Pulse Pressure, Arterial Stiffness, and Drug Treatment of Hypertension

Luc M.A.B. Van Bortel, Harry A.J. Struijker-Boudier, Michel E. Safar

Abstract—Epidemiological studies in the past decade have stressed the importance of pulse pressure as an independent risk factor for cardiovascular morbidity and mortality. We briefly review the epidemiological evidence and discuss in more detail the pathophysiological basis for this observation and the therapeutic consequences. We focus on the vascular determinants of increased pulse pressure. Both longitudinal and cross-sectional components of the vascular system contribute to the shape of the arterial pressure wave and, thereby, to pulse pressure. The primary longitudinal component is the architecture of the arterial tree, which determines the major reflection sites for the pressure wave. The cross-sectional architecture of the vascular system consists of a geometric (diameter) and a structural (composition vessel wall) component. Both diameter and composition of the vessel wall vary greatly when going from central to more peripheral arteries. We review the implications for the functional properties of various arterial segments. Finally, we discuss the therapeutic consequences of targeting pulse pressure rather than mean blood pressure with various drug classes. Among the antihypertensive agents, nitrates, NO donors, and drugs that interfere with the renin-angiotensin-aldosterone system may offer useful tools to lower pulse pressure, in addition to mean blood pressure. Future developments may include non-antihypertensive agents that target collagen or other components of the arterial wall matrix. However, large-scale clinical trials will have to confirm the therapeutic value of these agents in the treatment of increased pulse pressure and arterial stiffness. (Hypertension. 2001;38:914-921.)

Key Words: antihypertensive agents ■ arterial stiffness ■ epidemiology ■ pulse pressure ■ blood pressure

Hypertension is a cardiovascular (CV) risk factor, the mechanisms of which are generally attributed to the reduction in the caliber or number of small arteries or arterioles with a resulting increase in total peripheral resistance and mean blood pressure (MBP). MBP, the product of cardiac output and total peripheral resistance, refers to steady phenomena, considering pressure and flow as constant over time. This definition does not take into account that blood pressure and flow fluctuate during the cardiac cycle. In clinical practice, pressure is defined in terms of systolic (SBP) and diastolic (DBP) blood pressure, which refer to a pulsatile phenomenon, with SBP and DBP representing the extremes of the blood pressure oscillation around a mean value, the MBP. In fact, the blood pressure curve may be considered as the summation of a steady component, MBP, and a pulsatile component, the pulse pressure (PP).1 Besides the pattern of left ventricular ejection, the determinants of PP (and SBP) are the cushioning capacity (compliance) of arteries and the timing and intensity of arterial wave reflections.1 Compliance of arteries depends on arterial volume and the elastic properties (distensibility) of arterial walls. Compliance and distensibility are quantitative arterial wall properties. The term “stiffness” is used as an alternative to indicate qualitatively the elastic vessel wall properties.

In the past, DBP was considered as the better guide to determine the severity of hypertension. Epidemiological studies in the past decade have directed attention to SBP as a more adequate marker for CV risk,2 and it has also been shown that increased PP is an independent CV risk factor.3 Increased PP appears to be the most powerful measure available to identify those hypertensive patients at greatest risk for subsequent myocardial infarction.4–6 The predictive value has been consistently shown even in treated hypertensive subjects.7–9 Although the control of DBP (≤90 mm Hg) is easily obtained in large populations of hypertensive subjects, the ability to control SBP (≤140 mm Hg) is achieved to a much lesser extent.10–13

The purpose of this short review, which is focused on PP and arterial stiffness in hypertension, is 3-fold: (1) to assess, on the basis of epidemiological findings, if increased PP should be treated per se, independently of MBP; (2) to discuss the structural and functional factors influencing PP in relation to the hypertensive vascular biology; and (3) to analyze the therapeutic approaches that may be required to treat selec-
tively increased SBP and PP in populations of hypertensive subjects.

**PP and Aortic Stiffness as Independent Predictors of CV Risk**

On the basis of cross-sectional and longitudinal studies, there is epidemiological evidence that SBP and DBP increase markedly with age. However, after the age of 50 to 60 years, the rise in DBP tends to disappear, and DBP may even decrease with age. Thus, PP increases more markedly with age than does MBP. This finding may have important consequences in pathophysiology: (1) the increase of SBP with age enhances end-systolic stress and further promotes cardiac hypertrophy, thus increasing the oxygen demand of the myocardium, whereas (2) the decrease in DBP with age compromises the coronary perfusion and thus favors myocardial ischemia, particularly in the presence of stenosis of coronary arteries. These 2 different aspects, which have been extensively investigated in terms of pulsatile arterial hemodynamic studies, were recently confirmed in a number of epidemiological studies.

In a French population of untreated normotensive and hypertensive adults, a pulsatile component index, defined as a strong correlate of PP, was derived through principal-components analysis of SBP and DBP. During a 10-year follow-up, the pulsatile component index was independently associated with an increased risk of death from coronary artery disease. The relationship was mainly significant in women age ≥55 years. In another prospective evaluation of hypertensive patients either treated or untreated, those in the highest tertile of PP before the initiation of therapy (≥63 mm Hg) during an average follow-up of 5 years had an increased risk of myocardial infarction. In a later study, multivariate analysis revealed that PP is an independent predictor of myocardial infarction. Finally, PP behaves as a CV risk factor, regardless of whether it was measured with office sphygmomanometry or ambulatory monitoring.

From the MRC trial (Medical Research Council trial of treatment of hypertension in older adults) and the Framingham study, Millar et al and Franklin et al, respectively, concluded that in patients with hypertension, brachial PP is a stronger risk factor than SBP for myocardial infarction. The best predictor function of all possible linear combinations of SBP and DBP was shown to be similar to PP, suggesting that their association was real and not merely a statistical artifact caused by the correlation between SBP and PP. Further analysis showed that the predictor value of PP was due to both an increase in SBP and a decrease in DBP. Using the populations of the EWPHE (European Working Party on Hypertension in the Elderly) and SYST-EUR (SYStolic hypertension in elderly in EURope trial) trials in the elderly, Blacher et al showed that CV risk was positively correlated with SBP. However, at any given value of SBP, CV risk was higher when DBP was lower. A further confirmation for the role of PP was obtained by the long-term follow-up of Benetos et al. These authors showed that even after adjustment for age, gender, and other standard confounding factors, the cohort with an increase in SBP and a decrease in DBP during the follow-up had the highest CV mortality rate compared with the cohort in whom no change in either SBP and DBP was observed. The cohort with the second highest CV mortality rate was composed of subjects who had a combined increase in both SBP and DBP.

Because ventricular ejection and arterial stiffness are the main determinants of PP and because ventricular ejection tends to decrease with age, the question has arisen of whether pulse wave velocity (PWV), a classic marker of arterial stiffness, might be an independent predictor of CV mortality in subjects with hypertension, whether they have preserved renal function or end-stage renal disease. In subjects with end-stage renal disease, Blacher et al identified that the 2 dominant predictors of CV and all-cause mortality were aortic PWV and age at inclusion. Carotid artery stiffness could also be used as a predictor of CV mortality. In subjects with essential hypertension and preserved renal function, the situation is more complex because long-term follow-up is difficult to obtain. However, calculation of CV risk using Framingham equations indicates that in this category of subjects, the 10-year CV mortality rate consistently increases with the increase in aortic PWV. After adjustment for age and other standard confounding variables, PWV is the best theoretical predictor of CV mortality. These findings agree with a recent follow-up showing that the ratio between stroke volume and PP, an indirect marker of arterial stiffness, is an adequate independent predictor of CV risk.

Studies by Benetos et al have focused attention on the fact that brachial PP is a more potent predictor of CV risk in individuals with normal values of SBP (≤140 mm Hg) and DBP (≤90 mm Hg) than in hypertensive subjects. In these subjects, the odds ratios for CV and coronary mortality are even higher than those for hypertensive subjects. A major observation is that these results may be applied to hypertensive subjects on drug treatment. Even when normotensive blood pressure levels are achieved, an increased PP remains a significant independent predictor of CV mortality, particularly in diabetic subjects. This result is important to consider, because in populations of treated hypertensive subjects, death from CV disease events accounts for 68% of all deaths. Finally, it is important to reevaluate the role of PP in the results of the various therapeutic trials in the literature.

In earlier therapeutic trials, it was consistently shown that antihypertensive drug therapy prevented ≈40% of strokes, whereas the prevention of ischemic heart disease was much less effective. The reasons for this discrepancy remain the object of debate, but one of the main explanations is that the criterion of inclusion for therapeutic trials, DBP, has been an important bias introduced in the interpretation of the results. The subjects with the higher CV risk (ie, those with high SBP but, at the same time, low DBP) were excluded from the trials and therefore were not analyzed in the primary results and in the various meta-analyses of the literature. This bias was introduced not only at the inclusion of subjects at entry but also at the end of the follow-up. Indeed, the criterion of effectiveness for antihypertensive therapy was exclusively based on DBP, so that at the end of the trial, subjects with low DBP but, at the same time, elevated SBP (ie, with increased PP) were considered to have been “adequately” treated.
Pathophysiology of Increased PP

PP is determined by both cardiac and vascular factors. The cardiac ventricular ejection generates a primary pressure wave. Heart rate has an independent influence on the shape of this wave. The initial wave is propagated at a finite speed: PWV. Both longitudinal and cross-sectional components of the vascular system contribute to the shape of the subsequent wave, and thereby to PP.

Longitudinal vascular components that contribute to PP are related to the geometry of the vascular system. Any point of geometric discontinuity (branching) of the arterial tree generates a reflective wave that travels backward toward the ascending aorta. In young subjects with a low PWV, the reflected waves reach the aorta only after the closure of the aortic valves. The impact is then on DBP rather than on SBP. It leads to a “boosting” of coronary perfusion pressure. On the other hand, in patients with stiffer central arteries (eg, the elderly or hypertensive patients), PWV is increased considerably. In these patients, reflected waves will amplify left ventricular and systolic pressure and reduce aortic pressure during diastole. This dual alteration of SBP and DBP with a resulting increase in PP has indeed been observed during both the hypertensive and the aging process, although there are important differences between the 2 clinical situations. In the younger hypertensive population, there is a persistence of the PP gradient, causing PP to remain higher in peripheral than in central arteries, whereas mean arterial pressure is reset to a higher value. On the other hand, with aging the PP gradient tends to disappear due to a more rapid stiffening with age of central, and not peripheral, arteries. This results in an increase in the amplitude of the forward pressure wave and the existence of low reflection coefficients.

These differences in blood pressure behavior in the hypertensive and the aging process may be due to a number of factors in addition to arterial stiffness. Most of them are combined in old hypertensive subjects. First, the timing of wave reflections is influenced by the characteristics of the reflection coefficients of the pressure wave, which are principally located at the origin of resistance vessels. It is important to note that the control of peripheral vascular resistance, and hence of small arteries, is modified with age and hypertension, particularly through structural changes and alterations in endothelial and neurohormonal control. Second, the location of the same reflection sites may be substantially modified with aging and hypertension, due to the age- and pressure-induced increase in the caliber of arteries and the age-induced increase in the length of large vessels. These changes differ markedly in men and women and occur mainly at the site of central, but not peripheral, arteries. Third, pathological alterations may also produce reflection sites closer to the heart, as shown in the presence of calcified plaques, particularly at the site of arterial bifurcations (aorta, carotid and femoral arteries, origin of renal arteries). Finally, both aging and hypertension are associated with important alterations in microvascular architecture, although the impact of these changes on wave reflections has not yet been established. Taken together, these examples indicate that both increased arterial stiffness (coming from central arteries) and alteration of wave reflections (generated at peripheral large and small arteries) contribute independently to the predominant or selective increase in PP observed with age and hypertension (and mostly their combination).

In addition to cardiac and longitudinal vascular (wave reflections) components, the third factor determining PP is the cross-sectional architecture of the vascular system. This architecture consists of a geometric (diameter) and a structural (composition vessel wall) component. It is important to realize that both diameter and composition of the vessel wall vary greatly when going from the central to the more peripheral arteries. The role of vascular diameter in PP has been reviewed in depth elsewhere. The contribution of structural components is much less well defined, although the
The recent introduction of powerful molecular biological and histological approaches is rapidly influencing this field of research.

The basic morphological plan of larger arteries consists of cells and matrix arranged in 3 transmural zones: the intima, media, and adventitia. The intima consists at its luminal side of a single continuous layer of endothelial cells. A fenestrated sheet of elastic fibers, the internal elastic lamina, divides the intima from the media. In between, smooth muscle cells and various components of the extracellular connective tissue matrix are the predominant structural features. The intima does not contribute much to the mechanical behavior of the vessel wall but is a rich source of substances and signal transduction mechanisms that influence mechanical properties of the whole vessel wall.

The medial layer represents the main basis of mechanical properties of the peripheral elastic arteries. It is composed of a number of layers of elastic lamellae. The interlamellar zones consist of smooth muscle cells and a connecting molecular grid, consisting mainly of mucopolysaccharides. Vascular smooth muscle cells do not represent a homogeneous cell population. They may have different mixtures of phenotypes, including contractile, proliferative, synthetic, or apoptotic behavior. The relative occurrence of each of these phenotypes depends on age, location in the vascular tree, and prevailing pathological conditions. The contribution of the various types of smooth muscle cells to overall mechanical behavior of the arterial wall remains to be determined.

The third layer is the adventitia, which is abundant particularly in the more centrally located large arteries. It consists mainly of fibroblasts and collagen. The amount of collagen is determined at a young developmental stage. Collagen has a very low turnover but is subject to chemical modifications, such as breakdown, cross-linking, or glycation. Because collagen is a major determinant of stiffness of the large arteries, these various chemical modifications may have a profound influence on the mechanical properties of these arteries.

In the overall arterial tree, there is, for the same mean blood pressure, a progressive increase in stiffness from central to peripheral arteries. This physiological stiffness gradient, which is the consequence of the decrease in cross-sectional area and the increase in stiffness of the arterial vessels, is significantly attenuated in subjects with hypertension and in the elderly. Under these 2 conditions, the reduced gradient is exclusively due to a significant decrease in compliance and distensibility of central arteries compared with normotensive control subjects, whereas minimal changes are observed in the compliance and distensibility of peripheral medium-sized muscular arteries. In subjects with hypertension, the principal structural modification of the vessel wall is hypertrophy of the medial layer; in young hypertensives, the alterations of the mechanical properties result mainly from the elevated blood pressure itself, because reduced carotid compliance and distensibility disappear under isobaric conditions. However, in some territories, such as the femoral artery or even the aorta, intrinsic changes in stiffness (ie, increased stiffness under isobaric conditions) may be observed. In subjects with hypertension, adaptive mechanisms seem to be involved at the site of peripheral muscular arteries as the radial artery, because diameter is unchanged despite the elevated blood pressure, whereas in central arteries, diameter is increased in proportion with the level of blood pressure. In elderly hypertensives, medial hypertrophy involves a large increase in the extracellular matrix and adventitia. This histomorphometric pattern is associated with reduced compliance and distensibility independent of blood pressure level. In old subjects with hypertension, intrinsic changes in stiffness and, to a much lesser extent, blood pressure level are involved in the altered mechanical properties. Again, the latter are observed at the site of central, but not peripheral, arteries. Finally, with both aging and hypertension, endothelial alterations are noted. Although they may differ markedly in the hypertensive and the aging process as well as according to the vascular territory, a major role is attributed to changes in NO production and/or release. The latter is of particular importance for peripheral muscular arteries in which NO and endogenous vasoconstrictors are in constant interaction.

**Therapeutic Aspects of Increased PP**

On the basis of the data discussed here, it is obvious that any antihypertensive drug that reduces mean arterial pressure may decrease SBP through a decrease in DBP and a resulting passive decrease in arterial stiffness. This intervention is able to reduce substantially CV risk in hypertension, even in the elderly. Nevertheless, in the case of subjects with an isolated or disproportionate increase in SBP over DBP (ie, a selective increase in PP, as observed in older hypertensive subjects), the goal of treatment is rather to decrease SBP with maintenance of or even increase in DBP. Thus, the target mechanisms are the decrease in ventricular ejection, the active decrease in arterial stiffness, and the change in wave reflections. Not all classic antihypertensive drugs target these mechanisms. It is even possible to target these mechanisms without influencing peripheral vascular resistance or mean arterial pressure. We focus our subsequent discussion on drugs with potential direct effects on vessel wall stiffness or wave reflections.

**Changes in Stiffness and Wave Reflections Induced by Nitrates**

The antihypertensive effect of nitrates is well established in chronic hypertension. Earlier studies showed that nitrates cause a selective decrease in SBP over DBP in healthy volunteers as well as in subjects with borderline and sustained essential hypertension. Because the resulting baroreflex response is attenuated with age, a pronounced and selective decrease in SBP is frequently observed in old subjects with systolic hypertension. In 2 double-blind randomized placebo-controlled trials, the effect of isosorbide dinitrate (ISDN) was studied in elderly subjects with isolated systolic hypertension. In 1 study, ISDN caused a significant decrease in SBP, from the 8th to the 12th week of treatment. In the other study, the effect of ISDN after 8 weeks of treatment, without a reduction in DBP. In addition, ambulatory PP decreased with ISDN, whereas it did not change during placebo. Similar findings
have been observed in hypertensive middle-aged subjects using transdermal nitroglycerin or the long-acting agent molsidomine.49 The fact that nitrates decrease PP without decreasing DBP suggests that nitrates act in large part on large arteries without a substantial effect on small resistance vessels.

In the 2 studies in elderly persons with isolated systolic hypertension, no signs of tachyphylaxia were observed during ISDN treatment: the decrease in blood pressure was seen 8 and 12 hours after drug intake, and after active treatment was stopped, SBP returned toward baseline values.37 Because ISDN was administered orally at a dose of 20 to 40 mg at 8 AM and 8 PM in 1 study47 and in an eccentric schedule (at 8 AM and 2 PM) in the other,48 the long nitrate-free period might contribute significantly to the attenuation of the tolerance phenomenon55 and to the long-term antihypertensive effect. On the other hand, the well-known tachyphylaxia that occurs with nitrates might be more pronounced for the venous than for the arterial effects of nitrates. This hypothesis is suggested by the fact that in healthy volunteers, the increases in arterial diameter and compliance of the carotid and brachial arteries were at least similar after 8 days of ISDN 20 mg TID than after the first dose. In contrast, in the same study, venous tone, estimated by unstressed volume, decreased significantly after the first single dose of ISDN 20 mg but did not differ from baseline after 8 days of drug administration. Besides the possible tachyphylaxia, the well-known side effect of headache might be a disadvantage for the common use of nitrates. Although in 1 study in isolated systolic hypertension side effects were not significantly increased with ISDN than with placebo,47 in the other study,48 >20% of patients dropped out because of headache.

Nitrates increase arterial compliance of elastic and muscular arteries after a single dose and after 1-week administration in normotensive and hypertensive subjects.50–52 This increase in compliance is mainly due to an increase in arterial diameter. Distensibility and PWV, both measures of arterial stiffness, hardly change, especially in elastic arteries such as the aorta1 and the common carotid artery.50,51 The increase in arterial compliance is a main contributor to the decrease in SBP. In addition, the substantial increase in the diameter of peripheral muscular large arteries decreases early aortic wave reflections, thereby decreasing mainly central aortic SBP. Previous work by Taylor53 has shown that an increase in arterial cross-sectional area at peripheral bifurcations could theoretically produce this type of alteration through changes in peripheral reflection patterns. In clinical situations, such changes in central aortic SBP may be difficult to detect because the transmission of the pressure pulse is altered from the central aorta to brachial artery, making the changes less pronounced when brachial (and not aortic) blood pressure measurements are used. Finally, a major point to consider is that the decrease in central SBP is mainly caused by dilatation of peripheral muscular arteries proximal to the arterioles.1

Taken together, these findings indicate that the major sites of action of nitrates are muscular arteries (from the mediumsized arteries to the origin of arterioles). In muscular arteries, the action of vasoconstrictive compounds is physiologically counterbalanced by a concomitant NO production and/or release.42 A number of studies suggest that this mechanism is attenuated or even abolished with age. Thus, a major subject of research may be to determine the possible role of endothelium in the development of the high PP with age and the role of NO in its treatment.

A recent study with the NO donor sinitrodil in young healthy volunteers showed a dose-dependent increase in brachial artery compliance after a single oral dose.54 With sinitrodil 40 mg, brachial artery compliance increased by 27%, whereas this value was only 8% after ISDN 20 mg. In contrast, total peripheral resistance, determined by small resistance vessels, decreased by 11% after ISDN and only 7% after sinitrodil. Regarding a similar or smaller effect on resistance vessels, sinitrodil had a greater effect on the brachial artery than did ISDN, and sinitrodil is more selective to large arteries than is ISDN. As a consequence, it appears possible to develop drugs that act even more selectively on large arteries than nitrates. In addition, with sinitrodil 40 mg, 1 of 16 subjects complained of headache, whereas headache was present in 15 of 16 subjects after ISDN 20 mg. Drugs like the NO donor sinitrodil are presumably good candidates to decrease PP, thereby decreasing SBP and not decreasing, but perhaps even increasing, DBP. Such drugs may be of interest for the treatment of patients with isolated systolic hypertension, especially those patients with a low DBP and coronary artery disease.

Apart from NO donors, enhancers of NO production and/or release might be of interest. Recent studies suggest that some compounds, like the diuretic agent ciclofenicine50 and the selective β1-blocker nebivolol,56,57 may act as enhancers of NO production and/or release with resulting decrease in arterial stiffness.55,58

**Stiffness Changes Associated With Sodium and Renin-Angiotensin System**

Because angiotensin II stimulates the production of various types of collagen fibers,49 together with a number of growth factors,49 converting enzyme inhibition and angiotensin II type 1 (AT1) receptor blockade have been used as pharmacological tools to demonstrate that in vivo, the chronic inhibition of the effects of angiotensin II modifies arterial stiffness.61,62 Antihypertensive doses of the converting-enzyme inhibitor perindopril were shown to prevent the chronic accumulation of aortic collagen, whereas this result is not obtained with the nonspecific vasodilator hydralazine.62 The collagen reduction was noted even with nonantihypertensive doses of perindopril and paralleled the decrease in converting enzyme measured in the aortic tissue but not in the plasma.63 Further experiments clearly indicated that the collagen effect is not due to bradykinin but rather involves specifically the blockade of AT1 receptors.63 Finally, such findings were observed exclusively on a normal, but not a high, sodium diet,64 a situation during which the production of transforming growth factor-β1 is increased.65 In addition, when combined non-antihypertensive dosages of diuretic and converting-enzyme inhibitor are administered to spontaneously hypertensive rats, only the association of the 2 agents is able to prevent consistently carotid collagen accumulation and, at the same time, to decrease isobaric carotid stiffness.66
Thus, it is important to reevaluate the possible links among sodium, diuretics, and the extracellular matrix of arterial vessels.

Data on sodium-induced changes of arterial structure and function have been mostly obtained in genetic strains of hypertensive rats, such as stroke-sensitive and -resistant spontaneously hypertensive rats and Dahl salt-sensitive rats.67–70 In these models, increased sodium intake does not significantly modify intra-arterial blood pressure (with the exception of Dahl salt-sensitive rats) but decreases isobaric carotid distensibility or compliance and produces a drastic increase in wall thickness and extracellular matrix. Such alterations are prevented by a reduced-sodium diet or the administration of diuretics without any significant change in intra-arterial blood pressure level. Molecular biological studies indicate that the pressure-independent effects of sodium and/or diuretic compounds on the arterial wall are associated with changes in vascular smooth muscle cell phenotype.71

In clinical investigations, substantial links among genotype, arterial stiffness, sodium, and the renin-angiotensin system have been observed. Converting-enzyme inhibitors are able, in both hypertensive rats and humans, to induce a pressure-independent increase in diameter and, to a lesser extent, compliance and distensibility of peripheral muscular arteries.72 Such changes are observed even in the presence of diuretic compounds, whereas diuretics alone, administered to hypertensive middle-aged humans, cause few changes in arterial diameter and stiffness.73,74 Mostly, the large artery changes observed in response to converting-enzyme inhibition are more pronounced in the presence of some varieties of gene polymorphisms, such as the AT1 receptor gene polymorphism.75 In humans, the AT1 (A1166C) receptor gene polymorphism is associated with a more pronounced pressure-independent increase in arterial stiffness than in gender- and age-matched control subjects.75 In vivo and in vitro studies of human arterial rings have shown that the constrictive effects of angiotensin II and phenylephrine are significantly amplified by comparison with the other genotype subgroups.76 Finally, in hypertensive populations, subjects with AT1 receptor gene polymorphism exhibit a greater pressure-independent decrease in aortic stiffness than the other genotypic subgroup for the same degree of converting-enzyme inhibition, whereas a comparable effect is not observed with calcium-entry blockade.77

Stiffness Changes Induced by Spironolactone

In recent years, several in vitro investigations have indicated that aldosterone may act directly on large arterial vessels. Immunohistochemical methods have shown that the intensity of staining of mineralocorticoid receptors within the vascular wall predominates in the aorta and decreases with the size of the arteries.78 Endogenous vascular synthesis of aldosterone occurs in the rat mesenteric artery, even after adrenalectomy, and requires the presence of an intact endothelium. In this line of evidence, Benetos et al79 have observed that in both younger and older spontaneously hypertensive rats, spironolactone prevents in vivo both myocardial and aortic collagen accumulation with minimal changes in intra-arterial blood pressure. In contrast, in hypertensive humans, studies of 2 weeks duration did not identify a change in brachial artery stiffness after the administration of spironolactone.80 Long-term studies are needed in subjects with hypertension, particularly in the elderly, to confirm a decrease in arterial stiffness after spironolactone. Interestingly, in hypertensive subjects, increased aortic stiffness and increased plasma aldosterone have been shown to be statistically associated.80 In addition, a polymorphism of the aldolsynthase gene has been reported in association with a pressure-independent increase in aortic stiffness.81

Other Drugs

An approach to influence arterial stiffness totally independent of antihypertensive drug treatment is to target collagen metabolism. Because the turnover of collagen is extremely low, this may be a difficult target. However, recent progress has been made in the pharmacological interference with the formation of advanced glycation end products of collagen. These products are responsible for the arterial stiffening in conditions like diabetes82 and aging83 in animal models. Drugs that interfere with the formation of advanced glycation end products, such as aminoguanidine and ALT 711, have been shown in animal models to reverse arterial stiffening without influencing blood pressure.84,85 These data need clinical follow-up.

A final potential therapeutic target to influence arterial stiffness is hormone replacement therapy that includes estrogens. A recent review85 provides a balanced view on the possibilities and limitations of this approach.

Conclusions

Increasing evidence from epidemiological and pathophysiological research on the significance of arterial stiffening and raised PP as independent risk factors for CV disease creates new challenges for CV therapy. Thus far, pharmacotherapy has focused on blood pressure-lowering properties of antihypertensive drugs. The decrease in arterial stiffness is an attractive additional target.

References


Pulse Pressure, Arterial Stiffness, and Drug Treatment of Hypertension
Luc M.A.B. Van Bortel, Harry A.J. Struijker-Boudier and Michel E. Safar

Hypertension. 2001;38:914-921
doi: 10.1161/hy1001.095773
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/38/4/914

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/