Hypertension, Systolic Blood Pressure, and Large Arteries

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The authors of epidemiologic studies have long emphasized the close relationship between high systolic blood pressure (SBP) or diastolic blood pressure (DBP) and the incidence of cardiovascular (CV) disease. In the past, clinical hypertension was principally diagnosed based on the DBP level. The hemodynamic characteristics of the disease were attributed to a reduction of the caliber and/or number of small arteries, causing elevated peripheral vascular resistance and secondary adaptive changes of the structure and function of arterioles and the heart. Later, prospective studies on Framingham Heart Study populations redirected attention to SBP as a better guide than DBP to evaluate CV and all-cause mortality. In 1988 and later, we investigated a large population of patients treated for hypertension and where DBP was consistently and adequately controlled (<90 mm Hg). Approximately one third of the subjects exhibited a high SBP (>140 mm Hg) and pulse pressure (PP = SBP – DBP) for the same mean arterial pressure (MAP) as the remaining two thirds of the total population. The former group was characterized by significantly higher aortic pulse wave velocity (PWV) and degree of cardiac hypertrophy than the latter. Finally, it was shown that, in large populations, antihypertensive therapy frequently achieved adequate DBP control but that SBP was much more difficult to control. Those findings focused attention on the factors that modulate SBP and PP levels in hypertensive individuals, and therefore on the potential role of increased arterial stiffness and/or wave reflections in SBP and PP control, and hence CV morbidity and mortality.

A major function of the large arteries is to change the pulsatile pressure and flow coming from the heart into a steady pressure and flow at the periphery, to obtain optimal oxygenation of tissues. This major modification is a consequence of

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the so-called “Windkessel” effect. During systole, part of the stroke volume directly flows toward the periphery, causing systolic perfusion. The other part of the stroke volume is stored within the elastic thoracic aorta wall and restored during diastole, causing the resultant diastolic perfusion. The association of systolic and diastolic flows is responsible for continuous and steady peripheral perfusion, which contrasts with the alternative cyclic movement initiated by the heart. This “Windkessel” effect has major impact on SBP regulation, through the mechanisms of wave reflections and the development of systolic hypertension. This article is composed of the following four parts:

(1) Factors modulating central and peripheral SBP and PP in hypertensive subjects;
(2) Mechanisms enhancing PP variations in this population;
(3) Analysis of pulsatile arterial hemodynamics as predictors of CV risk; and
(4) Pulsatile hemodynamics and strategies lowering CV risk in the treatment of hypertension.

FUNCTIONAL AND STRUCTURAL FACTORS INFLUENCING CENTRAL SYSTOLIC BLOOD PRESSURE AND PULSE PRESSURE

This section summarizes briefly the principal factors modulating SBP and PP and acting on large arteries in hypertensive subjects. Increased SBP and PP are the main clinical characteristics of hypertension in the elderly.

The Systolic Blood Pressure and Pulse Pressure Arterial and Arteriolar Circuit

As we mentioned earlier, at the end of ventricular ejection, the pressure in the aorta falls much more slowly than in the left ventricle because the large central arteries, particularly the aorta, are elastic, and thus act as a reservoir during systole, storing part of the ejected blood, which is then forced out into the peripheral vessels during diastole.1,2,9,10 More specifically, the pulsatile load is borne primarily by elastin-containing central arteries, which fulfill the bulk of the cushioning function by expanding during systole to store some, but not all, of each stroke volume, and then contracting during diastole to facilitate peripheral run-off of the stored blood, thereby supporting diastolic blood flow to peripheral tissues.

![WAVE TRAVELING](image)

**Fig. 1.** Progression of the pressure wave along the arterial tree. Three steps are involved: propagation, reflection, and summation of the incident and the reflected waves. (From Safar ME, Lacolley P. Disturbance of macro- and microcirculation: relation with pulse pressure and cardiac organ damage. Am J Physiol Heart Circ Physiol 2007;293:H1–7; with permission.)
Then, the pressure pulse generated by ventricular contraction travels along the aorta as a wave (Fig. 1). It is possible to calculate the velocity of this wave (ie, pulse wave velocity, PWV) from the interval between two BP curves located at two different sites in the arterial tree, particularly the aorta. Because a fundamental principle is that pulse waves travel faster in stiffer arteries, PWV measurement is considered the best surrogate to evaluate arterial stiffness. It estimates 3 to 5 m/s in young persons at rest, but increases considerably with age. Given that peripheral arteries are markedly stiffer than central arteries, an important limitation of PWV determinations is the large heterogeneity of the arterial wall components at its different sites.

When several BP measurements are made simultaneously at different points all along the aorta, the pressure wave changes shape as it travels down the aorta. Whereas SBP actually rises with distance from the heart, the DBP and MAP fall slightly (about 4 mm Hg) during the same course along the aorta trajectory (see Fig. 1). Thus, pressure-oscillation amplitude between systole and diastole, which is PP, nearly doubles. This SBP and PP amplification along the vascular tree is a physiologic finding, approximately 14 mm Hg between the thoracic aorta root and the brachial artery, and continuing in aortic ramifications out to about the third-generation level of branches. Thereafter, both PP and MAP drop sharply to the levels found in the microcirculation, a territory in which steady flow is nearly achieved.

If an individual’s body length is about 2 m at most, and aortic PWV is approximately 5 m/s, something must happen to the BP-curve shape within each beat if heart rate is 60/min. What happens is the generation of wave reflections and their summation with the incident wave, as summarized in Fig. 1. The incident wave is driven away from the heart through the highly conductive arteries. However, it encounters an impedance mismatch at the junction of the high conductive artery and high resistance arterioles, blocking its entry into the arterioles and it is reflected, traveling backward toward the heart. Thus, the shape of every pulse wave results from the summation of the incident (forward-traveling) and reflected (backward-traveling) pressure waves.

**Age, Wave Reflections, and Systolic Hypertension**

Reflected waves may be initiated from any discontinuity of the arterial or arteriolar wall, but are mainly issued from high-resistance vessels.\(^1,9,10\) Pulse-wave propagation and

![Fig. 2. Characteristics of the pressure wave in young and old subjects for the same cross-sectional area of the blood pressure curve (ie, the same mean arterial pressure). Aix: Augmentation index is the supplement of SBP owing to the reflected wave and located between the two arrows indicated within the figure. (From Nichols WW, O’Rourke MF, McDonald DA. McDonald’s blood flow in arteries. Theoretical, experimental and clinical principles. 4th edition. Sydney: Hodder Arnold; 1998. p. 54–401. Copyright © 1998. Reproduced by permission of Edward Arnold (Publishers) Ltd.)](image-url)
reflection vary considerably according to age. In young adults at their maximum height and maximum elasticity of their central arteries (low PWV), the summation of the incident arterial pressure wave and the reflected wave results in progressive PP amplification, so that SBP is higher in the brachial artery than the ascending aorta (Figs. 1 and 2). This hemodynamic profile contrasts with MAP and DBP, which decline minimally in vessels at increasing distance from the heart at all ages (see Figs. 1 and 2). Note that, in the thoracic aorta, because PWV is relatively low, the reflected wave comes back during diastole, thereby maintaining DBP and boosting coronary perfusion. Hence, an optimal arterial function is maintained, along with adequate coronary perfusion.

The pattern of wave reflections and the pulse wave shape are directly dependent on aging and arterial stiffness. The development of increasing arterial stiffness (high PWV) and altered wave reflections with aging and hypertension completely abolishes the differences between central and peripheral PP by age 50 to 60 years (see Fig. 2), with major consequences on ventricular load and coronary perfusion. The increased velocity of the aortic pulse wave means that the reflected waves return to the aortic root earlier, during late systole. In that situation, the reflected waves summate with the forward-traveling wave to create an increase or “augmentation” of the central SBP and ventricular load (see Fig. 2). In elderly persons with isolated systolic hypertension, aortic SBP can be elevated by as much as 30 to 40 mm Hg as a result of the early return of the wave reflection.1,2 Furthermore, because the backward pressure returns in systole, and not in diastole, as a consequence of enhanced PWV, DBP and coronary blood flow tend to be reduced, a situation favoring coronary ischemia.

Arterial Remodeling, Wave Reflections, and Their Cardiovascular Consequences

An arterial wall is a complex tissue composed of different cell populations capable of structural and functional changes, in response to direct injury and atherogenic factors, or to modifications of long-term hemodynamic conditions. The principal geometric modifications induced by hemodynamic alterations are changes of the arterial radius (r) lumen and/or arterial wall thickness (h) owing to activation, proliferation, and migration of vascular smooth muscle (VSM) cells, and rearrangements of cellular elements and extracellular matrix (ECM).11–18 Whereas acute changes of tensile or shear stress (= v/r, with v = blood velocity) induce transient vasomotor-tone and arterial diameter adjustments, chronic alterations of mechanical forces lead to modifications of the geometry and composition of the vessel walls, as observed in hypertension, particularly in the elderly.13,14 To maintain tensile stress (T) within physiologic limits, arteries respond by thickening their walls (Laplace’s law: \( T = \frac{P}{r^2/h} \), where \( P \) = pressure). Experimental and clinical data indicate that acute and chronic augmentations of arterial blood flow induce proportional increases of the vessel lumen, whereas diminished flow leads to reduction of the inner arterial diameter.14,15 The presence of the endothelium is a major prerequisite for normal vascular adaptation to chronic changes of blood flow and pressure. Finally, although the alterations of tensile and shear stresses are interrelated, tensile stress changes primarily induce (as in hypertension) hypertrophy and sclerosis of the arterial media, whereas shear stress changes principally modify the dimensions and structure of the intima (atherosclerosis).

Hypertensive remodeling is characterized by the increased wall/lumen (h/r) ratio of arterioles, which represent the site of vascular resistance and also the origin of wave reflections (see Figs. 1 and 2).14–18 Regression of arteriolar hypertrophy is associated with diminution of vascular resistance and reflection coefficients, and thereby lower SBP, PP, and augmentation index (Aix), a classical marker of wave reflections (see Fig. 2).16–18 This process occurs approximately after 1 year of treatment with
MECHANISMS OF PULSE PRESSURE DIFFUSION AND VARIATION

It has recently been shown that PP interacts with the arterial wall through transduction mechanisms independent of MAP. Indeed, at any given MAP value, the arterial wall becomes much stiffer in the presence than in the absence of pulsatile stimulus. Furthermore, calcifications and attachment molecules are able to enhance arterial stiffness independently of both systemic MAP and changes in elastin and/or collagen within the vessel wall. All these factors contribute to PP widening.

Cyclic Mechanical Factors and the Arterial Wall

Since the pioneering studies of Glagov, many investigations have examined the effect of cyclic forces on the arterial wall, particularly on endothelial cells exposed to pulsatile shear stress in vitro. The role of cyclic shear stress (as opposed to steady stress), and the importance of stimulus duration and graded responses to mechanical forces have been demonstrated especially concerning NO and superoxide anions. Cyclic mechanical strain has also been analyzed, mostly using cultured VSM cells. Long-term cyclic distention enhances the mechanical properties of collagen-based medial components and even heightens collagen and fibronectin (Fn) accumulations in animal or human VSM models. The vessel-wall materials become stronger and stiffer than those obtained under static conditions.

A distinct feature of VSM cells is their phenotypic plasticity, particularly during the transition from the contractile to the synthetic phenotype of VSM-cell cultures in the absence of mechanical forces. Exposing cultured VSM cells to cyclic stretch can restore the expression of high-molecular-weight caldesmon and other markers of differentiated VSM cells. A certain degree of stretch is required to preserve the VSM contractile state. Hence, the failure to maintain a threshold level stretch is likely to contribute to VSM-cell transformation.

Stretch initiates complex signal-transduction cascades leading to gene transcription and functional responses, via interaction of integrins with extra cellular matrix (ECM) proteins, or by stimulating G-protein receptors, tyrosine kinase receptors, or ion channels (reviewed in Lehoux and colleagues). The intracellular pathways reported to be activated in VSM cells by cyclic stretch include, mainly, the mitogen-activated protein kinase cascades and nuclear factor-kappa B, which has been studied at both VSM and endothelial levels. More recently, steady and cyclic modes of stretch were shown to transduce differently in the aorta: the former implicating focal adhesion kinase and the latter free radicals derived from oxidative stress and the presence of inflammatory factors (Fig. 3).

Finally, the transcriptional profile of mechanically induced genes in VSM cells subjected to a uniform biaxial cyclic strain was studied. Cyclic stretch was found to stimulate the expression of a number of genes, including vascular endothelial growth factor and plasminogen activator inhibitor-1, but to negatively regulate others, such as ECM metalloproteinase-1 and thrombomodulin.

Wall Material, Stiffness, Calcifications, and the Role of Attachment Molecules

In recent years, studies on rodents showed that, particularly in old age, diabetes mellitus and/or in subjects on a high-sodium diet, arterial calcifications (not addressed in this article) and attachment molecules (between VSM cells, or VSM cells and ECM
proteins, or between collagen fibers), contribute per se to stiffening the vascular wall.\textsuperscript{2,26}

Cross-links may stabilize collagen fibrils, preventing slippage of adjacent molecules under applied tensile stress\textsuperscript{2} and contributing to increased arterial stiffness through the formation of end-glycation products.\textsuperscript{27} In elderly subjects with systolic hypertension, drugs involving collagen cross-link breakers acutely reduce arterial stiffness and PP, without any change of MAP.\textsuperscript{27} Glycosaminoglycans exhibit viscoelastic properties, which make them good candidates for flow-sensing molecules, binding sodium and calcium ions in their helicoidal chains.\textsuperscript{28} In the carotid arteries of spontaneously hypertensive rats (SHR), chronic high-sodium diet results in the reduction of arterial hyaluron and enhanced aortic stiffness.\textsuperscript{29}

Because integrins transmit inside-out and outside-in signals capable of modulating vascular responses, it has been suggested that adhesion molecules, such as Fn and its integrin receptor(s), might contribute per se to changing arterial wall stiffness. For instance, Fn-ECM polymerization increases tensile strength of model tissue.\textsuperscript{30–32} In young and old SHR, aortic Fn measurements indicate that more attachment sites between VSM cells and ECM proteins might contribute to enhanced arterial rigidity.\textsuperscript{2,26} On a normal-sodium diet, angiotensin-converting enzyme inhibition (ACEI) led to lower MAP and PP, together with reduction of aortic Fn and \(\alpha_2\beta_1\) integrin, and increase of isobaric arterial distensibility.\textsuperscript{31} On ACEI plus high-sodium diet, MAP was significantly reduced, but PP, arterial stiffness, and aortic Fn remained elevated. Similar results were obtained when chronic aldosterone administration was combined with high-sodium diet for Sprague - Dawley rats.\textsuperscript{32} In the latter experiment, the enhancements of Fn and stiffness were reversed by administration of the selective aldosterone-antagonist eplerenone.\textsuperscript{32}

Local changes of the attachments between VSM cells and ECM proteins along with arterial calcifications might independently modulate the stiffness of each artery taken individually. All these pathophysiological mechanisms might also contribute to the development of new wave-reflection sites, particularly in aged people. Finally, the extent of abnormal arterial stiffness and wave reflections in each individual is largely influenced by the vascular territories involved and the subject’s age. In some cases, as in obese persons and/or those with insulin resistance, arterial stiffness is enhanced with minor changes in wave reflections.\textsuperscript{1,2} In most cases, both parameters are increased in parallel. For all patients, bidirectional interactions develop between higher PP and enhanced wall stiffness, thereby creating a vicious circle and raising the risk of

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**Fig. 3.** Simplified view of mechanotransduction mechanisms. See text.\textsuperscript{21,23,24}
CV complications.\textsuperscript{1,2} Finally, increased stiffness and pulsatility may lead to target-organ damage every time PP is transmitted to the corresponding organ. This process requires the loss of organ autoregulatory mechanisms, whose study is beyond the scope of this article.

**PULSATILE ARTERIAL HEMODYNAMICS AS INDEPENDENT PREDICTORS OF CARDIOVASCULAR RISK**

This paragraph shows that brachial PP, aortic PWV, and even at a higher extent, central PP and wave reflections are independent predictors of CV risk in the elderly.

**Brachial Pulse Pressure**

In a 1989 French study including normotensive and untreated hypertensive adults,\textsuperscript{33} a pulsatile-component index, defined as a strong correlate of brachial PP, was derived by principal-components analysis of SBP and DBP measurements. An association was found between the pulsatile-component index and electrocardiographic evidence of left ventricular hypertrophy. During 10 years of follow-up, the pulsatile-component index was independently associated with an increased risk of death from coronary artery disease (CAD), but not from stroke. The relationship was found to be particularly consistent for women older than 55. In another prospective study evaluating hypertensive subjects,\textsuperscript{34,35} those in the highest brachial PP tertile before starting therapy (≥ 63 mm Hg) had an enhanced risk of myocardial infarction and, to a lesser extent, stroke. This result was obtained during an average follow-up of 5 years. In a later study, multivariate analysis revealed that brachial PP as a categorical (but not continuous) variable was an independent predictor of myocardial infarction. Finally, that association was observed, regardless of whether PP was measured by sphygmomanometry or ambulatory BP measurements over 24 hours.\textsuperscript{36}

Franklin and colleagues\textsuperscript{37} for the Framingham Heart Study, Millar and colleagues\textsuperscript{38} for the Medical Research Council trial, and Blacher and colleagues\textsuperscript{39} for the European Working Party on High Blood Pressure in the Elderly, Syst-China, and Syst-Eur trials, showed, almost simultaneously, that, after 50 to 60 years of age, brachial PP was a stronger CV risk factor than SBP alone for myocardial infarction in populations of hypertensive individuals. The best predictor function of all possible linear combinations of SBP and DBP was shown to be similar to that of PP, indicating that their association was not a statistical artifact caused by the correlation between SBP and PP.\textsuperscript{37–39} Furthermore, one report\textsuperscript{39} clearly indicated that CV risk was not only attributable to a SBP increase but also specifically to a DBP decline. As shown in Fig. 4, CV risk rises sharply with SBP. However, at any given SBP value, CV risk is higher when DBP is lower.\textsuperscript{39} This important finding was confirmed by the result of a longitudinal study,\textsuperscript{40} which indicated that, during 20 years of follow-up, subjects with higher CV mortality were those whose SBP rose and DBP declined, and their CV-mortality rate was significantly higher than that for those individuals whose SBP and DBP increased.\textsuperscript{41} Finally, it was demonstrated that, in the elderly, neither SBP nor DBP was superior to PP for predicting coronary risk\textsuperscript{37} and PP was found to be an independent predictor of CV mortality, even for individuals with recurrent myocardial infarction, congestive heart failure, or myocardial dysfunction.\textsuperscript{41–45} Finally, brachial PP was shown also to be an independent predictor of CV risk in subjects with end-stage renal disease, diabetes mellitus,\textsuperscript{46,47} or even systemic vasculitis.\textsuperscript{48}

In a population of 19,083 normo- or hypertensive men followed for 20 years, Benetos and colleagues\textsuperscript{49,50} not only confirmed that elevated brachial PP was a strong predictor of myocardial infarction but also that this predictive value was even observed in
a normotensive population, especially in men older than 55. Those findings were also applied to treated hypertensive individuals. Pertinently, even when normotensive BP values (SBP ≤ 140 mm Hg; DBP ≤ 90 mm Hg) were obtained with successful drug therapy, elevated PP predicted a higher CV-mortality rate, especially for diabetic patients. Furthermore, according to many therapeutic trials conducted on elderly hypertensive subjects, CV mortality was indeed substantially lowered but, at the end of the trials, the population was characterized by low DBP as opposed to SBP, which remained high (> 140 mm Hg). These findings suggest to what extent the presence of drug treatment might be partly responsible, together with age, for the hemodynamic profile associating low DBP and high SBP, ie, increased PP.

**Aortic Pulse Wave Velocity**

In older populations, PP is poorly influenced by ventricular ejection, which tends to decline with age, whereas, in contrast, arterial stiffness tends to increase. However, until recently, it was not known whether aortic PWV, a classic index of arterial stiffness and wave reflections, was an independent predictor of CV mortality in hypertensive individuals.

Based on the characteristics of 201 patients with end-stage renal disease (ESRD), logistic-regression and Cox analyses identified three predictors of CV mortality: aortic (and not limb) PWV, and age and duration of hemodialysis before entry. Lipid abnormalities, anemia, and low DBP influenced risk to much smaller degrees. After adjusting for age, duration of hemodialysis, preexisting CV disease, left ventricular hypertrophy, BP, serum albumin, and hemoglobin levels, the odds ratios for PWV (> 12 m/s) were 5.6 (95% confidence interval [CI] 2.4–11.9) for all-cause mortality, and 5.9 (95% CI 2.3–15.5) for CV mortality. These results provided the first evidence that, in ESRD patients on hemodialysis, enhanced aortic stiffness (but also PP) was a major independent predictor of CV mortality. Similar findings were observed in this population using, in the place of aortic PWV, carotid wall–material stiffness as an index of vascular...
wall–material stiffness. That analysis indicated that, while the wall/lumen ratio of the common carotid artery did not predict CV risk, carotid stiffness itself (and not wall thickness) was a highly significant predictor of CV mortality.\textsuperscript{55} Finally, the predictive value of carotid stiffness was subsequently extended to carotid wave reflections.\textsuperscript{56} Similar observations were obtained for ESRD patients with diabetes mellitus\textsuperscript{57} and in kidney-transplant recipients.\textsuperscript{58}

Identifying predictive factors contributing to essential hypertension is complex because long-term longitudinal studies with aortic PWV measurements are difficult to conduct, mainly because of patient mobility but also to the paucity of mechanisms involved. However, the calculating CV risk with Framingham equations can partly resolve this difficulty.\textsuperscript{59} In a study on 530 hypertensive subjects,\textsuperscript{60} the odds ratio of carrying a high CV risk based on various known factors was evaluated. The CV risk assessed using Framingham equations was linearly associated with the PWV increase. Furthermore, aortic PWV was shown to be the best predictor of CV mortality. The odds ratio of being at high risk of CV mortality (> 5% for 10 years) for patients with PWV greater than 13.5 m/s was 7.1 (95% CI 4.5–11.3). That study\textsuperscript{60} provided the first evidence that a single aortic PWV measurement could be a strong independent predictor of CV risk for hypertensive patients. The results of longitudinal studies\textsuperscript{61,62} confirmed that aortic PWV is a significant and independent predictor of CV risk, more potent than PP itself.

To assess the prognostic significance of aortic PWV above and beyond the other traditional CV risk factors, a sex- and age-stratified random sample of 1678 Danish subjects, 40 to 70 years old, was investigated.\textsuperscript{63} Cox regression was used to evaluate the prognostic value of PWV, office PP, and 24-hour ambulatory PP, with adjustment for MAP and other covariates. Over a median follow-up of 9.4 years, fatal and nonfatal CV end points, CV mortality, and fatal and nonfatal CAD concerned 154, 62, and 101 patients respectively. Adjustments were made for sex, age, body mass index, MAP measured in the office (conventional PP and PWV), or by ambulatory monitoring (24-hour PP), smoking, and alcohol consumption. After these adjustments, PWV maintained its prognostic significance for each end point ($P < .05$), whereas office and 24-hour PP lost their predictive value ($P > .19$), except for office PP in a context of CAD ($P = .02$) (Fig. 5). For each increment of one PWV standard deviation (3.4 m/s), the risk of an event increased 16% to 20%. According to sensitivity analyses, PWV still predicted all CV events after standardizing to a heart rate of 60 beats per minute, after adjustment for 24-hour MAP instead of office MAP, and/or after additional adjustment for the total-to-HDL serum cholesterol ratio and diabetes mellitus at baseline. Thus, in a general Danish population, PWV predicted a composite of CV outcomes above and beyond traditional CV risk factors, including 24-hour MAP. Similar findings were obtained for other populations of diabetic and nondiabetic subjects.\textsuperscript{64–66}

Central Pulse Pressure, Aortic Stiffness, and Coronary Artery Disease

Numerous studies have shown in the past significant associations between CAD and enhanced aortic or carotid stiffness.\textsuperscript{1,2,67,68} Because, in most cases of CAD, brachial, and not aortic, BP was measured\textsuperscript{1,2,67,68} and because brachial PP is physiologically higher than aortic PP for the same MAP,\textsuperscript{1,2} most of those earlier studies did not clearly demonstrate that aortic PP was the main hemodynamic parameter significantly predicting CAD.

As we stated previously, studies on pulsatile arterial hemodynamics showed that, whereas MAP remains nearly constant along the arterial tree, PP rises markedly from central (thoracic aorta and carotid artery) to peripheral (brachial) arteries. That
Physiologic amplification can be explained by the pressure-wave propagation along arterial vessels associated with the progressive artery-diameter decline and arterial stiffness increase, resulting in modifications of wave-reflections timing and/or amplitude. Therefore, aortic PP is expected to be more relevant to the investigation of CV risk than brachial PP, because it is closer to the heart, coronary arteries, and carotid arteries, which are the most important sites of CV events.\textsuperscript{1,2} Aortic, but not brachial, pulsatility has been shown to be independently associated with CAD in patients undergoing coronary angiography after angioplasty.\textsuperscript{69–72} In 409 subjects followed for 4 to 5 years by Jankowski and colleagues,\textsuperscript{73} a 10-mm Hg aortic PP increase was associated with a corresponding 13% increase of CV events. In atherosclerotic subjects, central wave reflections were shown to be independent predictors of CAD.\textsuperscript{74} In ESRD patients, aortic PWV and carotid wave reflections (and/or central PP) were shown to predict independently CV mortality.\textsuperscript{1,2,74} Finally, in the same patients and in elderly subjects with essential hypertension, central PP was demonstrated to be an independent predictor of mortality.\textsuperscript{75} Taken together, all these findings suggested that central PP was superior to brachial PP to predict coronary risk and indicated that, during long-term antihypertensive drug therapy, serial central BP determinations are required to predict CV complications.\textsuperscript{2}

**PULSATILE ARTERIAL HEMODYNAMICS AND RISK-REDUCTION STRATEGIES IN HYPERTENSION**

The main therapeutic trial demonstrating the predictive role of aortic stiffness in hypertensive subjects was conducted on ESRD patients on hemodialysis.\textsuperscript{76} The objective of that trial was to lower CV morbidity and mortality through a therapeutic regimen involving, successively, salt and water depletion by dialysis; then, after randomization,
ACE inhibition or calcium-channel blockade; and, finally, the combination of the two agents and/or their association with a beta-blocker. Using that protocol, it was possible to evaluate, over long-term follow-up (51 months), whether or not the drug-induced MAP reduction was associated with a parallel diminution of arterial stiffness impacting on CV risk. During follow-up, it was clearly shown that survivors’ MAP, PP and aortic PWV were lowered in parallel. In contrast, for patients who died from CV events, MAP had been reduced to the same extent as in survivors, but neither PWV nor PP had been significantly modified by drug treatment. Thus, survival of ESRD patients was significantly better when aortic PWV declined in response to BP lowering. The adjusted relative risks for all-cause and CV mortality rates in those with unchanged PWV in response to BP changes were, respectively, 2.59 (95% CI, 1.51–4.43) and 2.35 (95% CI, 1.23–4.51) \( (P < .01) \). The prognostic value of PWV sensitivity to BP reduction on survival was independent of age, BP changes, and blood-chemistry abnormalities. The results indicated that arterial stiffness was not only a risk factor contributing to the development of CV disease but that it was also a marker of established, more advanced, and less reversible arterial lesions. This interpretation was supported by the loss of aortic PWV sensitivity to BP lowering for non-survivors, compared with survivors whose arterial stiffness remained responsive to BP reduction. Finally, in that trial, prolonged survival seemed to be more closely associated with the use of an ACEI than other drugs or the number of drugs per se. The use of beta-blockers and/or dihydropyridine calcium-channel blocker had no direct impact on the outcomes.\(^7\)

The Reason study\(^1\)\(^6\),\(^7\)\(^7\) was the first to investigate the long-term interactions among PP, arterial stiffness, and wave reflections in relationship to drug treatment and end-organ damage (cardiac mass) in hypertensive subjects. ACEI perindopril (Per), associated with low-dose indapamide (Ind) was compared for 1 year of treatment with the beta-blocking agent atenolol. For the same DBP and MAP decreases, Per/Ind lowered SBP and PP more than atenolol. The reduction was more pronounced centrally (carotid artery) than peripherally (brachial artery). Although the two drug regimens lowered PWV equally, only Per/Ind reduced the Aix.\(^7\)\(^7\) In addition, Per/Ind decreased cardiac hypertrophy more than atenolol, and that diminution was attributed to Aix, indicating that the reduction of cardiac end-organ damage mainly reflected the effect on central wave reflections.\(^7\)\(^7\)

The Conduit Artery Function Evaluation (CAFE) study, a subanalysis of the Anglo-Scandinavian Cardiac Outcomes Trial,\(^7\)\(^8\) conducted on 2073 subjects, showed that aortic PP, recorded noninvasively by radial tonometry and the application of generalized transfer functions, is a determinant of clinical outcome, independently of age, other traditional CV risk factors, and even peripheral PP.\(^7\)\(^8\) In agreement with the REASON study,\(^1\)\(^7\),\(^1\)\(^8\) the CAFE study results showed that treating subjects with a regimen based on the beta blocker atenolol and a diuretic versus one based on the calcium-channel blocker amlodipine and an ACEI had similar effects on brachial SBP and PP but different impacts on central aortic pressures.\(^7\)\(^8\) Even though brachial pressure reductions were similar for the two arms of the study, central SBP and PP decreases were greater for the perindopril (ACEI) arm. That study’s results not only demonstrated that brachial PP does not always reflect the impact of different pressure-lowering treatments on central aortic pressures, but also suggested that central changes in pressure might better predict clinical outcomes other than brachial pressures.\(^7\)\(^8\) Therefore, antihypertensive drug therapy should selectively lower SBP and PP through complex interactions between small and large artery effects, thereby opening the way to the development of new long-term CV-treatment strategies involving both small and large arteries.
REFERENCES


