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REVIEW

Role of nebivolol in the control and management of central aortic blood pressure in hypertensive patients

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Measurement of blood pressure (BP) using a brachial cuff sphygmomanometer is universally accepted for the diagnosis of hypertension and prediction of cardiovascular diseases. However, brachial systolic BP does not represent actual systolic BP in the central arteries which encounter cardiac load directly. Due to wave amplification from central to peripheral arteries, a significant difference exists between the two. Central BP measurements also account for arterial stiffness, vessel branching and vascular mechanics, unlike brachial BP. Emerging data suggests that hypertension can be diagnosed more accurately by central pressure indices as compared to brachial BP. Various non-invasive techniques are now available to measure central BP indices owing to recent technological advances. Recently, it has been reported that different classes of anti-hypertensive drugs display differential effects on brachial and central BPs. Nebivolol is a cardio-selective beta-blocker which targets central systolic BP and reduces it significantly along with brachial BP. In this article, we will review the current literature to evaluate the role of central BP to diagnose hypertension in detail. We will also assess the clinical evidence to evaluate the role of nebivolol in the management of elevated central systolic BP. Central BP indices offer better estimation of BP in central arteries and should be considered in routine clinical practice. Nebivolol has shown significant reduction in aortic pressure and wave reflection and improvements in endothelial dysfunction and arterial stiffness in hypertensive patients.

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INTRODUCTION

Cardiovascular disease is the cause of more than 17 million deaths every year worldwide, of which more than 9.4 million deaths are due to hypertension.[1] Hypertension is considered as a silent killer with no visible symptoms.[1] It is usually diagnosed with a brachial cuff sphygmomanometer.[2] However, in recent years, the validity of this method has come under scrutiny. It is generally assumed that brachial systolic pressure represents the actual pressure in central circulation; however, a considerable disparity exists in vascular mechanics at the level of micro and macro-circulation, which leads to a significant difference in blood pressure (BP) between peripheral and central arteries.[3] The Conduit Artery Function Evaluation (CAFE) study showed different effects of atenolol ± thiazide-based and amlodipine ± perindopril-based therapy on central aortic pressures and hemodynamics, even though a similar effect was seen on brachial BP.[4] Arterial stiffness, proximity of pressure wave reflection site and differences in heart rate were mentioned as the possible mechanism by investigators. Increase in arterial stiffness due to aging and both timing and magnitude of pressure wave reflections significantly contribute to the measured brachial BP, making it markedly different from the central pressure.[5]

The heart, brain and kidneys are closely associated with central arteries and experience the cardiac load first. Central BP indices reflect more accurately loading conditions of the left ventricular myocardium, coronary arteries and cerebral vasculature.[6] Emerging evidence suggests that central BP may diagnose hypertension, which is determined by central hemodynamics and vascular remodelling, more accurately than brachial BP.[7] It has also been observed that different anti-hypertensive drugs exert different effects on central and brachial pressure and reduction in morbidity and mortality in response to various anti-hypertensive drugs cannot be completely attributed to the reduction of peripheral BP.[7] Some anti-hypertensive drugs, notably beta-blockers, significantly reduce central BP along with brachial pressure. Nebivolol is a beta-blocker which significantly reduces central and brachial BP and displays additional vasodilating properties through the nitric oxide (NO) pathway. In this article, we will evaluate the role of central BP for the diagnosis of hypertension. We will also review current clinical evidence to

Central blood pressure indices

Augmentation index: ratio between augmentation pressure (AP) and central pulse pressure (PP).

Augmentation pressure: amount of pressure added to the systolic pressure peak based on the reflected wave.

Central blood pressure: blood pressure in the aorta near the heart.

Pulse wave velocity (PWV): measurement of aortic pulse velocity. It is the distance between carotid and femoral arteries divided by the transit time.

Pulse pressure amplification: difference between brachial and central PP.

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assess the role of nebivolol in reducing central BP in patients with hypertension.

CLINICAL RELEVANCE OF CENTRAL BLOOD PRESSURE INDICES

Numerous randomised controlled trials evaluated the potential of central BP and wave reflection indices for the prediction of hypertension and cardiovascular risk. Low central BP was found to be associated with a low risk of hypertension in a study conducted among 67 young patients with isolated systolic hypertension (ISH).[8] Central systolic pressure consistently and independently predicted cardiovascular mortality in a study that enrolled 1272 subjects.[9] ICARe Dicomano study ($n = 899$) reported that a higher carotid systolic BP and carotid pulse pressure (PP) predicted cardiovascular events and mortality better than brachial systolic BP and brachial PP in elderly patients.[10]

The STRONG heart study, which included 3520 patients, revealed that central PP was more strongly related to 3 arterial measures (plaque score, intimal-medial thickness and vascular mass) than brachial PP.[6] In a subgroup analysis among 2403 overt cardiovascular disease-free patients, central PP was found to be a better predictor of cardiovascular events than PP.[6] In the Czech Post-MONICA study ($n = 728$), non-invasively determined central pressure was found to be more strongly associated with left ventricular hypertrophy than brachial pressure in elderly patients.[11] Central PP, not mean BP or brachial PP, was found to be a strong independent determinant of carotid artery enlargement and wall thickening in a study that included 167 normal and hypertensive patients.[12] Another study which enrolled 67 normotensive patients reported that the late systolic augmentation of central pressure waveform was associated with an increase in left ventricular mass index independent of age and mean BP.[13]

Wave reflection indices such as augmentation index, pulse wave velocity (PWV), augmentation pressure and PP amplification (Box 1) have also been reported to predict multiple cardiovascular events better than brachial pressure (Figure 1).[5] In addition, wave reflection indices also reflect on arterial stiffness.[5] A meta-analysis of 11 longitudinal studies ($n = 5648$) revealed that central (aortic and carotid) pressures can independently predict cardiovascular outcomes and all-cause mortality and that augmentation index can predict all-cause mortality.[14] The Framingham heart study ($n = 2232$) reported that the risk of first cardiovascular event is increased by 48% in patients with a higher aortic PWV.[15] Aortic PWV also improved risk prediction by 0.7% when added to standard risk factors. However, augmentation index, central PP and PP amplification were not found to be associated with increased cardiovascular events in this study. Aortic PWV was found to predict cardiovascular outcomes better than traditional cardiovascular risk factors such as 24-h mean arterial pressure ($n = 1678$).[16] Moreover, results of Framingham Heart Study Offspring cohort ($n = 1759$) revealed that higher aortic stiffness, forward wave amplitude and augmentation index were associated with higher risk of incident hypertension, but initial BP was not found to be independently associated with the risk of progressive aortic stiffening.[17] Aortic augmentation pressure was also found to predict major adverse cardiac events.[18]

Central pressure, PWV and central PP have also been found to be a significant predictor of all cause and cardiovascular disease mortality in patients with end-stage kidney disease.[19] Carotid PP, brachial/carotid PP and PWV were found to be better predictor for all-cause mortality than brachial BP and PP in patients with end-stage kidney disease undergoing haemodialysis ($n = 180$).[20] Strong association between pulse wave measures and carotid intima-media thickness and plaque was reported in patients with chronic kidney disease ($n = 367$) as well.[21] Collectively, these observations suggest that central pressures and wave reflection indices are better predictor for hypertension, cardiovascular risk and renal diseases.

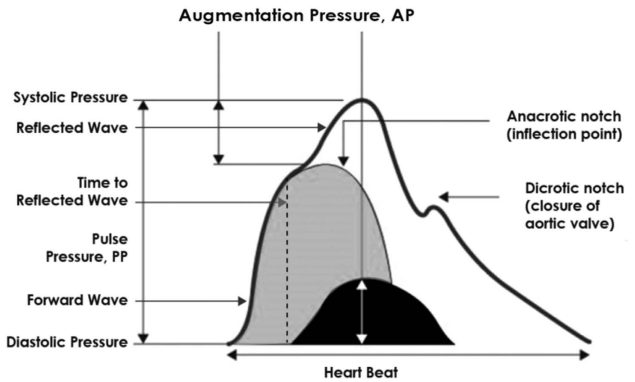

Figure 1. Central pressure waveform: systolic and diastolic pressures are the peak and trough of the waveform. Augmentation pressure is the additional pressure added to the forward wave by the reflected wave. Augmentation index is the ratio between augmentation pressure and central PP. The dicrotic notch represents closure of the aortic valve and is used to calculate ejection duration. The reflected wave in the central pressure waveform results in augmentation of systolic flow. Reflected pulse wave (black). (modified from Trudeau *et al*.[26])

PATHOPHYSIOLOGICAL BASIS OF CENTRAL BLOOD PRESSURE

Diastolic and mean arterial pressures are relatively constant throughout the arterial tree. However, the shape of the pressure waveform changes throughout the arterial tree. Brachial systolic BP is higher than aortic systolic BP by up to 20 mm Hg.[3] Systolic pressure amplifies as pressure wave moves away from the heart due to an increase in arterial stiffness from central to peripheral arteries. Various components of waveform are depicted in Figure 1. Left ventricle generates forward pressure waves/incident waves which passes down to the arterial tree. These pressure waves travel forward towards peripheral arteries from the ascending aorta at a speed termed as PWV. These pressure waves are reflected from high impedance site such as artery-arteriole junctions and arterial branching points to generate backward waves (Figure 2). Hence, the actual pressure waveform at any point of the arterial tree is the summation of forward and backward pressure waves.[7]

In normal, healthy, and compliant conduit arteries, the backward/reflected waves merge with the incident wave in the proximal aorta during the diastolic phase and enhances diastolic BP, which aids in coronary perfusion. This amplifying effect of wave reflection on central BP is known as the augmentation index (AIx). An increase in arterial stiffness due to aging and/or hypertension results in the narrowing of the upper portion of the wave, which leads to an increase in systolic pressure. As a result, the systolic peak becomes more prominent, PWV and incident wave increases, and reflected/backward waves merge with the incident wave, which then enhances the aortic systolic pressure. It also increases left ventricular afterload and compromises normal ventricular relaxation and coronary filling. The balance between vasoconstriction and vasodilation in the peripheral circulation changes the proportion of the incident wave that is reflected. This change may also result in the changes in reflected wave and central pressure.[7]

Central BP is subjected to greater variations due to changes in the functional and structural properties of the large and small arteries. Elasticity is not uniform within the arterial tree. The aorta is more elastic and distensible than the muscular arteries. This gradient in arterial stiffness produces the PP amplification from central to peripheral arteries along with wave reflection. The

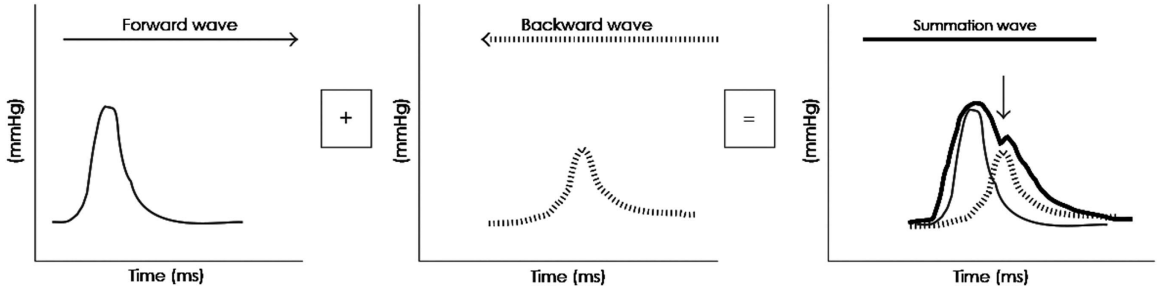

Figure 2. Arterial waveform (right) which is the summation of forward (left) and backward (i.e. 'reflected') wave (middle).

extent of systolic pressure amplification differs both within and between individuals owing to age, gender, height and heart rate. People with shorter stature and/or lower heart rates show less amplification of pulse wave and hence, higher central pressure. Moreover, multivariable regression models could explain only 70% of the variability in pressure amplification. McEniery *et al*. assessed aortic and brachial pressure in the Anglo-Cardiff Collaborative Trial II which included 10 613 volunteers. A significant and highly variable difference was found between aortic and brachial systolic pressures across all age groups.[3] In young subjects with high ISH, reduced large artery compliance and high augmentation index was observed, owing to changes in the proportion of the incident wave that is reflected (which depends on the tone of impedance vessels).[8] These subjects also showed impaired small artery compliance and increased total peripheral resistance, which increases central systolic BP.

In summary, brachial BP reasonably measures end-diastolic BP, but it does not measure the systolic pressure accurately. In addition, in peripheral arteries, the measured BP is amplified due to the branching structure and mechanical properties of the arteries and does not reflect the central BP accurately.[3] Furthermore, pressure at the central arteries, such as the ascending aorta and common carotid arteries, is the more significant pressure for cardiac function, as the heart pumps the blood against this pressure. Hence, brachial pressure does not reflect on actual BP in central arteries. Measuring central BP resolves many of the shortcomings of brachial BP and presents a better target for the treatment and diagnosis of hypertension.

ESTIMATION OF CENTRAL PRESSURE

Central pressure can be measured using both invasive and non-invasive techniques. Direct and invasive techniques include cardiac catheterisation and measurement of BP in the ascending aorta using a pressure-sensing catheter. Since these are highly invasive techniques, they are not suitable for routine clinical practice involving a larger population. Non-invasive techniques include analysis of applanated carotid and pulse waves. Applanation tonometry uses transcutaneous pressure transducers at the end of a probe which obtain pressure waveforms similar to those obtained using intra-arterial measurements. Then, carotid waveform is used as a surrogate for aortic pressure to measure pressure from radial, carotid and/or femoral arteries. Numerous caveats for its use include a highly operator-dependent technique, difficulty in obtaining good quality carotid waveforms (particularly in obese individuals) and the presence of a small degree of amplification between the carotid artery and the aorta, which may lead to an over-estimation of the aortic pressure. In pulse wave analysis, pressure waveforms are recorded at peripheral arteries and corresponding central aortic pressure is derived using a generalised transfer function, identification of the late systolic shoulder of the peripheral waveform, or a proprietary algorithm.[2]

Carotid-femoral PWV is widely used to assess arterial stiffness. It is the simplest, non-invasive, robust and reproducible method to measure arterial stiffness. PWV is the measurement of aortic pulse velocity and is measured by the distance between carotid and femoral arteries divided by the transit time. The distance travelled by the waves is measured to the surface between the two measurement sites. The final PWV is calculated using the formula PWV = D (metres)/Δt (seconds). Notably, it also provides measurements for amplification of the pulse wave between central and peripheral arteries, augmentation index and arrival time of reflected waves.[2]

IMPLICATIONS FOR THERAPY

Numerous randomised controlled trials have compared the efficacy of various anti-hypertensive drugs on brachial and central pressures. A double blind, 1-year follow-up, REASON (pREterax in regression of Arterial Stiffness in a controlled double-blind study) trial which included 471 hypertensive patients, reported that the normalisation of brachial systolic BP requires a significantly greater reduction of central BP with the combination of angiotensin converting enzyme inhibitor (ACE inhibitor) perindopril and the diuretic indapamide as compared to atenolol alone.[22] In addition, the perindopril-indapamide combination reduced the left ventricular mass more significantly than atenolol.[22] Mackenzie *et al*. also reported a similar effect of perindopril, lercanidipine, bendrofluazide and atenolol on brachial BP in patients with isolated systolic BP.[23] However, all four drugs had a differential effect on central BP and augmentation index.[23] Another double blind cross-over study concluded similar results with differential effects of ACE inhibitor, calcium channel blockers, diuretics, and beta-blockers on brachial and central BP.[24] A meta-analysis of 24 randomised controlled trials revealed that different anti-hypertensive drugs (beta-blockers, diuretics and combinations) reduce brachial BP more than central BP.[25] Results from these studies strongly suggest that anti-hypertensive drugs not only lower the brachial BP, they also affect the central BP indices, but the effect is substantially different on both.

EFFECT OF BETA-BLOCKERS ON CENTRAL BLOOD PRESSURE INDICES

Beta-blockers are commonly used for the management of hypertension as they effectively reduce brachial BP in hypertensive patients. Beta-blockers inhibit the activity of beta-1 receptors, which results in decrease in catecholamine outflow from the central nervous system, reduced force and rate of cardiac contraction, and inhibition of release of renin. Decreased levels of renin lead to inhibition of catecholamine and aldosterone release from adrenal glands and the formation of angiotensin-II, which decreases arterial vasoconstrictive tone.[26] In a meta-analysis that included 24 randomised controlled trials, the effect of anti-hypertensive drugs (beta-blockers, diuretics and combinations) on central and brachial BP was examined.[25] Combination therapeutic regimens that included beta-blockers significantly reduced

Table 1. Effect on central systolic BP and heart rate: nebivolol vs other anti-hypertensive drugs

Reference	*Study drugs*	*No. of patients*	*Results*
Polonia *et al.*[27]	ARB vs carvedilol/nebivolol vs Atenolol	242	Central SBP (after therapy) ARB 139 ± 9 mm Hg Carvedilol/nebivolol 135 ± 10 mm Hg[a] Atenolol 145 ± 11 mm Hg Heart rate (after therapy) ARB 82 ± 11 beats per min Carvedilol/nebivolol 69 ± 11 beats per min[a] Atenolol 61 ± 9 beats per min
Kampus *et al.*[29]	Nebivolol vs Metoprolol	80	Central SBP (after therapy) Nebivolol 122.4 ± 12.47 mm Hg[b] Metoprolol 124.6 ± 16.57 mm Hg[b] Brachial SBP (after therapy) Nebivolol 129.3 ± 8.33 mm Hg[b] Metoprolol 134.1 ± 4.62 mm Hg Heart rate (after therapy) Nebivolol 60.1 ± 7.47 beats per min[b] Metoprolol 64.6 ± 9.75 beats per min[b]
Dhakam *et al.*[31]	Nebivolol vs atenolol vs placebo	16	Central SBP (after therapy) Nebivolol 127 ± 3 mm Hg[c] Atenolol 125 ± 3 mm Hg Placebo 131 ± 2 mm Hg Brachial SBP (after therapy) Nebivolol 137 ± 3 mm Hg[c] Atenolol 136 ± 3 mm Hg Placebo 149 ± 2 mm Hg Heart rate (after therapy) Nebivolol 57 ± 1 beats per min[d] Atenolol 61 ± 2 beats per min Placebo 80 ± 3 beats per min
Mahmud and Feely[33]	Nebivolol vs Atenolol	40	Central SBP (after therapy)[e] Nebivolol 122 ± 2 mm Hg Atenolol 128 ± 4 mm Hg Placebo 131 ± 2 mm Hg Brachial SBP (after therapy)[f] Nebivolol 136 ± 3 mm Hg Atenolol 136 ± 4 mm Hg Heart rate (after therapy)[g] Nebivolol 63 ± 1 beats per min Atenolol 60 ± 1 beats per min Augmentation index (%; after therapy)[g] Nebivolol 33 ± 3 Atenolol 28 ± 2

Abbreviations: ARB, angiotensin receptor blockers, SBP, systolic blood pressure. [a]$P < 0.03$ compared to atenolol. [b]$P < 0.001$ compared to baseline. The difference in central systolic BP compared to baseline was only significant in the nebivolol-treated patients (P 0.3 for metoprolol). [c]$P < 0.4$ compared to atenolol. [d]$P < 0.01$ compared to atenolol. [e]$P < 0.6$ compared to atenolol. [f]$P < 0.21$ compared to atenolol. [g]$P < 0.05$ compared to atenolol.

central to brachial amplification.[25] Beta-blockers and diuretics were found to significantly lower central systolic BP more than brachial systolic BP.[25] In a retrospective study, Polonia *et al*. found that vasodilating beta-blockers such as carvedilol and nebivolol lowered systolic central BP and wave reflections more than atenolol.[27] Vasodilating beta-blockers show a favourable effect on central BP indices as compared to other anti-hypertensive drugs. However, old generation beta-blockers do not display favourable effects on aortic stiffness, metabolic profile and exercise capacity.[5]

EFFECT OF NEBIVOLOL ON CENTRAL BLOOD PRESSURE INDICES

Nebivolol is a third generation beta -blocker. It is a racemic mixture of D- and an L-isomer (1:1), of which d-nebivolol have highly selective antagonistic activity for $beta_1$-adrenergic receptor.[5] In addition, nebivolol also displays significant vasodilation properties via the L-arginine pathway. It induces NO release and acts as a potent anti-oxidant. Nebivolol offers an effective hemodynamic profile and better tolerability in patients with hypertension. Various randomised clinical trials studied the effect

of nebivolol treatment on central BP and waveforms and compared effect of different β-blockers on central BP and waveforms (Table 1). In a study with 13 hypertensive patients, a significant reduction in central aortic pressures (systolic BP, 131.5–111.6 mm Hg; diastolic BP, 96.3–81.7 mm Hg; mean arterial pressure, 111.3–94.0 mm Hg (all $P < 0.0001$) and PP, 35.2–29.7 mm Hg ($P < 0.01$) from baseline was observed within 15 days of initiation of nebivolol treatment.[28] Kampus *et al*. reported a significant reduction in central systolic and diastolic BPs, central PP and left ventricular wall thickness after 1 year of nebivolol treatment in a randomised, double-blind study that enrolled 80 hypertensive patients.[29] In another study comprised of 50 pre-hypertensive patients, it was reported that nebivolol caused a significant reduction in central aortic systolic ($P = 0.011$), diastolic ($P = 0.009$) and mean arterial BP ($P = 0.002$) as compared to placebo, during the 8-week follow-up period.[30]

Dhakam *et al*.[31] compared effect of nebivolol and atenolol treatment on central BP in 16 treatment-naive hypertensive patients. Although both drugs significantly reduced brachial BP and arterial stiffness, nebivolol reduced aortic PP more than atenolol ($P = 0.02$).[31] Caglar and Dincer showed that nebivolol significantly reduced the left ventricular mass index than ramipril.[32] It has been suggested that nebivolol-mediated vasodilation and structural remodelling of the small arteries leads to a reduction in reflection site intensity and a decrease in central BP indices.[29] Moreover, heart rate reduction is lower with nebivolol than other beta-blockers which may lead to reduced wave reflection and improvement in arterial stiffness.[5]

Wave reflection plays a major role in central hemodynamics as described earlier in this paper. Several studies have evaluated effect of nebivolol on indices of wave reflection. Mahmud *et al*. reported a significant decrease (11.7%, $P = 0.05$) in augmentation index (AIx) in a randomised clinical trial that included 40 untreated hypertensive patients who received nebivolol.[33] In another single arm, open labelled study, nebivolol significantly reduced AIx and carotid PWV.[28] Furthermore, nebivolol has been shown to improve small artery distensibility (a marker for arterial stiffness) in hypertensive patients. Nebivolol has been shown to increase the small artery distensibility index in a single-blind, placebo-controlled, cross-over study that enrolled 20 hypertensive patients.[34] In another clinical study ($n = 29$), nebivolol increased carotid artery distensibility and cross-sectional compliance of the common carotid artery resulting in better control of the systolic pressure pulse.[35] Of note, improved carotid artery distensibility may provide protection against atherosclerotic complications of hypertension. Nebivolol also significantly reduced PWV compared to metoprolol (-1.4 ± 1.9 m s^{-1} vs -0.1 ± 2.2 m s^{-1}; $P = 0.005$) in beta-blocker naive hypertensive patients ($n = 19$).[36] Other central BP indices were not evaluated in this study.

The reduction in AIx and augmentation pressure in patients treated with nebivolol was due to an increased bioavailability of NO in the vascular wall of medium-sized muscular arteries.[33] The endothelium-dependent vasodilatation property of nebivolol can be attributed to the L-arginine-nitric oxide-dependent pathway.[5] Nebivolol improves the endothelial function by increasing NO synthesis through a stimulation of constitutive NO-synthase (eNOS) and by reducing oxidative inactivation of NO.[5] Decreased NO levels or an increased oxidative stress is associated with the changes in mechanical properties and structural alterations in the large arteries.[5] Increased NO levels also affect small resistance arteries, increase PP amplification and reduce wave reflection.[5,29] Improved endothelial function leads to reductions in arterial stiffness and systemic vascular resistance.[5,28] Furthermore, vasodilation by nebivolol mildly reduced the heart rate as compared to other beta-blockers, which decreased wave reflection and improves arterial stiffness.[5] Peripheral vasodilation by nebivolol also helps in reducing cardiac afterload and reverting adverse arterial remodelling.[29]

OUTSTANDING ISSUES

Central BP measurement has yet to be incorporated into standard clinical practice guidelines as a method for diagnosing hypertension. Several issues have been raised regarding the integration of central BP into everyday clinical practice. Although various easy-to-use devices are available to measure central BP non-invasively, a standard approach for validation of these devices has not been established yet. Whether these devices should be validated against invasively determined aortic pressure remains to be determined. Estimates of 'true' central pressure irrespective of brachial pressure may result in higher central pressure measurements, whereas central pressure measurements relative to brachial pressure may produce under-estimated 'true' aortic pressure. Hence, the number of BP indices which can be measured using these devices also require consensus among experts. In addition, a standard approach needs to be developed to calibrate peripheral waveforms to better understand the brachial-radial and aortic-carotid amplification. Another concern regarding central BP is to set standard 'cut-off' values for central pressure since the BP is normally distributed. However, a reference range of central BP for age and gender is difficult to set as it may indicate that age-dependent increase in BP is physiological rather than pathological and hence is without increased risk of any cardiovascular disease.[2]

Furthermore, various factors such as age, gender and heart rate differentially impact the degree of pressure amplification towards peripheral arteries. Hence, it is necessary to validate the predictive ability of central BP in a variety of populations and disease conditions. In addition, clinicians require a better understanding of calculated central pressure indices such as augmentation index and amplification for various conditions with regards to aging, drug treatment and physiological variations, to avoid errors in clinical judgement. Notably, several large population studies have used PWV measurements to evaluate central waveforms. Numerous commercial devices are in practice to measure PWV and central BP non-invasively. With the availability of these simple and non-invasive methods, it is easier to measure PWV and central BP in clinical setting with relatively inexpensive equipment and modest training.[14]

PERSPECTIVE

The criterion for surrogate markers of BP is satisfactorily fulfilled by both brachial and central BP. However, central BP presents as a better surrogate for hypertension and cardiovascular risk because central BP indices are more sensitive to alterations in both functional and structural properties of small and large arteries. Analysis of pulse wave and central BP has shown more relevance in diagnosis and treatment of hypertension, in observing the hemodynamic effects of atherosclerotic risk factors, and in predicting cardiovascular events and outcomes. Hence, central BP and pulse wave reflection indices have more pathophysiological relevance than brachial BP. With the availability of non-invasive and easy-to use methods for the measurement of central BP and wave reflection indices, these can easily be incorporated in clinical practice. These indices will be useful adjunct to brachial BP measurement to predict hypertension and cardiovascular risk and effect of anti-hypertensive therapy. However, large, diversified population-based studies are required to establish cut-off values for central BP indices. Vasodilating anti-hypertensive drugs such as nebivolol offers a distinct advantage over other anti-hypertensives with the combination of beta-1 blockade and NO-mediated vasodilation activity. It significantly reduces aortic pressure and wave reflection and improves

endothelial dysfunction and arterial stiffness. Moreover, its neutral or favourable effects on glucose and lipid metabolism present it as a valuable therapeutic agent for the management of central BP in hypertensive patients.

What is known about topic?

- Brachial blood pressure (BP) may not provide accurate measurement of pressure on central arteries which experience the cardiac load directly.
- Central BP indices can predict the cardiovascular risk.
- Nebivolol, a third generation β-blocker has significant vasodilatory activity through L-arginine/NO pathway.

What this study adds?

- Discusses central BP indices and their contribution to the prediction of numerous pathological conditions.
- Summarises clinical evidence regarding differential effects of antihypertensive drugs on central BP indices.
- Reviews available clinical data regarding effects of beta-blockers, particularly nebivolol, on central BP, arterial stiffness, augmentation index and pulse wave velocity.

CONFLICT OF INTEREST

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