Mechanism(s) of Systolic Blood Pressure Reduction and Drug Therapy in Hypertension

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Antihypertensive drug therapy is a major modality of cardiovascular (CV) disease prevention, especially for stroke, congestive heart failure, and renal insufficiency. Coronary risk is also consistently prevented by antihypertensive treatment, but to a lesser extent.1–4 The Prime Study2 has shown that drug-induced blood pressure (BP) reduction in hypertensive subjects is associated with a significant decrease of coronary risk. However, when treated and untreated subjects are compared, at any given value of systolic BP (SBP), this risk remains higher in treated than in untreated subjects, suggesting the persistence of residual coronary complications. Results of therapeutic trials also indicate that coronary risk is associated with a particular hemodynamic pattern in treated hypertensive subjects.5 Although diastolic BP (DBP) is significantly lowered by drug treatment to 90 mm Hg (80% of the patients), SBP remains above 140 mm Hg in 60%, indicating an increase of pulse pressure (PP), which is the difference between SBP and DBP.4 It is widely accepted that SBP and PP rise sharply with age and that this increase is a major manifestation of vascular aging and stiffening, which are now considered major predictors of CV risk, independent of the mean BP (MBP) level.4 The purpose of this review is to analyze the mechanism(s) of SBP in untreated and chronically treated hypertensive subjects and to determine which pathophysiological factors are susceptible to attenuating consistently coronary and CV complications in hypertensive populations.

Pathophysiological Modifications of SBP
Along the Arterial Tree

Ventricular ejection in humans is associated with 2 principal events. First, the coronary circulation is transiently interrupted, as the principal consequence of cardiac contraction, and, second, an acute shock of stroke volume against the aortic wall is observed (Figure 1). Then, the BP curve may be considered as a wave, which travels along the arterial tree at a given speed, the pulse wave velocity (PWV). The PWV level is an indirect measurement proportional to aortic stiffness: the higher the PWV, the stiffer the arterial wall and the higher the SBP at any given stroke volume value. Thereafter, 2 major events characterize the BP curve (Figure 1). First, at each discontinuity of the arterial wall, the “incident” pressure wave may be reflected. Second, the summation of the incident and the “reflected” waves determine the shape of the BP curve at each site of the arterial tree. With age, this shape is more and more influenced by the reflected wave, which returns toward the heart at the same PWV as the incident wave.5

Pressure waves are reflected at every discontinuity of the arterial wall, but reflections predominate at the sites of arteriolar bifurcations, where the geometry and stiffness of vessel wall material determine the reflection angle and, therefore, the value of its coefficient. Herein, the major factors to consider are not only the distensibility and the diameter of each arteriolar branch of the bifurcation, but also their exact location.1,4 With age, the reflection sites are closer to vital organs, such as the heart, brain, and kidney, so that wave reflections may contribute more to organ damage.5 Wave reflections occur at every location where vasomotor tone and pulsatility are present and disappear almost completely at precapillary and capillary levels (diameter: <150 μm), that is, when blood perfusion becomes almost completely steady. However, even under such conditions, the capillary beds are quite important to consider for several reasons6: (1) their density is constantly reduced in hypertensive subjects; (2) capillaries may participate substantially in the magnitude of vascular resistance, mainly in the myocardium; and (3) capillary perfusion mediates oxygen transport and delivery, as well as many other factors responsible for immune, inflammatory, or even thrombotic responses. Thus, the arteriocapillary network strongly influences the autoregulation of vital organs and, at the same time, initiates the return of reflected waves toward the heart.1

From a pathophysiological viewpoint, the reflected pressure wave is markedly influenced by vascular aging.4 When subjects are young and have quite elastic conduit arteries (low PWV), the reflected wave returns slowly toward the heart, that is, during the diastolic period. Its principal consequence is to boost coronary perfusion during this period without changing the cardiac afterload. On the other hand, when the subjects are old and have stiff arteries, the reflected wave returns very rapidly toward the heart (high PWV), that is, during systole.1,4 In this setting, coronary perfusion, which normally occurs only during diastole, is consistently reduced and favors coronary ischemia. Furthermore, in the central

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arteries, the reflected pressure wave becomes superimposed on the forward wave during systole and causes an additive increase of SBP, called the “augmentation pressure.”

This pathophysiological process, which may be accentuated by reduced heart rate and left ventricular ejection time, favors the development of cardiac hypertrophy. The increase of cardiac mass, in turn, enhances the myocardial intercapillary distance and disturbs oxygen transport and delivery, finally contributing to hypoxia and oxidative stress. The presence of atherosclerosis, thrombosis, and/or ischemia, which certainly may accelerate the process.

In recent years, all of these pathophysiological mechanisms, which act predominantly through conduit vessels, have been considered important for the following reasons. First, the BP curve normally involves 2 different components: a steady component, which is represented by MBP and is governed exclusively by small arteries and the degree of vascular resistance, and a pulsatile component, which is represented by PP and mainly influenced by arterial stiffness and wave reflections. Second, the transduction of mechanical signals within the arterial wall differs consistently, whether BP is steady or pulsatile. Although steady pressure seems to act particularly through vascular focal adhesion kinase, pulsatile pressure acts rather through the action of free radicals and oxidative stress. Third, epidemiological findings in humans have shown that, within the various mechanical factors associated with CV risk, it is important to distinguish between the following: first, those related to MBP, SBP, or DBP (when studied alone) and, second, those related to PP, arterial stiffness, and wave reflections. The latter, which are more complex than the former, are mostly observed in subjects on a high-sodium diet and/or in the elderly or in patients with type 2 diabetes mellitus, systolic hypertension, chronic renal insufficiency, or multifocal atherosclerotic disease, that is, having numerous CV disorders in which oxidative stress is present.

### Figure 1.
Pressure wave traveling along the arterial tree, involving the following: (1) propagation of the incident wave at a given speed (PWV), (2) wave reflection at arteriolar sites, and (3) backward (reflected) pressure wave, which summates with incident wave, giving the arterial BP curve. Note that, as a consequence of arterial stiffness and wave reflections, SBP and PP are higher in central than in peripheral arteries. Under drug treatment, PWV is reduced as a consequence of decrease in pressure distension; reflection coefficients are reduced as a consequence of reduced wall on lumen ratio of arterioles (under ACEI); such changes lead to reduction of central SBP and PP through change in the amplitude and timing of reflected pressure wave.

#### WAVE TRAVELING

(1) Propagation (PWV)

(2) Reflection sites

(3) Reflected wave (Summation of incident and reflected waves)

SBP Reduction and Antihypertensive Drug Treatment

The roles of arterial stiffness and wave reflections in the mechanisms of SBP reduction in subjects under antihypertensive drug therapy were demonstrated from 2 different randomized, double-blind therapeutic trials. First, during the long-term follow-up of subjects with end-stage renal failure, it was shown that the difference between deceased and alive patients was not the degree of MBP reduction (which was comparable in the 2 groups of subjects) but rather in the combined reductions of SBP, PP, and arterial stiffness (which were observed only in survivors). Second, in subjects with essential hypertension, the Conduit Artery Function Evaluation Study showed that both brachial and mostly aortic PP were able to predict CV outcomes significantly and independently. In both trials, an angiotensin converting-enzyme inhibitor (ACEI) was used. In the Conduit Artery Function Evaluation Study, the ACEI was associated with a calcium-channel blocker, which was at the origin of based treatment and was compared with an association of diuretic and β-blockers. In subjects with end-stage renal disease, only the presence of ACEI and not other antihypertensive agents was able to predict CV outcomes. However, for all of the subjects, an important prerequisite was necessary for the interpretation of data: the extent of SBP and PP amplifications, that is, to determine separately brachial and central (carotid) SBP and PP, should have to be evaluated. Physiologically, as a consequence of arterial stiffness and wave reflection modifications along the arterial tree, SBP and PP are constantly higher in peripheral (brachial) than in central (carotid artery and thoracic aorta) arteries. The difference is ~11 to 14 mm Hg. Thus, central BP measurements are needed to evaluate drug efficacy in therapeutic trials. For instance, it has been shown that ACEI reduces both brachial and carotid SBP and PP, with even more pronounced central rather than brachial effects. In contrast, because of heart rate slowing and resulting earlier wave reflections, the β-blocking agent atenolol poorly modified central PP, whereas BP reduction at
the brachial artery site is nearly at the same extent as for the other antihypertensive agents.

The primary results of 1 year of monitoring for brachial and carotid SBP and PP all together in subjects with essential hypertension were obtained from the Reason Study. That controlled trial compared the \( \beta \)-blocking agent atenolol to low doses of the combination of the diuretic indapamide (Ind) with the ACEI perindopril (Per). After 1 year, for the same DBP reduction, Per/Ind lowered brachial and carotid SBP and PP more than atenolol. The reductions of carotid SBP and PP were more pronounced than those of brachial SBP and PP, but that effect was seen exclusively with Per/Ind. Although carotid and aortic PP did not change significantly under atenolol, Per/Ind achieved a significant diminution. The 2 drug regimens obtained the same aortic PWV reduction as a result of the comparable decreases of MBP and DBP. The major difference between the regimens was that Per/Ind lowered the carotid augmentation index, a classic marker of carotid wave reflections, but atenolol did not. Cardiac output, ventricular ejection, and vascular resistance did not differ between the 2 regimens after 1 year of treatment.

The Reason Study elucidated for the first time the mechanism of SBP reduction under Per/Ind. Primarily, with the 2-drug regimen protocol, aortic PWV slowing because of the diminution of pressure distension in an elastic artery was similar. This hemodynamic profile is in contrast with the case of muscular arteries in which ACEI but not \( \beta \)-blocking agents are able to reduce PWV. Second, the wave-reflection changes resulting from reduction of peripheral (arteriolar) reflection coefficients were the principal factors to consider in explaining the difference between atenolol and Per/Ind regarding SBP reduction. Indeed, ACEI, but not atenolol, is known to lower these reflection coefficients significantly. In the Reason Study, this reduction could be strongly anticipated, because after 1 year of drug treatment, structural arteriolar changes had reversed, but muscular and mainly musculoelastic arteries were much less extensively modified. These agents lowered carotid mass to a greater extent than \( \beta \)-blocking agents like atenolol. Regarding the ACEI perindopril, the regression of cardiac hypertrophy was shown to be consistently mediated by lowering of central SBP and PP but not of brachial BP. This finding is quite logical to consider, because the heart “sees” central but not peripheral BP. In contrast, numerous studies have not only highlighted the substantial differences in cardiac mass under treatment comparing \( \beta \)-blocking agents and renin–angiotensin system blockers but also have pointed to the role of nonmechanical factors in the mechanisms of regression of cardiac hypertrophy. Nowadays, measurements of brachial and central BP and wave reflection are considered important prerequisites to determine whether central BP measurements or, on the opposite, nonmechanical factors, are responsible for the difference in cardiac mass under drug treatment of hypertension. In clinical practice, these determinations are particularly important to consider in treated subjects, because PWV progression with age is accelerated in hypertensive patients.
and this process undoubtedly favors the development of cardiac hypertrophy.\textsuperscript{25} This enhanced progression is significantly more pronounced in subjects with metabolic syndrome, that is, in subjects with insulin resistance and/or oxidative stress\textsuperscript{26} (Figure 3). Whether this process could explain the high coronary and CV risk observed in subjects with type 2 diabetes and/or metabolic syndrome merits consideration. Another aspect related to cardiac mass is the presence, in untreated hypertensive patients, of myocardial capillary rarefaction. In clinical practice, the thinning of the capillary network is influenced not only by the degree of cardiac hypertrophy but also by the sodium content of the diet.\textsuperscript{27} A low-sodium diet and/or diuretic treatment may reverse capillary rarefaction, suggesting new specific indications for salt and water depletion in treated hypertensive subjects.\textsuperscript{28}

Regarding renal damage, because efferent arteriolar resistance is greater than afferent resistance in normal individuals, the pressure drop across the glomerular microcirculation of the kidney is relatively small. MBP and PP in the glomerulus are relatively high, \textasciitilde 60\% of arterial values.\textsuperscript{29} These higher pressures ensure the maintenance of the glomerular filtration rate but expose the glomerular capillary to the potentially damaging effect of elevated glomerular pressure.\textsuperscript{29} In the normal subject, renal blood flow is adequately autoregulated over a wide range of perfusion pressures.\textsuperscript{30–32} The combination of myogenic tone in the afferent arteriole and tubuloglomerular feedback mechanism mediates most of this autoregulation, which has traditionally been defined mainly in terms of steady pressure. Animal experiments showed that myogenic tone in the afferent arterioles is affected not only by steady pressure but also by SBP and PP.\textsuperscript{31,32} Thus, in animal models or humans with PP elevated out of proportion with MBP, renal hemodynamics might be directly influenced by the higher PP, as observed experimentally in the remnant kidney.\textsuperscript{31,32} In humans, we have shown that this hemodynamic profile is observed with advancing age beyond the fifth decade and, therefore, represents a distinct possible mechanism for the age-related decline of renal function.\textsuperscript{33} A similar mechanism is also expected to occur in type 2 diabetic subjects, and even obese individuals in whom significantly increased arterial stiffness and pulsatility are frequently observed very early, during the course of disease development.\textsuperscript{1,4,34}

Concerning brain damage, everybody knows that it is easier to achieve stroke prevention than renal or cardiac protection,\textsuperscript{3} because antihypertensive treatment effectively lowers the frequency of strokes, mainly in association with MBP reduction. Recent meta-analysis has shown that the efficacy of β-blocking agents is less pronounced on strokes than that of blockers of the renin-angiotensin system or mostly calcium entry blockers.\textsuperscript{4} Thus, for stroke prevention, β-blocking agents should be considered major antihypertensive agents less than in the past, even independent of their adverse effects on central PP.\textsuperscript{35}

**Perspectives**

This review has shown that the status of large arteries, studied in term of arterial stiffness and wave reflections, is of major importance to obtain an effective SBP reduction during chronic antihypertensive therapy. For the first time, clinical data clearly indicate that the reversibility of structural arteriolar changes may be an important prerequisite to obtain an adequate SBP reduction in hypertensive subjects. This possibility is obtained using calcium entry blockers and/or inhibitors of the renin–angiotensin system.\textsuperscript{14,15} On the opposite, with β-blocking agents or diuretics given alone, there is no reversibility of structural arteriolar changes,\textsuperscript{14,15} and an adequate SBP reduction is difficult to obtain. Furthermore, traditional β-blocking agents like atenolol do not decrease central PP, a factor contributing to maintain an increased cardiac load. Taken together, these findings suggest that, during long-term antihypertensive therapy, it is important to frequently evaluate central BP measurements. Mostly it is worth noting that, in the past, a very small number of antihypertensive agents have been developed to improve, per se, arterial stiffness and/or wave reflection. Clinical and experimental studies should have to consider this aspect to improve further CV risk in the future.

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**Disclosures**

None.

**References**


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