ATCOR

April 2021

Central Aortic Pressure Monitoring as an Essential Component of Hypertension Management

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 (>130/80 mm Hg), approximately 45% of adults in the United States have hypertension or have been prescribed medication for hypertension.[2] The CDC reports that hypertension is under control in only 24% 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 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 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. Non-invasive pulse wave analysis (PWA) is a technique that transforms the data from peripheral arterial pressure waveforms

obtained into an evaluation of central aortic pressures. The calculations are obtained through a generalized transfer function that corrects for pressure wave amplification in the upper limb. Variables calculated include central aortic systolic and diastolic pressures, augmentation index (ratio expressing the relationship of forward and backward traveling waves in the central aorta), central aortic pulse pressure (systolic minus diastolic pressure). Peripheral (brachial) blood pressures are highly correlated to central pressures; however, brachial systolic pressures are generally higher than central (aortic) pressures with diastolic pressures being similar. The difference between the peripheral and central pulse pressure is referred to as pulse pressure amplification.

The technology for non-invasive assessment of central aortic pressures through PWA is currently available and approved by the United States Food and Drug Administration (FDA). In recognition of the clinical utility of PWA, a Current Procedural Terminology (CPT) code has been established. The SphygmoCor® XCEL system is a dual arterial pressure monitoring medical device consisting of brachial blood pressure and central aortic pressures (using partial cuff inflation to record the outgoing brachial waveform), which can be obtained in the clinic in the same patient session. The SphygmoCor® XCEL is the only FDA cleared medical device for non-invasive central arterial pressure waveform analysis for all adults. The SphygmoCor® System incorporation of PWA was developed as complementary to brachial pressure measurements to help guide treatment decisions designed to prevent or reduce long-term target organ damage and cardiovascular events resulting from increased aortic pressure.

The objective of this document is to summarize data that demonstrate the clinical need to incorporate PWA into the care of all patients with hypertension, the specific variable from PWA selected that can be readily incorporated into hypertension management decisions, and the threshold values used for such decisions.

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. The focus of this document and discussion is directed towards the diagnosis and monitoring of blood pressure for the purpose of guiding treatment decisions. 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.

Incorporation of non-invasive measurements of central aortic pressures can improve hypertension management in the following areas:

- Refine monitoring requirements
- Reduce over-treatment
- Improve under-treatment
- Reduce costs of management (e.g. medication costs, monitoring such as ambulatory blood pressure monitoring (ABPM))

Incorporation of pulse wave analysis (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 proposal focuses on using central aortic blood pressure. However, the other variables from PWA 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. While the corresponding cSBP and pSBP values differ (pSBP being higher in absolute mm Hg), the two variables are highly correlate and provide complimentary physiologic and clinical information. Diastolic pressures (central and peripheral) are generally similar and do not often diverge so that the additional consideration of central aortic diastolic pressure will likely contribute only minimally to the current approaches to treatment. Augmentation Index (AIx, difference between (a) reflected wave added to incident wave, and (b) incident pressure during systole) is not included in the proposed draft central pressure guideline as there is less information on a threshold value and a large investment in education would be required. AIx is also dependent on heart rate, although corrections can be applied. While some studies suggest that the predictive value of AIx may be higher than cSBP, overall, there does not appear to be significant incremental value. Pulse pressure (difference between systolic and diastolic values) has been shown to predict adverse outcomes but has not been included in this document as it is not considered in current blood pressure management guidelines.

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.[5-10] Reductions in blood pressure has been definitively demonstrated to reduce vascular end-organ damage, morbidity, and mortality.[11-13] A comprehensive meta-analysis encompassing 306,273 participants from 74 trials demonstrated that blood pressure lowering pharmacotherapy reduced mortality and cardiovascular disease based on a threshold (baseline) systolic blood pressure > 140 mm Hg.[11] They further noted that pharmacotherapy was not associated with any benefit in primary prevention at systolic blood pressures below 140 mm Hg although there may be additional protection in patients with coronary artery disease. A recent study (SPRINT)[13] suggests that the thresholds for initiation of pharmacotherapy should be lower and is referred to in hypertension management guidelines.[13,14] 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 mm Hg) and recommend pharmacotherapy at lower thresholds where a patient has known risk factors for cardiovascular disease (i.e. 130 to 139 mm Hg).[14]

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 highly but incompletely correlated to peripheral systolic pressures with correlation coefficients of up to 0.97 although a published review from 2014 indicated a range from 0.6 to 0.9.[15-17] In absolute numbers, central systolic pressures are expected to be lower than peripheral systolic pressures.

Multiple studies, including meta-analyses, have evaluated 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.[18-23] A meta-analysis conducted by Wang et al indicated that central blood pressure appears to have a higher predictive value for end-organ damage.[24] 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.[25] 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.[25]

Wang and colleagues evaluated the relationship of central and peripheral pressures to end-organ damage in 1,272 subjects.[23] 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. With adjustment for age, sex, heart rate, body mass index, current smoking, glucose, lipids, carotid-femoral pulse wave velocity, left ventricular mass, intima-media thickness, and glomerular filtration rate, only cSBP consistently independently predicted cardiovascular mortality (hazard ratio=1.30 per 10 mmHg increase).[23]

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.[26] The age- and risk-factor-adjusted pooled relative risk of total CV events was 1.088 (95% CI 1.040– 1.139) for a 10 mm Hg 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). When compared with brachial pulse pressure, central pulse pressure was associated with marginally but not significantly higher relative risk of clinical events (p = 0.057).[26]

A more recent meta-analysis assessed 24 prospective studies with 146,986 individuals.[27] The adjusted pooled hazard ratio of total cardiovascular events was 1.10 (95% confidence interval [CI] 1.04–1.16) for a 10 mmHg increase of cSBP, 1.12 (95% CI 1.05–1.19) for a 10 mmHg increase of central pulse pressure and 1.18 (95% CI 1.09–1.27) for a 10% increase of central augmentation index. The hazard ratio of all-cause mortality was 1.22 (95% CI 1.14–1.31) for a 10 mmHg increase of central pulse pressure and 1.19 (95% CI 1.05–1.34) for a 10% increase of central augmentation index. The authors concluded central hemodynamic variables are independent predictors of cardiovascular disease and all-cause mortality.[27]

A prospective study 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.[28] A total of 1,327 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. brachial sBP that was statistically but not clinically significant.

McEniery and colleagues have performed a systematic review and individual participant data meta-analysis from 15 studies for the purpose of evaluating central aortic pressures for the prediction of cardiovascular events.[29] The report is perhaps the most comprehensive and statistically detailed meta-analysis on the subject to date. At this time, the report is under peer-review and has been provided to CardieX with permission from the authors. Study-specific associations of central and peripheral systolic (SBP) and pulse pressure (PP), and augmentation index (AIx) with cardiovascular (CV) events, were determined using Cox proportional hazard

models, and random effect models to estimate pooled effects. Of 22,433 participants, 908 had a myocardial infarction, 641 a stroke and 1,844 a CV event. The pooled hazard ratio (HR) [95% CI] for combined CV events per SD increase in SBP, after adjustment for physiological confounders and cardiovascular risk factors, was 1.16 [1.06, 1.26] for peripheral sBP (SD 21.0 mmHg) and 1.20 [1.09, 1.33] for central sBP (SD 21.8 mmHg). Adjustment of central sBP for peripheral sBP was also associated with an increased HR for CV events (1.17 [1.00, 1.37]). In summary, central sBP was predictive of CV events even after adjustment for physiological confounders including adjustment for brachial sBP and is therefore an independent predictor of CVD events.

The substantial 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 hgiher than peripheral SBP in some studies, and uniformly at least as high as peripheral SBP in others. Given the knowledge, experience, and correlations of peripheral and central systolic pressures, it is intuitive that 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.

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 mm Hg, elevated BP >120 – 129/<80 mm Hg, Stage 1 hypertension: 130 – 139/80 – 89 mm Hg, and Stage 2 hypertension >140/90 mm Hg.[14]

Table 1	Systolic BP	Diastolic BP
NICE (2019)		
Normotension	<140	<90
Stage 1 Hypertension	≥140	≥90
Stage 2 Hypertension	≥160	≥100
Severe hypertension	≥180	or ≥120
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

Table 1: Current staging of hypertension by NICE, ESH/ESC and ACC/AHA. Adapted from NICE, ESH/ESC and ACC/AHA guidelines.[30]

ACC, American College of Cardiology; AHA, American Heart Association; BP, blood pressure; ESC, European Society of Cardiology; ESH, European Society of Hypertension; NICE, National Institute for Health and Care Excellence

Expert recommendations based on agreed upon thresholds are provided for brachial BP goals for adults with confirmed hypertension as follows:[14]

- With known cardiovascular disease (CVD) or 10-year atherosclerotic CVD (ASCVD) event risk of 10% or higher, a BP target of <130/80 mm Hg is recommended.
- Without additional markers of increase CVD risk, a BP target of <130/80 may be reasonable.

The specific recommendations are included as a reference (Appendix A).[14] 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.

Cheng and colleagues published an analysis demonstrating central aortic BP<110/80 mmHg as optimal, 110-129 / 80-89 mm Hg as prehypertension (corresponding to "elevated" and Stage 1 hypertension in the 2017 Guidelines) and >130/90 mm Hg 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), the authors determined diagnostic thresholds for central blood pressure by 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 mm Hg) was clinically and statistically elevated (hazard ratio: 3.08, 95% confidence interval 1.05 to 9.05). Modeling demonstrated that central BP > 130/90 mm Hg 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 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.[16] This cross-sectional study involved 10,756 subjects without overt cardiovascular disease. In the cohort, 7,348 subjects received no antihypertensive, antidiabetic or lipid-lowering drug treatment, and were used for the analysis. The cSBP values in those without cardiovascular risk factors other than hypertension was 125.8±37.^{2} (mean±2 SD, n=3,760) mm Hg. The values obtained from subjects with no cardiovascular risk factors were 112.6±19.2 (n=1,975) mm Hg for optimal and 129.2±14.9 mm Hg for normal brachial blood pressure categories (n=697). The reference values of optimal and normal cSBP categories were reported as 112.6+19.2 mm Hg and 129.2+14.9 mm Hg.[16] The study provides further support for cSBP

reference values and threshold values based on risk and is corroborative data for the threshold of >130 mm Hg 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 mm Hg was recommended as a reasonable upper limit of normal based on data that demonstrated a corresponding brachial systolic pressure of 140 mm Hg.[31] 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) is proposed to be > 130/90 mm Hg; however, justification is available to consider a threshold of >125 mm Hg.

Threshold values for management decisions are supported by the aforementioned reports, but target goals are also 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.[25,27]

Booysen et al reported an upper threshold for cSBP of 112 mm Hg in a study of 1,169 participants.[25] In patients with a normal/high-normal BP with cSBP values that were less than 95% confidence interval 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.[25] Lamarche and colleagues recently reported a prospective study that examined the predictive value of central systolic blood pressure for cardiovascular events.[28] The study included 13,461 participants available central BP and follow-up data from administrative databases but without cardiovascular disease or antihypertensive medication. A total of 1,327 major adverse cardiovascular events occurred during follow-up (median approximately 9 years). Central and brachial systolic pressures of 112 mm Hg (95% CI 111.2–114.1) and 121 mm Hg (95% CI 120.2–121.9) were identified as optimal BP thresholds.[28] The data indicate that a target goal for central systolic pressure should be 112 mm Hg, which would be consistent with the previously described reports.

Yu et al investigated the prevalence of central hypertension and its association with end-organ damage in 1,983 elderly people.[32] 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 mm Hg (brachial pressure) and 130/90 (central aortic pressure) for risk evaluation and treatment decisions.[32] 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 mm Hg (possibly >125 mg) should be considered clinically equivalent to the brachial systolic pressure threshold of >140 mm Hg (Stage II hypertension as per the 2017 AHA guidelines). Furthermore, a normal central systolic pressure of 112 mm Hg can be considered as clinically equivalent to a brachial pressure of 120 mm Hg for the purpose of establishing treatment goals.

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 (ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM)) is referred to as white-coat hypertension. In recognition of the importance of white coat hypertension, the US Centers for Medicaid and Medicare Services has provided reimbursement for ABPM for suspected white coat hypertension since 2001.[33] In 2019, CMS expanded ABPM coverage to include masked hypertension.[34] The prevalence of white-coat hypertension is somewhat variable among published research. A meta-analysis of 7 studies with 11,502 participants indicated a prevalence of 13%.[35] A national registry study indicated that 35% of untreated patients can be classified as having WCH.[36] A report of national and international registries reported a prevalence between 10% and 50%.[36] The incidence is increased in the elderly, men, elevated lipids and obesity.[37] The phenomena is likely predominantly due to a vasopressor response to catecholamines that occurs during a clinic visit. Other factors may contribute although the relative contribution of such factors remains to be defined; however, poor measurement technique, reliance on the first measurement in a clinic, and small cuff size should be considered. Data suggests that patients with WCH may be at increased risk of adverse cardiovascular consequences relative to a truly normotensive population, which may be intermediate relative to patients meeting current criterion for hypertension.[38,39,40] 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.[35] Recommendations for patients with white-coat hypertension include non-pharmacologic treatment and monitoring.[14] 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.[39] If the patient's total cardiovascular risk is low and there is no hypertension-mediated end-organ damage, drug treatment may not be necessary. Recommendations include monitoring and lifestyle modification, as patients with WCH may subsequently develop sustained hypertension and thereupon require pharmacotherapy.[14]

The European Society of Hypertension has recommended that an office brachial BP measurement of at least 140/90 mmHg and a mean 24-hour ambulatory blood pressure of less than 130/80 mmHg is diagnostic of white-coat hypertension.[38] The 2017 ACC/AHA Guidelines indicate that white coat hypertension can be diagnosed if the difference between clinic and home BP exceeds 20/10 mm Hg.[14] It is important to recognize that the phenomena of an elevated clinic-based blood pressure relative to a home-based measurement also occurs in patients with a diagnosis of hypertension and receiving pharmacotherapy. Therefore, more specific terminology would be "white coat uncontrolled (or untreated) hypertension" and "treated white coat hypertension".

Table 2: Summary of Current Status of White Coat Hypertension30

Definition	ESH: clinic BP>140/90 mm Hg + mean 24-hour BP<130/80 mm Hg ACC/AHA: clinic BP>130/80 + daytime ambulatory or home BP<103/80 mm Hg NICE: clinic BP>140/90 mm Hg + daytime ambulatory or home BP<103/80 mm Hg
Etiology	Psychological factors (stress, anxiety)
Physiology	Poorly understood, sympathetic and endocrine factors implicated
Relevance*	Increased risk of sustained hypertension Worse target organ damage Some studies – higher rates of CVD
WCH	Syst-Eur and HYVET trials suggest treating WCH in patients >60 and >80 years old, respectively, might confer some protection to CV events

ACC: American College of Cardiology, AHA: American Heart Association, ESH: European Society of Hypertension, NICE: National Institute for Health and Care Excellence, WCH: White Coat Hypertension

*Cardiovascular (CV) clinical relevance compared to people with normal blood pressure

The white coat effect has been specifically examined in older adults taking antihypertensive medication. As part of the Hypertension Optimal Treatment (HOT) trial, the white coat effect was 22 and 15 mmHg for systolic and diastolic blood pressures respectively (i.e., difference from clinic to ABPM).[40] The elevation in blood pressure attributed to white coat hypertension was 36 and 12 mmHg for systolic and diastolic blood pressures relative to ABPM in the HYVET study and, 22 and 2 mm Hg (systolic and diastolic) in the Syst-Eur ABPM study.[41,42]

The study by Yu et al[32] was discussed in the previous section but is highly applicable with regard to the issue of white coat hypertension. As noted previously, 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. The concordant hypertension group demonstrated higher end-organ damage compared to the concordant normal pressure group. Measures of end-organ damage were significantly associated with the concordant hypertensive group compared to isolated brachial hypertension or isolated central hypertension as follows:[33]

- left ventricular hypertrophy: 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)*

*Values expressed as adjusted odds ratios (95% CI)

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.

Saladini and colleagues studied a cohort of 354 young to middle age 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. The control group consisted of 34 participants with normal blood pressure.[43] 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 mm Hg). 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 mm Hg was used and when the model included ambulatory blood pressure.[43] The study reinforces the clinically relevance of including central pressure measurement in the assessment and management of hypertension.

It is therefore clear that office-based measurements may provide over-estimations 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 (transportation to and from a clinic) and the need to have a fully cooperative patient for the 24-hour 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). The SphygmoCor® XCEL system provides both peripheral and central pressures in the same office-based setting and may represent a highly cost-effective approach to improving hypertension management.

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:

a. 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

b. 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.

c. Confirmation that increased treatment may not be needed.
   Scenario: Borderline high peripheral pressures and normal central pressures

d. 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)

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 a 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.[44] 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-hour 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.[44] 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.

While 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 (ASCOT).[45] 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 mm Hg; 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 mm Hg; 95% CI, 3.3 to 5.4, p<0.0001; difference in central aortic pulse pressure = 3.0 mm Hg; 95% CI, 2.1 to 3.9, p<0.0001). Central pulse pressure was associated with a

composite outcome of total cardiovascular events/procedures and development of renal impairment (post-hoc analysis, $p<0.05$). 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).[45]

The publications and data described above indicate that the adjunctive measurement of central pressures provides clinically important patient care information. The provision of both peripheral and central pressures can occur during the same office visit, is available within a dual arterial pressure monitoring device (SphygmoCor® XCEL), is clinically appropriate, and a cost-effective approach to managing hypertension, particular with regard to medication treatment decisions.

Reduced Morbidity Association with Overtreatment of Hypertension

Overtreatment of hypertension may readily occur if office-based cuff measurements are misleadingly high. All medications are associated with side effects specific to the medication (e.g., cough in angiotensin converting enzyme inhibitors, constipation in calcium channel blockers); however, all anti-hypertensive medications have the potential for hypotension and consequences thereof. Elderly patients are more susceptible to hypotension and adverse consequences from hypotension. Furthermore, the association of blood pressure with cardiovascular events appears to be bimodal with higher rates at both low and high blood pressures.[46] In a study of 10,001 patients followed for approximately 5 years, patients with a pre-existing history of coronary artery disease and a low blood pressure (110–120/60–70 mmHg) had an increased risk of cardiovascular events other than stroke.[46] Several studies have noted an increased mortality in elderly patients related to lower treated blood pressure.[47,48] Reduced kidney function was associated with lower blood pressures in older subjects.[49] Older hypertensive patient have an increased risk of postural hypotension, balance and gait impairment, confusion, and dizziness.[50] Finally, an increased risk for injuries related to falls may result from overly aggressive treatment of hypertension.[50]

In summary, prescription of anti-hypertension medications has the potential of significant benefit but as with all medications, may be associated with adverse consequences and should always be judicious and carefully considered, particularly in the elderly. Assessment of central pressures provides relevant information that informs prescription medication needs.

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). As previously stated, cuff brachial measurements are a surrogate (albeit an extremely useful surrogate) for the true pressure transmitted to vital organs (i.e. pressures within the aorta). Despite the success of using cuff brachial pressures to guide management decisions, hypertension related vascular disease continues to be a prominent socioeconomic burden. As well, over and undertreatment represent additional costs that are not often considered. 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. Non-invasive central aortic pressure measurement is a confirmation of whether the brachial blood pressure during a clinic visit 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 (SphygmoCor® XCEL) is a cost-effective approach to confirmation of normotension, hypertension, and white coat hypertension.

Economic implications include:

a. Reduced additional costs for confirmation of white coat hypertension.

b. Avoidance of medication costs for treatment of hypertension when white coat hypertension is present. Reduced costs due to avoidance of medication side effects.

c. Potentially earlier aggressive treatment when there is confirmation of hypertension with associated reduction in socioeconomic costs due to subsequent reduced morbidity.

d. Guidance to attempting trials of medication reduction in treated patients who may have low or low-normal central pressures and normal brachial pressures.

Summary and Conclusions

The following is a summary of the key discussion points:

- 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 highly correlated to brachial systolic pressures; however, central systolic pressures cannot be reliably inferred from brachial pressures
- 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 extensive published data on prediction of risk, the correlations of central and brachial systolic pressures, the improvement of health outcomes resulting from lowering elevated brachial systolic pressure, it is clinically appropriate to conclude that lowering of elevated central systolic pressures will reduce the risk of cardiovascular events and morality.
- 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 as the dual arterial pressure SphygmoCor® XCEL device, the only FDA cleared medical device for non-invasive central arterial pressure waveform analysis for all adults, can provide both brachial and central aortic pressures in the same clinic setting.
- Incorporation of PWA into the treatment paradigm for hypertension has the following advantages:

  a. 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

  b. Avoiding initiation of medication when white coat hypertension is suspected.
  Scenario: Elevated brachial pressure and normal central pressures

  c. Confirmation that increased treatment may not be needed.
  Scenario: Borderline high peripheral pressures and normal central pressures

  d. 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)

In conclusion, based on current technology, the availability of a non-invasive dual arterial pressure measurement system, the compelling clinical rationale and the extensive clinical published research, incorporation of central aortic pressure monitoring, monitoring should be a part of the care of all patients with hypertension.

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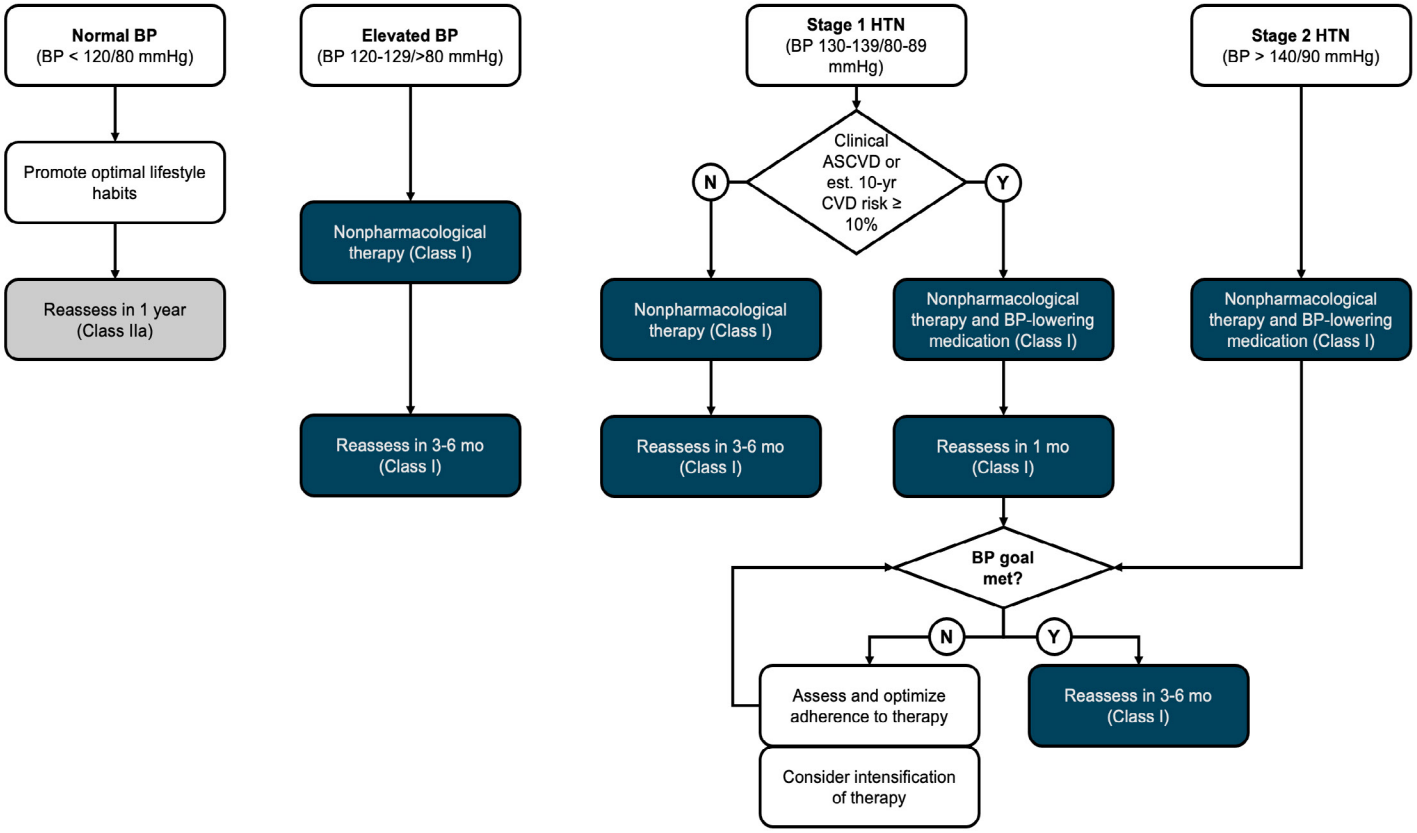
APPENDIX A

Blood Pressure Thresholds and Recommendations for Treatment and Follow-Up

Adapted from: Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, et al. 2017 ACC/AHA/AAPA/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation 2018;138:e484-e594. doi: 10.1.1161/CIR.0000000000000596.



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