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REVIEW

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Central hypertension is a non-negligible cardiovascular risk factor

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Abstract

High blood pressure (BP) confers cardiovascular risk. However, the clinical value of central BP remains debatable. In this article, we aim to briefly review the prognosis, diagnosis, and treatment of central hypertension. Central and brachial BPs are closely correlated. In most prospective investigations, elevated central and peripheral BPs were similarly associated with adverse outcomes. Outcome-driven thresholds of the central systolic BP estimated by the type I device were on average 10 mmHg lower than their brachial counterparts. Cross-classification based on the central and brachial BPs identified that nearly 10% of patients had discrepancy in their status of central and brachial hypertension. Irrespective of the brachial BP status, central hypertension was associated with increased cardiovascular risk, highlighting the importance of central BP assessment in the management of hypertensive patients. Newer antihypertensive agents, such as renin–angiotensin–aldosterone system inhibitors and calcium channel blockers, were more efficacious than older agents in central BP reduction. Clinical trials are warranted to demonstrate whether controlling central hypertension with an optimized antihypertensive drug treatment will be beneficial beyond the control of brachial hypertension.

KEYWORDS
cardiovascular risk, central blood pressure, isolated central hypertension

1 | NTRODUCTION

According to the Global Burden of Disease Study, high systolic blood pressure (BP) accounted for 10.8 million global attributable deaths in 2019, and remains a leading risk factor among the 20 analyzed risk factors or clusters of risk factors, such as air pollution, high plasma glucose, high body mass index, tobacco smoking, etc.[1,9] Although BP is routinely measured at the brachial artery in clinical settings, discrepancies between brachial and central BPs have been noticed in their absolute values,[2] associations with target organ damage[3] and adverse outcomes,[4] and effects of BP lowering agents.[5,6] The anatomic proximity of the aorta to heart, brain, and kidney gives rise to the hypothesis that central BP might be a better reflection of pulsatile pressure load of the target organs and a better predictor of outcomes than peripheral BP. However, up to now the evidence supporting the hypothesis remains inconsistent.[7,8]

Central BP can be directly and accurately measured with catheters; however, the application of the method is restricted due to its invasive nature. In the last 3 decades, various non-invasive methods of central BP estimation via pulse wave analysis have been developed. As recommended by the ARTERY Society task force, the dedicated devices can be categorized into 2 types.[9] The type-I device purports to give an estimate of central BP relative to measured brachial BP, providing relatively accurate pressure difference between central and peripheral sites, while the type-II device purports to estimate the intra-arterial central BP, providing relatively accurate absolute central BP values despite inaccuracy at the peripheral site.[9] Nevertheless, up to now, almost all the non-invasive estimations of central BP relied on the calibration with brachial BP.[9,10] Given the very close correlation between central and brachial BPs, it might not be surprising that at the population level central BPs were not more strongly associated with outcomes than their brachial counterparts.[7,8] Nevertheless, elevated central BP remains a consistent and significant risk factor for cardiovascular morbidity and mortality across studies. Based on the central and brachial BP status, patients could be cross-classified as concordant or discordant normotensive or hypertensive.[11–13] Emerging evidence indicated that such cross-classification might improve risk stratification and have its clinical significance,[14] which shed some light on the application of central BP measurement. In this article, we aim to briefly review the prognostic value of central versus brachial BP in prospective population studies and discuss about the diagnosis and treatment of central hypertension in individual patients.

2 | CENTRAL VERSUS BRACHIAL BP AS A RISK FACTOR

The first meta-analysis comparing the associations of clinical outcome with central versus brachial BP was published in 2010.[7] The comparisons involving 4574 subjects from 5 studies revealed that central pulse pressure was associated with a marginally but non-significantly higher relative ratio of clinical outcome than brachial pulse pressure (1.318 versus 1.188, $P = .057$), whereas the risk estimates for central and brachial systolic BPs were similar (1.236 versus 1.204, $P = .62$).[7] Subsequent comparison studies[15–18] reported negative results by including both central and brachial BP variables in a single model, which might complicate the interpretation due to collinearity. In the Framingham Heart Study involving around 2200 participants followed up for a median of 7.8 years, central pulsatile pressures, either calibrated from carotid pressure waveforms[15] or derived using radial artery tonometry and a generalized transfer function,[16] were not related to cardiovascular events after adjustment for common risk factors including brachial systolic BP. Similarly, in the Western Denmark Heart Registry,[17] which included 21,908 patients with stable angina pectoris undergone coronary angiography and followed up for a median of 3.7 years, both invasive aortic systolic BP and office cuff systolic BP were associated with stroke in patients with diabetes mellitus (hazard ratio per 10 mmHg, 1.14 and 1.18, respectively) and with myocardial infarction in patients without diabetes mellitus (1.05 and 1.07, respectively). However, in models including both BP measurements, aortic BP lost statistical significance and did not improve risk classification. Analyses on the aortic pulse pressure in the cohort produced similar results.[18]

To further clarify whether central arterial properties could contribute to risk stratification using a powerful meta-analysis of individual rather than aggregate data, the International Database of Central Arterial Properties for Risk Stratification (IDCARS) was constructed.[19] Of the 5608 subjects from 9 studies in Europe, Africa, Asia, and South America, 255 experienced a cardiovascular endpoint and 204 died during the follow up for a median of 4.1 years.[8] The Pearson correlation coefficient between central and brachial BPs was .97 for systolic and .95 for pulse pressure. The adjusted standardized hazard ratios of the primary cardiovascular endpoint were 1.50 (95% CI, 1.33–1.70) for central systolic BP, 1.49 (95% CI, 1.33–1.67) for peripheral systolic BP, 1.36 (95% CI, 1.19–1.54) for central pulse pressure, and 1.34 (95% CI, 1.19–1.51) for brachial pulse pressure. Adding central BPs to a model with brachial BPs did not increase the model fit (generalized $R2$ increments $\leq$.003%).[8] Once again, it showed that, at least in adult populations, central and brachial BPs were associated with cardiovascular complications at a similar strength.

3 | DIAGNOSTIC THRESHOLDS OF CENTRAL BP

Although the relationship between cardiovascular outcomes and BP, irrespective of central or peripheral, are continuous, thresholds are needed to make clinical decisions on the diagnosis and treatment of hypertension. Several studies[20–23] proposed thresholds based on the distribution of central BP in "healthy" or "reference" populations. In the Reference Values for Arterial Measurements Collaboration with the data from 77 studies worldwide,[20] central BP was measured with various devices including the SphygmoCor, Omron HEM-9000AI, PulsePen, and direct carotid tonometry. The 90th percentiles of central systolic BP for the optimal, normal, and high-normal categories were 110, 125, and 135 mmHg, respectively, for women and 111, 122, and 132 mmHg, respectively, for men in a total of 18,183 "normal" subjects.[20] Based on the mean values of the entire group and

TABLE 1 Thresholds of central versus brachial blood pressures

Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)	
Brachial	Central	Brachial	Central
120	110	70	70
130	120	80	80
140	130	90	90
160	150	100	100

According to ref. [14], the thresholds of central systolic blood pressure yielded similar 5-year risk of a composite cardiovascular event as the corresponding brachial values. Diastolic blood pressure is similar throughout the arterial tree. Thresholds are therefore same for brachial and central diastolic blood pressures.

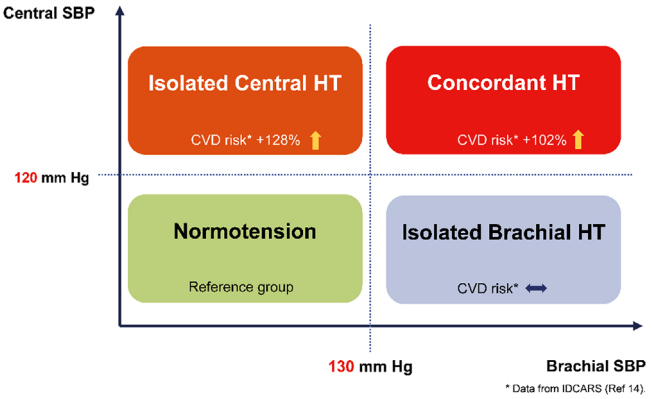

FIGURE 1 Cross-classification of central and brachial blood pressures

the 90th percentiles of the truly normotensive group among the 2423 untreated adults without overt cardiovascular disease, the International Academic 24-H Ambulatory Aortic Blood Pressure Consortium (i24abc.org) proposed 135 mmHg as the upper normal limit for the 24-h central systolic BP calibrated with brachial mean and diastolic arterial pressures, and 120 mmHg for that calibrated with brachial systolic and diastolic pressures.[23] Of note, the proposed thresholds relied heavily on the characteristics of the so-called healthy population and ignored the associations of cardiovascular endpoints with central BPs.

In the year 2013, Cheng et al. first determined mortality-driven thresholds for central BP.[24] Central BPs were estimated with carotid artery tonometry in the derivation cohort and with the SphygmoCor software and radial artery tonometry in the validation cohort. The central systolic/diastolic cutoffs were 110/80 mmHg for optimal BP and 130/90 mmHg for hypertension corresponding to the brachial cutoffs of 120/80 and 140/90 mmHg, respectively.[24] Along similar lines, the IDCARS collaboration determined the thresholds by considering both fatal and nonfatal endpoints in multiethnic populations.[14] Central systolic BP estimated by the type-I device (SphygmoCor) of 110.4 (95% CI, 109.0–111.9), 120.2 (119.3–121.0), 129.9 (129.5–130.3), and 149.4 (148.2–150.6) mmHg yielded similar 5-year risk of composite cardiovascular events as the brachial systolic BP of 120, 130, 140, and 160 mmHg, respectively.[14] Taken the results of 2 outcome-based studies together,[14,24] the rounded thresholds for central systolic BP were approximately 10 mmHg lower than their brachial counterparts, and those for diastolic BPs were similar between the central and brachial arterial sites (Table 1). Nonetheless, it is important to note that the proposed thresholds may only be applied to the central BP estimated by the type-I device, especially the SphygmoCor system, and need to be tested in future studies using various devices.

4 | CROSS-CLASSIFICATION OF CENTRAL AND BRACHIAL HYPERTENSION

Using the brachial and central BP thresholds mentioned above, subjects could be cross-classified as having isolated brachial hypertension, isolated central hypertension, and concordant normotension or hypertension (Figure 1). The prevalence of central and brachial hypertension may vary with the diagnostic thresholds applied. Indeed, among the 2742 adults aged 19 years or older, the prevalence rates of isolated central (≥130/90 mmHg) and isolated brachial hypertension were 2.3% and 8.9%, respectively, if the 2017 American College of Cardiology/American Heart Association guidelines criteria for brachial hypertension (≥130/80 mmHg) was used, and 7.35% and .3% if the 2018 European Society Cardiology/European Society Hypertension guidelines criteria (≥140/90 mmHg) was used instead.[25] However, regardless of the brachial threshold, subjects with isolated central hypertension had a significantly greater 10-year risk score of coronary heart disease than concordant normotensive subjects, and those with concordant hypertension had the highest risk score.[2,12] In 1983 community-dwelling elderly Chinese, only patients with concordant hypertension had significantly higher levels of left ventricular mass index, carotid-formal pulse wave velocity, and urinary albumin–creatinine ratio than those with concordant normotension.[13]

Recently, the IDCARS investigators explored the prognostic relevance of the cross-classification of central and brachial hypertension. With concordant normotension as reference, the multivariable-adjusted hazard ratio (95% CI) for the primary cardiovascular endpoint was 1.30 (.58–2.94, $P = .52$) for isolated brachial hypertension, 2.28 (1.21–4.30, $P = .011$) for isolated central hypertension, and 2.02 (1.41–2.91, $P < .001$) for concordant hypertension.[14] The concordant normotension, concordant hypertension, isolated brachial hypertension, and isolated central hypertension, respectively, accounted for 43.1%, 48.2%, 5.0%, and 3.7% of the 5576 study participants.[14] The mean age of the corresponding patients was 47.8, 60.5, 47.3, and 57.3 years, respectively. In elderly, pressure amplification from central to peripheral arteries decreases and the difference between central and brachial BP becomes small,[26] therefore the prevalence of isolated brachial or isolated central hypertension may vary with age. Patients with isolated brachial hypertension, in the literature also referred to as "spurious systolic hypertension," were predominantly tall and young men characterized with hyperkinetic circulation involving elevated stroke volume and fast heart rate, and some featured with increased arterial stiffness, high body mass index, and other metabolic

disorders.[27,28] In contrast, patients with isolated central hypertension were more likely female, shorter, had a slower heart rate, and more frequently reported the use of β-blockers compared to those with isolated brachial hypertension,[14] which is consistent with previous findings that shorter stature[29] and lower heart rate[4,6,30] augmented pressure wave reflections and were associated with higher central pressure.

5 | TREATMENT OF CENTRAL HYPERTENSION

Since central BP elevation is related to adverse outcomes, and various classes of antihypertensive agents have different treatment effects on central BPs, there is growing interest in the treatment of central hypertension.[2,5,6] Recently, we performed a meta-analysis of 20 published randomized controlled trials to compare newer (renin–angiotensin–aldosterone system [RAS] inhibitors and calcium-channel blockers [CCBs]) with older antihypertensive agents (diuretics and β- and α-blockers) regarding their effects on central hemodynamics.[6] The analyses showed that compared with older drugs, RAS inhibitors and CCBs more efficaciously ($P < .001$) reduced central and brachial systolic BPs by a weighted mean difference of −5.63 mmHg (−6.50 to −4.76 mmHg) and −1.97 mmHg (−2.99 to −.95 mmHg), respectively, and central PP −3.27 mmHg (−4.95 to −1.59 mmHg), augmentation index −6.11% (−7.94% to−4.29%), and augmentation pressure −3.35 mmHg (−5.28 to −1.42 mmHg).[6] The difference in the effects of agents on heart rate and vasodilatation, which are 2 important regulators of central hemodynamics, might explain the observations at least in part. Furthermore, encouraging results have been reported that an even newer antihypertensive drug class, that is, angiotensin receptor neprilysin inhibitor (ARNI), was more effective in reducing central systolic and pulse pressures by about 4 mmHg compared with olmesartan.[31,32]

However, up to now, there is still no direct evidence that targeting central hypertension would be clinically beneficial to patients. To study whether antihypertensive treatment would improve clinical outcomes in patients with coronary heart disease and isolated central hypertension, a multicenter randomized placebo-controlled clinical trial (ANTICIPATE, www.chictr.org.cn/ChiCTR2000035758) has been designed and is currently ongoing in China. According to the design of the trial, eligible patients should have stable coronary heart disease or unstable angina pectoris and normal untreated or treated brachial systolic/diastolic BP (<140/90 mmHg) but high invasive central systolic BP (≥130 mmHg). Approximately, 2000 patients would be randomly assigned to active antihypertensive treatment with alisartan and amlodipine besylate or placebo for 48 weeks. The primary composite outcome consists of acute myocardial infarction, stroke, cardiac revascularization procedures, hospitalization due to heart failure or angina, and death from cardiovascular causes. The ANTICIPATE trial will be helpful to elucidate the efficacy and safety of controlling isolated central hypertension in patients with coronary heart disease.

6 | CONCLUSIONS AND PERSPECTIVES

At the population level, central and brachial BP are similarly and significantly associated with clinical outcomes. The cross-classification of central and brachial hypertension can help to identify patients at high cardiovascular risk. Even in the presence of brachial normotension, an assessment of central BP might improve risk stratification and optimize antihypertensive drug treatment. All these might be especially true for Asian patients who are characterized by stronger associations between BP and outcomes[33,34] and by higher central BP probably due to shorter stature than other ethnicities.[29] With advanced technology, simultaneous ambulatory monitoring of brachial and central hemodynamics is now available for clinical use.[23] Given large amount of evidence showed that the 24-h ambulatory BP was a better cardiovascular risk predictor than the office BP, irrespective of at brachial[35] or central[36–38] sites, it is warranted to explore if the ambulatory central BP outperforms ambulatory brachial BP in risk stratification and hypertension management. Ultimately, direct interventional evidence is needed to demonstrate whether targeting central hypertension with an optimized antihypertensive drug treatment would be beneficial beyond the control of brachial hypertension.

AUTHOR CONTRIBUTIONS

Yi-Bang Cheng and Yan Li prepared the first draft of manuscript. All authors critically commented and revised the manuscript and gave final approval.

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CONFLICT OF INTEREST

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