Pulsology Reloaded

Commentary on Similar Effects of Treatment on Central and Brachial Blood Pressure in Older Hypertensive Subjects

Vittorio Palmieri, Riccardo Pini, Maria Chiara Cavallini

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) Study,[1] the Second Australian National Blood Pressure Trial (ANBP2),[2] and the Anglo-Scandinavian Cardiovascular Outcome Trials[3] have shown that different antihypertensive treatments may have different impacts on the rate of events in hypertension while achieving comparable brachial blood pressure (BP) reduction. Thus, although brachial BP estimation by classic Riva–Rocci cuff sphygmomanometer and the Korotkoff auscultatory technique have provided almost all of our knowledge on epidemiology, prognosis, and treatment of hypertension,[4,5] recent trials[1–3] are revealing intrinsic limitations of the conventional approach, because the real goal of treatment in hypertension is the reduction in the number and the rate of untoward events.

More recently, the Conduit Artery Function Evaluation (CAFE) Study[6] described higher central BP as a key factor explaining the greater number and rate of events with atenolol than with amlodipine plus perindopril. Central pressure waveform and BP values can be estimated by applanation tonometry, a method supported by solid theoretical principles and modeling studies in experimental settings.[7] Analysis of the systolic portion of the carotid pressure waveform allows for obtaining indices of the arterial viscous-elastic properties that correlate with end-organ damage and clinical outcomes in hypertension.[8] Therefore, the indices of arterial waveform reflection and mechanics and central BP assessed by applanation tonometry have the potential to add significant information for risk stratification beyond and above brachial BP. In fact, the conclusions of the CAFE Study were well received.[9] In addition, applanation tonometry has also been associated with 2D-guided M-mode vascular ultrasonography to assess simultaneously the viscous-elastic properties of the carotid artery, the intima–media thickness, and quantification of atherosclerosis.[8] Assessment of cardiovascular target organ damage is curial for a global risk assessment integrating the staging of hypertension by measures of BP.[5]

In this issue of *Hypertension,* Dart et al[10] reported that hydrochlorothiazide and enalapril, at doses that caused comparable brachial BP reduction, had similar impact on central BP. Thus, the authors concluded that central BP was not the factor explaining the better outcome in hypertensive subjects randomly assigned to enalapril than in those randomly assigned to hydrochlorothiazide reported previously in the main ANBP2 Study.[2] Dart et al[10] evaluated 479 older hypertensive subjects from the larger ANBP2 Study,[2] who had paired evaluations of brachial and central BP at baseline after 4 years of antihypertensive treatment.[10] Questions arise. How strong is the evidence that different antihypertensive treatments may have substantially different impacts on central and brachial BPs? Furthermore, is central BP the only determinant of different outcome associated with different antihypertensive treatments achieving comparable BP reduction? Is the case of ANPB2[10] compared with CAFE[6] a matter of taking the "blue pill" or the "red pill," as in the cult movie *Matrix*?

Antihypertensive treatment was significantly different between the CAFE (amlodipine plus perindopril versus atenolol plus bendroflumethiazide potassium[6]) and the ANBP2 substudy (hydrochlorothiazide versus enalapril[10]), which may have contributed to the discrepancy. An early study in a small sample of patients with hypertension with age comprised between 65 and 85 years showed that traditional β-1 adrenoreceptor block was able to reduce brachial but not central BP compared with placebo.[11] However, another previous small study showed that perindopril and atenolol were both efficacious in reducing central BP, although by different mechanisms.[12]

Notably, Morgan et al used radial applanation tonometry to derive central pressure waveform and estimate central BP,[11] whereas Pannier et al[12] used carotid applanation tonometry for a direct reproduction of the central pressure waveform. The CAFE Study[6] used radial applanation tonometry and pulse wave analysis to back calculate central BP,[13] applying the notion that pulse pressure increases from central to periphery.[14] In fact, in the CAFE Study, central pulse pressure was lower than its brachial counterpart. In contrast, in the ANBP2, central BP was estimated by carotid applanation tonometry.[10,15] Interestingly, in the current study by Dart et al,[10] brachial pulse pressure tended to be equal or even lower than central pulse pressure, which may raise concern and certainly fuels debate on the reliability of those measurements. On the other hand, on a theoretical basis, it may be argued that the radial applanation tonometry detects a difference between central and peripheral BP, because it extrapolates central BP by the transfer function[13] in which a difference between the 2 BPs is built in. In addition, partic-

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ipants in the ANBP2 substudy by Dart et al[10] were, on average, 10 years older than those evaluated in the CAFE Study,[6] which may have contributed to the differences in findings between the 2 studies, because it is known that the difference between central and peripheral BP becomes smaller with older age.[16] Moreover, end-study brachial BP was significantly lower in the CAFE Study[6] than in the ANBP2 substudy[10]; mean BP contributes to passive arterial stiffness, which may have, in turn, blunted a potential response of central BP to antihypertensive treatments in the ANBP2 substudy.[10] Furthermore, the study by Dart et al[10] is based on a pairwise design, whereas the CAFE Study[6] included patients who reached end points. Previously, Dart et al[15] showed that brachial, and not central, BP was related to total fatal and nonfatal cardiovascular events in the ANBP2; therefore, the authors commented that the pairwise design did not introduce significant survival effects in the present ANBP2 substudy.[10] Notwithstanding, in the present ANBP2 substudy,[10] the lack of difference in outcome by study design between the treatment arms might have selected negatively those at higher risk of fatal cardiovascular events because of higher central BP. Thus, at the moment, we have 2 different trials offering 2 different results.

A crucial issue is whether central BP is better than brachial BP as a predictor of cardiovascular outcome in hypertension. In the CAFE Study,[6] in Cox proportional-hazard models adjusted for age and baseline risk factors, central pulse pressure was only slightly better than brachial pulse pressure as a predictor of the composite end points, including development of renal impairment, a peculiarity of that study. Moreover, in the CAFE Study,[6] the augmentation index, a parameter potentially relevant to represent mechanistically the different impact of atenolol versus amlodipine plus perindopril on cardiovascular outcome in hypertension,[12] was not stronger than central pulse pressure as a predictor of events. Preliminary data from the Strong Heart Study supported the superiority of central over brachial BP as an independent predictor of cardiovascular outcome.[17] Nevertheless, wider brachial pulse pressure was associated with higher cardiovascular mortality independent of traditional risk factors, left ventricular hypertrophy, and depressed ejection fraction in Strong Heart Study participants without overt coronary heart disease.[18]

In hypertension, other factors may help explaining different outcomes with different treatments. Hypertension is associated with cardiovascular organ target damage, in turn related to increased risk of atherothrombosis, that is, stroke and myocardial infarction,[19] the most common cardiovascular events associated with higher BP.[20] In the Heart Outcomes Prevention Evaluation Study, only a small part of the benefit of the treatment with the angiotensin-converting enzyme inhibitor ramipril could be attributed to the magnitude of the brachial BP reduction; it is likely that angiotensin-converting enzyme inhibitors exert additional effects on the cardiovascular system that may include antagonizing the direct effects of angiotensin II on vasoconstriction, the proliferation of vascular smooth muscle cells and rupture of plaques, improving vascular endothelial function, reducing left ventricular and carotid remodeling, and enhancing fibrinolysis.[21] In the LIFE Study, losartan was more efficacious than atenolol essentially in stroke prevention,[1,22] a typical manifestation of atherothrombosis, particularly in diabetic patients with hypertension, and independent of brachial BP reduction.[23] This may relate to mechanisms including more beneficial impact of losartan over atenolol on new-onset diabetes, left ventricular hypertrophy regression, left atrial diameter, new-onset and recurrence of atrial fibrillation, impact on vascular structure and mechanics, thrombus formation, and platelet aggregation.[24]

Therefore, we may need to reload pulsology and wait for more evidence on whether central BP is or is not the factor explaining different outcomes with different antihypertensive treatment above and beyond BP reduction. Meanwhile, we should lower our patients' brachial BP to the recommended targets and prescribe antihypertensive treatment taking into account hypertension-associated clinical conditions, especially in older patients, patients with diabetes, and in those with known target organ damage,[4,5] in whom angiotensin-converting enzyme inhibitors and/or angiotensin II type 1 receptor blockers reduce the rate of cardiovascular events beyond and above brachial BP reduction.[1–3,6]

Disclosures

None.

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