Current Perspectives on Arterial Stiffness and Pulse Pressure in Hypertension and Cardiovascular Diseases

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Blood pressure (BP) is a powerful cardiovascular (CV) risk factor that acts on the arterial wall and is responsible in part for various CV events, such as cerebrovascular accidents and ischemic heart disease. In clinical practice, 2 specific and arbitrary points of the BP curve, peak systolic BP (SBP) and end-diastolic BP (DBP), are used to define the CV risk factor. Because the goal of drug treatment of hypertension is to prevent CV complications, it appears likely that the totality of the BP curve, not simply 2 specific and arbitrary points, should be considered to act mechanically on the arterial wall and therefore should be used to propose an adequate definition of high BP.

A current approach consists of considering the BP curve as the summation of a steady component, mean blood pressure (MBP), and a pulsatile component, pulse pressure (PP).1 MBP, the product of cardiac output multiplied by total peripheral resistance, is the pressure for the steady flow of blood and oxygen to peripheral tissues and organs. The pulsatile component, PP, is the consequence of intermittent ventricular ejection from the heart. PP is influenced by several cardiac and vascular factors, but it is the role of large conduit arteries, mainly the aorta, to minimize pulsatility. In addition to the pattern of left ventricular ejection, the determinants of PP (and SBP) are the cushioning capacity of arteries and the timing and intensity of wave reflections.1 The former is influenced by arterial stiffness, usually expressed in the quantitative terms of compliance and distensibility.1 The latter result from the summation of a forward wave coming from the heart and propagating at a given speed (pulse wave velocity, or PWV) toward the origin of resistance vessels and a backward wave returning toward the heart from particular sites characterized by specific reflection coefficients.1

Over the past few years, arterial stiffness and wave reflections have been widely investigated in old and/or hypertensive subjects for several reasons. First, whereas DBP was considered in the past as the better guide to determine disease severity, epidemiological studies have directed attention to SBP as a more informative CV risk factor, particularly in patients older than 50 years of age, and it has been shown that PP is an independent marker of CV risk, mainly for myocardial infarction.2 Second, in subjects >50 years of age, ventricular ejection tends to be reduced, so that arterial stiffness and amplitude and timing of wave reflections become the main determinants of increased SBP and PP. Third, whereas drug control of DBP is consistently obtained in large populations of hypertensive patients, the ability to control SBP is observed much less frequently.3 Finally, increased PP is also a predictor of CV risk in subjects with recurrent myocardial infarction and congestive heart failure.2-4 From the hemodynamic factors that influence PP, 2 have been shown to independently predict CV risk: aortic stiffness, measured from aortic PWV,6,7 and early return of reflected waves to the heart, evaluated from pulse wave analysis.8

The purpose of this review is to discuss the structural and functional factors that influence arterial stiffness, wave reflections, and PP within the fields of vascular biology and CV risk, independent of atherosclerosis. From these considerations, novel approaches may be proposed to further reduce CV risk in the aged population with hypertension and other CV diseases.

BP Propagation, an Information System Between the Proximal and Distal Parts of the Arterial Tree

BP is involved in 2 distinct functions of large arteries: the conduit function, which, on the basis of a pressure gradient, consists of supplying blood flow to peripheral tissues and organs; and a cushioning function, which is able to dampen the pressure oscillations that result from intermittent ventricular ejection (“Windkessel effect”).1,9 Although all the arteries of the vascular tree participate in these 2 functions, proximal arteries (ie, the aorta and its main branches) have a dominant role in cushioning, whereas distal arteries and arterioles contribute more to the distribution of blood. Nevertheless, the role of BP is not simply to passively distend the arterial tree. As derived from Von Foerster’s theories, BP is able to transfer energy and mechanical signals independently of neurohumoral factors.10 This aspect, largely derived from studies of impedance spectrum, pulsatile strain-stress relationships, and mechanotransduction, results from the propagation of the pressure wave at fast speed (5 to 7 m/s). The generation of the signals, which are frequency dependent,
involves 2 different mechanisms. The first is related to the development of a high-pressure wave by the left ventricle that ejects into the proximal aorta (proximal compartment). The second is indirect, arising from the distal compartment via the influence of arterial stiffness and wave reflections.

Ejection of blood into the aorta generates a pressure wave that is propagated to other arteries throughout the body. As in elastic conduits, this forward-traveling pressure wave may be reflected at all points of structural and/or functional discontinuity of the arterial tree. From these different points of discontinuity, mainly located in the distal arteries at the branching origins of arterioles, a reflected wave is generated that travels backward toward the ascending aorta. Thus, incident and reflected pressure waves are in constant interaction along the arterial circuit and are summed up into the actual pressure wave. The final amplitude and shape of the measured aortic BP wave are determined by the phase relationship (timing) between the 2 component waves. The timing of incident and reflected pressure waves depends on PWV, the traveling distance of pressure waves, and the duration of ventricular ejection. In young subjects, under physiological conditions, the backward pressure wave returns from the distal arterial compartment during diastole, making PP higher in peripheral than in central arteries. This physiological phenomenon, called PP amplification, is influenced by PWV. With heightened PWV, the reflecting sites of the distal compartment appear “closer” to the ascending aorta, and the reflected waves occur earlier, being more closely in phase with incident waves in this region. Such an earlier return of wave reflections means that the reflected wave affects the central arteries during systole and not during diastole. This disturbed signal results in an augmentation of aortic and ventricular pressures during systole and reduces aortic pressure during diastole. Hence, altered mechanical properties of the aortic wall influence the level of aortic SBP (which is increased) and DBP (which is decreased) as a consequence of early wave reflections. Finally, all these findings taken together indicate that a disturbed pressure signal arising from the distal arteries through disturbed wave reflections may alter the heart-vessel coupling and lead to increased CV risk. Evidence for this pathophysiological mechanism arises from studies of pulsatile arterial hemodynamics, as highlighted recently by the role of PWV and wave reflections as independent factors in CV risk in hypertension and various CV diseases.

Wave reflections alter the ventricular-vascular coupling not only through increased arterial stiffness and changed timing but also through modifications in their amplitude. Such possibilities depend on the reflectance properties of the arterial tree, which arise from the distal part of the arterial tree. They are influenced by the geometry, number, structure, and function of smaller muscular arteries and arterioles. Thus, acute and active arterial and arteriolar constriction results in earlier aortic wave reflections at the aortic level and hence increased PP. Taylor previously reported that an increase in the arterial cross-sectional area at peripheral bifurcations causes a delay of wave reflections, with subsequent selective decreases of SBP and PP through changes of peripheral reflection pattern. Thus, it can be hypothesized that a decrease in arterial cross-sectional area contributes to cause earlier wave reflections and increase SBP and PP through changes in peripheral reflection patterns. These alterations are influenced by several distally located structural and functional factors, involving mainly hypertrophy or remodeling of arterial and arteriolar vessels, and by a change in the number and branching angles of arterioles, modifications of the microenvironment (in particular sodium and other cations), reduced endothelium-mediated vasodilation, changes in matrix composition of small arteries and arterioles, and finally, genetically mediated alterations of vasomotor tone, arising from smooth muscle or endothelial cells. Age greatly influences all these modifications and tends to increase PP more rapidly in the central than in the distal compartment of the arterial tree, resulting in an age-dependent reduction of PP amplification. Reduction of PP amplification has been shown to be an independent predictor of CV mortality in hypertensive subjects.

In this context, the architecture of the microvascular network plays a pivotal role. It has become evident that the microvascular network is the primary determinant of long-term vascular resistance (VR). The number of small arteries and the way in which they branch, including the branching angle, contribute importantly to this process. In the developing microvascular bed, VR is strongly influenced by the nature of vascular growth, with a major distinction in effect of addition of new segments to existing terminal segments (vasculogenesis) and addition of a vessel onto an existing segment (angiogenic sprouting). These forms of terminal or segmental growth influence overall resistance properties of a vascular bed differentially. On the other hand, during aging and hypertension, there is a progressive loss of microvessels (rarefaction). Finally, it is possible that microvascular architecture acts not only on VR but also on BP propagation and its consequences. Early mathematical studies on wave reflection factors suggest an important microvascular location of reflection sites. Recent careful measurements by Christensen and Mulvany suggest that PP is transmitted much deeper into the microcirculation than was previously believed. These observations may have implications for drug treatment of hypertensive disease that may induce specific alterations in microvascular architecture.

Finally, several other reflecting sites, located in larger arteries, play a role in the mechanism of disturbed wave reflections and the resulting increased PP. Under physiological conditions, these reflection sites probably have a minimal impact. However, they may become prominent in various pathological situations, such as those created by aortic coarctation or traumatic amputation of the lower limbs or atherosclerotic alterations involving multiples sites. For instance, changes in the geometry of the aorta, in particular the accelerated age- and pressure-induced increase of their cross-sectional area (abdominal aneurysm) and the age-induced increase of their length (and hence tortuosities), may modify the amplitude and timing of wave reflections. Interestingly, these changes may differ markedly in men and women, and in women, they are largely influenced by the reduced length of the arterial tree and by hormonal factors, such as the loss of estrogen. Finally, the presence of calcified plaques, partic-
ularly at aortic, carotid, and femoral bifurcations and at the origin of renal arteries, may also produce reflection sites closer to the heart, thereby modifying wave reflections and increasing PP.

In summary, it appears that elastic arteries buffer the pulsations, muscular arteries actively alter propagation velocity, and arterioles serve as major reflection sites. Each of these alterations (or their combination) enables a cross-talk between the proximal and distal compartments of the arterial tree, which leads to the predominant or selective increases of SBP and PP observed in aged and/or hypertensive populations at high CV risk. In the presence of decreased ventricular ejection, these frequency-dependent factors disturb the heart-vessel coupling, increase the load of the heart, and favor cardiac hypertrophy, coronary ischemia, and ultimately CV death. It is now clear that future research should focus on a better localization of reflection sites. Modern imaging technologies, such as MRI of the entire vascular tree in living subjects, will play an important role in this future research. In addition, molecular imaging methodologies may give important new information on the in vivo contribution of the various components of the vessel wall to the propagation of the BP wave and on the discontinuities of the arterial wall as a function of the distance from the heart.

**Structural Features of the 2 Compartments of the Arterial Tree**

The basic architecture of arteries is usually described in terms of cross-sectional arrangement of cells and extracellular matrix. The latter consists, within the media, of lamellae of elastic material with intervening layers of vascular smooth muscle (VSM) cells, collagen fibers, and ground substance. However, the distribution of elastin and collagen varies markedly along the longitudinal aortic axis. In the proximal aorta, elastin is the dominant component, whereas in the distal aorta, the collagen-to-elastin ratio is reversed, and in peripheral arteries, collagen predominates. The transition occurs rapidly over the distal 5 cm of the thoracic aorta above the diaphragm and over a similar distance in the branches leaving the arch of the aorta. Thereafter, VSM cells largely predominate. Thus, it is anatomically justified to divide the arterial tree into 2 compartments, proximal and distal. During development, VSM cells of different embryonic origin clearly reflect the differences in anatomic locations. In the avian abdominal aorta and small muscular arteries, the smooth muscle cells are of mesodermal origin, whereas those of the aortic arch and thoracic aorta are mainly derived from the ectodermal cardiac neural crest. The participation of VSM cells of ectodermal origin is essential in the formation and organization of elastic laminae and tenso-receptors in the great vessels. These changes of VSM cells as a function of distance from the heart have been further confirmed by studies of the chemical properties and of gene expression of elastin and collagen along the aorta.

Theoretically, the characteristics and amounts of collagen are determined at a very young developmental stage and thereafter remain quite stable because of very low turnover. Nevertheless, the proportion of collagen type I and III differs markedly between the different species and has a substantially differential mechanical effect on stiffness and distensibility of the vessel wall. In addition, several neurohumoral factors, particularly those related to the angiotensin II and aldosterone systems, may modulate collagen accumulation. Collagen may also be subjected to important chemical modifications, such as breakdown, cross-linking, or glycation, resulting in marked changes in stiffness. Finally, in central conduit arteries, large amounts of collagen are observed in the adventitia, thus contributing to alter arterial mechanical properties. Collagen is principally responsible for the discontinuities of the vessel wall, mainly at the vessel bifurcations. It greatly modifies arterial rigidity and the transit of wave reflections, thereby increasing thoracic aorta PP. In turn, the increased cyclic stress causes fragmentation and fracture of elastin and calcifications, particularly in the elderly.

Extracellular matrix is responsible for the passive mechanical properties of the arteries, particularly in the aorta and its main branches. In a cylindrical vessel, when the transmural pressure rises, a curvilinear pressure-diameter curve ensues, theoretically caused by the recruitment of elastin at low pressure and of collagen fibers at high pressure. Nevertheless, other molecules, through their role in cell-cell and cell-matrix attachments, may contribute to the tridimensional repartition of mechanical forces within the arterial wall. An illustrative example is given by the role of the different connexin (Cx) isotypes along the aortic axis. In the rat, proximal elastic arteries, the main smooth muscle cell type, consist of desmin-negative cells with high levels of Cx43, whereas in small to medium muscular arteries, the main cell type is desmin-positive cells with low levels of Cx43. In mice lacking desmin, isotonic carotid stiffness is increased in association with enhanced vessel wall viscosity. In rat models, an increased sodium diet is associated with increased isotonic systemic stiffness and reduced aortic proteoglycans. On the other hand, chronic aldosterone excess produces increased isotonic carotid stiffness and arterial fibronectin, a process reversed by the aldosterone antagonist eplerenone.

Finally, VSM cells do not represent a homogenous population. For the same genomic background, they may have different mixtures of phenotypes, not only with contractile and synthetic but also with proliferative and apoptotic behavior. The relative occurrence of each of the phenotypes depends not only on age but also on location in the vascular tree and prevailing (pathological) conditions. Contractile properties, which are mainly expressed in the distal arterial compartment, are responsible for the active mechanical properties of conduit vessels. Changes in VSM tone may occur either directly or through signals arising from endothelial cells. The endothelium is a source of substances, particularly nitric oxide (NO), and of signal transduction mechanisms that necessarily influence the biophysical properties of conduit arteries. NO is the principal mediator, dilating larger arteries more than smaller arteries. Whereas the role of flow- and endothelium-dependent dilation is not restricted to a particular vessel category, the role of mediators arising from the endothelium predominates in muscular distal arteries. In such vessels, the site and the pattern of wave reflections are influenced by the local differential effects of NO and vaso-
constrictive (norepinephrine, angiotensin, endothelin) compounds.\textsuperscript{36} Research that relates arterial stiffness, the reflectance properties of the arterial system, and VSM tone is just emerging and may greatly contribute to influence our knowledge on the mechanisms of systolic hypertension. A combination of pharmacological, transgenic (selective activation or knockout of specific genes), and protein antibody approaches now provides powerful tools to unravel the molecular basis of the mechanical behavior of the proximal and distal compartments of the arterial tree.

**Arterial Stiffness, Cardiovascular Diseases, and Genomic Control**

Physiologically, MBP is almost the same throughout the arterial tree. However, there is a progressive increase of vessel stiffness from the proximal to the distal arterial compartment. This hemodynamic profile results from the combination of several factors: the continuous decrease of the vessel cross-sectional area along the various branching points of the arterial tree, the progressive increase in rigidity of vascular wall material (mainly the changes in elastin/collagen ratio), and the physiological rise in PP from central to peripheral arteries due to closer reflection sites. Because compliance and distensibility are larger in the proximal than in the distal compartment, a given reduction of distensibility between these 2 compartments may be observed. For instance, in humans, the stiffness gradient between the carotid and the radial artery approximates 25% in normal subjects of middle age.\textsuperscript{1,9,37} With age, this gradient is significantly decreased because of a reduction of compliance and distensibility in the central but not the peripheral arteries.\textsuperscript{1,9} This age-related increase in stiffness in central but not peripheral arteries is observed without change in MBP and reflects intrinsic alterations of the vessel wall of central arteries with age, involving enlargement of mean diameter with reduction of pulsatile diameter, huge development of the extracellular matrix of the vessel wall, and reduction of PP amplification.\textsuperscript{9} The latter relates to the more rapid increase with age of aortic than peripheral PP because of both the increased stiffness of the arterial wall and altered reflectance properties with age. Finally, as a consequence of the age-dependent enlargement of aortic diameter, proximal compliance is less reduced with age than proximal distensibility.

Ageing is the dominant process altering vascular stiffness, wave reflections, and PP. However, there is an extreme variability of these age-dependent changes from one population to another.\textsuperscript{39} This variability is highly influenced by the association of other CV diseases and concomitant risk factors. In subjects with hypertension, for instance, the mechanical factor represented by high BP contributes greatly to the stiffness changes observed in younger subjects, whereas the intrinsic alterations of the vascular wall play a more important role in older subjects.\textsuperscript{1,9} Increased isobaric stiffness of central arteries is a major underlying factor to consider in patients with diabetes and end-stage renal disease and in subjects with multiple atherosclerotic alterations.\textsuperscript{6,8,9,37} The stiffness changes are even more difficult to evaluate in other CV diseases, such as congestive heart failure or aortic dissection.\textsuperscript{39,40}

The genetic background of stiffness changes is now beginning to be considered as a potential factor of importance. However, this genetic background is not easy to analyze. First, the same genotype is expressed in each arterial compartment by potentially different phenotypes. The prominent secretory properties of VSM cells in the proximal compartment and prominent contractile properties in the distal compartment are an example of this. Second, different gene expression patterns, mainly those related to collagen and elastin connective tissue, may contribute to the differential mechanical behavior of the proximal and distal arteries. Third, the different gene expressions are possibly influenced by mechanical factors,\textsuperscript{30} particularly cyclic stress.\textsuperscript{41}

In humans, monogenic disorders such as Marfan disease\textsuperscript{42} now represent an important source of knowledge about the influence of single-gene effects on vascular stiffness. Furthermore, several recent studies have suggested that arterial mechanics are influenced by specific gene polymorphisms or combinations thereof. They may be divided into 2 categories: those related to the pathophysiology of high BP, such as the renin-angiotensin-aldosterone system, the endothelial NO synthase system, and the α-adducin systems;\textsuperscript{43–46} and those related to CV aging, particularly those related to elastin, collagen, and telomere length.\textsuperscript{47–49} However, results regarding the association of individual gene polymorphisms with arterial behavior are still controversial. Recent research suggests that combinations of 2 or 3 specific polymorphisms acting on the same BP control mechanism can affect vessel wall properties profoundly. The Figure presents a scheme of how 3 genetic variants in combination may exert a powerful effect on a single physiological mechanism, in this case the activity of the sodium-potassium pump.\textsuperscript{46} This combination of polymorphisms gives a strongly increased risk for hypertension and abnormal vascular mechanics.\textsuperscript{46} Again, the increased risk is observed in the central more than in the peripheral arterial compartment.

Such examples suggest that a dominant paradigm for future studies is to determine simultaneously the genetic and environmental factors that modulate the increase of PP, arterial stiffness, and wave reflections with age and therefore influence CV risk. Large populations should be investigated, with evaluations of the role of younger (children) and older people,
gender, body mass index, geographic repartitions, and associated CV diseases.

Conclusions
On the basis of the evidence discussed above, a more precise description of the arterial tree in relation to CV risk may be proposed. The proximal compartment (the aorta and its main branches) is characterized by low stiffness and is composed of VSM cells originating from the neural crest and involving prominent secretory properties (elastin and collagen). This compartment is highly sensitive to age and changes in BP. It differs substantially from the distal compartment, which is characterized by a higher stiffness. The distal compartment is the major source of wave reflections, and is mainly composed of VSM cells with contractile properties, which are highly sensitive to vasoactive substances, particularly those of endothelial origin. BP does not have simply a unique passive role, which is to maintain an open and flow-carrying arterial circuit. Indeed, the 2 compartments of the arterial tree are interconnected by an information system that consists of BP propagation, from which frequency-dependent mechanical signals arise independently of and in addition to conventional neurohumoral signals. This information system is based on arterial stiffness, wave reflections, and PP. Their message is related to CV survival and longevity. Genetic and environmental factors, themselves graduated from the central to the peripheral compartment, are both involved in the modulation of the increase in PP and arterial stiffness with age and in the magnitude of CV longevity. Novel therapeutic approaches available to reduce the increase in PP and arterial stiffness with age have been proposed recently and should be developed further.50 These approaches involve converting enzyme inhibitors in association with diuretic compounds, nitrate derivatives, agents acting on collagen cross-linking, spironolactone and vasopeptidase inhibitors. Therapeutic trials using such medications will be necessary to demonstrate an improvement in morbidity and mortality on the basis of influencing vascular stiffness and increased PP.

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References

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