Central blood pressure and hypertension: role in cardiovascular risk assessment

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ABSTRACT

Although the differences between central and peripheral BP (blood pressure) have been known for decades, the consequences of decision-making based on peripheral rather than central BP have only recently been recognized. The influence of cyclic stretch (owing to cyclic changes in BP) on the aortic wall in atherosclerosis has been documented at every stage of its development. Apart from mediating atherosclerosis progression and plaque instability, the pulsatile component of BP is the main mechanism leading to plaque rupture and, consequently, to acute coronary syndromes and other vascular complications. The principal goal of the present review is to evaluate the role of central BP measurements, principally systolic and pulse pressure, for cardiovascular risk assessment. Recent findings suggest that the pulsatile component of BP (when represented by central pulse pressure or central pulsatility) is one of the most important factors determining event-free survival. Results of several prospective studies (using both invasive and non-invasive measurements of central BP) indicate not only an independent predictive value of central pulse pressure, but also its advantage over brachial pressure. Recent evidence suggests that some antihypertensive drugs can influence central BP more consistently when compared with peripheral BP. This is especially true for agents acting on the renin–angiotensin system. Nevertheless, large prospective studies aiming at the comparison of the predictive value of peripheral and central BP in the general population, as well as studies comparing the effectiveness of hypertension management based on peripheral compared with central BP measurements, are needed before algorithms based on central BP can be recommended for clinical practice.

INTRODUCTION

Brachial artery BP (blood pressure) measurement is of major value for the screening and diagnosis of clinical hypertension. However, in recent years, the assessment of CV (cardiovascular) risk in therapeutic trials and in meta-analyses in subjects with hypertension has led to the development of more sophisticated methods of BP measurement, raising several important questions [1]. First, for risk assessment, especially in subjects over 55 years of age, DBP (diastolic BP) becomes less useful than the other BP components, as it falls with age, leaving SBP (systolic BP), PP (pulse pressure) or MBP (mean BP) as possible candidates to discriminate CV risk better. Secondly, it is the aortic, not the brachial artery, pressures against which the heart pumps. Thus
The cushioning function is due to the viscoelastic continuous perfusion of peripheral organs and tissues. Draining this volume during diastole, thus permitting storing part of the stroke volume during systole and modulate the volume of blood ejected from the ventricles, arteries, mainly the aorta, can instantaneously accommodate the volume of blood ejected from the ventricles, storing part of the stroke volume during systole and draining this volume during diastole, thus permitting continuous perfusion of peripheral organs and tissues. The cushioning function is due to the viscoelastic properties of the arterial (mainly aortic) walls and is influenced by three factors: ventricular ejection, arterial (aortic) stiffness and wave reflections [1].

**Mechanotransduction of steady and pulsatile stretch**

From the above physiological description, it is logical to accept that arteries are permanently exposed to a basal stretch, which is related to MBP. MBP is paired to a pulsatile component, PP, since the heart represents a cyclic pump.

Stretch initiates complex signal transduction cascades leading to gene transcription and functional responses, via the interaction of integrins with extracellular matrix proteins or by stimulation of G-protein receptors, tyrosine kinase receptors or ion channels (reviewed in [2,3]). The intracellular pathways reported to be activated by stretch in VSMCs [VSM (vascular smooth muscle) cells] include mainly the MAPK (mitogen-activated protein kinase) cascades and NF-κB (nuclear factor κB) [3], which have been extensively studied at both VSM and endothelial levels. Steady and cyclic modes of stretch have been shown to transduce differently in the aorta, the former implicating FAK (focal adhesion kinase) and the latter free radicals derived from oxidative stress and the presence of inflammatory factors [4–6]. Furthermore, the transcriptional profile of mechanically induced genes in VSMCs subjected to a uniform biaxial cyclic strain has been studied widely [2,7]. Cyclic stretch is found to stimulate the expression of a number of genes, including VEGF (vascular endothelial growth factor) and PAI-I (plasminogen activator inhibitor-1), but to negatively regulate others, such as extracellular MMP-1 (matrix metalloproteinase-1) and thrombomodulin.

Nowadays, the differential effects of steady and pulsatile forces on mechanotransduction should be considered as obvious, even if several findings have been investigated mainly in vitro [3,8], with the corresponding in vivo findings remaining relatively scarce. Most of these are simply deduced from human epidemiological investigations, indicating that pulsatile stress, as represented by PP, wave reflections and/or arterial stiffness, represents a more adequate predictor of CV risk than steady stress [1–8]. In humans, steady stress is traditionally represented by the height of brachial SBP or DBP [8]. The independent role of pulsatile stress and its relationships with free radicals and atherosclerosis have been recognized more recently and constitutes one of the main objectives of the present review.

It should be emphasized that the influence of cyclic stretch on atherosclerosis has been documented at every stage of its development [9]. PP was shown to be an important factor conditioning the infiltration of the arterial wall by lipids [10]. Cyclic stretch stimulates the expression of adhesion molecules in endothelial cells, which...
facilitates the migration of inflammatory response cells into the vascular wall, as well as the production of scavenger receptors, thereby facilitating the transformation of macrophages into foam cells [9,11]. The activity of metalloproteinases in the atherosclerotic plaque also depends, at least partly, on the cyclic stretch of the arterial wall. The influence of vascular wall stretch on migration and proliferation of VSMCs was also documented, as well as its impact on the production of glycosaminoglycans by the same cells [9,12]. Moreover, apart from mediating atherosclerosis progression and atherosclerotic plaque instability, the pulsatile component of BP is the main mechanism leading to plaque rupture and, consequently, to acute coronary syndromes and other vascular complications [9]. In the present review, the mechanical analysis will be limited to tensile stress. Indeed, in most situations, changes in tensile and shear stress are associated, but the clinical applications of the latter remain limited [1–4].

**PATHOPHYSIOLOGICAL BASIS OF CENTRAL BP**

Currently, several arguments suggest that central BP is more relevant than peripheral BP for the determination of CV risk assessment [13,14].

The pressure wave generated by the left ventricle travels down the arterial tree and then is reflected at any discontinuity of the arterial wall, mainly the multiple resistance arterioles and their bifurcations (Figure 1). Consequently, the pressure waveform recorded at any site of the arterial tree is the sum of a forward travelling waveform generated by LV (left ventricular) ejection and a backward travelling wave, the ‘echo’ of the incident wave, reflected at peripheral sites [1,13]. This modelization leads, for the mathematical description of the total arterial tree, to define a reflection point common to the myriads of pressure waves and its physiological consequence: the relationship between brachial and central BP, which is characterized by "pressure wave amplification" (Figure 1) [1]. Typically DBP and MBP change little across the arterial tree; however, as a consequence of the transmission of the pressure wave and reflections, SBP and PP are amplified as much as 10–14 mmHg when moving from the aorta to the brachial artery (Figures 1 and 2). This phenomenon, seldom considered in published clinical guidelines, has three major consequences related to: (i) CV complications of hypertension; (ii) the choice of antihypertensive agents, and (iii) the regulation of heart rate.

Regarding CV complications, when the large conduit arteries are healthy and compliant (young subjects), the reflected wave merges with the incident wave in the proximal aorta mostly during diastole, thereby augmenting aortic DBP and supporting coronary perfusion (Figure 3). In contrast, when the arteries are stiff (old subjects), wave travel is faster and the reflected wave merges earlier with the incident wave, augmenting aortic systolic, rather than diastolic, pressure (Figure 3). As a result, LV afterload is increased and coronary filling is compromised. Such a pathophysiological mechanism supports the idea that central BP is superior to brachial BP in the prediction of CV risk and acts on CV risk independently of atherosclerosis and other traditional CV risk factors [13–15].

The choice of drug treatment in hypertension is also influenced by wave reflections, both by their amplitude (i.e., the proportion of incident wave which is reflected) and their timing (as shown in Figures 2 and 3). Acutely, vasodilators reduce the amplitude of wave reflections and hence SBP [1]. This process is observed typically
with nitrates, but may also occur with angiotensin or calcium entry blockade. With the presence of chronic hypertension, arterial and arteriolar remodelling modifies the baseline characteristics (geometry, distensibility and structure) of reflection sites, mainly at the arteriolar level. Under drug treatment, central SBP will be consistently reduced if vascular remodelling and reflection coefficients are adequately corrected (by angiotensin or calcium entry blockade), but will remain elevated if the structural changes of the microvasculature and the reflection coefficients remain poorly modified despite drug treatment (β-blocking agents) [15]. This finding has been particularly observed in REASON (Regression of Arterial Stiffness in a Controlled Double-Blind Study) [15], where angiotensin blockade and β-blockade have been compared. After 1 year of drug treatment, only angiotensin system blockade, but not β-blockade, reduced arteriolar remodelling and reflection coefficient, resulting in a reduction in central SBP and PP.

Finally, BP and PP amplification is highly influenced by heart rate (Figure 3). Lowering of heart rate tends to reduce SBP and PP amplification and increase ventricular afterload, whereas tachycardia has an opposite effect. The decrease in heart rate produced by β-blocking agents prevents the reduction in central SBP and PP in subjects with hypertension, in contrast with angiotensin blockade which significantly reduces SBP and PP and does not modify heart rate [16].

**INVASIVE CENTRAL INDICES PREDICTING CV EVENTS**

For the evaluation of CV risk, BP measurements within central arteries are the most adequate to perform, although their principal difficulty is their invasive nature. As femoral access is widely used in invasive cardiology centres, this technique allows central BP measurements to be done only in the supine position. A fluid-filled system, which is used in clinical practice, may lead to some inaccuracies, and this is especially true when the dynamic

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**Figure 2** Propagation of the BP curve from the thoracic to the aortic bifurcation

Note the change in the shape of the BP curve with the amplification of SBP and PP and minor modifications of DBP and MBP. Major branches of the aorta are indicated. This Figure was reproduced from W.W. Nichols and M. O’Rourke, McDonald’s Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles, 4th edition (Arnold, 1998). Reprinted by permission of Edward Arnold (Publishers) Ltd.

**Figure 3** Aortic BP curve for younger and older subjects for the same cross-sectional area under the curves, i.e. same MBP and same cardiac time

In the older subjects, SBP is higher and DBP lower than in younger subjects, indicating reduced diastolic coronary perfusion and disturbed central wave reflection (=increased AIx). This Figure was reproduced from W.W. Nichols and M. O’Rourke, McDonald’s Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles, 4th edition (Arnold, 1998). Reprinted by permission of Edward Arnold (Publishers) Ltd.
response characteristics of the fluid-filled system is not adequate. Most of the latter limitations can be overcome with the use of a high-fidelity pressure transducer [1]. Unfortunately, no studies using a high-fidelity transducer and assessing the relationship between central BP and prognosis have been published to date.

In recent years, many studies have been focused on the presence of positive correlations between aortic PP and the extent of coronary atherosclerosis [17–19]. No such correlations were found for MBP. Importantly, central PP was correlated better with atherosclerosis when compared with SBP or DBP levels. Indeed, the BP–atherosclerosis relationship can be clearly seen when central, instead of peripheral, BP values are analysed. Central PP was found not to be correlated with coronary atherosclerosis in a group of patients with impaired LV systolic function [20]. This finding could probably be attributed to diminished stroke volume and/or ventricular ejection in patients with severe atherosclerosis, rather than to a lack of a PP–atherosclerosis association.

Chirinos et al. [21] have published the results of 300 men with angiographically confirmed CHD (coronary heart disease) in whom intra-aortic pressure was measured invasively at baseline. They found that a 10 mmHg increase in PP in the ascending aorta may be associated with an increase in all-cause mortality by 15%. It is worth noting that Chirinos et al. [21] did not find any independent relationship between brachial PP and CV risk. In the ABPS (Aortic Blood Pressure and Survival) study, 1109 subjects with confirmed CHD were followed for over 4.5 years [22]. In this group, central BP was a much better predictor of CV complications compared with LVEF (LV ejection fraction), kidney function, diabetes mellitus, age or coronary atherosclerosis [22]. As a number of potential confounders were taken into account (including coronary atherosclerosis and invasive treatment of coronary disease), that study was the first to show the independent predictive value of central PP (as measured invasively) in patients with CHD. These results suggested that a 10 mmHg increase in central PP value was related to an increase in the risk of major CV events by 13% [22]. Importantly, central invasive MBP, as well as non-invasive peripheral BPs, were not related to the risk of CV events. It should be underlined that, besides significant differences in the methods used in these studies, the findings by Chirinos et al. [21] and data from the ABPS study [22] provide similar conclusions. As indicated in Table 1, central PP was also shown to predict restenosis after PCI (percutaneous coronary intervention) in three out of four small studies investigating the association between central PP and restenosis [24–28].

PP is traditionally believed to represent the pulsatile component of BP [29]; however, PP is also significantly correlated with MBP [9], which confirms that, apart from being an index of cyclic within-beat variations of BP, PP contains also information on the absolute BP level. On the other hand, pulsatility (the PP/MBP ratio) and the pulsatility index (the PP/DBP ratio) are not correlated with MBP [9,17], which indicates that these parameters may be devoid of information on absolute BP levels. Importantly, these two indices have no units (being ratios). Indeed, although PP represents absolute changes in BP, pulsatility and the pulsatility index are related rather to relative changes. This observation may be of particular relevance for studies on the pathogenesis of atherosclerosis and its complications. Recently, ascending aortic pulsatility was shown to be related to the extent of coronary atherosclerosis irrespective of the presence of hypertension [30]. Importantly, pulsatility tends to be a better predictor of both coronary atherosclerosis and CV events when compared with central PP [20,22]. In the ABPS study population, central pulsatility, but not

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### Table 1: Studies assessing the relationship between an invasively determined pulsatile BP component and the risk of CV events

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Duration of follow-up</th>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakayama et al. [25]</td>
<td>53</td>
<td>3 months</td>
<td>Central pulsatility</td>
<td>Increase by 0.1 increases the risk of restenosis after PCI by 88%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Central PP</td>
<td>PP higher in patients with restenosis after PCI</td>
</tr>
<tr>
<td>Lu et al. [26]</td>
<td>87</td>
<td>6 months</td>
<td>Central pulsatility</td>
<td>Increase by 0.1 increases the risk of restenosis after PCI by 154%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Central pulsatility index</td>
<td>Increase by 0.1 increases the risk of restenosis after PCI by 60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Central PP</td>
<td>Increase by 1 mmHg increases the risk of restenosis after PCI by 6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Central PP</td>
<td>Increase by 10 mmHg increases the risk of restenosis after PCI by 72%</td>
</tr>
<tr>
<td>Jankowski et al. [27]</td>
<td>84</td>
<td>9 months</td>
<td>Central PP</td>
<td>Increase by 10 mmHg increases the risk of all-cause mortality by 15%</td>
</tr>
<tr>
<td>Philippe et al. [28]</td>
<td>96</td>
<td>—</td>
<td>Central or peripheral PP</td>
<td>No independent relationship with the risk of restenosis after PCI</td>
</tr>
<tr>
<td>Ueda et al. [23]</td>
<td>52</td>
<td>4.6 years</td>
<td>Central PP</td>
<td>No independent relationship with all-cause or CV mortality</td>
</tr>
<tr>
<td>Chirinos et al. [21]</td>
<td>324</td>
<td>3.2 years</td>
<td>Peripheral PP</td>
<td>Increase by 10 mmHg increases the risk of all-cause mortality by 15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No significant relationship with the risk of all-cause mortality</td>
<td></td>
</tr>
<tr>
<td>Jankowski et al. [22]</td>
<td>1109</td>
<td>4.6 years</td>
<td>Central PP</td>
<td>Increase by 0.1 increases the risk of major CV events by 13%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Central pulsatility</td>
<td>Increase by 0.1 increases the risk of major CV events by 18% and the</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>risk of CV death/MI/stroke by 15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peripheral PP or pulsatility</td>
<td>No significant relationship with CV risk</td>
</tr>
</tbody>
</table>

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central PP, was related to the risk of CV end points consisting of CV death, MI (myocardial infarction) or stroke [22]. Another important finding is that central pulsatility appears to be a better predictor of CV events compared with LVEF, coronary atherosclerosis or kidney disease. Indeed, it appears that the pulsatile component of BP is the most important factor in determining prognosis, at least for patients with CHD [22].

Another index measured invasively is AIX (augmentation index), which reflects both amplitude and timing of wave reflections (see Figure 3) [1]. However, in a considerable proportion of patients (in some studies up to 30% [31]), it is not possible to find the inflection point on the pulse wave curve due to almost perfect overlapping of the ascending arms of the primary and reflected pressure waves. In many cases, this difficulty makes it impossible to reasonably estimate augmentation and AIX in these subjects. Therefore results based on invasive measurements of AIX should be treated with caution; in fact they cannot be considered as totally conclusive.

In conclusion, routine measurement of intra-aortic pressure could provide clinically important information. The recent evidence suggests that central BP determination during coronary angiography provides more precise information regarding the risk of future CV events compared with the extent of coronary atherosclerosis or LVEF [22]. As central BP measurement during coronary angiography is not itself related to any risk to the patient and is easy to perform rapidly, ascending aortic BP measurements should be an integral part of results of invasive diagnostic procedures in patients with CHD.

NON-INVASIVE CENTRAL INDICES PREDICTING CV EVENTS

The non-invasive measurement of BP has provided a great impetus for the spread of central pressure estimation in clinical practice. Two major methodologies are available for this purpose (Table 2) [13–16,32,33]: (i) estimation of central pressure waveforms by direct non-invasive recording at the carotid artery (method A); and (ii) the application of generalized transfer functions for the indirect estimation of aortic pressure waveforms based on pressure wave recordings at the radial artery (method B). Method A can be applied by using two different techniques for the recording of carotid pressure waveforms: (i) applanation tonometry, which is based on recording the pressure that is applied by the arterial wall on a pressure transducer; and (ii) echo tracking for the recording of arterial distension waves, which is based on a recording of the vessel's changes in diameter indirectly produced by BP variation. Both techniques provide good agreement and precision regarding the estimation of central PP as assessed from invasive recordings. With regard to method B, generalized transfer functions [13–16,32] are commercially available as the SphygmoCor system (AtCor Medical); however, other research groups have also developed and validated their own transfer functions [32].

With regard to the use of transfer functions for the estimation of central pressure waves, a few shortcomings should be noted. The initially developed generalized transfer functions were indeed validated on the basis of invasively measured radial pressures [1]. Therefore generalized transfer functions, although very carefully generated, cannot be derived from large clinical studies and are based mainly on a small number of well-performed intra-arterial measurements. The inaccuracies in the estimation of central BP (when compared with intra-arterial measurements) are mainly attributed to the initial inevitable error that is introduced during the calibration of pressure waveforms by the non-invasive measurement of brachial BP [34]. The results published by the AAMI (Association for the Advancement of Medical Instrumentation) for the American National Standard for Blood Pressure Measurements [35] show that the auscultatory SBP and DBP only poorly represent intra-atrial pressure. The AAMI compared the two methods in five studies totalling 197 patients and found the average difference between arterial and cuff SBP ranged from 0.9 to 12.3 mmHg, with the S.D. ranging from 1.3 to 13.0 mmHg. Similar comparisons for DBP showed average differences from 8.3 to 18.0 mmHg, with the S.D. ranging from 1.1 to 9.3 mmHg. These inconsistencies are necessarily passed along the MBP and PP when they are calculated from the auscultatory SBP and DBP. Furthermore, depending upon the age of the patient, the brachial SBP and PP will differ from aorta pressures, making, in fact, these cuff pressures unreliable surrogates of aortic pressures.

Regarding central SBP and PP as non-invasive evaluations of CV risk assessments, the first studies were performed in patients with end-stage renal failure [24,32,36]. Non-invasive indices of central SBP and PP, as well as indices of wave reflections, were shown to be strong independent predictors of all-cause and CV mortality. In subjects with hypertension, but without chronic renal failure, findings from the SHS (Strong Heart Study) have shown that brachial PP, a simple indirect index of arterial stiffness, was associated with a higher CV mortality level, independent of traditional risk factors, LV hypertrophy and reduced ejection fraction in adults without overt CHD [37]. Results from the same study showed in a 5-year follow-up that the non-invasively-determined central PP predicted incident CV disease better than did the corresponding brachial PP, possibly because of a more accurate representation of the vascular load on the left ventricle [38]. The predictive value of central PP was significant even when subclinical atherosclerosis was taken into account [38].
Disturbed arterial wave reflections expressed by the central AIx (discussed above) (Figure 3) are independently associated with an increased risk of severe short- and long-term CV events in patients undergoing PCIs [39]. Nevertheless, in contrast with this evidence, a study conducted in elderly women with hypertension found negative results on the same subject [40]. However, it is well-established that the factors influencing AIx in humans differ markedly between men and women, mainly due to the shorter stature of the latter [41]. Moreover, the independent relationship between invasively measured central PP and CV risk was proved only in men [21,22]. The large CAFE (Conduit Artery Function Evaluation) study reported that central PP derived from radial artery applanation tonometry independently predicted CV outcomes in treated patients with hypertension [16]. Finally, highlighting the interplay between small and large arteries in the evaluation of CV risk determination, the structure of small arteries (which compose the main reflection sites in hypertension) was shown to be a predictor of CV events in patients with hypertension [42]. However, the result was observed exclusively in association with the presence of a high brachial PP, a surrogate index of the status of large arteries. Recently, a new non-invasively estimated parameter of central BP, central pulsatility (the central PP/central MBP ratio), was shown to be related to the coronary atherosclerosis, as well as to the previous MI [43].

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 on central BP and derived indices in more general populations or in other disease states. Finally, it would be desirable for future studies to address whether central BP may be measured using other new methods and provide incremental and independent prognostic value over other emerging biomarkers [44]. Routine central BP measurements in humans are important to consider, but they remain in their infancy.

**THERAPEUTIC IMPLICATIONS**

At present, the therapeutic applications of the studies described in this review remain modest. A certain number of currently used antihypertensive drugs have been shown to have significant effects on arterial stiffness and mostly on wave reflections, such as nitrates and their derivatives [1]. With the exception of their action on muscular peripheral arteries and arterioles, these agents appear to have little direct influence on central arterial mechanical properties. Nevertheless, they may act on central arteries through the mechanism of wave reflections with evident chronic reduction in PP in the elderly population [1].

Molecules acting on the RAS (renin–angiotensin system) and aldosterone appear to have a greater effect on central PP and arterial stiffness (independently of BP-lowering) than the other classes of drug (including calcium channel antagonists) [45]. All of these effects are evident when central, but not peripheral, measurements are performed. Regarding the RAS, it is well accepted that in rodents AngII (angiotensin II) infusion is associated with an increase in carotid arterial mass and stiffness, independent of an increase in MBP [29]. This response requires the presence of an active α-integrin on the carotid wall in order to be effective, as shown from the effect of angiotensin in knockout mice devoid of this compound. In rats, angiotensin blockade by an ACEI (angiotensin-converting enzyme inhibitor) or an AT1 receptor (AngII type 1 receptor) antagonist selectively reduces central PP and arterial stiffness, and even decreases PP more extensively than MBP [46,47]. This result was observed only in the presence of a normal-sodium diet. Regarding chronic
aldosterone, the perfusion of this hormone in the presence of a high-sodium diet selectively increased central PP and aortic stiffness in rats, a finding reversed in the presence of the aldosterone antagonist eplerenone [48].

Blockade of angiotensin and aldosterone prevent arterial fibrosis in SHRs (spontaneously hypertensive rats), but have minor effects on central PP and carotid stiffness when a high-sodium diet is present [47]. Indeed, under all of the conditions involving a high-sodium diet, increased arterial fibronectin expression develops at the site of the carotid arterial wall [46–48]. Finally, all of these observations suggest that carotid α-integrins play an associated role in the mechanism(s) of arterial stiffness and central PP change during angiotensin and/or aldosterone blockade through the formation of a carotid complex associating integrin and fibronectin.

In humans with hypertension, a combination of the ACEI perindopril with small doses of the diuretic indapamide reduces SBP more than the β-blocking agent atenolol for the same reduction in DBP [15]. The reduction in SBP during ACEI treatment is much more pronounced in the carotid artery compared with the brachial artery and is associated with a significant decrease in cardiac hypertrophy (in contrast with atenolol). A similar result was also observed with the same ACEI associated with the calcium channel antagonist amlodipine [16]. A significant decrease in CV outcomes was associated in parallel. Such findings have not been observed to the same extent with the β-blocking agent atenolol. Eprosartan was also shown to have a greater effect on central compared with brachial SBP [49]. In another small study, atenolol increased central PP when compared with nebivolol or placebo [50]. Currently, a new drug (an advanced glycation end-products cross-link breaker) called alagebrium is being investigated. This agent reduces the pulsatile BP component without influencing MBP. Alagebrium has been shown to increase arterial compliance, and reduce PP and pulsatility [51].

PROSPECTIVE VIEWS

Antihypertensive drug therapy has considerably improved the prognosis of CV prevention, but most of the statistical evaluations, however, indicate the persistence of a significant residual coronary risk [52–54]. Furthermore, drug treatment normalizes DBP (<90 mmHg) in more than 80% of cases, whereas SBP is normalized (<140 mmHg) in approx. 60% of cases [52,54]. Most international recommendations suggest improving CV prevention only through the association of various antihypertensive agents. The main consequence of these recommendations has been simply to decrease DBP further, but without any major improvement in SBP.

Currently, using either international or European guidelines, it is possible to evaluate the effectiveness of chronic drug treatment on brachial BP using well-established classifications of BP level. The results may be compared with those obtained on central BP measured in parallel in the same patients under the same conditions. Two main findings emerged from such results [55,56]. First, despite the fact that an optimal brachial BP reduction had been obtained, SBP and PP amplification became lower than normal in treated subjects, suggesting that, despite optimal brachial BP reduction, central BP remains too high under drug treatment (when compared with normal control values). Secondly, in the same patients with optimal brachial BP reduction under treatment, pulse wave velocity and wave reflections remain somewhat higher than in untreated controls. Clearly, the results indicate that traditional drug therapy is not sufficient to optimally reduce central BP, and that developing drugs acting specifically on arterial stiffness and wave reflections are important in order to obtain an optimal therapeutic effect in subjects with hypertension.

More specifically, the analysis of previous trials has shown that a reduction in SBP and PP may be centrally obtained with blockade of AngII and/or calcium channels, whereas β-blocking agents have little effects on central SBP and PP [14]. The same agents reduce microvascular structure markedly and cause simultaneous remodelling of the arteriolar reflection sites, an effect poorly obtained with β-blocking agents alone [57]. In contrast, diuretics undoubtedly may potentiate such effects. In one short-term study, hydrochlorothiazide was shown to decrease peripheral and central BP equally [58], and indapamide markedly improved wave reflections [45,47].

A number of algorithms are recommended to calculate CV risk in patients with CV risk factors [52–54]. All of these algorithms are based on brachial BP measurements. Large prospective studies aiming at the comparison of the predictive value of peripheral and central BP in large populations are needed before algorithms based on central BP can be recommended for clinical practice. Large epidemiological studies will probably answer the following question: should hypertension be diagnosed according to peripheral or central BP values? Finally, there is a need for studies comparing the effectiveness of hypertension management based on peripheral compared with central BP measurements.

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