

Central Blood Pressure Under Angiotensin and Calcium Channel Blockade

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Hemodynamic studies have shown that, in healthy subjects, there is a gradual widening of the height of the pressure waveform as it travels from the central (aortic) elastic arteries to the peripheral muscular arteries (brachial pressure waveform as it travels from the central (aortic) arterial sites. This finding is mainly attributed to the gradual increase (ie, amplification) of systolic BP (SBP) or pulse pressure (PP) along the arterial tree and is conventionally quantified as the ratio of the SBP or PP between the 2 sites (eg, SBP arm:SBP aorta)\(^1\) (Figure).

In the present issue of Hypertension, Matsui et al\(^2\) have shown the superiority of calcium channel blockers (CCBs) over diuretics using the following protocol: the angiotensin receptor blocker olmesartan was combined with the CCB azelnidipine and compared with the same olmesartan associated with the diuretic hydrochlorothiazide. Central SBP was shown to be lower (ie, normotensive). Furthermore, CCBs have attenuated the pressure wave reflection as measured by carotid-femoral pulse wave velocity, and pressure wave amplification and, thus, to heart rate or left ventricular ejection fraction.

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Central BP, SBP, and PP Amplification and Angiotensin II Blockade

The BP curve consists of 2 components: a steady and nonamplifiable component, the MAP, that depends on cardiac output and peripheral arterial resistance (microcirculation) and a pulsatile and amplifiable component (ie, the PP), that depends on large artery stiffness and pressure wave reflection (macrocirculation). It is essential to notice this distinction, because the transduction mechanisms governing MAP and PP differ markedly, involving apparently either focal adhesion kinase for MAP or oxygen free radicals for PP.\(^5\)

Angiotensin II (ANGII) blockade is mainly associated with a reduction of vascular resistance and MAP. In contrast, the effects on central and peripheral PPs have been poorly investigated despite their well-established interactions with oxygen free radicals. Studies on animal models and humans suggest that ANGII blockade is associated with reverse remodeling of both small and large arteries via specific mechanisms, including anti-inflammatory effects and mainly change of arterial attachments linking \(\alpha_\beta_1\)-integrin to its specific ligand fibronectin.\(^6\)\(^7\) Such effects are important to obtain a significant and selective reduction of central PP and arterial stiffness under ANGII blockade.\(^6\) In hypertensive rats on a low-salt diet (but not a high-salt diet), ANGII blockade by valsartan normalizes central PP (<50 mm Hg) but not MAP for the same drug dosage.\(^7\) In hypertensive subjects under ANGII blockade, carotid-brachial SBP and PP amplifications are increased. ANGII blockade improves or even normalizes the structure of small resistance arteries and, at the same time, reduces pressure wave reflections, suggesting a cause-and-effect relationship between the 2 factors.\(^3\)\(^8\) In the study by Matsui et al,\(^2\) ANGII inhibition by olmesartan may have greatly contributed to independently lower central PP and aortic stiffness. The same mechanisms are not observed under CCB blockade.\(^6\)

Evidence on the Mechanism of Action of a CCB on Central BP and Amplification

The amplification phenomenon is a direct result of the distortion (ie, alteration in the morphology) of the pressure waveform as it travels distally, attributed mainly to the existence of an elasticity gradient along the arterial bed and the presence of reflected pressure waves.\(^1\) The SBP amplification is inversely related to large artery stiffness, as assessed by carotid-femoral pulse wave velocity, and pressure wave reflections, as assessed by the augmentation index, a classic marker of wave reflections. The mechanism by which these parameters affect the SBP amplification is largely related to the “timing synchronization” of the forward and reflected waves and, thus, to heart rate or left ventricular ejection.

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In a large population of treated hypertensives, it has been shown recently that SBP amplification is primarily modulated by heart rate and large artery stiffness.\(^9\)

In the present study, Matsui et al\(^2\) have provided evidence on the mechanism of the reduction of SBP and PP amplification by a CCB, namely by reducing the pulse wave velocity and augmentation index. In line with previous findings showing that aortic stiffness is the major predictor of brachial SBP reduction,\(^10\) the present data highlight the predominant role of aortic stiffness as a predictor of central SBP reduction. The CCB is a powerful vasodilating agent, increasing the large artery diameter independent of BP reduction and of any endothelium-dependent effect.\(^6\) Reduction of pressure wave reflections is the second important mechanism of central SBP reduction by CCB.\(^2\) Although heart rate was decreased in the olmesartan/azelnidipine arm, thus favoring an earlier timing of wave reflections in systole, augmentation index was reduced. This may be explained partly by the prolonged time of return of the reflected wave because of lower pulse wave velocity. Another possibility is that the long-term drug treatment causes regression of arteriolar hypertrophy, as is usually observed under CCB treatment.\(^3\) This might cause a distal shift of reflection sites or decrease of the reflection coefficients, thus lowering amplitude of wave reflections.\(^3\) The same possibility may be observed with ANGII blockade but not with diuretic or traditional \(\beta\)-blocking agents given alone.\(^3,8\) Whether azelnidipine has such effects, most likely via arteriolar vasodilation and structural changes, by altering baroreflex sensitivity, or even by acting synergistically with ANGII blockade, is a possibility that merits additional exploration.

**Clinical Implications and Perspectives**

In clinical practice, the amplification phenomenon has potentially important clinical implications regarding CV risk assessment, stratification, and treatment.\(^1\) First, for a given brachial SBP, higher SBP amplification, per se, is associated with lower CV risk. Second, a large proportion of hypertensive subjects may be misclassified concerning their BP-associated CV risk when based solely on brachial SBP. Third, we have shown that, in treated hypertensive subjects, the effective (even optimal) control of brachial SBP is not constantly associated with normalization of central hemodynamic parameters (eg, SBP amplification, pulse wave velocity, and augmentation index), when compared with untreated normotensive subjects. This process implies the presence of residual CV risk, particularly in the coronary circulation.\(^11\)

Finally, recent studies have clearly indicated that central BP (or its amplification) is superior to brachial BP in terms of risk assessment. However, 2 important questions remain the object of debate. First, what is the most powerful central hemodynamic parameter predicting CV risk? Second, which central parameters might have superiority over peripheral BP in terms of CV risk reduction strategies? The topic of central hemodynamics is emerging, and more studies, particularly regarding CV outcomes, are urgently needed.

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**Disclosures**

None.

**References**


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