Central Blood Pressure Measurements and Antihypertensive Therapy
A Consensus Document

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The 2003 European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension included 2 important novel recommendations: assessment of the total cardiovascular risk should be taken into account in the management of the hypertensive patient, and quantification of risk should include subclinical target organ damage.

These guidelines acknowledged that central (aortic) blood pressure (BP), which is the pressure exerted on the heart and brain, may be different from the pressure that is measured at the arm. They also recognized that central pressure may be predictive of outcome in specific populations and differently affected by antihypertensive drugs. However, although these guidelines accepted that central augmentation index and pulse wave velocity may be important as measures of subclinical organ damage, they also stressed the need for prospective trials to establish their predictive values given that such studies were lacking at that time (2003).

After publication of these guidelines, additional data have strengthened the pathophysiological importance of central BP. Clinical studies have indicated that central BP may have predictive value independent of the corresponding peripheral (brachial) BP. More importantly, recent large-scale trials have shown that central hemodynamics may provide a worthwhile treatment target. In addition, central hemodynamics can now be reliably assessed noninvasively with a number of devices. Accordingly, because arterial stiffening and central hemodynamics are markers and manifestations of organ damage, the pertinent key question is whether the balance of evidence on their importance and issues related to clinical practice allows for implementation in patient management.

Pathophysiological Significance of Central Pressures
Central (aortic and carotid) pressures are pathophysiologically more relevant than peripheral pressures for the pathogenesis of cardiovascular disease. It is aortic systolic pressure that the left ventricle encounters during systole (afterload), and the aortic pressure during diastole is a determinant of coronary perfusion. Furthermore, the distending pressure in the large elastic-type arteries (aorta and carotid) is a key determinant of the degenerative changes that characterize accelerated aging and hypertension. In contrast, the muscular peripheral arteries, such as the brachial and the radial ones, are less influenced by these changes.

The pressure wave generated by the left ventricle travels down the arterial tree and then is reflected at multiple peripheral sites, mainly at resistance arteries (small muscular arteries and arterioles). Consequently, the pressure waveform recorded at any site of the arterial tree is the sum of the forward traveling waveform generated by left ventricular ejection and the backward traveling wave, the “echo” of the incident wave reflected at peripheral sites. When the large conduit arteries are healthy and compliant, the reflected wave merges with the incident in the proximal aorta during diastole, thereby augmenting the diastolic BP and aiding coronary perfusion. In contrast, when the arteries are stiff, pulse wave velocity increases, accelerating the incident and reflected waves; thus, the reflected wave merges with the incident wave in systole and augments aortic systolic rather than diastolic pressure. As a result, left ventricular afterload increases, and normal ventricular relaxation and coronary filling are compromised. Apart from changes in the timing of the waveforms merging, changes in the magnitude of the reflected wave and central pressures may result from changes in the proportion of the incident wave that is reflected, which
in turn depends on the balance between vasoconstriction and vasodilatation in the peripheral circulation.

Another important consideration regarding the relationship between brachial and central aortic pressure is “pressure wave amplification.” Typically, the diastolic and mean pressures change little across the arterial tree. However, systolic BP is amplified when moving from the aorta to the periphery (Figure 1).

Consequently, the pulsatile components of central and peripheral pressures (systolic BP and pulse pressure [PP]) may vary significantly. In general, brachial systolic and PP tend to overestimate central systolic and PP, especially in younger subjects who have more pronounced amplification. Substantial differences between central and brachial BP are also often also seen in older people, especially with tachycardia, exercise, use of vasoactive agents, or in those with systolic heart failure.

Techniques to Assess Central Hemodynamics

Although central pressures are ideally measured directly by using invasive devices, several methods have been devised currently to derive central pressures from analyses of applanated carotid and radial pulses or carotid distension waves. Among several commercial and noncommercial devices, the most widely used in clinical studies is the SphygmoCor device (AtCor Medical), which uses radial or carotid pulses and a validated generalized transfer function to estimate central pressures from the peripheral signal (Figure 2). When the applanated radial waveform is calibrated using direct intra-arterial pressures, the SphygmoCor calculations of aortic pressures are accurate, whereas the accuracy of this, as well as of other peripheral artery methods, decreases when the radial pulses are calibrated using inaccurate cuff pressures. This is also the case for carotid artery techniques. Alternatively, because mean BP remains virtually constant from central to peripheral arteries, the mean BP value computed from the area of the applanated carotid artery waveform can be calibrated using the mean BP obtained at the brachial artery level. Values of carotid pressures can then be derived. It should be emphasized that even when central pressures cannot be accurately calculated, these methods can display several features of the aortic (or carotid) pulse that are not dependent on the absolute values of BP, such as amplification of the pulse wave between central and peripheral artery, augmentation index, and arrival time of the reflected wave (the latter 2 are, however, dependent on identification of inflection point). Furthermore, because these features are also influenced by factors including heart rate, height, and age, modern computational capability could allow weighting of these factors in appropriate formulas. Potential problems related to the widespread application of arterial tonometry include appropriate training, supervision, and quality control, as they do for sphygmomanometry.

Arterial wave reflections indices and central pressures coupled with measurement of aortic pulse wave velocity, a direct measure of arterial stiffness, constitute a comprehensive and integrated approach of the study of arterial function. This is further highlighted by a possible differential ability to predict risk (augmentation index is better in younger persons and pulse wave velocity is better in older persons) or by situations where, contrary to the usual behavior, pulse wave velocity and wave reflection indices move in opposite directions.

Central Pressures and Central Indices as Markers and Predictors of Disease

Central hemodynamic variables have been shown to be independently associated with organ damage, incident cardiovascular disease, and events both in the general population and in various disease states. Tables 1 and 2 show such associations according to population studied, variable measured, and site and mode (invasive or noninvasive) of measurement.

Central Pressures and Central Indices as Markers of Disease and Predictors of Surrogate End Points

Increased aortic augmentation index is associated with coronary artery disease. Central pressures also correlate with cardiovascular risk not only in patients with atherosclerotic disease but also in apparently healthy subjects. The late systolic augmentation of the central pressure waveform is associated with an increase in left ventricular mass index.
independent of age and mean BP, and carotid systolic BP is an independent determinant of left ventricular wall thickness. Moreover, central pressure is also more closely related to other important cardiovascular intermediate end points, such as vascular hypertrophy, extent of carotid atherosclerosis, and the ascending aorta diameter in patients with Marfan syndrome than brachial pressure. Recently, higher carotid pressure augmentation in older individuals has been linked to increased flow pulsations entering the cerebral circulation, which may increase the risk of cerebral microvascular damage. In inflammatory disorders such as systemic vasculitis, augmentation index is a marker of disease activity, and it is independently associated with levels of C-reactive protein.

<p>| TABLE 1. Cross-Sectional and Longitudinal Studies Indicating the Independent Value of Central Hemodynamics as Markers of Disease and Predictors of Surrogate Cardiovascular End Points |</p>
<table>
<thead>
<tr>
<th>Source</th>
<th>Year, Country</th>
<th>Population</th>
<th>Design</th>
<th>Parameter</th>
<th>End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saba et al16†</td>
<td>1993, United States</td>
<td>Normotensives</td>
<td>Cross-sectional</td>
<td>Carotid AIx</td>
<td>LVMI, carotid thickness</td>
</tr>
<tr>
<td>Boutouyrie et al17†</td>
<td>1999, France</td>
<td>Hypertensives</td>
<td>Cross-sectional</td>
<td>Carotid PP</td>
<td>Carotid thickness</td>
</tr>
<tr>
<td>Boutouyrie et al18†</td>
<td>2000, France</td>
<td>Hypertensives</td>
<td>Longitudinal (9-month FU)</td>
<td>Carotid PP</td>
<td>Carotid IMT reduction with treatment</td>
</tr>
<tr>
<td>Roman et al19</td>
<td>2000, United States</td>
<td>Normotensives, Hypertensives</td>
<td>Cross-sectional</td>
<td>Carotid systolic BP</td>
<td>Relative LV wall thickness</td>
</tr>
<tr>
<td>Waddell et al20†</td>
<td>2001, Australia</td>
<td>CAD</td>
<td>Cross-sectional</td>
<td>Carotid BP</td>
<td>Extent of CAD</td>
</tr>
<tr>
<td>Nishijima et al21‡</td>
<td>2001, Japan</td>
<td>Suspected CAD</td>
<td>Cross-sectional</td>
<td>Aortic fractional PP</td>
<td>Incident CAD</td>
</tr>
<tr>
<td>Nurnberger et al22</td>
<td>2002, Germany</td>
<td>Healthy + CVD</td>
<td>Cross-sectional</td>
<td>Carotid AIx</td>
<td>CV risk scores</td>
</tr>
<tr>
<td>Philippe et al23†</td>
<td>2002, France</td>
<td>CAD</td>
<td>Cross-sectional</td>
<td>Aortic PP</td>
<td>Extent of CAD</td>
</tr>
<tr>
<td>Hayashi et al24*</td>
<td>2002, Japan</td>
<td>Suspected CAD</td>
<td>Cross-sectional</td>
<td>Aortic AIx</td>
<td>Incident CAD</td>
</tr>
<tr>
<td>De Luca et al25†</td>
<td>2004, REASON Study</td>
<td>Hypertensives</td>
<td>Longitudinal (1-year FU)</td>
<td>Carotid PP</td>
<td>LVMI reduction</td>
</tr>
<tr>
<td>Weber et al26</td>
<td>2004, Austria</td>
<td>Suspected CAD</td>
<td>Cross-sectional</td>
<td>Aortic PP, Ax</td>
<td>Incident CAD</td>
</tr>
<tr>
<td>Jankowski et al27*</td>
<td>2004, Poland</td>
<td>CAD</td>
<td>Cross-sectional</td>
<td>Aortic PP</td>
<td>Extent of CAD</td>
</tr>
<tr>
<td>Danchin et al28†</td>
<td>2004, France</td>
<td>Suspected CAD</td>
<td>Cross-sectional</td>
<td>Aortic PP</td>
<td>Incidence and extent of CAD</td>
</tr>
<tr>
<td>Booth et al29</td>
<td>2004, United Kingdom</td>
<td>Systemic vasculitis</td>
<td>Cross-sectional</td>
<td>Aortic AIx</td>
<td>Disease activity</td>
</tr>
<tr>
<td>Roman et al30†</td>
<td>2007, United States</td>
<td>High-risk</td>
<td>Cross-sectional</td>
<td>Aortic PP</td>
<td>Carotid IMT and mass</td>
</tr>
<tr>
<td>Hashimoto et al31†</td>
<td>2007, Japan</td>
<td>Hypertensives</td>
<td>Longitudinal (1-year FU)</td>
<td>Aortic AIx</td>
<td>LVMI reduction with treatment</td>
</tr>
</tbody>
</table>

AIx indicates augmentation index; CAD, coronary artery disease; CV, cardiovascular; FU, follow-up; IMT, intima–media thickness; LV, left ventricular; LVMI, left ventricular mass index.

*Central pressure measured directly.
†These studies have shown incremental value of central indices over peripheral BP.

independent of age and mean BP, and carotid systolic BP is an independent determinant of left ventricular wall thickness. Moreover, central pressure is also more closely related to other important cardiovascular intermediate end points, such as vascular hypertrophy, extent of carotid atherosclerosis, and the ascending aorta diameter in patients with Marfan syndrome than brachial pressure. Recently, higher carotid pressure augmentation in older individuals has been linked to increased flow pulsations entering the cerebral circulation, which may increase the risk of cerebral microvascular damage. In inflammatory disorders such as systemic vasculitis, augmentation index is a marker of disease activity, and it is independently associated with levels of C-reactive protein.

TABLE 2. Longitudinal Studies Indicating the Independent Value of Central Hemodynamics as Predictors of Events

<table>
<thead>
<tr>
<th>Source</th>
<th>Year, Country</th>
<th>Population</th>
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<th>Parameter</th>
<th>End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakayama et al32*</td>
<td>2000, Japan</td>
<td>CAD-PTCA</td>
<td>Longitudinal (3-mo FU)</td>
<td>Aortic fractional PP</td>
<td>Restenosis</td>
</tr>
<tr>
<td>Lu et al33*</td>
<td>2001, China</td>
<td>CAD-PTCA</td>
<td>Longitudinal (6-mo FU)</td>
<td>Aortic PP</td>
<td>Restenosis</td>
</tr>
<tr>
<td>London et al34†</td>
<td>2001, France</td>
<td>ESRD</td>
<td>Longitudinal (52-mo FU)</td>
<td>Carotid AIx</td>
<td>CV mortality</td>
</tr>
<tr>
<td>Safar et al†</td>
<td>2002, France</td>
<td>ESRD</td>
<td>Longitudinal (52-mo FU)</td>
<td>Carotid PP, PP amplification</td>
<td>All-cause and CV mortality</td>
</tr>
<tr>
<td>Ueda et al35*</td>
<td>2004, Japan</td>
<td>CAD-PTCA</td>
<td>Longitudinal (6-mo FU)</td>
<td>Aortic AIx</td>
<td>Restenosis</td>
</tr>
<tr>
<td>Chirinos et al36†</td>
<td>2005, United States</td>
<td>CAD-PTCA</td>
<td>Longitudinal (3.2-y FU)</td>
<td>Aortic AP</td>
<td>CV mortality and events</td>
</tr>
<tr>
<td>Weber et al37†</td>
<td>2005, Austria</td>
<td>CAD-PTCA</td>
<td>Longitudinal (2-y FU)</td>
<td>Aortic AP</td>
<td>CV mortality and events</td>
</tr>
<tr>
<td>Dart et al38</td>
<td>2006, Australia</td>
<td>Elderly female hypertensives</td>
<td>Longitudinal (4.1-y FU)</td>
<td>Carotid AIx, brachial BP</td>
<td>CV mortality and events during treatment</td>
</tr>
<tr>
<td>Williams et al39†</td>
<td>2006 CAFE Study</td>
<td>Hypertensives</td>
<td>Longitudinal (4.8-y FU)</td>
<td>Aortic PP</td>
<td>CV mortality and events</td>
</tr>
<tr>
<td>Roman et al40†</td>
<td>2005 and 2007, United States</td>
<td>High-risk</td>
<td>Longitudinal (4.8-y FU)</td>
<td>Aortic PP</td>
<td>CV mortality and events</td>
</tr>
</tbody>
</table>

ESRD indicates end-stage renal disease; PTCA, percutaneous transluminal coronary angioplasty; AIx, augmentation index; CAD, coronary artery disease; CV, cardiovascular; FU, follow-up.

*Central pressure measured directly.
†These studies have shown incremental value of central indices over peripheral BP.
Central Pressures and Central Indices as Predictors of Events

Recent data from the Strong Heart Study confirm that peripheral PP, a simple index of arterial stiffness, is associated with a higher cardiovascular mortality independent of traditional risk factors, left ventricular hypertrophy, and reduced ejection fraction in adults without overt coronary heart disease. Furthermore, data from the same study showed in a 5-year follow-up that the noninvasively determined central PP better predicts incident cardiovascular disease than does the corresponding brachial PP, possibly because of a more accurate representation of the vascular load on the left ventricle. Central pressures and wave reflection indices are also strong independent predictors of all-cause and cardiovascular mortality in patients with end-stage renal failure. Moreover, in patients with coronary artery disease, wave reflections as expressed by central augmented pressure are powerful and independent predictors of recurrent acute coronary events or death. Pulsatility of the ascending aortic pressure waveform is a powerful predictor of restenosis after angioplasty. Increased arterial wave reflections expressed by augmentation index are independently associated with an increased risk of severe short- and long-term cardiovascular events in patients undergoing percutaneous coronary interventions. In contrast to the aforementioned evidence, a recent study conducted in elderly hypertensive women found that carotid augmentation index is not predictive of outcome. However, the large Conduit Artery Function Evaluation (CAFE) Study reported that central PP derived from radial artery applanation tonometry independently predicts outcome in treated patients with hypertension. Highlighting the interplay of small and large arteries in risk determination, the structure of small arteries (which compose the main peripheral reflecting sites) was a predictor of events in patients with hypertension. It should be noted, however, that evidence for a specific central pressure component or index does not necessarily apply to the others, and, thus, they should not be used interchangeably. Furthermore, there is clearly a need for additional studies of central pressures and indices in more general populations or in other disease states. Finally, it would be desirable for future studies to address whether central pressures provide incremental and independent prognostic value over other emerging biomarkers.

Implications for Therapy

BP reduction, per se, is the major determinant of the benefit of antihypertensive treatment. This has been shown by data from placebo-controlled trials, trials that compared more intensive versus less intensive BP-lowering strategies, and trials comparing different active regimens, and it is further supported by large meta-analyses of studies on antihypertensive treatment. However, during the last decade, important multicenter trials gave rise to the hypothesis that new antihypertensive drugs, such as blockers of the renin–angiotensin system, may reduce cardiovascular outcomes beyond (peripheral) BP control. Particularly, in the Heart Outcomes Prevention Evaluation (HOPE), Losartan Intervention For Endpoint reduction in hypertension (LIFE), and the Australian National Blood Pressure 2 (ANBP2) studies, the observed clinical benefit tended to be greater than that expected from the decrease in peripheral BP. These potential effects “beyond BP control” are perhaps accounted for by protective properties of different drugs that affect subclinical organ damage or intermediate end points, such as arterial properties or central BP, for which
there is evidence that they are related to cardiovascular morbidity and mortality. Effects on central pressures may not be evident by pressure measurements in the periphery, because the reflected wave is added to a different part of the central waveform. This may explain why drugs with similar reduction in peripheral pressures have a differential impact on cardiovascular outcomes. In this context, a short-term (4-week treatment) study showed that, in contrast to \( \beta \)-blockers, angiotensin-converting enzyme inhibitors and calcium blockers may be more effective in reducing aortic systolic BP than that indicated by brachial pressure measurements. Furthermore, more recent studies comparing the acute effects of angiotensin-converting enzyme inhibitors (ramipril) and the short-term (6-week) effects of angiotensin receptor blockers (eprosartan) with atenolol showed that, for a similar fall of brachial pressure, inhibitors of the renin–angiotensin axis may cause a significantly greater fall of central pressures. Interestingly, the pREterax in regression of Arterial Stiffness in a controlled double-blind (REASON) trial, which compared a perindopril–indapamide combination against atenolol, showed that normalization of brachial systolic BP is achieved with a significantly greater reduction of carotid systolic BP after a 12-month treatment with the combination. In this study, compared with atenolol, the perindopril–indapamide combination was associated with a greater fall in left ventricular mass, and this was related to carotid but not brachial BP.

The notion that BP-lowering drugs can have substantially different effects on central aortic pressures and hemodynamics despite a similar impact on brachial BP and that central rather than peripheral BP should be a treatment target in trials was highlighted by the recent CAFE Study, a major substudy within the Anglo-Scandinavian Cardiac Outcome Trial, which examined the impact of a conventional regimen (atenolol±thiazide) versus a contemporary one (amlodipine±perindopril). In the CAFE Study, despite similar effects in peripheral BP, there were substantial reductions in central aortic pressures and hemodynamic indices in favor of theamlodipine-based treatment. Because there were no differences in carotid–femoral pulse wave velocity and the pressure at the inflection point (height of P1, studied in a subgroup of patients), these changes were predominantly attributed to lower pressure wave augmentation because of decreased pulse wave reflection. Central aortic PP was a determinant of clinical outcome in this study. These findings are in line with the enhancement of the relationship between events and BP reduction when allowance is made for a greater reduction in central than brachial pressure occurring with arterial dilating drugs (Figure 3, right). Because \( \beta \)-blockers are less effective than other drugs in preventing major cardiovascular events, especially stroke, the recent recommendations for the treatment of hypertension suggest against their use for initial treatment of hypertension. It is currently unknown whether this is a class effect (including those \( \beta \)-blockers with vasodilating properties) or whether this only pertains to atenolol, the main \( \beta \)-blocker used in clinical trials of hypertension.

Other studies have also shown that surrogate end points can be predicted by indices of central hemodynamics after therapy. Aortic and radial augmentation index, as well as amplification of the pulse between central and radial arteries, were superior to conventional cuff measures in predicting reduction in left ventricular mass during antihypertensive therapy. Furthermore, the reduction in carotid wall diameter and hypertrophy with antihypertensive treatment was related to carotid PP but not to mean BP.

Implementation in Clinical Practice
Both peripheral and central BP fulfill the criteria of a surrogate marker (type 2 marker). Accordingly, regarding the theoretical basis, central BP is pathophysiologically more relevant than the corresponding peripheral BPs. Furthermore, current, noninvasive, validated, and easy-to-use techniques can estimate central BPs and wave reflection indices. Reproducibility is very good (please see http://hyper.ahajournals.org), but improvement is desirable. In addition, because peripheral BP is perhaps the most firmly established cardiovascular risk predictor, the question of whether central BP provides incremental value over and above peripheral BP is pivotal. Evidence is growing that this may be indeed the case, but more data are needed with regard to each central pressure index. Finally, the CAFE Study has provided the first randomized, prospective event-based evidence that central BP and related indices may be a useful guide to treatment. Nevertheless, more studies are needed.

Before implementation into clinical practice, determination of normal values for wave reflections indices and central BPs is mandatory. Importantly, the recently published Anglo-CardiFF Collaborative Trial and the European Project on Genes in Hypertension, as well as ongoing studies (European Network for Noninvasive Determination of Large Arteries, National Institute of Aging, and Framingham) are making important progress in this direction.

Perspectives
The prognostic value of brachial BP is well established. However, there is mounting evidence suggesting that central pressure and indices correlate more closely with intermediate measures of cardiovascular risk than brachial pressure and that they independently predict future cardiovascular events. Moreover, despite similar effects on brachial pressure, antihypertensive drugs have differential effects on central pressure. This may explain the superiority of vasodilating drugs in recent outcome trials. However, extension of the existing data regarding the superiority of central pressures over and above brachial BP in a wider range of populations and disease states is desirable. Inclusion of a parameter in patient assessment and management should serve various purposes, such as advancement of science, physician education, and practicality of use in a range of settings, whereas cost should also be taken into consideration. Assessment of central pressures meets these criteria to a varying degree at present. Definition of terms such as central and peripheral BP, arterial stiffness, wave reflections, and systolic BP and PP amplification should be readily available to both clinicians and researchers and introduced in the guidelines on hypertension and cardiovascular risk. Although brachial BP remains our point of reference, there is a definite sense that efforts to investigate
and advance from the status quo of cuff BP measurements should be pursued. Acquired evidence of this sort would allow for supportable recommendations to the committees whose responsibility it is to issue guidelines for the evaluation and management of hypertension.

Disclosures
M.F.O. is the founding director of AtCor Medical, the manufacturer of systems for analyzing the arterial pulse. The remaining authors report no conflicts.

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20. Waddell TK, Dart AM, Medley TL, Cameron JD, Kingwell BA. Carotid pressure is a better predictor of coronary artery disease than brachial pressure. Hypertension. 2001;38:927–931.


