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REVIEW

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Viewpoint: The Case for Non-Invasive Central Aortic Pressure Monitoring in the Management of Hypertension

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Abstract

Elevated central aortic pressure indices (e.g., systolic pressure and pulse pressure) predict cardiovascular (CV) events and mortality in addition to structural changes (e.g., left ventricular hypertrophy, carotid intima-media thickness and reduced glomerular filtration rate). These elevated risks have been shown in multiple studies to be superior to, and in others, at least as high as that associated with brachial pressures. Threshold values for the diagnosis of elevated central arterial pressures have been defined and can be considered target goals of treatment. Measurements of central arterial pressures can be incorporated into the current approaches to hypertension management utilizing currently available non-invasive devices that measure central pressures during the measurement of brachial BP. The objective of this review is to outline the rationale and evidence supporting incorporation of central aortic pressure monitoring into the care of patients with hypertension.

Keywords: Blood pressure, Hypertension, Central aortic blood pressure, Management, Pulse wave analysis

1 Background

Hypertension remains a common disorder responsible for substantial vascular morbidity and mortality. In 2018, hypertension as a primary or contributing cause was responsible for approximately 500,000 deaths in the USA [1]. According to the current definition for hypertension ($\geq$ 130/80 mmHg), approximately 45% of adults in the United States have hypertension or have been prescribed medication for hypertension [2]. The Centers for Disease Control and Prevention reports that hypertension is under control in only 22% of patients [2].

The Medical Expenditure Panel Survey, a United States nationally representative database, was analyzed to estimate annual healthcare expenditure for patients with hypertension using data from 2003–2014 [3]. The database included a total of 224,920 adults, 37% of whom had hypertension [3]. Average annual medical expenditure attributable to hypertension was $9,089 per diagnosed patient. Patients with hypertension had $1,920 higher annual adjusted incremental expenditure, 2.5 times the inpatient cost, 2 times the outpatient cost, and 3 times the prescription medication expenditure. Specifically, for prescription medications, the annual expenditure was $2,371 for individuals with hypertension compared with $814 for those without hypertension. Overall, the estimated adjusted annual incremental cost was $131 billion per year higher for adults with hypertension relative to adults without hypertension [3].

Management of hypertension through sphygomanometric cuff measurement of peripheral (brachial artery) pressures has dramatically but incompletely improved the ability of health care providers and their patients to control hypertension and reduce associated end-organ damage. Multiple issues likely contribute to the ongoing socioeconomic burden of hypertension despite the availability of multiple

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effective medications and widespread educational efforts. Such issues include, but are not limited to, case finding (early diagnosis), continuity and continued follow-up of care, affordability of care, medication adverse effects, medication compliance and challenges in modifying lifestyle behavior.

An underappreciated but clinically relevant area to consider is the precision and reliability of current monitoring which is based on brachial blood pressure measurements, including patient and health care provider factors. Cheng and colleagues placed the issue in context and noted that cuff brachial blood pressure measurement "is not so much a surrogate, but a compromised measure that is recorded because of technical limitations" [4]. The reference is to cuff pressures being a surrogate for central (i.e. aortic) blood pressures, which represent the actual pressures that are transmitted to organs effected by hypertension (e.g. heart, brain, kidney) due to the closer proximity of the ascending aorta to vital organs.

The central aortic pressure pulse reflects more accurately the cardiac load, which will have an impact on the left ventricular myocardium, coronary artery, and cerebral vasculature [5, 6]. In addition, there are significant difference in the pressure pulse between the central aorta and the peripheral arteries like the brachial artery. Early studies showed when injecting a fast-acting vasodilator drug (glyceryl trinitrate), the central systolic pressure decreases significantly in some cases to approximately 20 mmHg with almost no change in brachial systolic pressure [7].

The relationship between central aortic and peripheral pressure waveforms had been described in a mathematical transfer function, which can be generalized and applied to an adult population [8]. Non-invasive pulse wave analysis (PWA) is a technique that applies the transfer function on the peripheral arterial pressure waveforms to obtain central aortic pressure waveform with cardiovascular related features. Central pressure waveform features calculated include central aortic systolic and diastolic pressures, augmentation index (the ratio of the extra pressure load due to wave reflection relative to the pulse pressure), central aortic pulse pressure (systolic minus diastolic pressure), end-systolic pressure, mean pressures in systole and diastole, and subendocardial viability ratio (the ratio of the area under the curve during diastole to systole) (Fig. 1). Even though peripheral (brachial) blood pressures correlate with central pressures in large cohorts, significant variability exists in systolic pressure [9] such that central pressures cannot be reliably inferred from brachial pressures in individual cases [10]. Additionally, brachial systolic pressures are generally higher than central (aortic) pressures due to wave reflection resulting from the difference in arterial properties between the two arteries. The ratio of the peripheral to central pulse pressure is referred to as pulse pressure

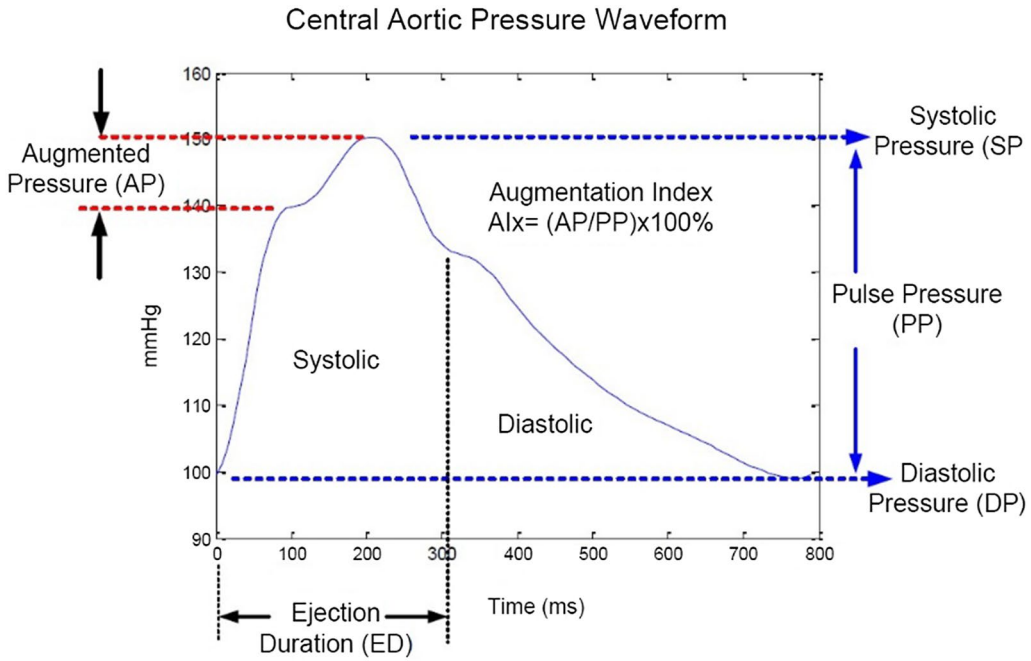

Fig. 1 Central aortic pressure waveform with cardiovascular related features

amplification, which studies have shown to be associated with cardiovascular disease and events [11–13].

The technology for non-invasive assessment of central aortic pressures through PWA had been validated in invasive studies [14, 15] and is currently available and approved by the United States Food and Drug Administration (FDA). Systems that incorporate PWA is considered as complementary to brachial pressure measurements and can help guide treatment decisions designed to prevent or reduce long-term target organ damage and cardiovascular events resulting from increased aortic pressure.

2 The Need for Evaluation of Central Aortic Pressures

Despite dramatic success in the diagnosis and management of hypertension, the disease continues to be associated with a high socioeconomic burden globally as noted in the previous section. Related issues that provide compelling examples of the need include the problem of white-coat hypertension (in-office blood pressure measurements elevated relative to home-based readings), direct and indirect medication adverse effects in the case of over-treatment (i.e., symptoms that lead to medication discontinuation, morbidity such as hypotension, metabolic effects, and organ adverse effects). PWA is an additional tool that can be seamlessly adapted to the current cuff brachial blood pressure monitoring paradigm, which has the following potential utility: a) reduce over-treatment, b) improve under-treatment, c) reduce costs of management (e.g., medication costs, monitoring such as ambulatory blood pressure monitoring (ABPM)). PWA has also shown significant benefits in treatment and management of chronic heart failure [16].

Incorporation of PWA into routine clinical care requires an evidence-based guidance for how to use PWA in patient management. The guidance should fit into existing algorithms for the management of hypertension and be supported by sufficient evidence to justify the clinical utility of PWA. The following sections focuses on using central aortic blood pressure in hypertension management. However, the other central pressure waveform features from PWA, such as augmentation pressure and subendocardial viability ratio can certainly contribute to further understanding of the physiology and potential impacts of elevated pressures.

Central aortic systolic blood pressure (cSBP) fits within the current paradigm for utilizing peripheral (brachial) systolic blood pressure (pSBP) in that management decisions are currently guided by predefined pSBP thresholds as well as diastolic BP thresholds in all national and international hypertension guidelines. However, given the significant difference between cSBP and pSBP and the high variability of cSBP within hypertension pSBP class [10], measuring cSBP can differentiate patients with risk even if they have the same pSBP [17, 18].

Central pulse waveform shape that results from PWA is determined by ventricular ejection pattern and the elastic and geometric properties of the arterial tree [19]. The features can provide a significant insight into the status of the arteries and its effect on cardiac function, which may assist in identifying risk and contribute to hypertension management decisions.

3 Central Aortic Pressure as a Predictive Measure of Cardiovascular Risk

Peripheral (brachial) blood pressure elevation has been proven to be a prominent risk factor for vascular-related end-organ damage, morbidity, and mortality [20–25]. Blood pressure reduction has been definitively demonstrated to reduce vascular end-organ damage, morbidity, and mortality [26–28]. A comprehensive meta-analysis encompassing 306,273 participants from 74 trials demonstrated that antihypertensive drugs reduce mortality and cardiovascular disease based on a threshold (baseline) systolic blood pressure $\geq$ 140 mmHg [26]. They further noted that no benefit was documented for pharmacotherapy in primary prevention of CV disease at systolic blood pressures below 140 mmHg although benefit may be present in those with coronary artery disease. A recent study (SPRINT) [28] suggests that the thresholds for initiation of pharmacotherapy should be lower and is referred to in hypertension management guidelines [28, 29]. With reference to systolic blood pressure, the 2017 Guidelines for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults recommend follow-up monitoring and lifestyle modifications at lower pressures (i.e. systolic blood pressures 120 to 139 mmHg) and recommend pharmacotherapy at lower thresholds where a patient has known risk factors for cardiovascular disease (i.e., 130 to 139 mmHg) [29].

Threshold values have been defined that represent the targets for initiation of treatment (lifestyle treatments such as diet and exercise, and pharmacotherapy) and values have been defined for the goals of treatment. However, sparse data has been published on how and what target values should be used for recommending reductions in pharmacotherapy.

End-organ damage associated with hypertension is related to central pressures and is physiologically intuitive, as such pressures are directly transmitted to vital organs. Central systolic pressures are correlated to peripheral systolic pressures with the correlations

varying from 0.6 to 0.9 [30–32]. Despite the correlation, prediction of aortic systolic pressures based on brachial systolic pressures cannot be reliably inferred as demonstrated by McEniery et al. using data from over 10,000 subjects participating in the Anglo-Cardiff Collaborative trial [10]. The study by McEniery reinforces the variation in central systolic pressure that may occur within the same category of peripheral systolic pressure and that central and peripheral pressures are related but not interchangeable.

Multiple studies, including meta-analyses, have evaluated central blood pressure (cBP) variables and suggested that cBP has a higher predictive value for cardiovascular events relative to peripheral blood pressure, with others uniformly demonstrating that non-invasive cBP is at least as predictive as peripheral blood pressure [5, 6, 33–35]. A meta-analysis conducted by Wang et al. indicated that central blood pressure appears to have a higher predictive value for end-organ damage [37]. In a study of 1,169 participants, the group of patients with a normal/high-normal peripheral BP with cSBP values that were less than the 95% confidence interval (CI) of healthy participants with optimal BP values (45% of those with a normal/high normal BP), had no evidence of target organ changes [38]. In patients with a normal/high-normal BP with cSBP values that exceeded optimal threshold values, left ventricular mass index was increased and estimated glomerular filtration rate was decreased. The report demonstrated that central pressure may have higher predictive value for end-organ damage related to hypertension [38].

Wang and colleagues evaluated the relationship of central and peripheral pressures to end-organ damage in 1272 subjects [36]. Carotid intima-media thickness and glomerular filtration rate were more strongly related to central pressures than peripheral pressures. A total of 130 participants died with 37 dying from a cardiovascular cause. Peripheral and central blood pressure predicted all-cause and cardiovascular mortality. After adjustment for demographic, as well as biochemical and physiologic disease related variables (heart, kidney, arterial, etc.), cSBP was the only BP variable that consistently and independently predicted death from cardiovascular disease (hazard ratio = 1.30 per 10 mmHg increase) [36].

Vlachopoulos et al. reported a meta-analysis of 11 studies that incorporated central hemodynamics and had followed 5,648 subjects for a mean of 45 months [39]. cSBP was associated with a pooled relative risk of total CV events of 1.088 (95% CI 1.040–1.139) for a 10 mmHg increase of cSBP, 1.137 (95% CI 1.063–1.215) for a 10 mmHg increase of central pulse pressure, and 1.318 (95% CI 1.093–1.588) for a 10% absolute increase of central augmentation index (AIx). Central pulse pressure relative to brachial pulse pressure was numerically associated with a higher relative risk of clinical events ($p = 0.057$) [39].

A more recent meta-analysis assessed 24 prospective studies with 146,986 individuals [40]. Adjusted pooled hazard ratio (95% confidence interval [CI]) were determined total cardiovascular events based on changes for the following variables: cSBP (per 10 mmHg increase) = 1.10 (1.04–1.16), central pulse pressure (per 10 mmHg increase) = 1.12 (1.05–1.19), and central augmentation index (per 10% increase) = 1.18 (1.09–1.27). For all-cause mortality, the hazard ratio (95% CI) based on (a) central pulse pressure (per 10 mmHg increase) was 1.22 (1.14–1.31) and (b) based on AIx (per 10% increase) was 1.19 (95% CI 1.05–1.34). The authors concluded that central hemodynamic variables are independent predictors of cardiovascular disease and all-cause mortality [40].

A prospective study by Lamarche et al. published in 2021 evaluated the predictive value of cSBP for cardiovascular events in 13,461 patients using available central blood pressure measurements and follow-up data from administrative databases [41]. A total of 1327 major adverse cardiovascular events occurred during follow-up (median approximately 9 years). The hazard ratio for risk of major adverse cardiovascular events was 1.16 (95% CI 1.09–1.22) for cSBP and 1.15 (95%CI 1.09–1.22) for brachial sBP for a one standard deviation increase. Modeling data evaluating area under the curve for risk indicated a slightly higher risk using cSBP vs. pSBP that was statistically but not clinically significant. Nevertheless, the study provided further data based on "real-world" data verifying the predictive value of central BP for adverse cardiovascular outcomes.

Another variable that can provide additional data regarding cardiovascular risk is Augmentation Index, (AIx), which is the ratio of the central systolic pressure to the pressure at the first inflection during cardiac ejection (Fig. 1). AIx (adjusted to heart rate of 75 beat per minute) has been demonstrated to be associated with coronary artery disease severity in patient with high Framingham score, and an increased incidence of death, myocardial infarction, and stent restenosis in patient undergoing coronary angiography [42, 43].

Several limitations should be acknowledged regarding the aforementioned studies. Published investigations often examine associations to surrogate endpoints (e.g., carotid intima-medial thickness, left ventricular mass index and glomerular filtration rate) rather than long-term outcome studies, or do not have sufficient power and duration of follow-up for definitive conclusions regarding clinical endpoints of most interest such as major cardiovascular events and mortality. Regarding the

clinical endpoint publications especially meta-analyses, only summary data is without the ability to assess individual patient responses (i.e., patient level data).

The data in multiple peer-reviewed publications demonstrate an increased risk for cardiovascular events with elevated central pressures, particularly cSBP and it is therefore reasonable to conclude that reductions in hypertension based on cSBP will be associated with reduced CV events, as has been proven with brachial blood pressure. Furthermore, the predictive value of cSBP is higher than pSBP in multiple studies, and uniformly at least as high as pSBP in others. While the supportive data should not be considered definitive, an objective of treatment should be to lower central systolic pressures to values (or thresholds) that correspond to the targets set for peripheral systolic pressures for the purpose of reducing vascular risk.

4 Threshold Values for Central Systolic Blood Pressure

Management decisions for the treatment of hypertension are based on specific values for systolic and diastolic brachial pressures regardless of age and gender. The 2017 ACC/AHA Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults specify the following: normal BP: < 120/80 mmHg, elevated BP > 120–129/ < 80 mmHg, Stage 1 hypertension: 130–139/80–89 mmHg, and Stage 2 hypertension ≥ 140/90 mmHg [29]. The 2018 ESH/ASC Guidelines provide additional levels of hypertension and has some differences in nomenclature (Table 1).

Expert recommendations based on agreed-upon thresholds are provided for brachial BP goals for adults with confirmed hypertension as follows [29]: (a) with known CV disease or 10-year atherosclerotic CV disease (ASCVD) event risk of 10% or higher, a BP target of < 130/80 mmHg is recommended, (b) without additional markers of increase CV disease risk, a BP target of < 130/80 may be reasonable. Given the high correlation to brachial pressures and the predictive value for CV events, thresholds for management decisions based on central systolic pressures can be determined. Guidelines do not exist for central BP thresholds; however, published research indicates a degree of consistency that can be used for establishing central BP management targets.

Cheng and colleagues published an analysis demonstrating central aortic BP < 110/80 mmHg as optimal, 110–129/80–89 mmHg as prehypertension (corresponding to "elevated" and Stage 1 hypertension in the 2017 Guidelines) and ≥ 130/90 mmHg as hypertension (corresponding to Stage 2 hypertension in the 2017 Guidelines) [4]. The analysis utilized a derivation cohort and then validated the results against a second independent cohort (validation cohort). In the derivation cohort (1,272 individuals and a median follow-up of 15 years), diagnostic thresholds for central blood pressure were determined using guideline-endorsed cut-offs for brachial blood pressure with a bootstrapping method (resampling by drawing randomly with replacement) and an approximation method. The thresholds from the derivation cohort were tested in 2,501 individuals with median follow-up of 10 years (validation cohort) for prediction of cardiovascular outcomes [4]. The analyses (derivation and validation cohort) yielded similar threshold values for central aortic pressures. Relative to optimal (central BP < 110/80 mmHg), the risk of cardiovascular mortality in subjects with hypertension (central BP ≥ 130/90 mmHg) was clinically and statistically elevated (hazard ratio: 3.08, 95% CI 1.05 to 9.05). Modeling demonstrated that central BP ≥ 130/90 mmHg was associated with the largest contribution to the prediction of cardiovascular events.

The authors discussed the clinical relevance of central pressures and noted "…in current international guidelines, the classification of cuff BP values disregards age, sex, and other cardiovascular risk factors. In our multivariate model, the results were consistent after accounting for these factors. In line with current clinical practice and considering the higher clinical events in the aged population, we now propose diagnostic thresholds of CBP without age and sex specification" [4]. In reference to spurious systolic hypertension and white coat hypertension, the authors recognized the clinical utility of measuring central aortic BP in that

Table 1 Current staging of hypertension by ESH/ESC and ACC/AHA. Adapted from NICE, ESH/ESC and ACC/AHA guidelines

	Systolic BP	Diastolic BP
ESH/ESC (2018)		
Optimal	< 120	< 80
Normal	120–129	80–84
High Normal	130–139	85–89
Grade 1 Hypertension	140–159	and/or 90–99
Grade 2 Hypertension	160–179	and/or 100–109
Grade 3 hypertension	⩾180	and/or ⩾110
ACC/AHA (2017)		
Normotension	< 120	and < 80
Elevated BP	120–129	and < 80
Stage 1 Hypertension	130–139	or 80–89
Stage 2 Hypertension	≥140	or ≥90

ACC, American College of Cardiology; AHA, American Heart Association; BP, blood pressure; ESC, European Society of Cardiology; ESH, European Society of Hypertension

the diagnosis can be inferred based on a high cuff (brachial) BP and low/normal central BP [4].

Takase and colleagues evaluated the distribution of central blood pressure values in a population study of Japanese subjects [31]. This cross-sectional study involved 10,756 subjects without overt cardiovascular disease. The analysis used data from 7,348 subjects who were not receiving antihypertensive, antidiabetic or lipid-lowering drug treatment. Optimal brachial BP was defined as systolic < 120 and diastolic < 80 mmHg. Normal BP was defined as systolic < 130 and diastolic < 85 mmHg. The cSBP values in those without cardiovascular risk factors (other than hypertension) was 125.8 ± 37.2 (mean ± 2 SD, $n = 3{,}760$) mmHg. For subjects with no cardiovascular risk factors the numbers were 112.6 ± 19.2 ($n = 1{,}975$) mmHg for optimal and 129.2 ± 14.9 mmHg for normal brachial blood pressure categories ($n = 697$). Therefore, the inference is that reference values of optimal and normal cSBP categories can be considered as approximately 113 mmHg and 129 mmHg respectively [31]. The study provides further support for cSBP reference values and threshold values based on risk and is corroborative data for the threshold of ≥ 130 mmHg as published by Cheng et al. [4].

North American Artery is a professional society whose purpose is to "encourage, support, and understanding of vascular structure and function and its application to clinical medicine, research, and pharmaceutical and medical device development". The organization includes national and international experts in the field of hypertension. The organization sponsored a symposium on the clinical use of PWA in which a central aortic systolic value of 124 mmHg was recommended as a reasonable upper limit of normal based on data that demonstrated a corresponding brachial systolic pressure of 140 mmHg [44]. While slightly more stringent than the value noted above, it is still similar to what was proposed by the other investigators.

Based on the totality of the data, a threshold for the diagnosis of hypertension (corresponding to Stage 2 Hypertension in the 2017 guidelines) can be considered as ≥ 130/90 mmHg; however, justification is available to consider a threshold of ≥ 125 mmHg. Target goals are desirable for the widespread utility of central pressures as a complementary approach to blood pressure management. Incorporating cSBP into brachial BP treatment goals should lead to more precise and reliable patient management. The previous studies have documented what is considered optimal central pressures, which can be considered the target goal. Several other reports exist that corroborate the values noted [38, 40].

Booysen et al. reported an upper threshold for cSBP of 112 mmHg in a study of 1169 participants [38]. In patients with a normal/high-normal BP with cSBP values that were less than 95% CI of healthy participants with optimal BP values (45% of those with a normal/high normal BP), no target organ changes were noted. In patients with a normal/high-normal BP with cSBP values that exceeded optimal threshold values, left ventricular mass index was increased and estimated glomerular filtration rate was decreased. The report demonstrated that central pressure may have higher predictive value for end-organ damage related to hypertension [26]. The previously discussed report by Lamarche and colleagues recently identified central and brachial systolic pressures of 112 mmHg (95% CI 111.2–114.1) and 121 mmHg (95% CI 120.2–121.9) as optimal BP thresholds based on cardiovascular risk [41]. Data indicate a consistency around a target goal for central systolic pressure of 112 mmHg.

Yu et al. investigated the prevalence of central hypertension and its association with end-organ damage in 1983 elderly people [45]. Brachial hypertension was defined as ≥ 140/90 mmHg or using antihypertensive medications. Central hypertension was defined by central BP ≥ 130/90 mmHg or using antihypertensive medications. Both normal brachial and central pressures occurred in 28.4% of subjects, concordant brachial and central hypertension occurred in 67.9%, isolated brachial hypertension (normal central pressures) in 2.3% (consistent with white coat hypertension group), and isolated central hypertension in 1.4% of subjects (consistent with masked hypertension group). Measures of end-organ damage were significantly associated with the concordant hypertensive group (left ventricular hypertrophy: adjusted odds ratios [95% confidence interval] = 2.03 [1.55, 2.68], left ventricular diastolic dysfunction: 2.29 [1.53, 3.43], urinary albumin-creatinine ratio > 30 mg/g: 1.97 [1.58, 2.44]), compared to isolated brachial hypertension or isolated central hypertension. The study results demonstrated that groups can be distinguished based on concordance and discordance of hypertension using threshold values of 140/90 mmHg (brachial pressure) and 130/90 mmHg (central aortic pressure) for risk evaluation and treatment decisions [45]. While the discordant groups were a minority of the population, the data indicate that both measurements of central and peripheral pressures should be reviewed given that treatment decisions often constitute a life-commitment to pharmacotherapy.

In summary, threshold values that represent a decision point for medication prescription for hypertension can be determined based on published data from multiple studies involving an overall large population. A central

systolic pressure of ≥ 130 mmHg (possibly ≥ 125 mg) should be considered clinically equivalent to the brachial systolic pressure threshold of ≥ 140 mmHg (Stage II hypertension as per the 2017 AHA guidelines) (Table 2). Furthermore, a normal central systolic pressure of 112 mmHg can be considered as clinically equivalent to a brachial pressure of 120 mmHg for the purpose of establishing treatment goals.

5 Central Aortic Pressure for Evaluation of White Coat Hypertension (WCH)

An elevated blood pressure in an office setting with normal values for home assessed blood pressure values (ABPM) or home blood pressure monitoring) is referred to as white-coat hypertension (WCH). A meta-analysis of 7 studies with 11,502 participants indicated a prevalence of 13% [46]. A report of national and international registries reported a prevalence between 10 and 50%. [47] The incidence is increased in the elderly, men, elevated lipids, and obesity [48]. Data suggests that patients with WCH may be at increased risk of adverse cardiovascular consequences that may be somewhere in between those meeting standard hypertension criteria [49–51]. However, the data is somewhat inconclusive. For example, a meta-analysis of over 11,000 participants found that the incidence of cardiovascular events was not significantly different between people with WCH and those with normal blood pressure [46]. The diagnosis currently requires confirmation with repeated office and out-of-office BP measurements, including ambulatory blood pressure monitoring. Nevertheless, it appears that the use of ambulatory blood pressure monitoring is exceedingly low given the documented prevalence of white coat hypertension. [50]

The study by Yu et al [45] was discussed in the previous section but is highly applicable with regard to the issue of white coat hypertension. Central hypertension was defined by central BP ≥ 130/90 mmHg or using antihypertensive medications. Measures of end-organ damage were significantly associated with the concordant hypertensive group compared to isolated brachial hypertension or isolated central hypertension [45]. The study results demonstrate that both brachial and central blood pressures must be evaluated for risk evaluation and treatment decisions. Discordant hypertension was not associated with left ventricular hypertrophy, left ventricular diastolic dysfunction and renal dysfunction. While the discordant groups were a minority of the population, both measurements must be considered given that treatment decisions often constitute a life-commitment to pharmacotherapy.

Table 2 Proposed central systolic blood pressure threshold values corresponding to the American Heart Association brachial systolic blood pressure threshold values

Hypertension stage	Central systolic BP
Normal	≤ 112 mmHg
Stage I	> 112 to < 130* mmHg
Stage II	> 130 *mmHg

*125 mmHg can be considered as the threshold

Saladini and colleagues studied a cohort of 354 young to middle-aged participants (18 to 45 years) who had isolated systolic hypertension (ISH), had never received treatment for hypertension and fell into the category of Stage 1 hypertension [52]. The control group consisted of 34 participants with normal blood pressure. The ISH population was divided into low (ISH-low) and high (ISH-high) central aortic systolic blood pressure based on the group median (120.5 mmHg). The duration of follow-up has 9.5 years. Hypertension requiring pharmacotherapy occurred in 54.0% of the ISH group and 14.7% of the control group. The odds ratio for developing sustained hypertension in the ISH-high vs. control was 6.0 (95% CI 1.5 – 24.0, p = 0.01). For the ISH-low vs. control group, the odds ratio was 1.1 (95% CI 0.2 – 5.3, p = 0.90). Importantly, the associations were still statistically significant when a threshold central systolic pressure of 125 mmHg was used and when the model included ambulatory blood pressure [52]. The study reinforces the clinical relevance of including central pressure measurement in the consideration of white coat hypertension in addition to hypertension in general.

Office-based measurements may provide overestimations of blood pressure (i.e., white coat hypertension) in patients who are and are not receiving treatment including pharmacotherapy for hypertension. Use of ABPM requires an additional expense (medical device, transmission and review of data, time to train patients and transfer of the device to and from a clinic, and the need to have a fully cooperative patient for the 24-h measurements. The use of PWA in the office setting can provide both confirmation of hypertension (elevated peripheral and central pressures) and the diagnosis of white coat hypertension (elevated peripheral systolic pressure and normal central systolic pressure) and may represent a cost-effective and practical approach to improving hypertension management.

6 Optimization of Pharmacotherapy for Hypertension

Other than lifestyle modification, pharmacotherapy is the primary treatment modality for hypertension. Treatment with combined (i.e., fixed dose combination) medications are often the mainstay of treatment. Nevertheless, despite the availability of multiple

medications and multiple classes of medications, suboptimal treatment and the consequences thereof are readily recognized as ongoing societal problems in terms of morbidity and socioeconomic costs. Specific issues related to prescription hypertension medications include undertreatment, overtreatment, compliance, drug cost, adverse events, and interactions with concomitant medications, all of which impact a patient's adherence behavior to prescribed treatment and the burden of hypertension. Optimizing prescription medication and the self-administration of therapy is critical to controlling hypertension.

Incorporation of PWA into the treatment paradigm for hypertension has the following advantages:

1. Confirmation of hypertension so that initiation of medication is more likely to be the correct decision for a patient.

• Scenario: Concurrent elevation in brachial and central pressures

2. Avoiding initiation of medication when white coat hypertension is suspected.

• Scenario: Elevated brachial pressure and normal central pressures, provided that an elevated heart rate does not confound the results.

3. Confirmation that increased treatment may not be needed.

• Scenario: Borderline high peripheral pressures and normal central pressures

4. Targeting when to consider reduction of medication.

• Scenario: Normal peripheral and low central pressures, or extended period of normal peripheral and normal central pressures (particularly in the setting of medication tolerance issues).

Although the above scenarios are based on physiologic principals, additional prospective data is needed for definitive proof of long-term clinical outcomes when using central pressure variables as proposed. In some cases, clinical data exists that is supportive; however, prospective randomized clinical trials of sufficient duration have not been performed examining each clinical situation as a primary outcome.

Previous sections in this document highlight the issues of confirmation of hypertension using both peripheral and central pressures for treatment decisions and when to delay or avoid medication prescriptions when white coat hypertension is suspected (e.g., emphasize scheduled monitoring, lifestyle counselling along with delaying or avoiding medications). Regarding medications, national and international guidelines focus on initiation and up-titration with almost no references or instruction on lowering medications. In the absence of intolerable adverse effects, hypertensive patients who start on drug treatment are essentially committed to life-long therapy. Changes thereafter consist of exchanging medication classes, increased dosing of a medication or the addition of another class of medications. However, given medication costs and potential adverse events, such lifelong decisions should be carefully considered with assurance of the appropriateness of the lifetime recommendation. Confirmation of hypertension with central blood pressure measurement should be considered for inclusion as part of care for this reason and for guidance as to the option of decreasing pharmacotherapy.

A thoughtful and practical example of how to incorporate central pressure monitoring in clinical practice can be found in the BP GUIDE study [53]. The study was a prospective randomized trial evaluating the use of central aortic blood pressure ($n=142$) compared with best-practice care without central pressure measurements ($n=144$) to guide hypertension management. Best-practice usual care included office, home, and 24-h ambulatory blood pressure. The group that had the addition of central aortic blood pressure guided management had a significant reduction in the amount of medication they required. In addition, 16% of patients in the central pressure guided group had all hypertension medications discontinued and maintained brachial blood pressure control. In the best-practice care only group, only 2% had all hypertension medications discontinued [53]. While the study size was relatively small, the data demonstrate that incorporating central pressure data into office practice can be clinically important to patient care.

Although not the focus of this discussion, it is relevant to note that incorporation of central pressure measurements may assist in the selection of anti-hypertensive medication classes. The CAFÉ Study was a sub-study of the Anglo-Scandinavian Cardiac Outcomes Trial [54]. The objective was to evaluate two hypertension lowering-regimens (atenolol/thiazide, amlodipine/perindopril) on central aortic pressures and hemodynamics. The study included 2,199 patients who had central aortic pressures and hemodynamic indexes on visits for up to 4 years. Brachial systolic pressures were similar between treatment groups (difference = 0.7 mmHg; 95% CI 0.4 to 1.7; p = 0.2); however, central pressures were reduced in the amlodipine regimen (difference in systolic pressure = 4.3 mmHg; 95% CI 3.3 to 5.4, $p<0.0001$; difference in central aortic pulse pressure = 3.0 mmHg; 95% CI 2.1 to 3.9, $p<0.0001$). A post-hoc analysis revealed an association between central pulse pressure and a composite of total cardiovascular events/procedures and development of renal impairment ($p<0.05$). The authors concluded that anti-hypertensive

medications appear to have different effects on central vs. peripheral blood pressure and such effects may explain differences in the clinical outcomes observed between treatment groups (i.e., superior effects of amlodipine/perindopril vs. atenolol/thiazide) [54]. This effect could, in part, explain the lower degree of regression of left ventricular hypertrophy with atenolol compared to losartan for similar reduction in brachial pressures in the LIFE study. [55]

The publications and data described above indicate that the adjunctive measurement of central pressures may provide clinically important patient care information. The provision of both peripheral and central pressures can occur during the same office visit through commercially available devices that measure both central and brachial pressures, appears to have clinical utility and is likely a cost-effective approach to managing hypertension, particular with regard to medication treatment decisions.

7 Clinical and Economic Implications

Brachial blood pressure monitoring and management decisions based on brachial pressures have had an enormous positive impact on the consequences of hypertension (predominantly cardiac, cerebral, and renal related diseases). Despite the success of using cuff brachial pressures to guide management decisions, hypertension-related vascular disease continues to be a prominent socioeconomic burden [1–3]. Furthermore, over and undertreatment represent additional costs that are not often considered [3, 56]. Cuff brachial blood pressure may overestimate the true cardiovascular risk of hypertension in the subset of patients with white coat hypertension, which is a common phenomenon [46–51]. Non-invasive central aortic pressure measurement represents the true pressures that are transmitted to organs at risk. A discrepancy such as a low central aortic systolic pressure is indicative of white coat hypertension, while the matching of elevated pressures serves as a confirmation of hypertension and reassurance that the treatment algorithm is applicable. The two non-invasive arterial blood pressure measurements (brachial and central aortic pressures) provided by the same device is a cost-effective approach to confirmation of normotension, hypertension, and white coat hypertension and has positive economic implications (Table 3).

The issues related to pharmacoeconomic implications would benefit from additional prospective studies where the addition of information from central pressures is the primary intervention.

8 Additional Considerations

It is also acknowledged that the proposals in this review would benefit from additional long-term data where the primary endpoints are specific clinical outcomes that have meaningful impact on health-related quality of life and the economics of health delivery. There are several approaches to the collection of prospective data other than the classical randomized clinical trial with sufficient power to test a specific hypothesis or address specific questions. Real-world evidence is increasingly recognized as a viable alternative to randomized controlled trials. Given that noninvasive central pressure measurement equipment is currently available and used, albeit not widely, real-world evidence can be generated, which can include matched cohort designs.

From a technology assessment view, the calibration of non-invasive central aortic pressure to brachial cuff values has the inherent feature of discordance between invasive and noninvasive values, which is predominantly due to the known general underestimation of cuff systolic pressure compared to brachial invasive pressure. Nevertheless, it is the central pressure in relation to the conventional brachial cuff pressure that is relevant in associated risk predictions as invasive pressure are generally obtained only in acute or life-threatening situations. Another consideration is that non-invasive determinations of central BP can be device dependent. We have focused our review on non-invasive central pressures based on the approach of using the generalized transfer function as we consider it the most accurate approach. There are other approaches and devices besides the transfer function [57]. As different devices may have different precision [57]; users of such systems should be cautious regarding direct comparability and applicability.

Table 3 Positive potential economic effects for the use of non-invasive monitoring of central pressures

Reduced additional costs for confirmation of white coat hypertension
Avoidance of medication costs for treatment of hypertension when white coat hypertension is present. Reduced costs due to avoidance of medication side effects
Earlier aggressive treatment when there is confirmation of hypertension with associated reduction in socioeconomic costs due to subsequent reduced morbidity
Guidance to attempting trials of medication reduction in treated patients who may have low or low-normal central pressures and normal brachial pressures

As previously stated, this paper is not a comprehensive review, and we wish to acknowledge that there are publications with data indicating central pressure associations with cardiovascular risk similar to but not statistically superior to peripheral pressure associations to cardiovascular risk [58,59]. Overall, the aim of this review and the pragmatic proposals is to encourage additional investigations that continue building the evidence for evaluation of central blood pressure monitoring for hypertension.

9 Summary and Conclusions

Hypertension is common and responsible for continued morbidity, mortality and high socioeconomic costs despite the widespread availability and use of cuff brachial artery measurements for diagnosis and monitoring. Elevated brachial arterial pressures predict CV events and mortality in addition to structural changes (e.g., left ventricular hypertrophy, carotid intima-media thickness and reduced glomerular filtration rate). Lowering elevated brachial arterial pressures through lifestyle modification and pharmacotherapy reduces the risk of cardiovascular events and improves survival. Central aortic systolic pressure is correlated to brachial systolic pressures; however, central systolic pressures cannot be reliably inferred from brachial pressures in individual measurements. Elevated central aortic pressure predicts cardiovascular events and mortality in addition to structural changes (e.g., left ventricular hypertrophy, carotid intima-media thickness and reduced glomerular filtration rate). The risk of adverse CV outcomes is associated with elevated central pressures and these risks have been shown in multiple studies to be superior, and in others, at least as high than that associated with brachial pressures. A recent meta-analysis, which incorporated multiple baseline factors including brachial systolic pressure, demonstrated that central systolic pressure is independently predictive of cardiovascular events and therefore provides additional risk information.

Based on the published data on prediction of risk, it is clinically appropriate to consider that lowering of elevated central systolic pressures may reduce the risk of cardiovascular events and mortality. Threshold values for the diagnosis of elevated central arterial pressures have been defined and have been referenced to the threshold values for the diagnosis of hypertension based on brachial pressures and for target goals of treatment. Measurements of central arterial pressures can be incorporated into the current approaches to hypertension management, particular considering the availability of dual arterial pressure devices can provide both brachial and central aortic pressures in the same clinic setting.

In conclusion, based on current technology, the availability of non-invasive dual arterial pressure measurement systems, the clinical rationale and the clinical published research, incorporation of central aortic pressure monitoring should be considered for the care of patients with hypertension.

Abbreviations

ABPM: Ambulatory blood pressure monitoring; ACC: American College of Cardiology;; AHA: American Heart Association; AIx: Augmentation index; ASCVD: Atherosclerotic CV disease; BP: Blood pressure; cBP: Central blood pressure; cSBP: Central aortic systolic blood pressure; CI: Confidence interval; CV: Cardiovascular; ESC: European Society of Cardiology; ESH: European Society of Hypertension; FDA: Food and Drug Administration; ISH: Isolated systolic hypertension; mmHg: Millimeters mercury; pSBP: Peripheral systolic blood pressure; PWA: Pulse wave analysis; WCH: White-coat hypertension.

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Conflict of interest

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