Effect of angiotensin II blockade on central blood pressure and arterial stiffness in subjects with hypertension

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Abstract: In hypertension, the blood pressure curve may be divided into two sets of components. The first set is mean arterial pressure, steady flow, and vascular resistance, thus acting on small arteries; the second set refers to large arteries, hence to pulse pressure, arterial stiffness, and wave reflections. The angiotensin-converting enzyme (ACE) inhibitor perindopril not only reduces mean arterial pressure but also acts specifically on pulse pressure. The effect on pulse pressure predominates on central rather than peripheral (brachial) large arteries, reducing aortic stiffness and most wave reflections. Such hemodynamic changes are not observed with standard β-blockade, which reduces aortic stiffness and brachial systolic and pulse pressure but not central pulse pressure and wave reflections. In hypertensive subjects, perindopril and other ACE inhibitors seem to predict more consistently the reduction of cardiovascular events, mainly of cardiac origin, than standard β-blockers alone. This effect is associated with the important biochemical finding that mechanotransductions of angiotensin and β-blockade are markedly different, acting in the former specifically on the α5β1 integrin complex and on the fibronectin ligand of arterial vessels.

Keywords: antihypertensive therapy, arterial stiffness, renal function

Introduction

Because they are the simple consequence of the well established auscultatory method, blood pressure (BP) measurements are usually obtained from the definition of only two specific points of the BP curve, ie, peak systolic BP and end diastolic BP. After the advent of antihypertensive therapy and following the results of therapeutic trials in populations of subjects with hypertension, it was proposed that cardiovascular effectiveness could be better evaluated from systolic BP than from diastolic BP. However, these standard definitions are oversimplified and now require substantial revision.

Blood pressure is the force applied per unit area on a given vessel, which determines the flow of blood. Pressure and flow result from the properties of the heart as a pump and the characteristics of the arterial system. However, pressure and flow vary during the cardiac cycle and are therefore called pulsatile pressure and flow. When the BP curve is submitted to Fourier analysis and written as a series of sine waves, these waves are called oscillatory pressure and flow. The zero term equals the mean value (mean arterial pressure) of BP, and the harmonics are the oscillatory terms, summarized by pulse pressure (pulse pressure = systolic BP – diastolic BP, see Figure 1).

After World War II, a group of cardiovascular physiologists suggested that the pulsatile BP curve could be better described when divided into two components, ie, a steady...
component (mean arterial pressure) and a pulsatile component (pulse pressure), as shown in Figure 1. This review focuses on, firstly, the description of the hemodynamics of untreated hypertension according to the basic principles defined from mean arterial pressure and pulse pressure, and, secondly, application of these principles to the study of angiotensin blockade. Perindopril was the first angiotensin-converting enzyme (ACE) inhibitor to be studied in subjects with hypertension using mean arterial pressure and pulse pressure. The role of the other ACE inhibitors in the mechanisms of angiotensin blockade is indicated in the Appendix.

Systemic hemodynamics in untreated hypertension

Large arteries have two distinct functions. The first consists of transporting blood from the heart toward peripheral tissues in order to satisfy their metabolic needs. This function requires the presence of a steady pressure gradient, represented principally by mean arterial pressure. In order to define this gradient, mean arterial pressure, calculated from the cross-sectional area under the BP curve divided by cardiac cycle time, is subtracted from central venous pressure, which is normally close to zero. The second function of large arteries consists of instantaneously accommodating the volume of blood ejected from the left ventricle of the heart, storing part of the stroke volume during systolic ejection, and carrying this volume during diastole, thereby ensuring continuous perfusion of organs and tissues at the peripheral level. This specific function of arteries is usually described in terms of elasticity or stiffness of the aorta or an individual artery and is usually associated with the generation of wave reflections.

Large artery elasticity or stiffness is usually determined from systolic and diastolic changes in artery diameter, coupled with measurement of local pulse pressure, which is the difference between systolic BP and diastolic BP. However, the most common method for evaluating arterial stiffness is based on the study of pulse wave velocity, ie, the velocity of the BP propagation wave along a given conduit artery, eg, the aorta. Pulse wave velocity can be determined from measurements of pulse transit time and the distance travelled by the pulse between the common carotid and femoral arteries. Aortic pulse wave velocity (carotid to femoral) can be measured by applanation tonometry, mechatransducer, or Doppler probes and is regarded as the gold standard for determining arterial stiffness, independent of wave activity. The technique of applanation tonometry is widely used to evaluate central BP and also wave reflections through the determination of the augmentation index, a noninvasive parameter (Figure 2). The augmentation index is a measure of the contribution that wave reflection makes to the central pressure wave. It is defined as the difference between the second and first peaks (P2-P1) corresponding to systolic BP and is expressed as a percentage of the pulse pressure. Therefore, the augmentation index is a quite indirect measure of systemic stiffness and is mostly a direct measure of wave reflection, a parameter defined later in this review.

It is widely accepted nowadays that the aortic BP curve represents the mathematical summation of an incident pressure wave, coming from the heart through ventricular ejection, and a reflected wave depending on a given arterial or arteriolar site characterized by three independent parameters, ie, the value of reflection coefficients, the degree of arterial stiffening, and the distance between the heart and the site of reflecting points (Figure 3). Under normal conditions, the complex interaction between these parameters is responsible for the physiologic amplification of the pressure pulse observed between central and peripheral arteries, whereas mean arterial pressure remains almost constant along the arterial tree. Under pathologic conditions, as frequently observed in elderly people, particularly those with hypertension, both increased arterial stiffening and reflection sites closer to the heart (ie, reflection sites at the level of arteriolar or arterial bifurcations) cause the backward pressure wave to return sooner (ie, during the systolic component of the aortic BP curve), resulting in a greater summation between the forward and backward waves and consequently a higher aortic pulse pressure and systolic peak. In older subjects with hypertension, such changes are responsible for a peculiar hemodynamic pattern involving a disproportionate increase of systolic BP over diastolic BP, with potentially a loss in pulse pressure amplification.

Finally, in the past, hypertension was simply defined from high mean arterial pressure, associated with elevated systolic
BP and diastolic BP. Mean arterial pressure divided by cardiac output enables calculation of vascular resistance, considered to be an index of the caliber of small arteries. Increased vascular resistance some decades ago was considered to be the unique and universal hallmark of hypertension. Nowadays, the buffering function of large arteries is also taken into consideration. This changing definition is due to the high frequency of systolic hypertension in the elderly, which generates mainly increased arterial stiffness and disturbed wave reflections but not necessarily increased vascular resistance.

**Hemodynamic effects of angiotensin II inhibition in hypertension**

The point to consider here is that the ACE inhibitor perindopril is able not only to decrease mean arterial pressure but also, through its effect on conduit arteries, to decrease brachial pulse pressure\(^5\)–\(^7\) and, even more selectively, central (carotid and aortic) pulse pressure (see Table 1).

We and others have shown in many previous clinical studies that ACE inhibitors may increase arterial diameter and decrease arterial stiffness independently of changes in mean arterial pressure.\(^8\)\(^9\) In addition, ACE inhibitors have been shown to act selectively on the backward aortic pressure wave, causing the reflected wave to return during the diastolic (but not the systolic) component of the BP curve, thus reducing aortic pulse pressure and systolic peak much more than brachial pulse and systolic BP. Thus, the decrease in arterial stiffness and change in the pattern of pulse wave reflections observed with perindopril contribute significantly to a decrease in BP through arterial (and not exclusively arteriolar) effects. Both in animals and in humans, there is strong evidence to support this assumption, particularly following long-term treatment with ACE inhibition. Firstly, in spontaneously hypertensive rats and in patients with

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**Figure 2** The augmentation index is the ratio of the difference between peak systolic blood pressure, shoulder of the ascending part of the blood pressure curve, and pulse pressure.\(^1\)–\(^4\) The augmentation index, measured as a percentage, represents the supplementary increase in systolic blood pressure due to wave reflections. This hemodynamic profile is observed in the elderly but not in young people (see also Figure 3).

**Figure 3** A classical and simple model for the definition of arterial stiffness and wave reflections. Top: a normal youthful arterial tree. Bottom: a stiffened arterial tree of an older person. The reflection of the pressure wave is represented by the diastolic wave in the first case (A) and by the late systolic wave in the second case (B). Coronary arteries are represented by hooks. PWV is an index of arterial stiffness and is dependent on degree of rigidity (thin line or thick line) of the arterial wall.\(^1\)–\(^4\)

**Abbreviation:** PWV, pulse wave velocity.
systolic hypertension and end-stage renal disease, ACE inhibition restores the aortic pulse pressure amplification normally observed from central to peripheral arteries, causing a more substantial decrease in carotid than in brachial systolic and pulse pressure.6,7 Secondly, in subjects with essential hypertension, ACE inhibitors decrease brachial systolic BP more than β-blocking agents for the same decrease in brachial diastolic BP and mean arterial pressure.10

REASON (Preterax in Regression of Arterial Stiffness in a Controlled Double-blind Study)11 was the first clinical trial to investigate the long-term effects of antihypertensive drug treatment on central systolic BP and pulse pressure, aortic stiffness, and wave reflections. It was conducted in middle-aged hypertensive subjects. Administration of perindopril, combined with a low dose of the diuretic indapamide, was compared with the effect of the β-blocking agent atenolol for one year. For the same diastolic BP and mean arterial pressure reduction, perindopril plus indapamide lowered systolic BP and pulse pressure more than atenolol (Figure 4). Moreover, the reduction was significantly more pronounced centrally (carotid artery) than peripherally (brachial artery, Figure 5). Although the two drug regimens lowered pulse wave velocity equally, only perindopril plus indapamide reduced central (carotid) pulse pressure and augmentation index.1–3,11,12 Central pulse pressure and augmentation index remained unchanged with atenolol. Furthermore, perindopril plus indapamide decreased cardiac hypertrophy more than atenolol. This effect was attributed to the augmentation index decline, indicating that the reduction of cardiac mass was related to central wave reflections.13–15 Furthermore, on drug treatment, the selective lowering of systolic BP (but not diastolic BP) with perindopril plus indapamide was significantly predicted by the baseline pulse wave velocity value. Thus, REASON emphasized the predictive values of pulse wave velocity, central systolic BP, and mean arterial pressure

| Table 1 The REASON study population (n = 181) with central (carotid) and brachial measurements11 |
|-----------------------------------------------|-----------------|-----------------|----------------|
| Brachial systolic BP (mmHg)                   | Perindopril plus indapamide | Atenolol         | P value        |
| Time                                          | M0               | M6              | M12            |
|                                               | 165.65 ± 1.40    | 162.18 ± 1.36   | 0.0786         |
| Carotid systolic BP (mmHg)                    | Perindopril plus indapamide | Atenolol         | P value        |
| Time                                          | M0               | M6              | M12            |
|                                               | 154.46 ± 1.95    | 152.37 ± 1.90   | 0.4431         |
| Aortic systolic BP (mmHg)                     | Perindopril plus indapamide | Atenolol         | P value        |
| Time                                          | M0               | M6              | M12            |
|                                               | 155.63 ± 1.83    | 151.23 ± 1.80   | 0.0891         |
| Brachial-carotid systolic BP (mmHg) amplification | Perindopril plus indapamide | Atenolol         | P value        |
| Time                                          | M0               | M6              | M12            |
|                                               | 9.40 ± 1.54      | 9.64 ± 1.50     | 0.9125         |
| Carotid augmentation index (%)                | Perindopril plus indapamide | Atenolol         | P value        |
| Time                                          | M0               | M6              | M12            |
|                                               | 29.09 ± 2.24     | 28.77 ± 2.16    | 0.9175         |
| Aortic augmentation index (%)                 | Perindopril plus indapamide | Atenolol         | P value        |
| Time                                          | M0               | M6              | M12            |
|                                               | 30.06 ± 0.98     | 30.30 ± 0.97    | 0.8616         |
| Pulse wave velocity (m/sec)                   | Perindopril plus indapamide | Atenolol         | P value        |
| Time                                          | M0               | M6              | M12            |
|                                               | 12.91 ± 0.26     | 12.46 ± 0.25    | 0.2161         |

Note: *Significant intergroup comparisons. Main cardiovascular parameters: adjusted absolute means ± standard error of means are presented at M0, M6, and M12.

Abbreviations: BP, blood pressure; M, month; REASON, Preterax in Regression of Arterial Stiffness in a Controlled Double-blind Study.
and pulse pressure in the mechanisms of BP reduction in hypertensive subjects. A confirmation of all these findings was obtained later from ASCOT (the Anglo-Scandinavian Cardiac Outcomes Trial) in which the role of central BP as predictive of cardiovascular events was further confirmed.

**Transduction within the arterial wall, pulse pressure, and angiotensin II blockade**

Mechanical forces involve pulsatile and steady pressure components but also have to integrate some biologic components, including those relating to structural and biochemical factors acting on arterial vessels. Focal adhesion formations of extracellular matrix and integrin-specific signaling in vascular smooth muscle cells are essential for mechanotransduction of angiotensin blockade within the arterial wall.

Dense plaques, which are composed of cytoskeletal proteins linked to the extracellular matrix by integrin receptors, are major sites of anchorage between vascular smooth muscle and the extracellular matrix. They represent key elements for interaction between mechanical forces and elastic materials. Integrins exist as αβ pairings. They interact with extracellular matrix components, including fibronectin (ligand for α5β1 and αvβ3), vitronectin (ligand for αvβ3), and laminin (ligand for α6β1). Interactions of specific extracellular matrix proteins with their integrin receptors play a central role in transmitting mechanical forces to vascular smooth muscle. Many of these integrins are capable of forming complexes with fibronectin, a glycoprotein that plays an important role in the organization and assembly of the extracellular matrix.

When cyclic mechanical strain is applied to matrixes containing different adhesion proteins, fibronectin produces one of the largest mitogenic responses in rat vascular smooth muscle. In addition, expression of fibronectin and its α5β1 receptor are increased in the spontaneously hypertensive rat aorta. The increase of fibronectin may reflect an increased number of mechanical attachments between the extracellular matrix and collagen fibers within the media. From a mechanical point of view, an increased number of cell matrix attachments promote increased stiffness and mechanical strength.

These changes have been studied in situations involving normal or increased sodium intake in the presence of angiotensin II and/or aldosterone stimulation and blockade. With a normal sodium diet, angiotensin or aldosterone blockade reduces mean arterial pressure and pulse pressure, and decreases collagen

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**Figure 4** Overall intention-to-treat population in REASON: adjusted values (±SD) in brachial SBP and DBP, measured each month in the perindopril plus indapamide and atenolol groups. There was no difference between groups for DBP but only for SBP and exclusively at month 12.

**Figure 5** Incidence of all renal events in ADVANCE according to achieved blood pressure levels, adjusted for age, gender, duration of diabetes, glycated hemoglobin, currently treated hypertension, history of macrovascular disease, electrocardiogram abnormalities (ventricular hypertrophy, Q waves, or atrial fibrillation), triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, body mass index, current smoking, current alcohol use, and study drug. Solid boxes represent estimates of event rates, centers of which are placed at the intersection of the point estimate and median systolic blood pressure value. Areas of the boxes are proportional to the number of events, and vertical bars represent 95% confidence interval. The rate of all renal events was significantly associated with achieved systolic blood pressure levels (P < 0.0001).

**Abbreviation:** ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR, Controlled Evaluation Study.
accumulation, fibronectin, and its integrin receptor. On a high sodium diet, mean arterial pressure, but not central pulse pressure, is reduced in association with collagen accumulation, increased fibronectin, and increased arterial stiffness.

It is worth noting that the mechanical contribution of mean arterial pressure and pulse pressure may vary markedly according to age or the vascular territory involved. Thus, pulse pressure mechanotransduction may predominate in the heart rather than in the brain or kidney because only the former territory involves active periodic autocollisions. Furthermore, with increasing age, reflection coefficients are located much closer to target organs (ie, the heart, brain, or kidney). This finding suggests that pulsatility and wave reflections may be transmitted to these organs in the presence of a defect in myogenic tone. This defect is commonly observed in subjects with type 2 diabetes mellitus, those with uninephrectomy or obesity, and often in older patients with systolic hypertension.28–31

This finding suggests that pulsatility and wave reflections may affect each particular organ locally, thereby modulating or interacting with a local hormonal system. A typical example would be subjects with hypertension and type 2 diabetes mellitus in whom perindopril reduces both systolic BP and renal events.

In conclusion, the renin–angiotensin–aldosterone system has been considered for many years only as a hormonal factor of the basis of hypertension and its treatment. With the development of antihypertensive therapy, the same system has come to be understood as a modulating antioxidative and anti-inflammatory factor contributing to the reduction of cardiovascular morbidity and mortality through its antifibrinotic effects, mainly observed in the elderly and particularly in the large arterial system. This system remains under investigation in older populations.

Acknowledgments
This work was performed with the help of INSERM (Institut de la Santé et de la Recherche Médicale) and GPH Cardiovascular (Groupe de Pharmacologie et d’Hémodynamique Cardio-vasculaire), Paris. Thanks are extended to Dr Anne Safar for helpful and stimulating discussions.

Disclosure
The author reports no conflict of interest in this work.

References
### Table 1 Differences between central and brachial systolic pressure changes related to angiotensin blockade

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Drug</th>
<th>Difference between central and peripheral systolic pressure change</th>
<th>Net difference between ACE inhibitor/sartan and other antihypertensive agents</th>
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<tr>
<td>Asmar et al32</td>
<td>184</td>
<td>Perindopril</td>
<td>-0.6 mmHg</td>
<td>7.6 mmHg</td>
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<td></td>
<td>170</td>
<td>Perindopril plus indapamide Atenolol</td>
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<tr>
<td>Williams et al17</td>
<td>1042</td>
<td>Amlodipine-perindopril</td>
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<tr>
<td>Morgan et al33</td>
<td>32</td>
<td>Perindopril</td>
<td>4.7 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>or enalapril</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deary et al34</td>
<td>30</td>
<td>Lisinopril</td>
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<tr>
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<td>ACE inhibitor</td>
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**Abbreviation:** ACE, angiotensin-converting enzyme.