Central Aortic Blood Pressure as an Indicator of Prognosis: An Asian Perspective

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Abstract

Brachial cuff sphygmomanometer remains the major method by which blood pressure (BP) is assessed clinically. However, this is a poor surrogate for central aortic BP. There is increasing evidence that central aortic BP can act as a marker of cardiovascular (CV) and peripheral vascular disease burden and that central pressures may be able to predict CV events and mortality. This, in turn, could have implications for the development and application of future pharmacological therapies. This review article examines the evidence surrounding the above and its controversies. It concludes that while central BP is an exciting new frontier, more research is required for central BP to become commonplace in clinical medicine.

Key words: Asian, augmentation, central blood pressure, prognosis, pulse wave velocity

Introduction

It is remarkable that despite considerable advances in technologies to assess the cardiovascular (CV) system, the technique for measuring blood pressure (BP) - through a brachial cuff sphygmomanometer - has remained unaltered for more than a century. Brachial BP remains firmly embedded in routine clinical practice in Asia and the rest of the world, and widely referenced in clinical care guidelines. There is good reason for this - the measurement of brachial BP is simple, and standardized, and therefore suited for screening of large populations, with a wide variety of devices now available for clinical use. However, it has long been recognized that brachial BP is a poor surrogate for central aortic pressure, which is invariably lower than corresponding brachial values. This concern has fuelled ongoing interest in pulse wave analysis for determining central BP and investigation into its potential superiority in CV risk prediction. The key question remains whether central BP measurement confers prognostic value beyond that provided by conventional BP. This review will discuss our current understanding of central BP and the evidence surrounding its prognostic significance with an Asian perspective.

Physiological Concepts

Concept of Systolic Pressure Amplification

Arterial pressure varies continuously throughout the cardiac cycle. Although diastolic and mean arterial pressures are relatively constant, systolic pressure may be >30 mmHg higher in the brachial artery than in the aorta.¹ This phenomenon of systolic pressure amplification arises due to an increase in arterial toward the periphery, as central arteries are highly elastic while peripheral arteries have more smooth muscle cells and are hence stiffer.²

Two Paradigms in Waveform Morphology

The first hypothesis of waveform morphology assumes that the arterial pressure waveform is a composite of a forward-traveling wave, generated by the left ejection fraction, and a backward-traveling reflected wave arising from mismatch in vessel stiffness.³,⁴ This change in impedance generates numerous reflected “wavelets” that sum together to augment systolic pressure in central arteries. The augmentation index (AIx),

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Received: 05-05-2018; Accepted 09-06-2018
which quantifies the extent of augmented pressure relative to central pulse pressure (PP), provides information about amplitude and timing of backward-traveling waves within the central arteries.\cite{1, 3} As augmentation pressure increases, aortic systolic BP increases, and PP amplification defined as the ratio of brachial to central BP decreases.\cite{3}

The second major paradigm initially viewed the arterial system as a two-element Windkessel model (resistance and compliance), where a central reservoir fills during systole and empties during diastole.\cite{5, 9} Although details of this model are beyond the scope of the review, it suffices to say that the model did not consider the contribution from impedance. Subsequently, Westerhof et al., in 2009, proposed adding an aortic characteristic impedance to form a three-element Windkessel model to improve the prediction of pressure and flow through the entire cardiac cycle.\cite{6}

**Variables that Affect Central Arterial Pulse Waveforms**

Irrespective of the precise mechanisms underlying the observed changes in central arterial pulse waveform, systolic pressure amplification within the arterial tree is not fixed and depends on multiple variables. These include age, gender, height and heart rate, as well as systemic diseases affecting the vasculature and physiological changes (diurnal variation, menstruation, changes with exercise, etc.). For example, PP amplification is higher in men in whom aortic systolic pressure measured invasively can be up to 30 mmHg lower than that in the brachial artery.\cite{17} Individuals with lower heart rates or shorter stature tend to have less PP amplification.\cite{7}

In large population-based studies, arterial pulse waveforms have also demonstrated variation with ethnicity.\cite{8, 10} A Singapore study showed that Malay and Indian diabetic patients have higher central arterial stiffness, in the form of carotid-femoral pulse wave velocity and Aix, compared to Chinese patients.\cite{8} These differences remained even after adjusting for glycated hemoglobin, proteinuria, and demographics. When compared to Caucasians, South Asians tend to have higher, multivariate-adjusted levels of aortic systolic BP, Aix, and novel central BP variables.\cite{10} These differences persist after adjustment for brachial BP, suggesting that central BP can capture ethnic variations in CV risk.

**Central Pressure as Marker of Disease**

**Coronary Artery Disease**

Cross-sectional studies of Chinese diabetic patients have shown that poor diabetic control is associated with higher Aix.\cite{11} In addition, the presence of hypertension, coronary heart disease, and ischemic stroke is independent risk factors for central BP increase.\cite{11} In the conduit artery function evaluation (CAFE) substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), investigators found that despite comparable achievement of brachial BP, hypertensives treated with amlodipine-perindopril achieved lower central BP than the atenolol-thiazide-treated group. Importantly, central PP was significantly associated with a composite outcome of total CV events and procedures and development of renal impairment. More recently, a multicenter Japanese observational study of >3500 treated hypertensives showed that those with central systolic BP in the top three quintiles had a significantly higher incidence of morbid CV events, even after adjustment for clinical covariates and brachial diastolic BP.\cite{12}

It remains uncertain how aggressive systolic brachial BP control should be. The action to control CV risk in diabetes trial showed no additional CV benefit in intensifying brachial systolic BP control to ≤120 mmHg.\cite{13} Since brachial BP does not fully reflect the hemodynamic milieu in the aorta, central BP may hold the missing key in hypertension risk prediction.\cite{13}

**Left Ventricular Hypertrophy**

Central BP may also be a better predictor of the left ventricular hypertrophy. In a small substudy of the PReterax in regression of arterial stiffness in a controlled double-blind (REASON) project, change in carotid PP but not brachial PP was associated with greater reduction in the left ventricular mass detected in the perindopril + indapamide arm as compared with the atenolol treatment arm.\cite{14} Similar observations were made in a substudy of ASCOT.\cite{15}

**Vascular Disease**

The strong heart study in American Indians demonstrated that compared to brachial BP, central systolic BP was more strongly related to vascular hypertrophy and extent of atherosclerosis.\cite{16} Longitudinal observation studies have confirmed that there is a stronger relation of carotid PP than brachial PP to carotid intima-media thickness.\cite{17} Moreover, with antihypertensive therapy, the reduction in carotid intima-media thickness relates better to the fall in central pressure.\cite{18}

**Central Pressure as Predictor of Events**

**CV Events**

The predictive value of central pressure has been investigated in only a handful of Asian studies \cite{Table 1}. Subjects studied included healthy community-dwelling individuals and patients with CV disease. In all these studies, there was a significant association between central systolic BP and central PP with diverse CV end points, ranging from restenosis following coronary angioplasty to CV mortality.\cite{19, 21} The strong heart study investigators observed that in over 2400 participants without overt CV disease, a central PP of >50 mmHg predicted an adverse CV outcome.\cite{16} Other studies have also demonstrated the incremental value of central over brachial pressures.\cite{14, 22} Surprisingly, the Framingham heart study failed to show any additional value of brachial/carotid amplification and central PP.\cite{23} However, this study was compromised by...
methodological issues, specifically the inappropriate use of the brachial artery rather than the radial or carotid arteries for applanation tonometry.

Mortality

Other than Wang et al., almost no Asian studies have examined the relation of central BP and arterial stiffness to mortality [Table 1]. A meta-analysis by Vlachopoulos et al. of mostly European and American studies found that the age- and risk factor-adjusted pooled relative risk of all CV events was about 1.1 for every 10 mmHg increase of central systolic pressure or central PP, and 1.32 for every 10% absolute increase of central Aix. They also concluded that central Aix predicted total mortality independent of brachial pressures. However, of the three studies pooled for this specific analysis, two (contributing ≥50% of sample size) actually showed no significant predictive value of Aix for mortality. More evidence should be accrued to show that Aix definitively impacts hard clinical outcomes such as mortality.

The meta-analysis of Vlachopoulos et al. also concluded that central aortic pressures had only marginal and not significant added value beyond brachial BP in predicting events. Likewise, the CAFE study reported similar predictive value of both central and peripheral PP for a composite CV and renal outcome.

The main issue with existing studies is that most are underpowered to show convincingly that central pressure or PP is clinically meaningfully superior to brachial pressures in predicting events, given that both have an excellent correlation. Clearly, a definitive outcome study is required, preferably using a validated operator-independent device, suited for use in a doctor’s office.

Pharmacological Reduction of Central Systolic BP

The CAFE ASCOT substudy and the REASON trial have clearly demonstrated that despite similar effects on brachial BP, antihypertensive drugs have differential effects on central BP. The reason trial showed that while all patients had normalization of brachial BP, patients randomized to perindopril + indapamide achieved a significantly greater reduction of central BP compared to those on atenolol. Such evidence may help to explain the excess risk associated with atenolol compared to other antihypertensives in outcome studies and provide support for the hypothesis that drugs which lower central BP most are the most effective.

Since then, numerous studies have examined the influence of all classes of BP-lowering drugs including repurposed agents such as nitrates on brachial versus central pressure. However, most of these studies are small, with varying methodology of central BP measurement, follow-up duration, and study end goals. There is limited evidence that nitrates may reduce central BP more than beta-blockers and that low-dose nitrate may reduce central BP without affecting brachial BP, which may be helpful in patients with poor ejection fraction or those prone to autonomic dysfunction. It has also been postulated that vasodilating beta-blockers may have greater capacity to reduce central systolic BP, potentially by reducing wave reflection. Nevertheless, the available data are conflicting with a recent meta-analysis concluding that differences in BP amplification between vasodilating and non-vasodilating beta-blockers are minimal after accounting for heart rate changes.

Conclusion

Several issues remain unresolved. “Cutoff” values for central BP are still not well defined, unlike with brachial BP. The application of age referenced “cutoff” values for central BP may also be misleading imply that the progressive age-related phenomenon of pressure amplification is physiological, rather than pathological. Furthermore, it is crucial to determine the shape of the relationship between central hemodynamic indices and risk. In addition, a standard approach to the validation of central BP measurement devices is still lacking, and even more so, validation against an Asian cohort. Devices made by Asian companies such as BPro modified tonometry sensor (HealthSTATS, Singapore) are promising but require more extensive evaluation.

In summary, the clinical relevance of differences between brachial and central pressure for the individual patient remains poorly answered at present. Several factors account for the current ambiguity, including the close correlation between these hemodynamic parameters, lack of a standardized approach for calibration and validation of existing methodologies for studying central aortic hemodynamics, and insufficient outcomes.
Central blood pressure as marker of prognosis

Ngoh, et al. Central blood pressure as marker of prognosis

Central pressure: Variability and impact of

High central blood pressure is associated with

Aortic pulse pressure is associated with

Selective reduction

table

. Importance of the aortic reservoir in

Evidence favoring central BP. Large studies are underway, but

until more evidence is available, brachial BP will remain the

point of reference for the management and prognosis of the hypertensive patient.

Acknowledgments

The authors have no conflicting interests to declare.

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How to cite this article: Ngoh CLY, Wong WK, Ling LH. Central Aortic Blood Pressure as an Indicator of Prognosis: An Asian Perspective. Hypertens 2018;4(2): 89-93.

Source of support: Nil, Conflict of interest: None

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