Role of Pulse Pressure Amplification in Arterial Hypertension: Experts' Opinion and Review of the Data

Alberto P. Avolio, Luc M. Van Bortel, Pierre Boutouyrie, John R. Cockcroft, Carmel M. McEniery, Athanase D. Protogerou, Mary J. Roman, Michel E. Safar, Patrick Segers and Harold Smulyan

Hypertension 2009;54;375-383; originally published online Jun 29, 2009;
DOI: 10.1161/HYPERTENSIONAHA.109.134379
Hypertension is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0194-911X. Online ISSN: 1524-4563

Role of Pulse Pressure Amplification in Arterial Hypertension

Experts' Opinion and Review of the Data

Alberto P. Avolio, Luc M. Van Bortel, Pierre Boutouyrie, John R. Cockcroft, Carmel M. McEniery, Athanase D. Protogerou, Mary J. Roman, Michel E. Safar, Patrick Segers, Harold Smulyan

Arterial hypertension is a major modifiable cardiovascular (CV) risk factor worldwide based on observational studies of brachial artery blood pressure (BP). In the latest guidelines of the European Society of Hypertension[1] for the management of arterial hypertension, aortic stiffness was introduced as an index of target organ damage. Three additional cardinal features of BP were also acknowledged: (1) systolic BP and pulse pressure (PP) may differ between the brachial artery and central arteries (ie, the aorta and its proximal branches), (2) the effects of antihypertensive drug treatment on brachial BP does not invariably reflect those seen on central BP, and (3) central BP is significantly related to CV events. Moreover, the guidelines acknowledged that noninvasive methods exist for the assessment of central hemodynamic parameters, such as central PP, and highlighted the need for large scale interventional studies that will further confirm the prognostic importance of central BP.

Two years ago, coincident with the 6th International Workshop on the "Structure and Function of the Vascular System," in Paris, a consensus document on the role of central BP in arterial hypertension was published.[2] It concluded that there is "mounting evidence suggesting that central BP and indices correlate more closely with intermediate markers of CV risk than brachial BP". It was also suggested that clinicians and researchers need to become familiarized with the disparity between peripheral and central BPs, ie, the phenomenon of pressure wave amplification. The present document is designed to address this need.

Pulse Wave Amplification: Basic Definitions

The left ventricle consumes energy by ejecting blood into the arterial system, thereby creating arterial blood flow and pressure. This phenomenon is easily conceived as a propagating pulse along the arterial bed. In daily clinical practice the arterial pulse, at a distinct site of the arterial tree (eg, at the brachial artery), is quantified as the variation in BP, ie, the systolic and diastolic BP. The most obvious feature of BP in the arterial system, generally neglected for decades in both clinical practice and research, is that it is a periodically oscillating wave (pulse wave [PW]) which travels from the heart toward the peripheral arteries.

The properties of the pressure PW can be readily understood when compared to a well-known wave, eg, the acoustic wave. As such, the pressure PW: (1) can be reflected and amplified, (2) has amplitude and frequency, and (3) these parameters can be analyzed in time (time-domain analysis, Figure 1a) and as sinusoidal harmonic components[3] (frequency-domain analysis, Figure 1b), both approach providing analogous results.[4]

Reflections of the forward propagating pressure PW occur at multiple sites of the arterial bed because of changes in arterial properties (eg, elasticity/stiffness gradient and vasomotor tone) or in the architecture of the arterial tree (eg, branching points, calcifications). The "reflection site" is more of a statistical notion than a physically discrete site at which reflection occurs. In the recordings of the pressure PW, the multiple reflected waves are integrated as a single combined reflected wave, which sums with the forward ejected wave and thus forms the final pattern of the pressure PW (Figures 1a and 2).

The fundamental frequency (ω) of the pressure PW corresponds to the periodicity of the ejecting source, ie, to the heart rate (Figure 1a). At distinct sites of the arterial bed, the amplitude of the pressure PW corresponds to the difference between the nadir (end diastolic BP) and the zenith (peak systolic BP), ie, to the PP (Figure 1a). The augmentation pressure (AP) corresponds to that part of the PP which is attributed to the summation of the reflected wave. The augmenting effect of the reflected pressure wave is conventionally provided by the ratio of the AP over the PP, defined

Received April 10, 2009; first decision April 29, 2009; revision accepted June 4, 2009.

From the Australian School of Advanced Medicine (A.A.), Macquarie University, Sydney; Heymans Institute of Pharmacology (L.V.B.) and Biofluid, Tissue and Solid Mechanics for Medical Applications (bioMMeda) Institute, Biomedical Technology (P.S.), Ghent University, Belgium; Université Paris Descartes, Assistance Publique-Hôpitaux de Paris, HEGP, Service de Pharmacologie (P.B.), and Hotel-Dieu Centre de Diagnostic et de Thérapeutique (M.E.S.), Paris, France; Wales Heart Research Institute (J.R.C.), Cardiff University, UK; Clinical Pharmacology Unit (C.M.E.), University of Cambridge, UK; Hypertension Center, 3rd Department of Medicine (A.P.), National and Kapodistrian University of Athens, Greece; Weill Cornell Medical College (M.J.R.), New York, USA; and State University of New York, Upstate Medical University (H.S.), Syracuse, USA.

Correspondence to A. Protogerou, MD, Hypertension Center, 3rd University Department of Medicine, 152, Mesogeion Ave, Athens 115 27, Greece. E-mail aprotog@med.uoa.gr

(*Hypertension*. 2009;54:375-383.)

Hypertension is available at http://hyper.ahajournals.org DOI: 10.1161/HYPERTENSIONAHA.109.134379

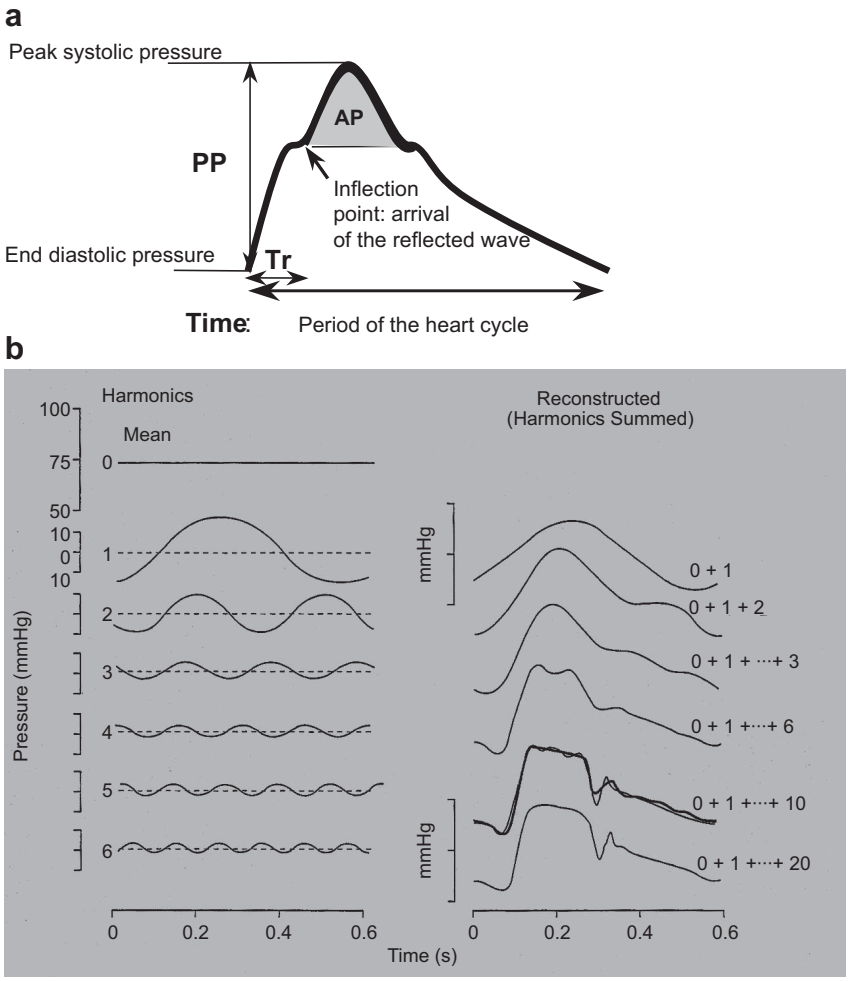

Figure 1. a, Pulse pressure wave at the aorta analyzed in time (time-domain analysis). The amplitude of the pressure wave corresponds to the pulse pressure (PP) and the fundamental frequency to the ratio: 1/period (sec) of the heart cycle. Tr indicates the time (sec) between the onset of the distally traveling (forward ejected) wave and the arrival of the proximally traveling (backward reflected) wave; AP (augmentation pressure, grey color), the increase of the pulse pressure wave due to the reflected wave. b, Pressure pulse wave (PW) at the ascending dog aorta analyzed in terms of sinusoidal harmonic components (frequency domain analysis). Left, The first 6 harmonics are presented. Right, Reconstruction of the pulse PW.

as the dimensionless augmentation index (AI). This quantification procedure is carried out by PW analysis (PWA) techniques and requires the identification of the inflection point (point of return of the reflected wave, Figure 1a). Ideally, the identification of the inflection point requires both flow and pressure measurement, as performed in wave separation[5] or wave intensity analysis.[6] The most widely used techniques of PWA use only pressure data and thus provide only approximations of the inflection point.[5]

The amplification of the pressure PW in the large elastic and smaller conduit arteries is associated with changes in the magnitude (amplitude) of each harmonic component of the wave. However, it can be conventionally understood in clinical practice as an increase in the whole amplitude of the pulse pressure as it travels distally, ie, a "gradual widening" of the PP between two sites of the arterial bed (eg, aorta and brachial artery, Figure 2). Amplification of PP with distance (spatial amplification) does not require additional energy input in the arterial system, and so, by definition, is more a distortion than true amplification, translated in an alteration in the morphology of the waveform. Mean BP remains almost unchanged (or slightly decreases because of viscous dissipation) between the two sites, reflecting the absence of any physiologically meaningful peripheral arterial resistance at the level of the large and middle sized conduit arteries.

The amplification (A) of the PW can be quantified as the ratio of the amplitude of the PP between a proximal (PP_1) and a distal (PP_2) location: $A = PP_2/PP_1$.

Assessment and Expression of Pulse Pressure Amplification in Research and Clinical Practice

The assessment of PP amplification is based on the sequential, or ideally simultaneous, assessment of both peripheral and central BP. This need arises primarily because: (1) PP amplification is highly variable within[7] and between subjects,[8] and (2) the applied linear regression models for the prediction of PP amplification explain less than 70% of the variability.[8,9]

The reference standard remains the invasive recording of both peripheral and central BP to detect the actual magnitude of amplification. However, this has obvious limitations and is not applicable to routine clinical practice. Noninvasive assessment of central BP has become widely available and officially recognized in recent years.[1] Although the available techniques have limitations,[10] it has been accepted that they may provide further complementary data to peripheral BP, regarding the management of arterial hypertension and CV risk.[1,2]

Two methods exist for noninvasive central BP assessment. The first method uses a radial-to-aorta mathematical trans-

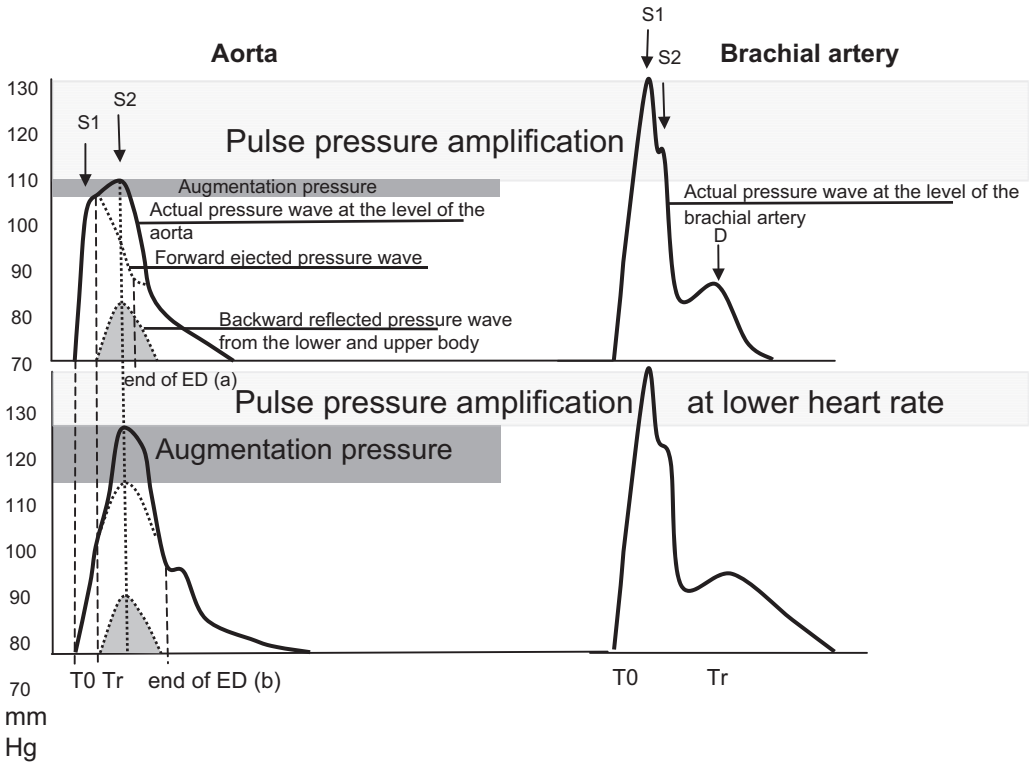

Figure 2. Schematic representation of: (1) the morphological differences of the pulse wave (PW) between the aorta and the brachial artery in young healthy subjects (upper panel) and (2) the effect of heart rate (upper panel versus lower panel) on systolic blood pressure (SBP) augmentation and PW amplification, for the same reflected pressure wave and similar pulse height of the forward ejected pressure wave (modified from Safar et al[74]). Aortic S1 indicates 1st systolic peak attributed to the forward wave; Aortic S2, 2nd late systolic peak attributable to the augmentation by the reflected pressure wave; brachial S2, systolic peak attributable to the reflected wave from the upper limb; D, accentuated diastolic wave attributable to the delayed arrival of the reflected wave from the lower body; ED, ejection duration; T0, onset of the forward ejected wave; Tr, time to return at the aorta of the backward reflected wave from the T0.

formation (generalized transfer function: GTF) of the pressure waveform, which has been derived and validated during invasive monitoring using frequency[11] or time[12] domain analyses. The GTF has been repeatedly tested and found reproducible in healthy[13,14] and in diseased[15,16] subjects, and after exercise.[17] Yet, debate continues as to whether the population-based radial-to-aorta GTF is valid in all patients and conditions. This 2-step method requires: (1) recording of the radial PW by applanation tonometry, and (2) its calibration by diastolic and mean or diastolic and systolic BPs. The GTF yields accurate results when invasive peripheral BP is used[18] for the calibration of the radial PW, even during physical exercise.[19] However, the major problem of this technique is that noninvasive BP recordings in the upper limb (usually the brachial artery) are used to calibrate the radial PW.[20] The output error (at the aorta) is associated with the input errors at the radial artery attributable to: (1) the under- or overestimation of actual (intraarterial) systolic and diastolic pressures, depending on which noninvasive method is applied,[21] and (2) the presence of brachial-to-radial pressure amplification.[22] Moreover, this output error may be magnified by the GTF in the setting of slower heart rates and higher BPs.[23] As a consequence, the assessed central PP is usually underestimated.[20,22,24,25]

The second method assesses systolic BP in the common carotid artery as a surrogate for the pressure in the ascending aorta. Because of the amplification phenomenon, the systolic BP is ≈2 mm Hg higher at the carotid artery than in the aorta.[26] This method is based on the observation that the mean and diastolic BPs, as well as the difference between them, are almost constant in the elastic/conduit arteries.[27,28] The carotid pressure PW is obtained directly at the common carotid artery (usually by applanation tonometry) and is calibrated by the noninvasively measured mean and diastolic BP. Diastolic BP can be obtained directly from readings at the brachial artery. Mean BP is optimally obtained by the integration of the brachial artery pressure curve after calibrating them with the brachial systolic and diastolic BP. If the radial pressure waveform is used, an additional error is introduced because of the presence of the brachial/radial systolic amplification.[22] If no brachial or radial pressure curves are available, the mean BP can be estimated as $MAP=DBP+0.4\times PP$.[29] Alternatively, the mean BP derived directly from automatic oscillometric devices seems to correlate well with mean aortic BP.[21] This second method negates the need for a GTF. However, because of anatomic reasons, reproducible PW recordings are more difficult to obtain at the carotid rather than radial site. If brachial or carotid artery PWs are not available, one alternative may be to obtain distension waves by echo-tracking, at least up to a pulse pressure of 70 mm Hg.[26]

Recently, it has been proposed that the second systolic peak on the radial PW curve correlates well with aortic systolic BP.[30] However, the application of this principle needs further validation.

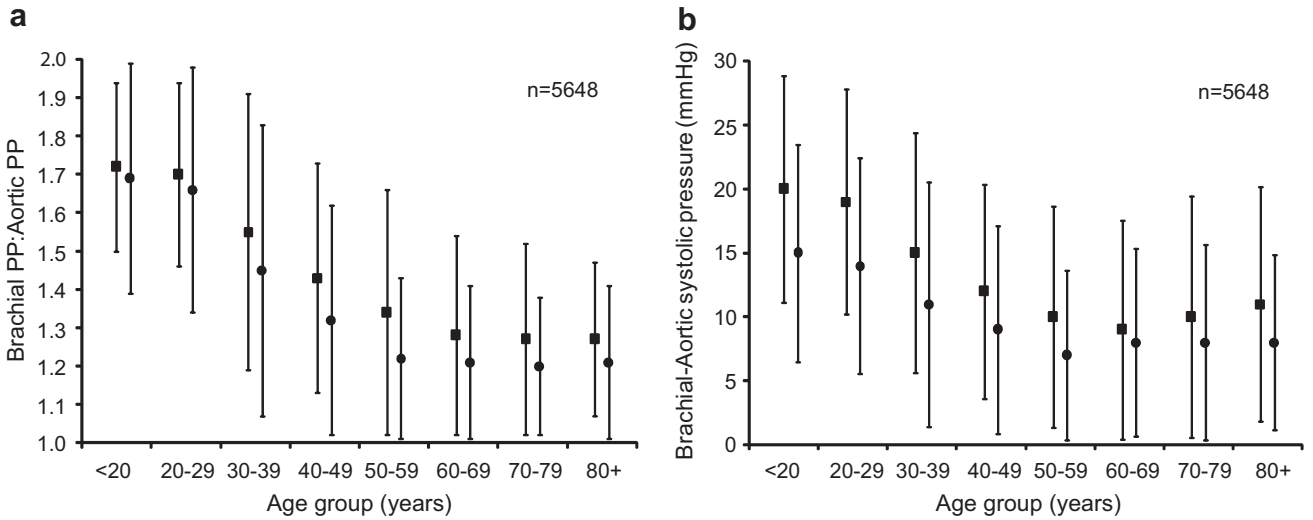

Figure 3. Data on healthy subjects from the Anglo-Cardiff Collaborate Trail II. Pulse pressure amplification values expressed according to age (10 years of strata) as: (1) the ratio of brachial/aortic pulse pressure, and (2) as the absolute difference brachial – aortic pulse pressure (mm Hg), in healthy subjects. Aortic blood pressure was measured by the SphygmoCor device by the application of a generalized transfer function and by calibration of radial pressure waveform by brachial systolic and diastolic blood pressure, obtained by a validated oscillometric device (HEM-705CP, Omron Corporation). ● for women (n=2869), ■ for men (n=2779). The data represent means ±2 SD (modified from McEniery et al[8]).

Limited evidence is available regarding the normal values for PP amplification between the aorta and the arteries of the arm. Population-based data from the Anglo-Cardiff Collaborative Trial (ACCT),[8] derived by the application of the GTF and by calibration of the radial PW by the brachial systolic and diastolic BP, obtained by a validated oscillometric device, suggest that the PP amplification values, expressed as the ratio of brachial/aortic PP, vary from 1.7 at less than 20 years of age to 1.2 at more than 80 years of age (Figure 3a). When expressed as the absolute change in mm Hg (brachial – aortic systolic AP) the amplification varies from: 20 mm Hg to 7 mm Hg (Figure 3b). Whether the relative and absolute expression of amplification have similar clinical relevance remains to be investigated. The absolute expression of amplification in mm Hg provides a more comprehensive approach of the phenomenon in terms of clinical practice; however, it might be modulated more by the level of BP.

The values of PP amplification provided by the ACCT[8] may be potentially overestimated because of the applied methodology. Lower values are reported in the Asklepios Study,[31] in which the method proposed by Kelly and Fitchett[27] was applied. Clearly, despite its demonstrated relevance for population studies, the calibration procedure still needs to be improved for individual subjects.

Morphology and Physiology of the Pressure Pulse Wave Amplification in the Upper Limb

The widening of PP between the central and peripheral arteries was originally described in invasive studies,[3,32,33] in both healthy volunteers and patients undergoing diagnostic catheterizations. These invasive recordings established the qualitative morphological differences of PW between the central and the peripheral arteries in young healthy subjects (Figure 2). It was also suggested that the modification of the pressure waveform was, in part, associated with the arrival of the reflected wave at the various sites of the arterial bed.[33] In addition, the clear disparity in the height of the PP as the wave traveled from the central aorta to the periphery was noted, because of the gradual increase of systolic BP.

The phenomenon of amplification of the PW is not restricted to the central arteries and the arteries of the upper limb (brachial, radial). It is observed between any two, more or less remote, conduit arteries in the systemic circulation. In the field of arterial hypertension, the amplification of pressure between the central arteries (to which the major organs are exposed) and the upper limb (where the BP is conventionally measured) is of great interest and has been extensively investigated. The data presented below apply to this segment of the arterial bed and should be extrapolated to other segments of the arterial bed cautiously. Moreover, the technical limitations of noninvasive measurements may limit interpretation.

The properties of each periodically oscillating wave are determined by the characteristics of (1) the generating source, (2) the means of travel, and (3) peripheral resistance. Therefore, in theory, the characteristics of the pressure PW are attributable to left ventricular contractility and chronotropy, properties of the large (diameter, length, wall visco-elasticticity) and small (peripheral resistance, remodeling) arteries, and the blood (viscosity). Because viscosity remains constant, it is of limited importance in variations in PP amplification.

Cross-sectional observational data in healthy subjects from the ACCT[34,35] and the Asklepios Study,[31] as well as data in subjects with hypertension[36] and metabolic syndrome,[37] have provided supportive evidence of the foregoing hypotheses. Amplification of the central-to-brachial PP is inversely related to: (1) large artery stiffness, as assessed by carotid-femoral pulse wave velocity (PWV) or total arterial compliance, (2) peripheral arterial resistance, and (3) characteristics of the reflected waves, such as the AI, the time to reflection

(Tr; Figure 2), and the reflection coefficient (an index which provides a measure of the magnitude of reflection at a distinct site). The role of aortic geometry is still investigated.[38] Interventional studies in subjects undergoing atrial pacing during cardiac catheterization,[39,40] as well as observational studies in healthy subjects[31,35] and those with hypertension[36] and metabolic syndrome,[37] showed that the higher heart rate is associated with higher PP amplification.

The mechanism by which these parameters affect the PP amplification is largely related to the "timing–synchronization" of the forward and reflected waves. Theoretically, for the same amplitude of the forward and reflected wave, a prolongation of the cardiac ejection phase attributable to slower heart rate is associated with higher augmentation of the peak systolic BP (Figure 2). This is attributed to earlier "timing" of the two waves within the systolic phase of the ejected wave. For example, for a given brachial systolic BP of 130 mm Hg, aortic systolic BP may increase from 110 to 120 mm Hg, depending on heart rate, and the PP amplification may decrease from 20 to 10 mm Hg (Figure 2). Of note, the "timing" – arrival time of the reflected wave (Tr) depends also on the PWV (thus arterial stiffness) and the distance covered by the reflected wave. In this respect another important modulator of the PP amplification is the "arterial length," ie, the actual distance between the heart and peripheral arteries, largely determined by height. This explains the lower amplification in shorter persons.

The relative contribution of each of the aforementioned parameters is extremely difficult to delineate in clinical practice and in experimental models, because these factors are closely interrelated. The AI measured in the aorta[31,41] or the radial artery[42] seems to be the factor most closely associated with PP amplification. This may be because this index synthesizes the combined impact of arterial stiffness, forward ejected wave from the left ventricle, reflected wave magnitude, heart rate, and timing of the waves. Even so, all the above parameters explain less than half of the variability of PP amplification,[31] and further investigation of the phenomenon is needed.

Nonmodifiable and Modifiable Factors Determining Pressure Pulse Wave Amplification

Aging is the main nonmodifiable factor associated with decreased PP amplification, as shown by cross sectional data from healthy subjects (Figure 3).[31,34,35] This is associated with the fact that "normal vascular aging" is the main modulator of large artery stiffening and increased wave reflections, although not in an age-dependent linear manner.[35]

Gender is the second important nonmodifiable determinant. Females exhibit lower PP amplification than males[8,31,35] (Figure 3). This observation is in line with the following: (1) females have higher AI, (2) height is consistently and positively associated with PP amplification, and (3) height is consistently and inversely associated with aortic AI. These observations may be explained only partly by delayed timing of the reflected wave in diastole, due to greater distance from the "major" site of reflections (effective reflecting distance) in males; other gender-related factors may play important roles as well.[43]

Accumulating evidence from cross-sectional studies suggests that subjects with traditional CV risk factors, such as hypertension,[8] diabetes mellitus,[8] hypercholesterolemia,[8,44] smoking,[8,45] or established CV disease[8] have lower PP amplification, which is independent of age, gender, height, and heart rate. Aside from physical alterations in the arterial wall attributable to these CV risk factors, an acute increase in mean BP may increase arterial stiffness and pressure wave reflections, thus leading to acutely reduced amplification. Indeed, there is an inverse relationship between mean BP and PP amplification in untreated hypertensive subjects,[31,35,37] although this relationship may be altered in treated hypertensive subjects.[41]

Hypertensive subjects with concomitant obesity and metabolic syndrome have exaggerated PP amplification.[37,46] However, these results are mainly driven by the presence of higher heart rates and blunted pressure wave reflections in such patients.

Together with heart rate, the nonmodifiable factors (aging and gender) appear to be more important predictors of PP amplification than traditional modifiable CV risk factors (hypertension, diabetes, smoking, hypercholesterolemia).[8] These data must be verified by longitudinal studies.

Clinical Implications of Pulse Pressure Amplification

There is now mounting evidence from cross-sectional and longitudinal, as well as invasive and noninvasive studies, that central, more than peripheral, BP is associated with target organ damage and potentially with CV risk.[2,47–52]

Indeed, for a given mean BP, lower PP amplification might be associated with unfavorable hemodynamic effects for the central arteries and the heart. For example (Figure 2), for a given brachial PP of 60 mm Hg, a subject with lower PP amplification is subjected to higher left ventricular afterload because of higher central PP.

Confirmatory evidence has been provided by prospective studies. In subjects with end-stage renal disease, low PP amplification, but not brachial PP, was an independent predictor of all-cause and CV mortality.[53] Moreover, the predictive power of PP amplification was superior to carotid PP. In untreated subjects with essential hypertension,[54] regression of left ventricular mass index after 1 year of drug treatment was independently associated with the increase of PP amplification, but not with the reduction in brachial PP. Further evidence is still awaited.

In clinical practice, arterial hypertension and BP-associated CV risk are stratified on the basis of brachial BP.[1] Because central BP tends to be more closely associated with intermediate markers of CV risk than brachial BP, classification of risk on the basis of central BP would appear to be important. This is not possible without direct assessment of the central BP, because of the marked variation in PP amplification within and between subjects.[7,8] Indeed, there is considerable overlap in aortic systolic BP between discrete categories of brachial systolic BP classified according to the international

guidelines. Cross-sectional data[8] show that 32% of men and 10% of women with normal brachial BP have aortic systolic BP similar to the aortic systolic BP of individuals with brachial BP within the limits of stage 1 hypertension. Conversely, individuals labeled as hypertensive based on brachial BP might actually have lower CV risk attributable to higher PP amplification and thus lower central BP. This apparent misclassification is likely to be clinically meaningful; confirmation by specifically designed longitudinal studies is awaited.

Isolated systolic hypertension (ISH), the most common phenotype of elevated BP in both adolescent/young and elderly hypertensives,[55,56] is primarily characterized by increased pulsatility of BP, as initially described 30 years ago,[57] rather than increased peripheral resistance. However, ISH in younger and older individuals can be distinguished clearly on the basis of PP amplification.[58,59] In the elderly (>60 years old), ISH is associated with increased aortic stiffness, early return of reflected waves, thus smaller PP amplification.[58] Nonetheless, aged individuals with ISH should be treated.[60] The underlying mechanism of ISH in adolescent/young adults is different[57] and still under investigation. PP amplification tends to be higher and wave reflection tends to be lower[59] in young subjects with ISH when compared with age matched normotensives and systolic/diastolic hypertensives. Increased stroke volume (hyperdynamic circulation) or relatively increased aortic stiffness may be the underlying cause.[55,57,59,61] Whether young subjects with ISH should be treated is not clear yet, but they should not be considered a "normal" population because diastolic BP and central systolic BP are higher in most cases[57,62] in comparison with normotensive subjects. The terms "spurious hypertension" or "pseudohypertension,"[62–64] initially proposed to describe young tall male subjects with elastic aortas who had ISH and normal central systolic BP,[64] may be applicable in special cases of extreme pulse pressure amplification, eg, >30 mm Hg. Because the normal levels of central systolic BP and PP are not yet defined, this term might be also misleading. Until the natural history of each potential subtype of ISH in adolescents and young adults is clarified, all subjects with ISH should be regarded as intermediate BP phenotypes and followed up to determine whether these individuals develop essential hypertension and target organ damage or regress to normotension.

Finally, the age-dependent decrease in PP amplification is likely to explain the low predictive value of brachial PP for CV events in young adults.[34]

Pulse Pressure Amplification and Implications of Drug Treatment

It is now accepted that the effect of antihypertensive drug treatment cannot be correctly evaluated solely by considering changes in brachial BP.[52,65] The available antihypertensive drugs reduce BP mainly by decreasing total peripheral resistance and cardiac output. However, there are additional effects of some antihypertensive drugs on central hemodynamics, beyond BP, which are associated with their ability to modify elasticity-associated arterial properties and wave reflections.[66] Two potential mechanisms may be responsible for the modification of wave reflections: (1) the reduction of the intensity of the wave (reduction of the reflection coefficient) or (2) the resynchronization of the timing of the reflected wave within systole, resulting in reduced systolic pressure augmentation. This latter mechanism may result from either a delay of the arrival of the wave (Tr), attributable to decreased PWV or a distal shift of the origin (effective reflecting distance) of the reflected wave, or of the shortening of the left ventricular ejection time (associated with tachycardia).

Table. Summary of the Available Evidence on the Effects of Antihypertensive Drug Classes on Pulse Pressure Amplification

Antihypertensive Drug Classes (No. of Available Studies*)	Reduction of Central BP Beyond Peripheral BP*	Change in BP Amplification
Diuretics (4)	0/2/2	Neutral/decrease
BBs (6)	0/6/0	Decrease
ACEIs (11)	8/1/2	Increase
ARBs (4)	2/0/2	Increase/neutral
CCBs (3)	2/0/1	Increase/neutral
Nitrates (3)	3/0/0	Increase

Modified from Protogerou et al.[69]

The studies are classified according to the effect (positive/negative/neutral) on central blood pressure (BP) reduction beyond peripheral BP.

*Only studies using monotherapy or single add-on treatment are included.

BB indicates β blockers; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; CCB, calcium channel blocker (dihydropyridine).

All classes of antihypertensive drugs might potentially decrease arterial stiffness passively, and thus decrease PWV, via the reduction of the distending mean BP. In this respect, all drugs might potentially increase PP amplification because of the resynchronization of the reflected pressure wave. However, there are important differences between the various classes of antihypertensive drugs regarding their effect on arterial stiffness and wave reflections.[67,68] As a consequence there are significant differences between the classes of antihypertensive drugs regarding their effect on PP amplification.

Most of the available evidence[69] derives from small invasive and noninvasive heterogeneous studies, which used various methodological designs, applied various methods for the assessment of PP amplification, and used various drug doses and for relatively short durations. Because modifications in arterial wall properties take place after long-term drug treatment,[70] there are considerable limitations regarding the extrapolation of the available data to daily clinical practice and it is not possible to draw definite conclusions regarding all classes of antihypertensive drugs.

The newer antihypertensive drugs (angiotensin converting enzymes inhibitors [ACEIs], angiotensin receptors blockers [ARBs], calcium channel blockers [CCBs]), as well as nitrates may increase PP amplification (Table). The common feature between these drug classes appears to be their arterial dilating capacity and their ability to reduce pressure wave reflections, as expressed by AI. Data concerning ACEIs are particularly convincing. ACEIs seem to act by decreasing wave reflections potentially attributable to chronic inverse remodelling of the small arteries leading to reduced reflection coefficients. There is also compelling evidence regarding the

detrimental effect of β blockers (BBs; mainly atenolol) on PP amplification. This is largely attributed to the associated bradycardia (longer systolic duration) and the consequent resynchronization of the reflected pressure wave relatively earlier in the systolic phase (thus increasing AI).[71] Indeed, a decrease in heart rate by 10 bpm is associated with an increase of aortic AI by 4%.[71] For the moment there are no convincing data that newer BBs with vasodilating properties are devoid of these effects.[71]

Most importantly, these class-specific effects on central hemodynamics (especially of BBs) may explain in part the difference in mortality and left ventricular structure which were observed in the ASCOT (as suggested by the CAFE substudy)[52] and REASON[72] trials, respectively.

Theoretically, other drugs with pleiotropic effects (antiinflammatory, antioxidants) eg, statins may have potentially favorable effects on arterial properties and increase PP amplification. However, this hypothesis remains to be proven.[73]

Perspectives

Despite the extensive physiological variability in BP and inaccuracies of office brachial BP readings, as conventionally used in clinical practice, brachial BP is a major predictor of CV risk. However, PP amplification between the aorta and the brachial artery is also an indisputable physiological phenomenon, arising from periodic oscillations of pressure waves, which travel and are reflected within arteries characterized by nonuniform visco-elastic properties. PP amplification is highly variable, within and between subjects, and modulated by nonmodifiable and modifiable factors: mainly vascular aging and heart rate. This disparity between central and peripheral PP highlights potentially important clinical implications regarding CV risk assessment, stratification, and treatment. Compared with BBs, vasodilating drugs exert a favorable effect on PP amplification, ie, for the same reduction of brachial PP, they reduce central PP, more than BBs. This may explain, in part, their superiority in recent clinical trials. Further clinical research designed to assess both central and peripheral BP is now required. The available methods for the assessment of central BP have limitations, mainly because of calibration issues. Nevertheless, combining the best available noninvasive methods at the upper limb and in the central arteries will allow PP amplification to be assessed as accurately as possible. Such assessments may then prove the superiority of central BP over peripheral BP and allow the identification of specific populations that might benefit more from the assessment of central BP.

Disclosures

None.

References

1. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2007 guidelines for the management of arterial hypertension. *J Hypertens.* 2003;21:1011–1053.
2. Agabiti-Rosei E, Mancia G, O'Rourke MF, Roman MJ, Safar ME, Smulyan HJ, Wang JG, Williams B, Vlachopoulos C. Central blood pressure measurements and antihypertensive measurements. A consensus document. *Hypertension*. 2007;50:154–160.
3. Nichols WW, O'Rourke MF. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*. V ed. London: Edward Arnold; 2005.
4. Swillens A, Segers P. Assessment of arterial pressure wave reflection: methodological considerations. *Artery Research*. 2008;2:122–131.
5. Segers P, Rietzschel ER, De Buyzere ML, De Bacquer D, Van Bortel LM, De Backer G, Gillebert TC, Verdonck PR. Assessment of pressure wave reflection: getting the timing right! *Pysiol Meas.* 2007;28:1045–1056.
6. Davies JE, Hadjiloizou N, Leibovich D, Malaweere A, Alastruey-Arimon J, Whinnett ZI, Manisty CH, Francis DP, Aguado-Sierra J, Foale RA, Malik IS, Parker KH, Mayet J, Hughes AD. Importance of the aortic reservoir in determining the shape of the arterial pressure waveform. The forgotten lessons of Frank. *Artery Res*. 2007;1:40–45.
7. Vlachopoulos C, Hirata K, O'Rourke MF. Pressure-altering agents affect central aortic pressures more than is apparent from upper limb measurements in hypertensive patients: the role of arterial wave reflections. *Hypertension*. 2001;38:1456–1460.
8. McEniery CM, Yasmin, McDonnell B, Munnery M, Wallace SM, Rowe CV, Cockcroft JR, Wilkinson IB. Central pressure: variability and impact of cardiovascular risk factors: the Anglo-Cardiff Collaborative Trial II. *Hypertension*. 2008;51:1476–1482.
9. Camacho F, Avolio A, Lovell NH. Estimation of pressure pulse amplification between aorta and brachial artery using stepwise multiple regression models. *Pysiol Meas*. 2004;25:879–889.
10. Papaioannou TG, Protogerou AD, Stamatelopoulos KS, Vavuranakis M, Stefanadis C. Non-invasive methods and techniques for central blood pressure estimation: procedures, validation, reproducibility and limitations. *Curr Pharm Des*. 2009;15:245–253.
11. Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *Eur Heart J*. 1993;14:160–167.
12. Chen CH, Nevo E, Fetics B, Pak PH, Yin FC, Maughan WL, Kass DA. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. *Circulation*. 1997;95:1827–1836.
13. Siebenhofer A, Kemp C, Sutton A, Williams B. The reproducibility of central aortic blood pressure measurements in healthy subjects using applanation tonometry and sphygmocardiography. *J Hum Hypertens*. 1999;13:625–629.
14. Crilly M, Coch C, Bruce M, Clark H, Williams D. Repeatability of central aortic blood pressures measured non-invasively using radial artery applanation tonometry and peripheral pulse wave analysis. *Blood Press*. 2007;16:262–269.
15. Savage MT, Ferro CJ, Pinder SJ, Tomson CR. Reproducibility of derived central arterial waveforms in patients with chronic renal failure. *Clin Sci (Lond)*. 2002;103:59–65.
16. Papaioannou TG, Stamatelopoulos KS, Gialafos E, Vlachopoulos C, Karatzis E, Nanas J, Lekakis J. Monitoring of arterial stiffness indices by applanation tonometry and pulse wave analysis: reproducibility at low blood pressures. *J Clin Monit Comput*. 2004;18:137–144.
17. Holland DJ, Sacre JW, McFarlane SJ, Coombes JS, Sharman JE. Pulse Wave Analysis Is a Reproducible Technique for Measuring Central Blood Pressure During Hemodynamic Perturbations Induced by Exercise. *Am J Hypertens*. 2008;21:1100–1106.
18. Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension*. 2001;38:932–937.
19. Sharman JE, Lim R, Qasem AM, Coombes JS, Burgess MI, Franco J, Garrahy P, Wilkinson IB, Marwick TH. Validation of a generalized transfer function to noninvasively derive central blood pressure during exercise. *Hypertension*. 2006;47:1203–1208.
20. Smulyan H, Siddiqui DS, Carlson RJ, London GM, Safar ME. Clinical utility of aortic pulses and pressures calculated from applanated radial artery pulses. *Hypertension*. 2003;42:150–155.
21. Smulyan H, Sheehe PR, Safar ME. A preliminary evaluation of the mean arterial pressure as measured by cuff oscillometry. *Am J Hypertens*. 2008;21:166–171.
22. Verbeke F, Segers P, Heireman S, Vanholder R, Verdonck P, Van Bortel LM. Noninvasive assessment of local pulse pressure importance of brachial-to-radial pressure amplification. *Hypertension*. 2005;46:244–248.
23. Papaioannou TG, Lekakis JP, Karatzis EN, Papamichael CM, Stamatelopoulos KS, Protogerou AD, Mavrikakis M, Stefanadis C. Transmission

of calibration errors (input) by generalized transfer functions to the aortic pressures (output) at different hemodynamic states. *Int J Cardiol*. 2006; 110:46–52.
24. Cloud GC, Rajkumar C, Kooner J, Cooke J, Bulpitt CJ. Estimation of central aortic pressure by SphygmoCor requires intra-arterial peripheral pressures. *Clin Sci*. 2003;105:219–225.
25. Davies JI, Band MM, Pringle P, Ogston S, Struthers AD. Peripheral blood pressure measurement is as good as applanation tonometry at predicting ascending aortic pressure. *J Hypertens*. 2003;21:571–576.
26. Van Bortel LM, Balkestein EJ, van der Heijden JJ, Vanmolkot FH, Staessen JA, Kragten JA, Vredeveld JW, Safar ME, Struijker Boudier HA, Hoeks AP. Non-invasive assessment of local arterial pulse pressure; comparison of applanation tonometry and echo-tracking. *J Hypertens*. 2001;19:1037–1044.
27. Kelly R, Fitchett D. Noninvasive determination of aortic input impedance and external left ventricular power output: a validation and repeatability study of a new technique. *J Am Coll Cardiol*. 1992;20:952–963.
28. Pauca AL, Wallenhaupt SL, Kon ND, Tucker WY. Does radial artery pressure accurately reflect aortic pressure? *Chest*. 1992;102:1193–1198.
29. Bos WJW, Verrij E, Vincent HH, Westerhof BE, Parati G, van Montfrans GA. How to assess mean blood pressure properly at the brachial artery. *J Hypertens*. 2007;25:751–755.
30. Pauca AL, Kon ND, O'Rourke MF. The second peak of the radial artery pressure wave represents aortic systolic pressure in hypertensive subjects. *Br J Aneasth*. 2004;92:651–657.
31. Segers P, Mahieu D, Kips J, Rietzschel ER, De Buyzere ML, De Bacquer D, Bekaert S, De Backer G, Gillebert TC, Verdonck P, Van Bortel LM, on behalf of the Asklepios investigators. Amplification of the pressure pulse in the upper limb in healthy, middle-aged men and women. *Hypertension*. 2009;54:414–420.
32. Kroeker E, Wood E. Comparison of simultaneously recorded central and peripheral arterial pressure pulses during rest, exercise and tilted position in men. *Circ Res*. 1955;3:623–632.
33. Remington J, Wood E. Formation of the peripheral pulse contour in man. *J Appl Physiol*. 1956;9:433–442.
34. Wilkinson IB, Franklin SS, Hall IR, Tyrrell S, Cockcroft JR. Pressure amplification explains why pulse pressure is unrelated to risk in young subjects. *Hypertension*. 2001;38:1461–1466.
35. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. Normal vascular aging: differential effects on wave reflection and pulse wave velocity. The Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol*. 2005;46:1753–1760.
36. Laurent P, Albaladejo P, Blacher J, Rudnichi A, Smulyan H, Safar ME. Heart rate and pulse pressure in hypertensive subjects. *Am J Hypertens*. 2003;16:363–370.
37. Protogerou AD, Blacher J, Mavrikakis M, Lekakis J, Safar ME. Increased pulse pressure amplification in treated hypertensive subjects with metabolic syndrome. *Am J Hypertens*. 2007;20:127–133.
38. Aortic diameter, wall stiffness, and wave reflection in systolic hypertension. Mitchell GF, Conlin PR, Dunlap ME, Lacourcière Y, Arnold JM, Ogilvie RI, Neutel J, Izzo JL Jr, Pfeffer MA. *Hypertension.* 2008;51: 105–111.
39. Albaladejo P, Copie X, Boutouyrie P, LalouxB, Declere AD, Snulyan H, Benetos A. Heart rate, arterial stiffness, and wave reflections in paced patients. *Hypertension*. 2001;38:949–952.
40. Wilkinson IB, Mohammad NH, Tyrrell S, Hall IR, Webb DJ, Paul VE, Levy T, Cockcroft JR. Heart rate dependency of pulse pressure amplification and arterial stiffness. *Am J Hypertens*. 2002;15:24–30.
41. Vergnaud AC, Protogerou AD, Blacher J, Safar ME. From 'optimal' to 'borderline' blood pressure in subjects under chronic antihypertensive therapy. *J Hypertens*. 2008;26:138–144.
42. Munir S, Guilcher A, Kamalesh T, Clapp B, Redwood S, Marber M, Chowienczyk P. Peripheral augmentation index defines the relationship between central and peripheral pulse pressure. *Hypertension*. 2008;51: 112–118.
43. Gatzka CD, Kingwell BA, Cameron JD, Berry KL, Liang YL, Dewar EM, Reid CM, Jennings GL, Dart AN. The ANBP2 investigators. Gender differences in the timing of arterial wave reflection beyond differences in body height. *J Hypertens*. 2001;19:2197–2203.
44. Wilkinson IB, Prasad K, Hall IR, Thomas A, MacCallum H, Webb DJ, Frenneaux MP, Cockcroft JR. Increased central pulse pressure and augmentation index in subjects with hypercholesterolemia. *J Am Coll Cardiol*. 2002;39:1005–1011.
45. Mahmud A, Feely J. Effect of smoking on arterial stiffness and pulse pressure amplification. *Hypertension*. 2003;41:183–187.
46. Vergnaud AC, Protogerou AD, Li Y, Czernichow S, Vesin C, Blacher J, Safar ME. Pulse pressure amplification, adiposity and metabolic syndrome in subjects under chronic antihypertensive therapy: the role of heart rate. *Atherosclerosis*. 2008;199:222–229.
47. Boutouyrie P, Bussy C, Hayoz D, Hengstler J, Dartois N, Laloux B, Brunner H, Laurent S. Local pulse pressure and regression of arterial wall hypertrophy during long-term antihypertensive treatment. *Circulation*. 2000;101:2601–2606.
48. Boutouyrie P, Bussy C, Lacolley P, Girerd X, Laloux B, Laurent S. Association between local pulse pressure, mean blood pressure, and large-artery remodeling. *Circulation*. 1999;100:1387–1393.
49. Roman MJ, Ganau A, Saba PS, Pini R, Pickering T, Deveraux R. Impact of arterial stiffening on left ventricular structure. *Hypertension*. 2000;36: 489–494.
50. Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T, Umans JG, Howard BV. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension*. 2007;50:197–203.
51. Jankowski P, Kawecka-Jaszcz K, Czarnecka D, Brzozowska-Kiszka M, Styczkiewicz K, Loster M, Kloch-Badełek M, Wiliński J, Curyło AM, Dudek D; Aortic Blood Pressure and Survival Study Group. Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. *Hypertension.* 2008;51:848–855.
52. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation*. 2006;113:1213–1225.
53. Safar ME, Blacher J, Pannier B, Guerin AP, Marchais SJ, Guyonvarc'h PM, London GM. Central pulse pressure and mortality in end-stage renal disease. *Hypertension*. 2002;39:735–738.
54. Hashimoto J, Imai Y, O'Rourke MF. Monitoring of antihypertensive therapy for reduction in left ventricular mass. *Am J Hypertens*. 2007;20: 1229–1233.
55. Sorof JM, Poffenbarger T, Franco K, Bernard L, Portman RJ. Isolated systolic hypertension, obesity, and hyperkinetic hemodynamic states in children. *J Pediatr*. 2002;140:660–666.
56. Franklin SS, Milagros JJ, Wong ND, L'Italien GJ, Lapuerta P. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES III). *Hypertension*. 2001;37:869–874.
57. Simon AC, Safar ME, Levenson JA, Kheder AM, Levy BI. Systolic Hypertension: Hemodynamic mechanism and choice of antihypertensive treatment. *Am J Cardiol*. 1979;44:505–511.
58. Nichols WW, Nicolini FA, Pepine CJ. Determinants of isolated systolic hypertension in the elderly. *J Hypertens Suppl*. 1992;10:S73–S77.
59. McEniery CM, Yasmin, Wallace S, Maki-Petaja K, McDonnell B, Sharman JE, Retallick C, Franklin SS, Brown MJ, Lloyd RC, Cockcroft JR, Wilkinson IB. Enigma study investigators. Increased stroke volume and aortic stiffness contribute to isolated systolic hypertension in young adults. *Hypertension.* 2005;46:221–226.
60. SHEP The Systolic Hypertension in the Elderly Program Cooperative Research Group: Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 1991;265: 3255–3264.
61. Eich RH, Peters RJ, Cuddy RP, Smulyan H, Lyons RH. The hemodynamics in labile hypertension. *Am Heart J*. 1962;63:188.
62. Hulsen HT, Nijdam ME, Bos WJ, Uiterwaal CS, Oren A, Grobbee DE, Bots M. Spurious systolic hypertension in young adults; prevalence of high brachial systolic blood pressure and low central pressure and its determinants. *J Hypertens*. 2006;24:1027–1032.
63. O'Rourke MF, Vlachopoulos C, Graham RM. Spurious systolic hypertension in youth. *Vasc Med*. 2000;5:141–145.
64. Mahmud A, Feely J. Spurious systolic hypertension of youth: fit young men with elastic arteries. *Am J Hypertens*. 2003;16:229–232.
65. Asmar RG, London GM, O'Rourke ME, Safar ME. Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patient: a comparison with atenolol. *Hypertension*. 2001;38:922–926.
66. Safar ME. London GM, for the clinical committee of Arterial Structure and Function, on behalf of the Working Group on Vascular Structure and Function of the European Society of Hypertension. Therapeutic studies and arterial stiffness in hypertension: recommendations of the European Society of Hypertension. *J Hypertens.* 2000;18:1527–1535.

67. Blacher J, Protogerou AD, Safar ME. Large artery stiffness and antihypertensive agents. *Curr Pharm Des*. 2005;11:3317–3326.
68. Mahmud A. Reducing arterial stiffness and wave reflection – Quest of the holly grail? *Artery Res*. 2007;1:13–19.
69. Protogerou AD, Stergiou GS, Vlachopoulos C, Blacher J, Achimastos A. The effect of antihypertensive drugs on central blood pressure beyond peripheral blood pressure. Part II: Evidence for specific class-effects of antihypertensive drugs on pressure amplification. *Curr Pharm Des*. 2009; 15:272–289.
70. London GM, Asmar RG, O'Rourke MF, Safar ME. on behalf of the REASON project Investigators. Mechanism(s) of selective systolic blood pressure reduction after low-dose combination of peripndopril/ indapamide in hypertensive subjects: Comparison with atenolol. *J Am Coll Cardiol.* 2004;43:92–99.
71. Dhakam Z, Yasmin, McEniery CM, Tim Burton, Brown JR, Wilkinson IB. A comparison of atenolol and nebivolol in isolated systolic hypertension. *J Hypertens*. 2008;26:351–356.
72. de Luca N, Asmar RG, London GM, O'Rourke MF, Safar ME. REASON Project Investigators. Selective reduction of cardiac mass and central blood pressure on low-dose combination perindopril/indapamide in hypertensive subjects. *J Hypertens.* 2004;22:1623–1630.
73. Williams B, Lacy PS, Cruickshank JK, Collier Dm Hughes AD, Thom S, Thurston H. for the CAFE and ASCOT investigators. Impact of statin therapy on central aortic pressures and hemodynamics – principal results of the Conduit Artery Function Evaluation study Lipid Lowering Arm: the CAFE-LLA study. *Circulation.* 2009;119:53–61.
74. Safar ME, Protogerou AD, Blacher J. Statins, central blood pressure, and blood pressure amplification. *Circulation*. 2009;119:9–12.

KEY WORDS: pressure amplification ■ wave propagation ■ arterial stiffness ■ wave reflection