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COMMENT

Gathering evidence on the prognostic role of central blood pressure in hypertension

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A conventional brachial blood pressure (BP) measurement is the standard method used to diagnose hypertension in clinical practice and to guide pharmacological strategies. Nevertheless, the development of noninvasive technologies to measure central BP has generated considerable interest in the field.

Many studies have shown the clinical relevance of the central BP indices acquired by noninvasive methods, including radial, brachial and carotid applanation tonometry, brachial cuff oscillometry, secondary systolic wave measurements in a radial pulse and the N-point moving average method [1]. The most widely used noninvasive technique is determination of the pulse waveform of the radial or carotid artery using applanation tonometry and its calibration via peripheral diastolic and systolic BP.

These techniques acknowledge the regional variation in the BP, and mathematical models validated by invasive monitoring are applied to derive the central pressures.

Because of the direct load imposed on the major target organs by hypertension, aortic pressures are likely more relevant to the underlying pathophysiology than the peripheral pressures.

A recent systematic review and meta-analysis [2] demonstrated that central BP reflects the hemodynamic stress on target organs more accurately than brachial BP. The pooled results of the cross-sectional data showed that central BP compared with brachial systolic BP was more closely associated with the left ventricular mass index (correlation coefficients $r = 0.30$, 95% confidence interval [CI]: 0.23–0.37 versus $r = 0.26$, 95% CI: 0.19–0.33, respectively; $p < 0.01$ for the difference) and the carotid intima-media thickness ($r = 0.27$, 95% CI: 0.19–0.34 versus $r = 0.23$, 95% CI: 0.16–0.30, respectively; $p < 0.01$ for the difference) [2].

Furthermore, many but not all studies examining the longitudinal relationship between central hemodynamic parameters and clinical outcomes support central BP as an independent predictor of higher cardiovascular risk [1].

The Strong Heart Study [3] demonstrated that aortic systolic BP and pulse pressure (PP) are independently associated with cardiovascular mortality and events and that the aortic PP is superior to the brachial PP in predicting outcomes. Conversely, a subset of the Framingham Heart study involving 2232 patients followed for 7 years showed that augmentation index, central PP, and carotid brachial PP amplification were not associated with risk of cardiovascular disease [4]. Similarly, in the second Australian National Blood Pressure (ANBP) Study, baseline brachial BPs predicted cardiovascular disease-free survival, while carotid augmentation index was not predictive of outcomes [5].

Some of the inconsistencies in these results are explained by differences in sample sizes, methodological aspects regarding estimation of central BP, and differences in use of survival adjusted models. Furthermore, the correlation between brachial and central BP presents statistical challenges in models comparing the two measures.

To this point, a meta-analysis [1] of longitudinal studies employing the measures of central hemodynamics revealed that individual studies had results that were not consistent with each other and when compared to the brachial BP, the central BP was not associated with a significantly higher risk of clinical events. Specifically, the central PP was associated with a marginally but not significantly higher relative risk (RR) of clinical events than the brachial PP (1.318, 95% CI: 1.221–1.423 versus 1.188, 95% CI: 1.104–1.280, respectively; $p = 0.057$), and central and

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brachial systolic BPs showed similar risk estimates (1.236, 95% CI: 1.128–1.354 versus 1.204, 95% CI: 1.104–1.313, respectively; $p = 0.62$) [1].

In this context, the analysis of the Antihypertensives and Blood pressure of Central Artery (ABC-J) II study by Eguchi et al. [6] published in the current issue of the journal adds new findings in this gray area.

Briefly, this prospective study of retrospectively collected data evaluated the predictive values of central BP for cardiovascular events in Japanese subjects that were treated for hypertension. Hypertensive patients enrolled in the study (1806 females and 1758 males, mean age 66.0 ± 10.9 years) met all of the following criteria: (1) a stable dosage of antihypertensive medication for at least 3 months; (2) available data on radial tonometry including radial augmentation index and central BP; and (3) age ≥ 35 years. Brachial BP and central hemodynamics were assessed using a semiautomatic tonometry device (HEM-9000AI; Omron Healthcare, Kyoto, Japan) [6].

During a median follow-up of 5 years, 64 incident cardiovascular events were observed (39 cerebral infarctions, 11 myocardial infarctions, 6 cerebral bleedings, 4 sudden deaths, 3 aortic dissections, and 1 undetermined stroke) and, in multivariable Cox regression models, high central systolic BP was associated with worse cardiovascular outcomes.

Although Eguchi et al. [6] have clearly acknowledged the limitations of their analysis, there are some fascinating findings in their report of the ABC-J II study that need to be mentioned.

First, the present analysis offers prognostic clues that could guide further work that attempts to better understand the pathophysiology of central BP. Indeed, at the core of their findings is evidence that the association between central BP and risk of cardiovascular events in treated hypertensive patients is more complex than expected. As reported by the authors [6], their survival models support the hypothesis that the effect of BP increases up to 140 mmHg, but then remains unchanging above that value. In other words, the relationship between central BP and cardiovascular outcomes was nonlinear, with a linear increase in risk up to a central systolic BP equal to 140 mmHg and a constant risk thereafter. At face value, it may be difficult to reconcile the current ABC-J II results with those of prior analyses demonstrating a linear relationship between central BP and cardiovascular risk [1]. As shown by the meta-analysis of 11 longitudinal studies cited in the preceding text [1] (Fig. 1), the risk of cardiovascular events significantly increased for every 10 mmHg rise of central systolic BP (RR: 1.08, 95% CI: 1.040–1.139). Similarly, in a recent study cohort of 1272 normotensive and untreated hypertensive patients, central systolic BP independently contributed to cardiovascular mortality with a hazards ratio of 1.303 (95% CI: 1.121–1.515) per increment of 10 mmHg increase in central systolic BP [7].

Second, although we question the risk grouping proposed in the present analysis of the ABC-J II patients with long-term follow-up [6], the results do not support the clinical significance of the *J*-curve phenomenon in hypertensive patients receiving antihypertensive therapy [8]. Specifically, the central systolic BP was divided into quintiles (Q1 < 112 mmHg; Q2 112–122 mmHg; Q3 122–131 mmHg; Q4 132–143 mmHg; Q5 ≥ 143 mmHg); when the patients in the second quintile (Q2) were set as a

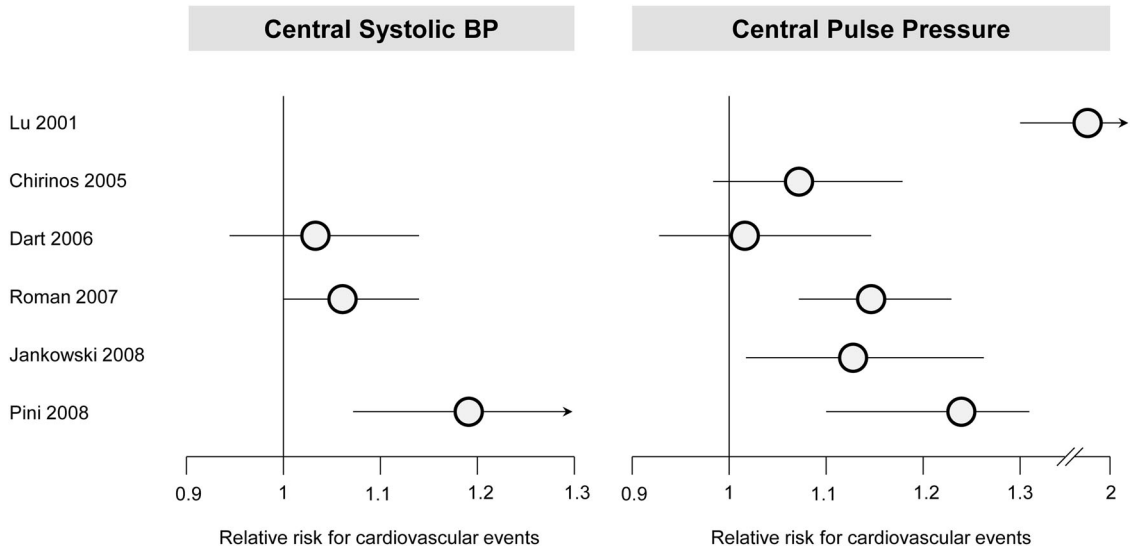

Fig. 1 Clinical studies estimating the predictive value of central blood pressure (BP) for cardiovascular outcomes. For individual studies, the relative risk and 95% confidence interval for a 10 mmHg increase in central systolic blood pressure (left panel) and pulse pressure (right panel) are reported. Data from ref. 1

reference, the patients in Q3 (HR 3.55, 95% CI: 1.29–9.78, $p = 0.014$), Q4 (HR 4.12, 95% CI: 1.53–11.10, $p = 0.005$), and Q5 (HR 2.87, 95% CI: 1.01–8.18, $p = 0.048$) had significantly higher incidences of CV events. Importantly, patients with a central systolic BP < 112 mmHg (Q1) showed a similar risk of cardiovascular complications when compared with patients in Q2. Notably, patients with extremely low BP, arrhythmias, advanced renal disease (estimated glomerular filtration rate < 15 ml/min/1.73 m^2), and history of heart failure (HF) were excluded from the analysis. This model has the potential to analyze the relationship between central BP and outcomes while excluding some effect modifiers that influence the presence (reverse causality) of a *J*-curve in predicting cardiovascular disease risk.

Finally, Eguchi et al. [6] performed receiver operating characteristic analyses to determine the appropriate cut-off value of central BP to predict cardiovascular events. As reported, the cut-off value of central systolic BP for which the Youden Index become maximal was 122.1 mmHg for a follow-up period of 1000 days and 123 mmHg for a follow-up period of 2000 days. However, the translation of the current brachial cut-off into a corresponding aortic value remains problematic for the phenomenon of pressure amplification and for the significant effects of age, heart rate, gender, and height on the difference between brachial and aortic systolic pressures (Fig. 2). Indeed, systolic BP is the parameter that changes moving toward the periphery; this phenomenon is related to the distortion of the pulse waveform that results from the interference of the forward ejected wave and the multiple reflected waves that are modified by the stiffness and diameter of arteries. Thus, defining normal and abnormal reference ranges for central BP requires further research.

In conclusion, the debate on central BP as an independent predictor of cardiovascular risk over and beyond clinical brachial BP measurements and other cardiovascular risk factors is still open and far from resolved. Moreover, a pertinent question is whether the guiding management of hypertensive patients using central BP in addition to brachial BP improves risk stratification. In this context, available data are sparse. A single study showed that central BP-guided management was associated with less medication use without adverse effects on left ventricular mass, aortic stiffness, or quality of life compared with brachial BP-guided management [9]. Another randomized pilot study in HF patients showed that medication titration guided by aortic central BP improved the exercise capacity [10]. Specifically, subjects with chronic HF were randomized to aortic pressure-guided treatment or conventional therapy. After a follow-up of 6 months, subjects randomized to active treatment experienced a greater improvement in peak oxygen consumption compared with the controls ($p = 0.025$) and were more likely to receive additional vasoactive therapies including nitrates, aldosterone antagonists, and hydralazine with no increased risk of hypotension or worsening renal function [10].

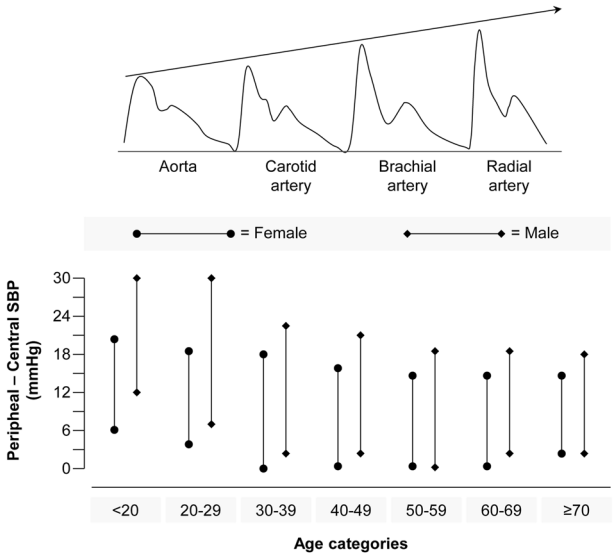

Fig. 2 Amplification of the pressure waveform (upper panel) moving from the aorta to the radial artery. Difference between peripheral and central systolic blood pressure (pSBP–cSBP) according to age categories and sex are also depicted (lower panel): values are given as 10th and 90th percentiles. Data from Herbert A, Cruickshank JK, Laurent S, Boutouyrie P; Reference Values for Arterial Measurements Collaboration. Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk factors. Eur Heart J. 2014; 35(44):3122-33 (27,253 patients with cardiovascular risk factors)

As more studies emerge demonstrating the value of central BP as a therapeutic target, it is possible that targeting central BP may become an important part of the armamentarium used to lower cardiovascular risk. Nevertheless, randomized clinical studies are further required to provide evidence that treatment decisions based on measurements of central BP result in better outcomes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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