and, therefore, that it is not valid to extrapolate central SBP from tail SBP. In contrast, in SHR studied under basal conditions no amplification is observed. This finding in SHR is not surprising. The levels of SBP and PP amplifications are proportional to the length of the arterial tree (42, 43). In hypertensive rats, the increased arterial stiffness and the resulting changes in wave reflections tends to attenuate amplification as a consequence of the reduced length of the arterial tree. Nevertheless, in SHR, SBP and PP amplifications have been noted after administration of vasoactive agents. Angiotensin-converting enzyme inhibitors and calcium-entry blockers, but not dihydralazine, markedly reduce central PP with practically no effect on the terminal aorta PP (60).

All these observations taken together show that pressure wave transmission should be considered for BP measurements in rats and more generally in small rodents. Rats and mice have the same MAP but the mouse PP is half that in rats together with a significantly higher heart rate (37).

Address for reprint requests and other correspondence: M. E. Safar, Médecine Interne 1, Groupe Hospitalier Broussais-G. Pompidou, Hôpital Broussais, 96, rue Didot, 75674 Paris Cedex 14, France (E-mail: michel.safar@brs.ap-hop-paris.fr).

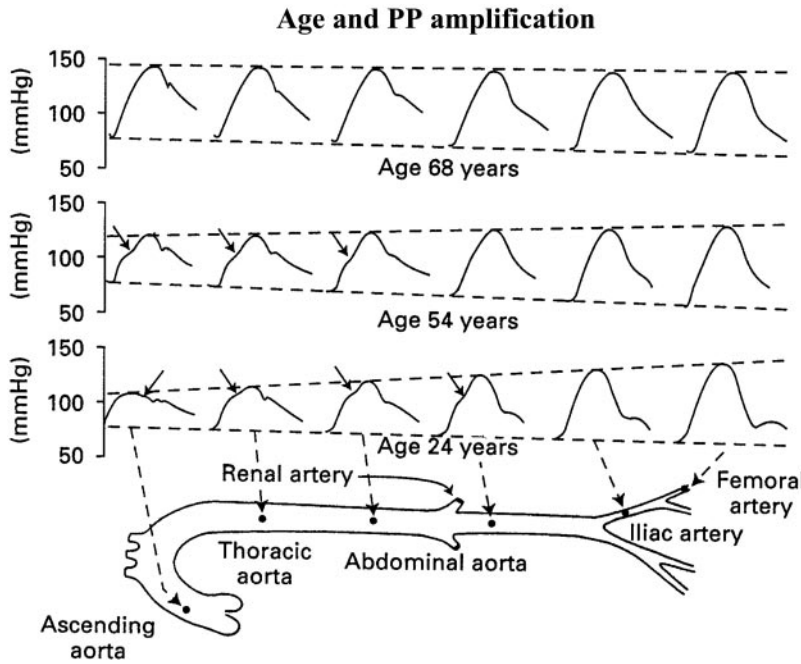

Fig. 1. Propagation of the pulse pressure (PP) wave from central to peripheral arteries at different ages in humans. In younger subjects (age: 24 yr), the rate of propagation is relatively low in arterial vessels, which become progressively narrower and less distensible. Because of the summation of the forward and the backward wave at each point of the arterial tree, peak systolic blood pressure (SBP) increases markedly from central to peripheral arteries, while end-diastolic blood presure (DBP) tends to be reduced and mean arterial pressure (MAP) remains unchanged. In older subjects (age: 68 yr), because of the more rapid propagation of pressure wave with resulting changes in wave reflections, the amplification of PP disappears, making that central and peripheral BP become identical. At 54 yr of age, the situation is intermediate between younger and older subjects (42).

Age-Associated Changes in SBP and PP in Rats

During the early phase of genetic hypertension in rats, there are major obstacles to accurately determine BP in such small animals. Whereas some authors have described a prehypertensive period, a number of other reports have indicated a significantly higher BP in SHR than in control rats before weaning (15, 17). In recent years, the use of intra-aortic BP measurements in conscious animals has clearly indicated that central BP increases with age more rapidly in SHR than in normotensive controls and that this increase involves enhancement of SBP, DBP, MAP, and PP but without any disproportional increase of SBP over DBP or PP over MAP (Fig. 2) (15).

The proportionally elevated SBP, DBP, MAP, and PP in SHR are known to decline spontaneously after 36 wk of age (36, 47). This finding is generally associated with a smaller stroke volume with aging and often considered to be due to incipient congestive heart failure (12, 47). In fact, SBP and PP are reduced with age to a lesser extent than MAP and DBP, which results in a statistically significant age-strain (SHR and WKY rats) interaction for SBP and PP but not MAP and DBP (36). Study of subpopulations of old (>60 wk) conscious SHR, which may be considered "survivors," has shown that, although aortic MAP remains relatively stable with aging, PP increases significantly from 52 to 78 wk of age (Fig. 2*B*). This observation indicates that, in rats, despite a decreased stroke volume with age, a parallel increase of aortic stiffness is able to produce an absolute PP increase in survivors (12). It should be noted that a significant increase of PP (but not MAP) with age has previously been reported in normotensive rats (38, 57).

In conclusion, few data are available on SBP and PP amplifications in rodents. Systolic hypertension can be seen in old survivors. However, in most populations, systolic hypertension is masked by the presence of decreased ventricular ejection and even congestive heart failure. These conditions emphasize the need to evaluate the mechanical properties of large arteries in old SHR.

Age-Associated Changes in the Mechanical Properties of Large Arteries in SHR

We and others (12, 15, 33, 36, 38) have shown that the carotid artery diameter and isobaric distensibility, and their age-related changes, do not differ significantly between WKY and SHR until the age of 12 wk, despite the higher BP and thicker arterial walls in SHR than control rats. In these young SHR, it seems likely that, in the presence of sympathetic constrictive influences, their normal isobaric distensibility contributes to the preservation of arterial function and is responsible for proportional increases of MAP and PP with age (12).

In contrast to the results obtained in young SHR, the isobaric aortic pulse wave velocity (PWV) and incremental elastic modulus are significantly increased in old (52–78 wk) SHR compared with age-matched controls (36). These findings indicate that in SHR the elastic properties of the aorta are intrinsically modified with aging independently of MAP level. This aortic stiffening cannot be attributed to wall thickening itself because the medial thickness-to-internal diameter ratio remains constant with age in both SHR and control rats (36). Therefore, other determinants of aortic wall elastic properties, i.e., the relative proportions of and/or interactions between smooth muscle cells and extracellular matrix, are affected during the aging of hypertensive rats. This process involves disproportional increases of collagen fibers and various adhesion molecules, such as fibronectin and proteoglycan, which contribute not only to increasing arterial stiffness but

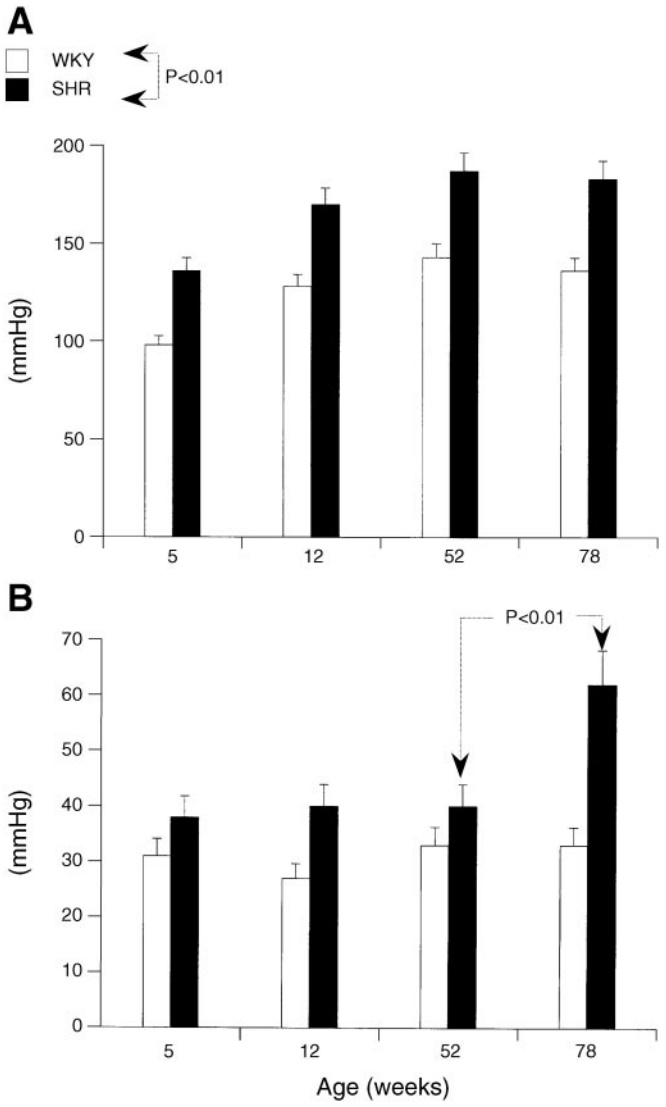

Fig. 2. Spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats: changes in MAP (*A*) and PP (*B*) with age. Note that after 12 wk of age, MAP remains stable in both strains, with higher MAP in SHR. Regarding PP, whereas the parameter remains stable in SHR till 52 wk of age, it increases markedly from 52 to 78 wk of age. This latter finding is observed in the small population of surviving animals (12).

also to altering the circulation of fluids in the interstitial milieu and favors cell death (51). It is noteworthy that, in such cases, cardiovascular (CV) death does not result from any lipid infiltration, as observed in atherosclerosis, but rather to other factors implied in the aging process. Thus rats have numerous biological factors capable of modulating arterial stiffening, SBP, PP, and PP amplification with age, and it is important to study these factors to develop novel approaches to treat hypertension.

BIOLOGICAL FACTORS MODULATING SBP AND PP IN RATS

Biological factors modulating SBP, PP, and PP amplifications have been studied mainly in genetic models of hypertension and involve mainly nitric oxide (NO) and vasoconstrictive agents, extracellular matrix, and sodium.

NO and Vasoconstrictive Substances

In anesthetized Sprague-Dawley rats, a bolus injection of NO synthase (NOS) inhibitor is able to significantly increase PWV, in parallel with an increase of BP (19). Because the BP changes are known by themselves to affect PWV, phenylephrine (PE) was administered in a control group to mimic the MAP changes induced by NOS inhibition, thus compensating for the pressure-dependent component of the PWV changes. Under those conditions, at each given level of MAP, PWV was significantly higher with NO blockade than with PE treatment. Similar findings have been reported using intra-arterial administration of suppressive doses of NO blocker in sheep (63). In Sprague-Dawley rats, the PWV changes were associated with an increase of central SBP and decrease of central DBP (i.e., PP increase) under NO blockade but not under PE (19). In elderly WKY rats with systolic hypertension, the increased SBP was reversed with L-arginine and angiotensin-converting enzyme inhibition (57). Taken together, these findings suggest that acute withdrawal of endogenous NO increases arterial stiffness independent of MAP changes and that an intact endogenous NO system is required to maintain arterial elasticity.

Studies on aortic reactivity in organ chambers have provided an explanation for the links between NO and arterial stiffness in rats. Young SHR aortic smooth muscle reaches maximal tension under norepinephrine (NE), and it is markedly higher in the absence than in the presence of endothelium (12) (Fig. 3). This heightened response, which is also produced by preincubation with a specific NOS inhibitor (12), indicates that NO modulates the SHR vascular smooth muscle cell response to the contractile agent NE. As previously observed in normotensive animals (14), NE acts on endothelial cells to increase NO production and/or release, thereby attenuating its own contractile effect on vascular smooth muscle. Numerous molecular biology studies on young SHR with sympathetic overactivity have shown that NO formation and/or release is upregulated (27, 35, 48) and should be considered a compensatory mechanism for the presence of neurogenic vasoconstriction. In vivo or in vitro NO blockade unmasks sympathetic overactivity, leading to increased arterial stiffness and PP (19). Finally, in young SHR, NO upregulation contributes to maintaining adequate arterial function and PP (12, 48).

The situation is completely different in aortic rings of 78-wk-old SHR. Compared with aortic rings from age-matched WKY or Wistar rats, the increase of maximal tension developed under NE obtained after deendothelialization (or under NO blockade) is significantly lower or even abolished (12) (Fig. 3). This observation suggests a modification with age of the interactions among endothelial function, arterial stiffness, and PP, an interpretation supported by several other results. First,

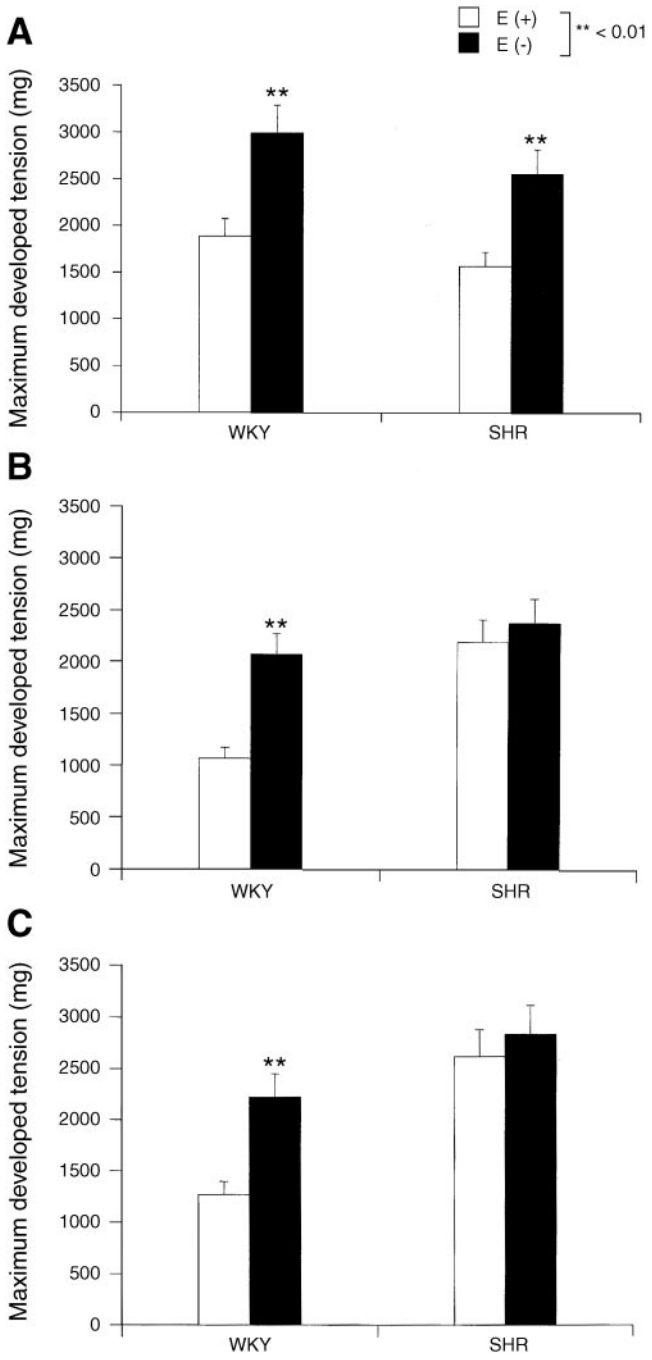

Fig. 3. SHR and WKY rats: maximum developed tension under norepinephrine (NE) before (E+) and after (E−) endothelium removal at 12 (*A*), 52 (*B*), and 78 wk (*C*). Note that at 12 wk of age, endothelium removal increases significantly maximum developed tension (**$P < 0.01$). This increase is no more significant in SHR of 52 and 78 wk (12).

under physiological conditions, the NO release is modulated both by frequency and amplitude of pulsatile flow, resulting in a PP decrease (8, 23). Second, this mechanism is disrupted in the elderly, in which conduit arteries are stiffened (46). Indeed, NO bioactivity and endothelial NOS mRNA and protein, which are markedly influenced by age and substantially lowered in the elderly (38), result in oxidative stress and are more substantially associated with pulsatile than with steady mechanical stress (3, 10, 13, 27, 35, 49, 51). Third, in old hypertensive rats and predominantly in men, exogenous NO donors acutely and selectively normalize PP with minor MAP changes and without any supplementary structural alteration of the hypertrophied arteries (see reviews in Refs. 42, 51, and 52). Finally, nitrates are known to dilate larger rather than smaller arteries, to decrease markedly arterial stiffness independently of MAP changes, and to produce a greater diminution of central than peripheral SBP, thereby increasing PP amplification (42, 52).

The endothelial NO-NE interaction can be easily studied in SHR, where its main characteristic is sympathetic overactivity. However, the interactions of NO with other vasoconstrictors, such as ANG II or endothelin, should also be considered. A specific receptor-mediated effect of ANG II on endothelial cells may be postulated. ANG II specifically constricts the carotid artery and increases cGMP levels via the ANG II type 1 (AT_1)-receptor subtype in the in vitro intact rat carotid artery (9, 31). The mechanism underlying this change is thought to be mediated through endothelial NOS stimulation by ANG II. ANG II-dependent NO production by the endothelial cells could modulate the peptide-induced smooth muscle cell contraction. Thus ANG II contractile and trophic vascular effects could be exaggerated under pathological heterogeneous conditions such as accelerated aging and contribute by themselves to the mechanisms of systolic hypertension.

SBP, PP, and Extracellular Matrix

The balance between rigidity and elasticity of all blood vessels is determined by the mechanical properties of extracellular matrix proteins. This balance involves not only elastin but also the formation of heterologous collagen I, III, and V fibrils synthesized by the smooth muscle cells of the arterial media. The texture and, therefore, the tensile strength of any tissue are characterized by the diameter of the fibrils and their ability to form bundles (26, 40, 44, 53). Collagen I is the most abundant and forms thick fibrils leading to rigidity, but the cross-linkage of this molecule with collagen III (and perhaps collagen V) decreases fibril diameter and increases the extensibility of the tissue. Hence, regulating the synthesis and thus the balance between collagens I and III is crucial for the mechanical properties of the blood vessel. This balance depends on the strict regulation of the biosynthesis and degradation of collagens I and III. For instance, the proportions of collagens I and III differ markedly within the arterial wall of Lyon and Japanese rats, resulting in a higher isobaric elasticity in the former (11).

In cell cultures, ANG II stimulates the production of various types of collagen fibers (25) and also several growth factors (22). In vivo, angiotensin-converting enzyme inhibition and ANG II AT_1 receptor blockade have been used as tools to demonstrate that the chronic blockade of the AT_1 receptor prevents the accumula-

Table 1. *Pharmacological agents capable of selectively reducing SBP and PP, and increasing arterial stiffness independent of MAP*

Mechanism(s) of Action	Compound	References
NO and endothelial function		
Nitrates*	Isosorbide dinitrate	16, 51, 62
	Sinitrodil	
Others	Nebivolol	12, 62
	Cycletanine	
Collagen and extracellular matrix		
Collagen content*	Blockers of renin-angiotensin system	1, 6, 28, 31
Collagen cross-linking*	Acteon	24
Sodium and related compounds*		
	Thiazide diuretics	56, 58
	Indapamide	2, 4, 18, 32
	Spironolactone	5, 29
	Sodium diet	28, 29, 34, 59

MAP, mean arterial pressure; systolic blood pressure; PP, pulse pressure; NO, nitric oxide. *Both experimental and clinical studies.

tion of aortic collagen in SHR (1, 6). This effect is independent of BP changes and bradykinin release but involves the blockade of either AT_1 or mineralocorticoid receptors or a combination of both (5, 6). Finally, such findings are observed exclusively on a normal, but not a high-sodium diet (28), a situation during which collagen accumulation is associated with an increase of isobaric arterial stiffness. Through their binding to cations, proteoglycans in the arterial wall may be one of the predominant contributors to this process (18).

Independently of the renin-angiotensin system, glycosylated end products may also participate in the biosynthesis and degradation of arterial collagen (24, 40). They may accentuate the cross-linking of collagen fibers and thereby increase isobaric arterial stiffness, particularly in experimental and human models of diabetes mellitus and aging. The drug aminoguanidine or derivatives can reverse the stiffness alterations (24).

Sodium and Arterial Stiffness

Most of the data on sodium-induced changes of arterial structure and function were obtained from genetic models of hypertension in rats. Tobian (59) was the first to show that, in stroke-prone SHR, high sodium intake is associated with more pronounced structural alterations of cerebral and renal arteries than when a low-sodium diet is consumed. Under high-salt conditions, the increased wall thickness involves a substantial increase of collagen content together with abnormal cross-linking and enhanced arterial stiffness (32, 40). These alterations are reversed with lowering of sodium intake without any change of intra-arterial MAP but in parallel with a reduced incidence of cerebrovascular accidents.

In stroke-resistant SHR, the temporal relationship between high BP hypertension and the appearance of vascular lesions during salt loading has been investigated starting at 5 wk of age (34). Neither intra-arterial BP nor vascular morphology of WKY rats is affected by 1% NaCl in the drinking water (34, 45). In SHR, BP is not affected by the addition of salt for at least 11 wk, but vascular morphology is significantly altered within 5 wk, resulting in significant thickening of the aortic media associated with increased arterial stiffness, marked modification of extracellular matrix, collagen, and proteoglycans (18, 34, 45). Similar results, associated with an isobaric increase of arterial stiffness have been obtained in Dahl salt-sensitive rats(4).

Taken together, these findings show pressure-independent interactions between sodium ions and arterial structure and function in various models of hypertension in rats. They also indicate that genetic factors, particularly those involving sodium sensitivity, are highly contributive to stiffness changes.

APPLICATIONS TO SYSTOLIC HYPERTENSION IN HUMANS

Hypertension in the elderly has two distinct features: isolated systolic hypertension with normal or low DBP and systolic-diastolic hypertension with a disproportional increase of SBP over DBP. Both of them result in a higher SBP and PP due to increased arterial stiffness and disturbed wave reflections (42, 52). Compelling evidence is now available that both varieties of hypertension involve a high degree of CV risk, as evaluated from PP and PWV measurements (50), and that drug treatment is highly effective against CV morbidity and mortality (55). In addition, Framingham studies (20) have shown that the age-related increase of SBP and PP vary widely from one individual to another after 50 years of age. The factors modulating this variability should be evaluated extensively if the goal of drug treatment is to adequately reduce CV risk. Thus, in older populations, the purpose of antihypertensive therapy should be not only to reduce BP as in younger populations, but mostly to prevent the accelerated increase of the SBP with age and to reduce the physiological decrease of DBP with age, hence to minimize the increase of PP with age, in populations at high CV risk.

As observed in animals, the accelerated increases of PP and PWV with age are modulated by a number of genetic and environmental factors. Some gene polymorphisms as those associating the C allele of the ANG II AT_1 receptor gene and the T allele of the constitutive

NOS (*G894T*) gene are accompanied by accelerated increases PP and arterial stiffness with age (30, 41). We have previously shown that the presence and/or the combination of the C and/or T alleles is associated with PP steeper increases with age than in the non-C, non-T allele subgroups (41). Thus, in individuals with a genetic predisposition, both an increase of ANG II-induced aortic collagen accumulation and impaired NO bioactivity might contribute to enhancing arterial stiffness, thereby increasing SBP and PP with age. In hypertensive subjects, the frequencies of these alterations have been underestimated, because in the majority of genetic studies, DBP, and not SBP, was used as the sole criterion of selection for the diagnosis of hypertension. In addition, other candidate genes have been described, particularly those combining the alleles of the angiotensin-converting enzyme and the α-adducin genes (56).

In humans, environmental factors also contribute to the increases of aortic stiffness and PP with age. In particular, it is well established that sodium sensitivity rises with age in parallel with the increase of PP. These effects have been noted in association with some gene polymorphisms, like those combining the angiotensin-converting enzyme and α-adducin genes (56). Finally, the role of genetic factors on the age-PP relationship is more pronounced in women than in men, possibly as a consequence of their constitutive short stature with resulting gender-related changes of arterial stiffness and wave reflections (41, 54).

In conclusion, it has been shown in this editorial that new aspects of the similarities and dissimilarities of hypertension in humans and rats may be noted. They mainly reflect changes in SBP, PP, and arterial stiffness associated with age. Furthermore, they suggest that the standard drug treatment of hypertension, which in the past focused on decreasing vascular resistance, is no longer adequate to obtain a parallel reduction in arterial stiffness. New aspects of CV pharmacology should be defined to respond to this important challenge as summarized in Table 1.

We thank Dr. Anne Safar for pertinent and in-depth discussions.

DISCLOSURES

This study was performed with the help of Institut National de la Santé et de la Recherche Médicale, Association Claude Bernard and Groupe d'Hémodynamique et de Pharmacologie Cardio-vasculaire, Paris.

REFERENCES

1. **Albaladejo P, Bouaziz H, Duriez M, Gohlke P, Levy B, Safar M, and Benetos A.** Angiotensin converting enzyme inhibition prevents the increase in aortic collagen in rats. *Hypertension* 23: 74–82, 1994.
2. **Asmar RG, London GM, O'Rourke ME, and Safar ME, and for the Reason project coordinators and investigators.** Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patients: a comparison with atenolol. *Hypertension* 38: 922–926, 2001.
3. **Bauersachs J, Bouloumie A, Mülsch A, Wiemer G, Fleming I, and Busse R.** Vasodilator dysfunction in aged spontaneously hypertensive rats: changes in NO synthase III and soluble guanylate cyclase expression and in superoxide anion production. *Cardiovasc Res* 37: 772–779, 1998.
4. **Benetos A, Bouaziz H, Albaladejo P, Guez D, and Safar M.** Carotid artery mechanical properties of Dahl salt-sensitive rats. *Hypertension* 25: 272–277, 1995.
5. **Benetos A, Lacolley P, and Safar ME.** Prevention of aortic fibrosis by spironolactone in spontaneously hypertensive rats (SHRs). *Arterioscler Thromb Vasc Biol* 17: 1152–1156, 1997.
6. **Benetos A, Levy BI, Lacolley P, Taillard F, Duriez M, and Safar ME.** Role of angiotensin II and bradykinin on aortic collagen following converting-enzyme inhibition in spontaneously hypertensive rats. *Arterioscler Thromb Vasc Biol* 17: 3196–3201, 1997.
7. **Black HR.** The paradigm has shifted to systolic blood pressure. *Hypertension* 34: 386–387, 1999.
8. **Canty JM and Schwartz JS.** Nitric oxide mediates flow-dependent epicardial coronary vasodilation to changes in pulse frequency but not mean flow in conscious dogs. *Circulation* 89: 375–384, 1994.
9. **Caputo L, Benessiano J, Boulanger CM, and Levy BI.** Angiotensin II increases cGMP content via endothelial angiotensin II AT1 subtype receptors in the rat carotid artery. *Arterioscler Thromb Vasc Biol* 15: 1646–1651, 1995.
10. **Cernadas MR, De Miguel LS, Garcia-Duran M, Gonzalez-Fernandez F, Millas I, Monton M, Rodrigo J, Rico L, Fernandez P, Defrutost, Rodriguez-Feo Ja, Guerra J, Caramelo C, Casado S, and Lopez-Farre A.** Expression of constitutive and inducible nitric oxide synthases in the vascular wall of young and aging rats. *Circ Res* 83: 279–286, 1998.
11. **Chamiot-Clerc P, Renaud JF, Blacher J, Legrand M, Samuel JL, Levy Bi, Sassard J, and Safar ME.** Collagen and III I and mechanical properties of conduit arteries in rats with genetic hypertension. *J Vasc Res* 36: 139–146, 1999.
12. **Chamiot-Clerc PH, Renaud JF, and Safar ME.** Pulse pressure, aortic reactivity and endothelium dysfunction in old hypertensive rats. *Hypertension* 37: 313–321, 2001.
13. **Chou TZ, Yen MH, Li CY, and Ding YA.** Alterations of nitric oxide synthase expression with aging and hypertension in rats. *Hypertension* 31: 643–648, 1998.
14. **Cocks TM and Angus JA.** Endothelium-dependent relaxation of coronary arteries by noradrenaline and serotonin. *Nature* 305: 627–630, 1983.
15. **Cunha R, Dabire H, Bezie I, Weiss AM, Chaouche-Teyara K, Laurent S, Safar M, and Lacolley P.** Mechanical stress of the carotid artery at the early phase of spontaneous hypertension in rats. *Hypertension* 29: 992–998, 1997.
16. **Duchier J, Iannascoli F, and Safar M.** Antihypertensive effect of sustained-release isosorbide dinitrate for isolated systolic hypertension in the elderly. *Am J Cardiol* 60: 99–102, 1987.
17. **Eccleston-Joyner CA and Gray SD.** Arterial hypertrophy in the fetal and neonatal spontaneously hypertensive rats. *Hypertension* 12: 513–518, 1988.
18. **Et-Taouil K, Schiavi P, Levy BI, and Plante GE.** Sodium intake, large artery stiffness and proteoglycans in the SHR. *Hypertension* 38: 1172–1176, 2001.
19. **Fitch RM, Vergona R, Sullivan ME, and Wang Y-X.** Nitric oxide synthase inhibition increases aortic stiffness measured by pulse wave velocity in rats. *Cardiovasc Res* 51: 351–358, 2001.
20. **Franklin SS, Gustin W IV, Wong ND, Larson MG, Weber MA, Kannel WB, and Levy D.** Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation* 96: 308–315, 1997.
21. **Frohlich ED, Pfeffer MA, and Pfeffer JM.** Systemic hemodynamics and cardiac function in spontaneously hypertensive rats: similarities with essential hypertension. In: *The Heart in Hypertension*, edited by Strauer BE. Springer-Verlag: Berlin and New York, 1981, p. 53–71.
22. **Gibbons GH, Pratt RE, and Dzau VJ.** Vascular smooth muscle cell hypertrophy vs hyperplasia: autocrine transforming growth factor-β1 expression determines growth response to angiotensin II. *J Clin Invest* 90: 456–461, 1992.
23. **Hutcheson IR and Griffith TM.** Release of endothelium-derived relaxing factor is modulated both by frequency and ampli-

tude of pulsatile flow. *Am J Physiol Heart Circ Physiol* 261: H257–H262, 1991.
24. **Kass DA, Shapiro EP, Kawaguchi M, Capriotti AR, Scuteri A, Degroof RC, and Lakatta EG.** Improved arterial compliance by a novel advanced glycation end-product cross-link breaker. *Circulation* 104: 1464–1470, 2001.
25. **Kato H, Suzuki H, Tajima S, Ogata Y, Tominaga T, Sato A, and Saruta T.** Angiotensin II stimulates collagen synthesis in cultured vascular smooth muscle cells. *J Hypertens* 9: 17–22, 1991.
26. **Kielty CM, Hopkinson I, and Grant ME.** Collagen. The collagen family: structure, assembly and organization in the extracellular matrix. In: *Connective Tissue and Its Inheritable Disorders: Molecular Genetic and Medical Aspects*, edited by Royce PM and Steinmann B. New York: Wiley-Liss, 1993, p. 103–147.
27. **Küng CF and Lüscher TF.** Different mechanisms of endothelial dysfunction with aging and hypertension in rat aorta. *Hypertension* 25: 194–200, 1995.
28. **Labat C, Lacolley P, Lajemi M, De Gasparo M, Safar ME, and Benetos A.** Effects of valsartan on mechanical properties of the carotid artery in spontaneously hypertensive rats under high-salt diet. *Hypertension* 38: 439–443, 2001.
29. **Lacolley P, Labat C, Pujol A, Delcayre C, Benetos A, and Safar M.** Increased carotid wall elastic modulus and fibronectin in aldosterone-salt treated rats-effects of Eplerenone. *Circulation* 106: 2848–2853, 2002.
30. **Lajemi M, Labat C, Gautier S, Lacolley P, Safar M, Asmar R, Cambien F, and Benetos A.** Angiotensin type 1 receptor-153 A/G and 1166 A/C II. gene polymorphisms and increase in aortic stiffness with age in hypertensive subjects. *J Hypertens* 19: 407–413, 2001.
31. **Levy BI, Michel JB, Salzmann JL, Poitevin P, Devissaguet M, Scalbert E, and Safar ME.** Angiotensine-converting enzyme inhibition on the arterial wall of adult spontaneously hypertensive rats. *Am J Cardiol Card* 71: 8E–16E, 1993.
32. **Levy BI, Poitevin P, Duriez M, Guez DC, Schiavi PD, and Safar ME.** Sodium, survival and the mechanical properties of the carotid artery in stroke-prone hypertensive rats. *J Hypertens* 15: 251–258, 1997.
33. **Lichtenstein O, Safar ME, Mathieu E, Poitevin P, and Levy BI.** Static and dynamic mechanical properties of the carotid artery from normotensive and hypertensive rats. *Hypertension* 32: 346–350, 1998.
34. **Limas C, Westrum B, Limas CJ, and Cohn JN.** Effect of salt on the vascular lesions of spontaneously hypertensive rats. *Hypertension* 2: 477–489, 1980.
35. **Marin J.** Age-related changes in vascular responses: a review. *Mech Ageing Dev* 79: 71–114, 1995.
36. **Marque V, Kieffer P, Atkinson J, and Lartaud-Idjouadienne I.** Elastic properties and composition of the aortic wall in old spontaneously hypertensive rats. *Hypertension* 34: 415–422, 1999.
37. **Mattson DL.** Comparison of arterial blood pressure in different strains of mice. *Am J Hypertens* 14: 405–408, 2001.
38. **Michel JB, Heudes D, Michel O, Poitevin P, Philippe M, Scalbert E, Corman B, and Levi BI.** Effect of chronic ANG I-converting enzyme inhibition of aging processes. II. Larges arteries. *Am J Physiol Regul Integr Comp Physiol* 267: R124–R135, 1994.
39. **Milnor WR.** *Hemodynamics* (2nd ed.). Baltimore, MD: Wilkins, 1989, p. 211–241.
40. **Mizutani K, Ikeda K, Kawai Y, and Yamori Y.** Biomechanical properties and chemical composition of the aorta in genetic hypertensive rats. *J Hypertens* 17: 481–487, 1999.
41. **Mourad JJ, Ducailar G, Rudnichi A, Lajemi M, Mimram A, and Safar ME.** Age-related increase of pulse pressure and gene polymorphisms in essential hypertension: a preliminary study. *J Renin Angiotensin Aldosterone Syst* 3: 109–115, 2002.
42. **Nichols WW and O'Rourke M.** McDonald's blood flow in arteries. *Theoretical, Experimental and Clinical Principles* (4th ed.). London, Sydney, Auckland: Arnold, 1998, p. 54–113, 201–222, 284–292, and 347–401.
43. **O'Rourke M.** Mechanical principles in arterial disease. *Hypertension* 26: 2–9, 1995.
44. **Parry DAD.** The molecular, and fibrillar structure of collagen and its relationship to the mechanical properties of connectivite tissue. *Biophys Chem* 29: 195–209, 1988.
45. **Partovian C, Benetos A, Pommies JP, and Safar ME.** Effects of a chronic high-salt diet on large artery structure: role of endogenous bradykinin. *Am J Physiol Heart Circ Physiol* 274: H1423–H1428, 1998.
46. **Peng X, Haldar S, Deshpande S, Irani K, and Kass DA.** Wall stiffness suppresses Akt/eNOS and cytoprotection in pulse-perfused endothelium. *Hypertension* 41: 378–381, 2003.
47. **Pfeffer MA and Frolich D.** Hemodynamic and myocardial function in young and old normotensive and spontaneously hypertensive rats. *Circ Res* 32, *Suppl* I: I28–I38, 1973.
48. **Radaelli A, Mircoli L, Mancia G, and Ferrari AU.** Nitric oxide-dependent vasodilation in young spontaneously hypertensive rats. *Hypertension* 32: 735–739, 1998.
49. **Ruschitzka F, Corti R, Noll G, and Lüscher TF.** A rationale for treatment of endothelial dysfunction in hypertension. *J Hypertens* 17, *Suppl* 1: S25–S35, 1999.
50. **Safar ME.** Systolic blood pressure, pulse pressure, and arterial stiffness as cardiovascular risk factors. *Curr Opin Nephrol Hypertens* 10: 257–261, 2001.
51. **Safar ME, Blacher J, Mourad JJ, and London GM.** Stiffness of carotid artery wall material and blood pressure in humans. *Stroke* 31: 782–790, 2000.
52. **Safar ME and London GM.** The arterial system in human hypertension. In: *Textbook of Hypertension*, edited by Swales JD. London: Blackwell, 1994, p. 85–102.
53. **Schwartz SM, Heimark RL, and Majesty MW.** Developmental mechanisms underlying pathology of arteries. *Physiol Rev* 70: 1177–1198, 1990.
54. **Smulyan H, Asmar RG, Rudnichi A, London GM, and Safar ME.** Comparative effects of aging in men and women on the properties of the arterial tree. *J Am Coll Cardiol* 37: 1374–1380, 2001.
55. **Staessen JA, Gasowski J, Wang JG, Thijs L, Den Hond E, Boissel JP, Coope J, Ekbom T, Gueyffier F, Liu L, Kerlikowske K, Pocock S, and Fagard RH.** Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 355: 865–872, 2000.
56. **Staessen JA, Wang JG, Brand E, Barlassina C, Birkenhäger H, Herrmann SM, Fagard R, Tizzoni L, and Bianchi G.** Effects of three candidate genes on prevalence and incidence of hypertension in a caucasian population. *J Hypertens* 19: 1349–1358, 2001.
57. **Susic D, Varagic J, and Frohlich ED.** Isolated systolic hypertension in elderly WKY is reversed with L-arginine and ACE inhibition. *Hypertension* 38: 1422–1426, 2001.
58. **The ALLHAT Officers, and Coordinators for the ALLHAT Collaborative Research Group.** Major outcome in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288: 2991–2997, 2002.
59. **Tobian L.** Salt and hypertension: lessons from animal models that relate to human hypertension. *Hypertension* 17, *Suppl* I: S152–S158, 1991.
60. **Tsoucaris D, Benetos A, Legrand M, London G, and Safar M.** Proximal and distal pulse pressure after acute antihypertensive vasodilating drugs in Wistar-Kyoto and spontaneously hypertensive rats. *J Hypertens* 13: 243–249, 1995
61. **Tsoucaris-Kupfer D, Benetos A, Legrand M, and Safar M.** Pulse pressure gradient along the aortic tree in normotensive Wistar-Kioto and spontaneously hypertensive rats: effect of nicardipine. *J Hypertens* 11: 135–139, 1993.
62. **Van Bortel LM, Struijker-Boudier HA, and Safar ME.** Pulse pressure, arterial stiffness, and drug treatment of hypertension. *Hypertension* 38: 914–921, 2001.
63. **Wilkinson IB, Qasem A, McEniery CM, Webb DJ, Avolio AO, and Cockcroft JR.** Nitric oxide regulates local arterial distensibility in vivo. *Circulation* 105: 213–217, 2002.