Recent Advances on Large Arteries in Hypertension

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Abstract—The most classic hemodynamic concept explaining the increased mean arterial pressure in hypertension reflects an increased total peripheral resistance dynamically and an increased wall-to-lumen ratio to suppress smaller arteries. However, a more current consideration takes into account not only that steady component but also the pulsatile component of blood pressure, a point that importantly modifies the traditional hemodynamic definition. Whereas mean arterial pressure is almost constant along the arterial tree, the pulse pressure increases markedly from the more central to the peripheral arteries, indicating that in vivo each artery should be characterized according to its own blood pressure curve. This important concept implies major modifications in the methods used to investigate the relationships between mechanical factors and large artery structure and function. It therefore seems reasonable that in hypertension the large arteries should no longer be considered as passive conduits but rather in terms of their active behavioral response to the mechanical forces to which they are subjected. New investigational aspects in hypertension therefore now involve not only genetic, cellular, and molecular mechanisms but also transductional hemodynamic mechanisms reflecting changing patterns in the extracellular matrix that influence structural remodeling of the vessels. **(*Hypertension*. 1998;32:156-161.)**

Key Words: hemodynamics ■ transduction ■ arteries ■ vessels ■ vascular remodeling

Early studies concerned with the hemodynamics of hypertension concentrated on the regulation of cardiac output, fluid volumes, and vascular resistances.[1] These investigations indicated the importance of the vascular wall, including that of veins.[1–3] Freis[1] emphasized aortic stiffness, and Tarazi et al[4] suggested measuring this stiffness using the ratio of pulse pressure to stroke volume. However, more recent studies concerned with large arteries in hypertension have focused on 3 more recent observations. First, older subjects with isolated systolic hypertension differed from younger ones in having a higher total peripheral resistance,[5] but when they had the same MAP and total peripheral resistance, there was less systemic arterial compliance.[6] Second, the acute administration of the antihypertensive agent dihydralazine to hypertensive patients reduced MAP and brachial artery diameter. In contrast, the antihypertensive drug diltiazem, causing the same fall in MAP in these subjects, produced an increased brachial artery diameter. This important difference suggested active changes in smooth muscle tone in the conduit vessel wall.[7] Third, prolonged antihypertensive therapy affects various hypertensive conduit arteries differently, since stroke is more readily and effectively prevented than target organ events in other vascular territories, such as the coronary circulation (even at the same reduction in arterial pressure).[8]

The earlier investigations of large arteries were focused mainly on invasive pulsatile arterial hemodynamics.[9] Thus, the definitions of vascular impedance and wave reflection required more sophisticated mathematical approaches, and these studies were focused on patients with cardiac problems. However, in 1970, O'Rourke[10] applied the concept of PP transmission to patients with hypertension, and the relevance of this approach to the study of large arteries in hypertension and of antihypertensive drugs provided novel approaches to cardiovascular pharmacology and therapeutics.[11] Finally, the introduction of ultrasonic devices in recent years has been a major advance, since it permits a new and dynamic analysis of arterial compliance and distensibility in animals and humans in vivo.[12–14]

It is now appropriate to suggest that the concept of arterial stress should be introduced into the area of hemodynamics of hypertension. This aspect of arterial function is perhaps as important as increased vascular resistance. This review has two objectives: (1) to emphasize the importance of large arteries in our understanding of the epidemiology and management of clinical hypertension and (2) to demonstrate that knowledge of pulsatile arterial hemodynamics is a necessary means for better understanding the current aspects of molecular biology and genetics in hypertension.

Pulse Pressure and the Definition of Hypertension

Computer analyses have shown that the arterial pressure curve may be divided into two components: a steady component, the MAP, and a pulsatile component, the PP (which is the difference between the systolic and diastolic pressures).[15] Epidemiological studies have recently emphasized the relevance of this description. Whereas MAP is an independent cardiovascular risk factor for any cardiovascular disorder,

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Selected Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AT_1 = angiotensin type 1 receptor
MAP = mean arterial pressure
PP = pulse pressure
PWV = pulse wave velocity
SHR = spontaneously hypertensive rats
SHR-SP = stroke-prone SHR
WKY = Wistar-Kyoto rats

including those affecting the brain, heart, and kidney, the arterial PP provides an independent predictor of cardiovascular risk for the heart, particularly for the prediction of myocardial infarction.[16–19]

PP is a very complex parameter. Whereas MAP remains fairly constant throughout the length of the arterial tree, PP is much higher in the peripheral than in the central arteries because of a significant increase in systolic pressure and a small fall in diastolic pressure. The aortic pressure curve is considered to be the sum of an incident pressure wave that is propagated at a given velocity (PWV) along the arterial tree and a reflected wave which travels backward from the peripheral reflecting sites toward the ascending aorta and the heart. These incidents and reflected waves interact constantly along conduit vessels, the lumen diameter and compliance of which are gradually reduced from central to peripheral arteries. Consequently, each artery is characterized by its own pressure curve and associated with its own mechanical consequences. The brachial blood pressure curve is only one of the curves that describe the arterial pressure in the entire circulation.

The amplification of the PP in the upper limbs is greatly influenced by the duration of the ventricular ejection period and therefore by heart rate.[10] Thus, in conditions associated with tachycardia, an elevated brachial arterial pressure, particularly increased systolic pressure, overestimates pressure levels in the aorta and more central arteries. This pattern may be one of the major factors explaining the significance of borderline or white coat hypertension.

On the other hand, the PP gradient along the entire arterial tree tends to disappear with age, due to a greater increase in the aortic PP with age than in the peripheral PP.[15] This most likely is due to an early return of the backward pressure wave toward the heart in the elderly because of the increase in the velocity of the aortic pulse wave with age. As the reflected pressure wave returns during the systolic component of the arterial pressure curve in older persons, it amplifies the aortic systolic pressure; this factor increases the end-systolic stress and serves to promote the further development of ventricular hypertrophy. This mechanism also helps to alter the elastic recoil of the aorta and to decrease the diastolic pressure, thus tending to impair coronary perfusion. These are some important reasons why increased PP (due to an increased systolic pressure and a decreased diastolic pressure) can be a strong predictor for coronary heart disease and myocardial infarction. For the same reasons, some trials of antihypertensive drugs were not as effective in demonstrating reduction of morbidity and mortality of coronary heart disease as for stroke[8,20]; the criterion of entry into such therapeutic trials was primarily diastolic pressure, and the populations studied did not include hypertensive patients with the major coronary risks (ie, those with increased systolic and low diastolic pressures[20]). This important hemodynamic point was emphasized by the Systolic Hypertension in the Elderly study, in which isolated systolic hypertension was the only criterion of entry, and drug treatment resulted in significant reductions in coronary events.[21]

Finally, these aspects of PP amplification show the need to encourage the use of new mechanical tools for describing cardiovascular risk in epidemiology. Not only must the heights of systolic, diastolic, and mean arterial pressures be considered, but also several additional parameters describing the arterial wall mechanics (eg, aortic PP, PP amplification, PWV, incremental elastic modulus, and the timing of wave reflections). Similarly, it will be important for us to include the major features of PP amplification in any future guidelines for the clinical management of hypertension.

Indices of Arterial Stiffness

Ultrasound Techniques

Ultrasound measurements have resulted in the development of dynamic indices of arterial stiffness in recent years.[22,23] This method has provided information that is very different from the static indices that are obtained by in vitro studies of arterial segments.[23] However, little has been done to differentiate between the relevance of static and dynamic pressure-diameter relationships of large conduit vessels.

Using in vivo carotid artery preparations of normotensive WKY and SHR,[24] the static hypertensive pressure-diameter curve is shifted toward higher values of diameter, indicating that arteries from normotensive and hypertensive animals differ in their structure and/or smooth muscle tone. However, at any given transmural pressure, the vessels can be stressed by applying a sinusoidal mechanical signal and measuring the change in diameter, thus leading to a dynamic pressure-diameter curve. One major characteristic of the dynamic curves is that their slope is always lower than that of the corresponding static curve.[24] Bergel[25] found this to be so for various arterial segments in vitro. This finding is not surprising, since the wall of any viscoelastic material, whether of physical or biological origin, has less time to reach its maximum potential strain when the stress is sinusoidal than it does in static tests. Thus, the ratio between the static and dynamic compliances provides a useful index of the viscosity of the arterial wall.

The frequency dependence of dynamic compliance has been recognized recently in vivo in normotensive rats. Atrial pacing has been used to show that the frequency dependence predominates on the elastic carotid artery, but it cannot be observed on the muscular femoral artery.[26] Finally, a clinical application of interest was obtained in a study on large populations of normotensive and hypertensive subjects in which there was a significant statistical association between reduced carotid distention (or increase in PWV) and high heart rate.[27] Because tachycardia is a strong predictor of cardiovascular mortality,[28] the statistical association between

increased arterial stiffness and increased heart rate provides an interesting link between cardiac rhythm, cardiovascular risk, and alterations in conducting vessels.

Measurements of PWV

Because the ultrasound techniques used to evaluate arterial stiffness take a long time to perform, a great deal of work has been done on PWV measurements in the territories of the aorta and the upper and lower limbs in which computerized automatic procedures provide an adequate reproducibility.[29] PWV is strongly influenced by age and arterial pressure, particularly in the aorta. Thus, statistical adjustments are needed for its interpretation. According to the Moens-Korteweg equation, PWV is influenced by 2 factors, the vascular geometry and the viscoelastic properties of the wall material, that act independently of age and blood pressure.[15]

Cross-sectional studies have shown that changes in PWV point to arterial changes independent of age and arterial pressure in several circumstances. First, patients with end-stage renal disease have higher PWV (aorta, upper and lower limbs) than gender-matched control subjects of the same age and arterial pressure.[30] Second, the polymorphism of the AT_1 receptor gene for angiotensin II was associated with significantly higher values of aortic PWV in hypertensive patients having the *cc* allele than in patients (with the same arterial pressure) having the *aa* and *ac* alleles.[31] Third, PWV may be increased in hypertensive patients with normalized arterial pressure receiving chronic antihypertensive drug therapy.[32]

Longitudinal studies have shown that PWV is poorly influenced by arterial pressure reduction in the arms and legs.[22] However, changes in aortic PWV are much more influenced by arterial pressure, even though they may be partly independent. This has been shown during pregnancy[33] or after the administration of certain pharmacological agents.[22] Finally, the major finding supporting the clinical relevance of arterial stiffness is the recent demonstration that in patients with end-stage renal disease, carotid elastic modulus was an independent predictor of cardiovascular mortality, a point clearly shown during this workshop.[34]

Accumulation of Aortic Collagen and Arterial Stiffness

The major structural change in the artery wall associated with increased arterial stiffness relates to increased collagen content. Because collagen turnover is slow, it is difficult to determine the contribution of collagen changes to the viscoelastic properties of the hypertensive arterial wall in vivo. Preventive (but not therapeutic) protocols have been developed recently in hypertensive rats[35] that may permit assessment of the relationships between the aortic wall collagen content, increased sodium intake, and the role of the renin-angiotensin system.

Increased sodium intake leads to ventricular and aortic hypertrophy in genetic hypertension in rats and to further development of extracellular matrix.[36–38] Although changes in arterial structures are associated with an increase in blood pressure in Dahl salt-sensitive rats,[39] there was no substantial change in intra-arterial blood pressure in the cases of SHR-SP or stroke-resistant SHR.[36–38] Moreover, excess dietary sodium intake in both the hypertensive and normotensive rats was associated with increased left ventricular mass without an increase in pressure.[37] A reduced sodium intake or administration of diuretics such as indapamide, chlorothiazide, or even spironolactone[40–42] reversed vascular hypertrophy and collagen accumulation in SHR and in SHR-SP in the absence of substantial changes in blood pressure. Determinations of nonmuscular myosin and EA III fibronectin in SHR-SP rats showed that increased sodium intake was associated with a loss of the contractile phenotype of vascular smooth muscle, independent of arterial pressure changes.[40] Investigations of pulsatile arterial hemodynamics in SHR and SHR-SP (under high sodium diet) suggest that the isobaric distensibility was identical in the 2 strains, whereas there was less vessel hypertrophy and collagen accumulation in SHR, suggesting that these rats had a stiffer wall material.[38] There was a parallel occurrence between the incidence of cerebrovascular accidents and the degree of sodium intake in SHR-SP, although blood pressure remains unchanged and the stiffness of wall material under high sodium diet is reduced in comparison with SHR.[38,40,41] These findings suggest that a reduced stiffness of the vascular wall material, possibly of genetic origin (but influenced by increased sodium intake), played a role in the incidence of strokes in SHR-SP independent of blood pressure.

Chronic inhibition of ACE decreased the accumulation of aortic collagen in SHR independently of any change in blood pressure.[35] This is not influenced by bradykinin blockade and is paralleled by a decrease in ACE in the vascular wall but not in the plasma. Studies on cultures of vascular smooth muscle cells have indicated that angiotensin II stimulates collagen synthesis.[43] In vivo studies using selective blockade of AT_1 receptors in SHR clearly indicate that the accumulation of collagen in the aorta is influenced by the blockade of this receptor.[44] We noted earlier that aortic PWV is critically increased in hypertensive patients having the *cc* allele of the AT_1 receptor gene for angiotensin II.[31] Inhibition of ACE not only decreased arterial pressure in these hypertensive patients but also markedly and selectively decreased aortic PWV.[45] Much work remains to determine the links between arterial stiffness, accumulation of aortic or ventricular collagen, sensitivity to sodium, and activation of the renin-angiotensin system.

Endothelium, Arterial Remodeling, and Laplace Law

Many studies carried out on hypertensive rats and humans have demonstrated abnormalities in resistance vessel structure associated with an increased reduction in media-to-lumen ratio.[46] Although these findings have been of great interest, the measurement methods suffer from several limitations.[47] A wire myograph generally has been used to study small arteries, and some of the conditions determined by this device are artificial, since the endothelial surface is exposed to the wire pressure and the vessel geometry is altered. The vessel shortens, so measurements of the media cross-sectional area may not reflect the values before experimental dissection. In contrast, large conduit arteries have several methodological advantages over small arteries for hypertension

studies.[22] First, operation blood pressure can be determined in vivo at the exact site where the arterial vessel is studied. Second, the viscoelastic properties of the arterial wall may be evaluated transcutaneously by ultrasound techniques under conditions of physiological blood flow, shear stress, smooth muscle tone, and endothelial function. Third, the arterial intima-media thickness may also be measured in vivo in hypertensive humans,[48,49] allowing calculation of circumferential wall stress and incremental elastic modulus. Finally, interactions between shear stress, circumferential stress, and arterial remodeling may be extensively studied in vivo.

Arteries are capable of structural and functional changes in response to alterations within their milieu or to changes in hemodynamic variables. Vascular remodeling may be considered as an adaptive process in response to long-lasting changes in arterial blood flow and/or pressure, whose ultimate effect tends to be maintenance of the constancy of tensile and/or shear stresses. The changes in shear and tensile stresses are interrelated, since any change in arterial radius produced by alterations in blood flow and shear stress induces changes in tensile stress (unless the pressure varies in the opposite direction). The geometric characteristics of vessel remodeling depend in large part on the type of hemodynamic stimuli applied to the vessel, as well as on the presence of intact endothelium. Experimental and clinical data indicate that acute and chronic augmentation in arterial blood flow induces proportional increase in the luminal area of the vessel, whereas the decrease in flow reduces arterial diameter.[50] The most classic example of flow-mediated remodeling includes arterial dilation associated with sustained high blood flow after creation of arteriovenous fistula.[51] Increase in arterial diameter is usually accompanied by an increase in tensile stress, one of the major determinants of vascular geometry and structure.

In hypertension, the effects of tensile stress are mediated by two mechanisms: an increase in intra-arterial pressure and a distention on the arterial diameter. According to the Laplace theorem, where wall stress is proportional to radius (R) and intra-arterial pressure (P) and inversely proportional to wall thickness, arterial wall hypertrophy serves as a compensatory mechanism to the increase of the PR product. Clinical and experimental studies in hypertensive animals and humans have shown that this purely mechanical aspect of the law of Laplace is not observed in vivo in the sense that there is little (central arteries) or no (peripheral arteries) increase in diameter, thereby causing a decreased wall-to-lumen ratio.[22,46–51] Because hypertensive large arteries are hypertrophied and the external tension is higher than the internal, this could prevent an increased arterial diameter. Another possibility is that altered endothelial function may keep arterial diameter constant through changes in shear stress and/or release of vasoactive compounds. An example of this possibility is given in the early phase of development in SHR, during which a transient increase in cardiac output and carotid blood flow has been reported.[52,53] Because there is no parallel increase in diameter of the carotid artery during this phase, and because this alteration occurs despite the increase in blood pressure, it has been suggested that the transient change in flow might prevent the pressure-induced increase in diameter through the mechanism of flow dilation (or constriction).[52] Finally, this mechanism has two characteristics: (1) it might help to maintain wall tension with a smaller hypertrophy than expected from the effect of purely mechanical factors and (2) it requires the presence of an intact endothelium.[52]

Experimental studies have demonstrated that endothelium plays an important and active role both in vascular remodeling and in the control of the viscous and elastic properties of the arterial wall.[54,55] Studying the effect of endothelium removal on carotid arterial compliance, Levy and collaborators[54,56] have shown that stripping the endothelial layer induces an increase in compliance and diameter. This suggests that endothelial cells act on the wall of arteries to keep the compliance within a given required level. While it has been shown repeatedly that decreased compliance has a negative impact on the left ventricular function and coronary perfusion, the abnormal increase in capacitive properties of the arterial system could in theory also produce negative effects on cardiovascular function. Under normal conditions, only 40% to 50% of blood ejected from the left ventricle is stored in capacitive arteries during the systolic interval. An abnormal increase in compliance could be responsible for an exaggerated arterial blood pooling during systole. This would produce alterations in PP transmission with decreased PWV and lengthening of the transmission of pressure head to peripheral circulation. Under this condition, the displacement of the blood column in the arterial tree would be more dependent on a direct "pushing" effect of stroke volume, abnormally increasing the inertial component of cardiac workload. On the other hand, Boutouyrie et al[55] have shown that destruction of endothelial layer is responsible for a huge increase in the viscosity of arterial wall, increasing the hysteresis of the arterial pressure-diameter relationship. This finding has two theoretical consequences: (1) to increase the capacity for blood pooling during the diastolic interval, thus altering the arterial recoil and diastolic runoff, and (2) to increase the dissipation of energy transmitted by the heart in an inefficient way. Finally, the combined effects of endothelial dysfunction and altered viscoelastic properties of arteries are to increase arterial blood volume during all phases of cardiac cycle, to increase the inertial component of afterload, and finally to increase the total cardiac workload.

In the past, endothelium was considered mainly as an interface between blood flow and vascular smooth muscle. We must now consider that the endothelium plays an active role as an interface between pulsatile blood pressure and diameter. In short-term situations, the increase in diameter after endothelium denudation clearly shows that vasoconstrictive compounds of endothelial origin are involved.[54] Such compounds remain as yet unidentified, although they are not inhibited by indomethacin.[56] In long-term situations, endothelium-induced structural change is a relevant possibility, since endothelial denudation is associated with a higher increase in wall thickness in younger rats with genetic hypertension than in controls, a process that is not observed in older rats.[57] In the case of large arteries in hypertension, it is difficult to determine the relative contribution of growth and antigrowth factors of endothelial or smooth muscle origin in

the mechanism of the Laplace law equilibrium. In parallel, we still need to know whether these alterations of conduit arteries are the initial events of future hypertensive complications.

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