Stiffness of Carotid Artery Wall Material and Blood Pressure in Humans
Application to Antihypertensive Therapy and Stroke Prevention

M.E. Safar, MD; J. Blacher, MD; J.J. Mourad, MD; G.M. London, MD

Background and Purpose—Because epidemiological studies show that increased pulse pressure and carotid wall–material stiffness are predictors of cardiovascular mortality independent of age, atherosclerosis, and conventional risk factors, the relationships between carotid wall stiffness and blood pressure are important to the optimization of cardiovascular prevention.

Summary of Review—In middle-aged hypertensive patients, mean and pulse pressures are increased, and systolic and diastolic pressures are increased to the same degree as mean pressure. Carotid hypertrophy is associated with normal wall stress, but no increased stiffness of wall material has been reported. With age, the normal wall stress is associated with a larger diameter and a stiffer material of carotid but not peripheral arteries. The stiffer wall involves calcifications, large amounts of collagen, and fragmentation and rupture of elastic tissue, which results in increased pulse-wave velocity and alterations of amplitude and timing of wave reflections and thus causes a disproportionate increase in systolic and pulse pressure. During this period, acutely administered nitrates in elderly subjects are able to reduce selectively systolic and pulse pressures without altering diastolic and mean blood pressure and composition of the carotid wall.

Conclusions—New therapeutic approaches acting mainly on the wall of large arteries are needed to treat hypertension in elderly patients and prevent stroke and myocardial infarction. These drugs could either selectively lower pulse pressure through changes in wave reflections (as nitrates do) or decrease arterial wall stiffness through modification of the composition of material (such as compounds that act on collagen cross-linking). (Stroke. 2000;31:782-790.)

Key Words: arterial wall hypertension

In humans, hypertensive cardiovascular complications result mainly from alterations in small and large arteries. Antihypertensive drug therapy prevents approximately 40% of strokes in treated subjects, whereas prevention of ischemic heart disease is much less effective.1 Because the same complications occur in normotensive subjects, vascular alterations are commonly attributed to factors associated with hypertension, such as aging or atherosclerosis. However, growing evidence suggests that the hypertensive vessel wall is significantly thicker and stiffer than that in normotensive controls and that this alteration occurs early in the course of the disease.2-3 In the carotid-cerebral circulation, studies of spontaneously hypertensive rats have focused on changes in distensibility of cerebral arterioles and the role of local pulse pressure in modification of vessel structure.4 However, these experimental findings are difficult to extrapolate to the human context of antihypertensive therapy because they cannot be directly related to cardiovascular risk. Many recent studies have shown that the structural and functional alterations of the conduit arteries of the carotid-cerebral circulation may be adequate markers of cardiovascular risk independent of conventional risk factors as diabetes, plasma lipids, and tobacco consumption.3,5,6 More specifically, increased pulse pressure and increased stiffness and thickness of the common carotid arterial (CCA) wall were shown to be significant and independent predictors of cardiovascular complications,6-9 mainly for myocardial infarction6 but also for stroke.10 Thus, in humans, the question arises as to whether stiffness changes in hypertensive carotid arterial vessels may be an early marker for future cardiovascular complications and could be a target for drug therapy for hypertension. To answer to this question, appropriate methods are needed in humans that can differentiate between vascular changes that result from atherosclerosis or aging and those caused by high blood pressure.

In animal models, evaluation of such differences presents no major difficulty, because genetic or experimental hypertension in rats is never accompanied by atherosclerosis.
Basic Concepts in Arterial Structure and Function

The medial layer constitutes most of the thickness of an artery such as the CCA. During growth and development, in parallel with the rise in blood pressure, the number of medial smooth-muscle cells increases rapidly, and they become organized into lamellar units. When comparing adults of different species, the number of lamellar units and the overall wall thickness reflect the size of the animal and the diameter of the vessel. The calculated tension per lamellar unit is relatively constant for a wide range of species and vessel sizes. Hypertension causes an increase in thickness in the arterial media that serves to normalize the rise in wall tension. According to the law of Laplace, tension (T) in the wall of a cylindrical vessel is a function of steady (mean) transmural pressure (TP) and internal radius (r), as follows: 

\[ T = TP \times r \]

Dependent on wall thickness \( h \), circumferential stress exerted by the tissue is \( T/h \). In hypertension, hypertrophy of conduit arteries such as the CCA, with normal or increased internal diameter and increased external diameter, is the most common finding, regardless of topography of the vessel. Arterial remodeling, as defined by reduced diameter and unchanged medial cross-sectional area, is not a common feature.

In hypertension, the number of lamellar units remains relatively constant and increased wall thickness results from changes in both cellular mass and extracellular matrix and their geometries. With aging, central arteries such as the CCA progressively stiffen because of thickening of the media with accumulations of collagen fibers and calcium deposits and degeneration of the elastic laminae. A loss of distensibility occurs, in association with a progressive dilatation of arteries predominantly due to fragmentation and rupture of elastin fibers, an aspect sometimes considered to be specific to the aging process independent of high blood pressure. All of these changes, which are most pronounced in the aorta and the CCA, are often attributed to the fatigue effect of cyclic stress and pulse pressure acting during many decades.

Experimental and, to a lesser extent, clinical studies have indicated that increased pulse pressure might contribute to the expansion of the extracellular matrix and even to atherosclerotic damage. Major manifestations of these changes are the rise of systolic and pulse pressures and the disappearance of pulse pressure amplification, findings documented by longitudinal studies in rats and in normotensive and hypertensive humans. Finally, all of these changes alter the biomechanical properties of the arterial wall, and therefore wall-material stiffness, a parameter usually evaluated from the determination of incremental elastic modulus (\( E_{inc} \)).

Circumferential stress is used to determine \( E_{inc} \), provided that arterial wall motion is detected and thus the strain-stress relationship of the artery as the CCA can be established. The circumferential strain of an artery can be defined as

\[ \frac{(d-d_0)}{d_0} \]

where \( d \) is observed internal diameter and \( d_0 \) is baseline internal diameter. Usually, \( d \) is defined as the diameter of the retracted, totally unloaded vessel, the diameter at low or 0 mm Hg pressure, or the unstressed diameter. The stress-strain ratio can be used to compute the Young modulus of elasticity (ie, the stretching force per unit of cross-sectional area required to elongate a strip of a vessel wall 100%). However, for materials with nonlinear strain-stress relationships, such as arterial vessels, the slope of the strain-stress curve is used to determine \( E_{inc} \). For instance, within the limits of the present definitions, carotid \( E_{inc} \) is related to carotid PWV by the Moens-Korteweg equation:
dures.34 Second, the mechanical properties of the arterial wall cannot be evaluated as with static preparations. First, with dynamic pressure-diameter curves, approaches have several disadvantages compared with in vitro vessels29 (Figure 1). Note that, in such preparations, the and the wall thickness are evaluated under baseline conditions, which the length of the vessel is controlled, the distending pressure is measured at zero pressure to allow a true determination of strain. In animals and humans, vascular wall stiffness can be estimated in vivo by use of ultrasonic determination of wall thickness and of the dynamic pressure-diameter curve within the systolic-diastolic range of the operational blood pressure.29–33 The determination is made under living conditions (ie, without altering blood flow, smooth-muscle tone, and endothelial integrity). Diastolic diameter is usually accepted to represent baseline diameter. Systolic-diastolic changes in internal diameter of various large arteries such as the CCA or radial artery can be recorded with high-resolution echotracking techniques.30–33 Such approaches have several disadvantages compared with in vitro preparations. First, with dynamic pressure-diameter curves, unstressed diameter cannot be evaluated as with static procedures.34 Second, the mechanical properties of the arterial wall under fully relaxed conditions cannot be determined. Third, because in hypertension blood pressure is by definition higher than in controls, this pathology requires that $E_{\text{inc}}$ should be evaluated in 2 different situations: under operational conditions (ie, at the blood pressure of the living animal or human); and, more adequately, for the same wall stress as controls. Finally, for measurement of carotid $E_{\text{inc}}$, the classic assumption of equal stiffness in all directions may be highly questionable, a major point that we and others have previously and extensively discussed.28,35,36 Taken together, these findings indicate that $E_{\text{inc}}$ should be considered to be only an “effective” measurement for clinical applications.

Despite these methodological limitations, recent epidemiological studies have emphasized the major interest of 3 different markers of arterial stiffness (brachial pulse pressure, carotid $E_{\text{inc}}$, and aortic PWV), as important tools for clinical research. First, several groups7,9,10,37–39 have shown that in large populations of normotensive and hypertensive subjects, increased brachial pulse pressure is a strong predictor of cardiovascular mortality as a results of myocardial infarction and, to a lesser extent, stroke.7,10 The finding is independent of the level of mean pressure and of the presence of other cardiovascular risk factors, such as age, tobacco consumption, and metabolic disorders. Second, in subjects with hypertension and end-stage renal disease, increased carotid $E_{\text{inc}}$ and aortic PWV (but not increased brachial pulse pressure) were shown to be independent predictors of cardiovascular mortality.8,40 Finally, by use of the equations of Anderson from the Framingham study,41 such results were extended to the larger population of normotensive and hypertensive subjects with normal renal function.42 Indeed, for such subjects, a single measurement of aortic PWV was shown to predict the risk of cardiovascular death at 10 years. Taken together, such epidemiological findings clearly indicate that brachial pulse pressure and carotid stiffness can separately predict cardiovascular risk in subjects with normal or high blood pressure and therefore are of major interest in cardiovascular prevention, including the areas of myocardial infarction and stroke.7,10

**CCA in Clinical Hypertension**

For the evaluation of arterial thickness and stiffness in Subjects with clinical hypertension, 2 different straight, superficial, and cylindrical arteries have been widely studied: the CCA and the radial artery.43 The latter, composed almost exclusively of vascular smooth muscle, exhibits no pathology, no atherosclerotic plaque, and little effect of age. Thus, when radial artery hypertrophy is observed in the presence of clinical hypertension, this hypertrophy can be attributed entirely to high blood pressure, exactly as it is observed in spontaneously hypertensive rats. The situation is quite different for the musculoelastic common carotid artery, in which not only hypertension can be responsible for carotid hypertrophy but also many other cofactors (eg, dyslipidemia, diabetes mellitus, and tobacco consumption).30,31,43,44 Despite these drawbacks, both arteries should be investigated, because the radial artery serves as a model of a peripheral muscular artery and the carotid artery represents a central musculoelastic artery.
Carotid and Radial Arterial Wall Hypertrophy With Normal Wall-Material Stiffness in Middle-Aged Subjects With Essential Hypertension

Previous clinical studies have shown that in middle-aged subjects with hypertension, both carotid and radial arteries are hypertrophied and constitute an adaptive phenomenon as a consequence of the law of Laplace. In the presence of high blood pressure and increased (carotid) or normal (radial) artery-lumen diameter, hypertrophy compensates to maintain normal wall stress. In these hypertensive subjects, little change in wall-material stiffness has been reported under operational conditions (Figure 2), and even decreased values have been observed under isobaric conditions. However, these findings are limited to the circumferential direction (due to cross-sectional measurements) and might differ in the longitudinal axis. Levels of compliance and distensibility differed in accordance with the topography of the vessels; for the radial artery, normal (operational conditions) or increased (isobaric conditions) values have been reported, whereas for the carotid artery, reduced (operational conditions) or normal (isobaric conditions) values were observed.

In middle-aged hypertensive patients, the mechanisms responsible for such minor changes in remain difficult to elucidate, given that increased wall thickness might modify vascular stiffness. Several mechanisms have been proposed in recent years. In particular, investigators have identified how mechanical forces are sensed and transduced into biochemical signals. Located at the cell surface (and in connection with basal membrane), integrins are likely to be the key mechanosensors, but ion channels and other unknown stretch receptors presumably also transduce the mechanical signal. As a result, several intracellular signaling pathways, such as the focal adhesion pathway, are activated and thereby might contribute to modulation. On the other hand, changes in smooth-muscle tone of either endothelial or muscular origin may contribute, independent of mechanical factors, to adaptive modifications of . For instance, sympathetic stimulation, such as that due to catecholamine release, contributes to a decrease in the diameter of the internal mammary and radial arteries with reduction in radial isobaric , but with no change in isobaric mammary artery , given that the mammary artery is a musculoelastic artery such as the CCA (Figure 1). Nitric oxide donors, either endogenous (of endothelial origin) or exogenous (nitrate compounds), also alter smooth-muscle tone, and, unlike norepinephrine, increase the diameter and distensibility of peripheral arteries such as the brachial and the femoral arteries. Finally, several studies of large arteries have shown that interaction between norepinephrine and endothelial nitrite oxide (NO) is a dominant basis for local control of vascular tone and, hence, diameter and stiffness of blood vessels.

Carotid and Radial Arterial Wall Hypertrophy and Increased Wall-Material Stiffness in Patients With End-Stage Renal Disease

In end-stage renal disease (ESRD), wall-material stiffness is increased in both carotid and radial arteries. This increase is independent of mechanical factors, because it is observed for the same blood pressure or wall stress as those of normotensive controls (Figure 2). Vascular hypertrophy is associated with increased (carotid) or normal (radial) artery diameter and significantly reduced isobaric and operational compliances and distensibilities. Structural and functional alterations of the arterial wall may be responsible for the increased arterial stiffness independent of the presence of conventional cardiovascular risk factors such as lipid or tobacco consumption. In subjects with ESRD, diabetes and calcifications are dominant factors that contribute to stiffening of the arterial wall as already identified in central and peripheral arteries. In particular, diabetes may contribute by forming advanced glycosylation end-products, thereby altering collagen cross-linking and, hence, arterial mechanical properties. These vascular abnormalities can be prevented experimentally by administering the protein cross-linking inhibitor aminoguanidine. Calcifications are usually associated with increased arterial stiffness, especially when diffuse deposits are observed, as in rat models of calcium overload and patients undergoing hemodialysis, which have strong alterations of calcium metabolism.

Alternatively, several biochemical compounds that are specifically altered in ESRD may modify the interstitial space, particularly that of the arterial wall, which results in modification of the structure and function of the vessels. In patients undergoing hemodialysis, overhydration, as expressed by interdialytic weight gain, is associated with increased aortic PWV independent of blood pressure changes. On the other hand, hyperhomocysteinemia and increased plasma endothelin are significantly correlated with PWV of the lower limbs and aorta, respectively. Finally, increased plasma endothelin is significantly associated with carotid wall thickness.

Carotid and Radial Arterial Wall Hypertrophy and Increased Wall-Material Stiffness in the Elderly

In hypertension in the elderly, the situation is more complex. Although both carotid and radial arterial hypertrophies are present, increased wall-material stiffness has been found only in the carotid artery. Although the radial artery is not influenced by age and blood pressure, these 2 variables significantly influence carotid . Nevertheless, increased carotid stiffness and occur even in the presence of
normal or low circumferential wall stress. This observation implies a major role for nonhemodynamic factors in the mechanism of increased carotid $E_{\text{inc}}$.

The increased $E_{\text{inc}}$ is usually related to the aging process, with an increase in secretory properties of smooth muscle cells and a resulting accumulation of rigid material such as collagen fibers and calcifications. Some authors have suggested that the observed lumen enlargement contributes to maintaining Windkessel function of the central conduit arteries despite significantly decreased distensibility. Nevertheless, recent experimental data have shown that not only is vascular structure modified in elderly populations but also that the endothelium plays an important role in the remodeling and vasomotor control of the viscoelastic properties of the arterial wall. First, stripping the endothelial layer in pressurized arteries of young spontaneously hypertensive rats induces an increase in arterial diameter in parallel with increases in compliance and viscosity of the arterial wall, which suggests that, through the release of vasodilating and predominantly vasoconstricting factors, an intact endothelium is necessary to maintain arterial diameter and stiffness within a given required range. Second, studies of aortic rings in organ chambers as well as in vivo studies have shown that local constrictive effects of angiotensin and norepinephrine are usually counterbalanced by the formation or release of NO of endothelial origin.

Third, in young, spontaneously hypertensive rats with sympathetic overactivity, upregulation of NO has been demonstrated and is considered to be a defense mechanism against hypertension-induced vasoconstriction, thus helping to keep arterial diameter within the normal range. Finally, in old rats (as in elderly humans) with spontaneous hypertension, increased blood pressure involves a disproportionate increase in systolic and pulse pressure over diastolic blood pressure, associated with increased arterial stiffness, increased endothelium-dependent contraction under norepinephrine, and alteration of the NO and NO-synthase biological activities independent of structural changes.

From these data, we postulate that the reduction in NO formation or release with age, which is well established in rodents and humans, favors in advanced age the role of contracting factors, thereby contributing to increased arterial rigidity independent of structural changes. Two other arguments favor this possibility. First, the NO disturbance is associated with reduced relaxation effects of cGMP. Second, Gaballa et al have shown that, in old rats, carotid $E_{\text{inc}}$ is increased not only under passive conditions but also is modulated by norepinephrine. In the latter case, this increase is observed only along the longitudinal axis of the vessel, which indicates a norepinephrine-induced change in anisotropy. Taken together, such findings clearly indicate a contributing role of endothelium in the mechanical properties of the conduit arteries and, more specifically, in the mechanisms altering arterial stiffness in old hypertensive rats.

In clinical situations, age-induced vascular alterations have been described extensively in the overall population of elderly subjects, regardless of whether they are normotensive or hypertensive. Thus, more specific mechanisms might be involved to explain the higher degree of wall-material stiffness observed in elderly subjects with systolic hypertension.

At first approximation, several environmental or genetic factors could be involved independent of mechanical factors. Avolio et al have established that, in humans, increased sodium intake but not increased plasma cholesterol is associated with a significant reduction of aortic distensibility, a result observed even after adjustment for age and blood pressure, which thereby suggests the possibility of sodium-induced structural alterations in large vessels. In various models of genetic hypertension in rats but not in their normotensive controls a significant increase in aortic wall thickness and extracellular matrix has been reported in parallel with increased sodium diet, whereas no or minimal changes in systemic blood pressure were observed. Subsequently, in these animals, reduced sodium intake or administration of thiazide diuretics or spironolactone prevented structural vascular alterations without any change in systemic blood pressure. This observation is particularly relevant in stroke-prone hypertensive rats, in which the incidence of cerebrovascular accidents is also significantly lowered. In spontaneously hypertensive rats, such structural alterations of the vessel wall are obtained not only by modulating sodium intake but also by administration of estrogens to castrated or intact males, thus altering vascular mechanical properties. Genetic factors may be involved in the mechanisms of arterial stiffening. In a subpopulation of hypertensive subjects, a polymorphism of the AT1-receptor gene of angiotensin II has been identified. The $cc$ allele subgroup was shown to be significantly associated with an age- and pressure-independent elevation of PWV, with more significant alterations in older versus younger subjects. From a therapeutic viewpoint, this polymorphism is important to consider because a diminution of aortic collagen accumulation has been reported in spontaneously hypertensive rats treated long term with calcium-entry blockers or angiotensin-converting enzyme inhibitors.

In the latter case, aortic collagen reduction was observed even with nonantihypertensive doses of converting-enzyme inhibitor. Furthermore, blockade of AT1 receptors but not bradykinin receptors was shown to be responsible for reduction of aortic collagen in vivo. Finally, in the human hypertensive population, when converting-enzyme inhibitors are used, a selective decrease PWV is observed in the $cc$ allele subgroup of subjects with the AT1-receptor gene polymorphism, whereas a comparable result was not obtained with calcium-entry blockers.

Independent of aging and hypertension, atherosclerosis may favor development of aortic collagen, particularly in advanced stages, when diffuse alterations and calcifications are present. In contrast, during early changes, particularly when foam cells predominate, atherosclerosis does not contribute to an increase in the stiffness of arterial-wall material in hypertensive subjects.

Taken together, these findings suggest that, in hypertensive subjects, the determination of vascular hypertrophy and increased wall-material rigidity should be considered independently for clinical evaluations. Vascular hypertrophy is an adaptive process present in all kinds of hypertension as a consequence of the law of Laplace. Increased wall-material
stiffness is indeed associated with vascular hypertrophy. However, this stiffness occurs only at the site of central (and not peripheral) arteries such as CCA and involves more severe varieties of hypertension, particularly those with disproportionate increases of systolic over diastolic blood pressure, which are observed mainly in the elderly and in patients with diabetes or ESRD.

**Wall-Material Stiffness and Level of Blood Pressure**

In hypertension in the elderly and in patients with diabetes or ESRD, mean arterial pressure may be either increased or normal. However, systolic and diastolic blood pressures are not increased to the same degree as mean pressure, and a specific pattern is generated of disproportionate increases of systolic over diastolic blood pressure or even of isolated systolic hypertension. In these populations, arterial hypertension is strongly associated with increased wall-material stiffness. As we showed earlier, the latter is not generated by pressure-induced mechanical factors. On the other hand, it is generally admitted that increased rigidity of the arterial wall may be responsible for the high systolic peak and disproportionate increase of pulse pressure. Nevertheless, studies have proposed that, as a supplementary mechanism, increased pulsatile pressure favors vascular hypertrophy and increased wall-material rigidity, thus creating a vicious circle.

Therefore, it is important to dissociate the 2 different phenomena of vascular hypertrophy and increased wall-material stiffness and to identify for each of them the corresponding features of elevated blood pressure. To do this, it is necessary to recall several aspects of pulsatile arterial hemodynamics, as classically observed in aged and hypertensive subjects.

The aortic and CCA blood pressure curve is widely accepted to be a result of the mathematical summation of 2 pressure waves: (1) an incident pressure wave that propagates along the arterial tree from the heart toward the peripheral vessels after ventricular ejection and (2) a reflected wave that returns from peripheral (resistant) vessels toward the heart. Whereas the forward wave is simply influenced by the pattern of ventricular ejection and aortic stiffening, the effect of the reflected wave depends on 3 different parameters: the reflection coefficients, the degree of arterial stiffening and resulting PWV, and the distance between reflection points and the heart. For given reflection coefficients, increased PWV and, additionally, reflection sites closer to the heart, cause an earlier return of the backward pressure wave toward the heart, which results in a higher aortic pulse pressure and systolic peak. This latter pattern, which is the dominant characteristic of hypertension in the elderly, clearly indicates that the major factors that contribute to a selective increase in pulse pressure and that are responsible for the disproportionate increases of systolic over diastolic pressure are elevation of PWV and the mostly subsequent alteration of the amplitude and timing of the reflected wave. PWV is influenced by blood pressure alone but is also independently influenced by the rigidity of wall material; at a given blood pressure, the more rigid the arterial-wall material, the higher the PWV.

According to the Moens-Korteweg equation, PWV depends not only on wall thickness and $E_{\text{inc}}$, but also on the arterial radius. Indeed, within the approximations of a linear model, for a given $E_{\text{inc}}$ and wall thickness, PWV may be lower if the arterial radius is increased. In that situation, the disproportionate increase in systolic over diastolic blood pressure is expected to disappear. This hemodynamic alteration is readily obtained in animals and humans with the acute administration of nitrates, which exert a preferential action on larger versus smaller arteries. When nitrates are used, large arteries dilate even when the mean arterial pressure is significantly lowered, and this change may be observed without substantial change in ventricular ejection, vascular resistance, or blood flow velocity. In healthy volunteers, nitrate-induced smooth-muscle relaxation of the brachial artery is associated with increased isobaric distensibility, but without any change in isobaric $E_{\text{inc}}$. In fact, nitrates, and more specifically nitroglycerin, exhibit a specific pattern that exerts little effect on larger elastic arteries such as the aorta and the CCA but has progressively increasing dilator effects on smaller arteries, from the smaller conduit muscular arteries through resistance arterioles (which are little affected by the compound). As shown extensively by several research groups, acute nitroglycerin selectively decreases aortic and carotid peak systolic and pulse pressures as a consequence of reduced amplitude and increased delays in wave reflections, with a more pronounced effect on pulse pressures in central (CCA) versus peripheral arteries. More specifically, in elderly subjects with systolic hypertension, acute nitroprusside reduces systolic and pulse pressures without altering diastolic blood pressure, whereas no comparable effect is observed in younger subjects with systolic hypertension. Furthermore, such a selective decrease in systolic and pulse pressures in the elderly is not observed to the same extent with other vasodilating agents, such as converting-enzyme inhibitors or calcium-entry blockers.

Taken together, these findings support 2 important conclusions. First, the conclusion that blood pressure changes produced by nitrates are obtained predominantly in the elderly and are not observed to the same extent with other vasodilating drugs favors our previous hypothesis that in elderly hypertensive subjects, endothelium alterations and arterial stiffening are strongly interconnected. Second, acutely administered nitrates pharmacologically lower the increased pulse pressure observed in the elderly exclusively through reduction of peripheral wave reflections and therefore without altering the composition or passive stiffness of the arterial-wall material.

**Prospective Views of Cardiovascular Pharmacology and Therapeutics**

During the last decade, increased brachial pulse pressure, carotid $E_{\text{inc}}$, and aortic PWV have been identified to be independent cardiovascular risk factors, mainly for myocardial infarction and stroke. However, it remains to be determined whether decreasing pulse pressure, carotid $E_{\text{inc}}$, or aortic PWV will be target goals for treatment of hypertension in the elderly. In fact, from the present analysis of the mechanical properties of CCA, it appears that the treatment of
hypertension in the elderly should focus on changes in the structure and function of conduit arteries rather than the structure and function of arterioles. In turn, this procedure might improve the degree of cardiovascular prevention, particularly of stroke and myocardial infarction.

One approach results from the study of nitrates, which selectively reduce brachial and, to a greater extent, aortic systolic and pulse pressures without altering diastolic and mean blood pressures. In fact, the nitrate-induced decrease of pulse pressure is achieved in the elderly not only in acute but also in long-term treatments but has never been tested in terms of effectiveness against cardiovascular risk. In hypertension in the elderly, only chronic thiazide diuretics and calcium-entry blockers are known to decrease cardiovascular morbidity and mortality by lowering brachial systolic and pulse pressures. However, in such therapeutic trials, brachial diastolic blood pressure is decreased at the same time. Instead, in the elderly, the aim of treatment is to preserve diastolic blood pressure, because its lowering contributes to maintaining an elevated pulse pressure. This has deleterious consequences to the coronary circulation that potentially can result in myocardial ischemia. Thus, use of more appropriate drugs (for instance, drugs that act on the age-induced changes in endothelial function) and more appropriate doses of conventional agents such as diuretics or nitrate-like compounds need to be evaluated. Recent studies have shown that, for a given antihypertensive agent, the decrease in diastolic blood pressure is more pronounced than the decrease in systolic blood pressure, which indicates that the curves that relate drug dosage to pulse pressure should be better identified. Thus, for conventional antihypertension drugs, new protocols should be developed to evaluate this possibility in cardiovascular pharmacology.

A new approach in drug treatment is to modify or prevent the development of arterial-wall structure, namely by reducing the thickness or changing the composition of the arterial wall or through a combination of both; hence, modifying $E_{mc}$ independently of blood pressure changes. With age, reducing the increase in wall thickness and delaying increases in $E_{mc}$ and PWV should be key targets of treatment, to thus restore, with time, a normal composition of the vessel wall. This goal seems to be easier to obtain in muscular arteries such as the radial artery than in musculoelastic arteries such as the CCA. The analysis presented in the present study, converting-enzyme inhibitors or AT$_1$-receptors blockers, alone or in combination with diuretics, potentially may be active agents, particularly in a specific genetic context. On the other hand, new molecules, such as those acting on collagen cross-linking, need to be tested on the wall of large arteries to develop novel treatment strategies.

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