ATCOR

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The Role of Central Aortic Pressure Monitoring in the Management of Patients with Chronic Kidney Disease

Executive Summary

- Chronic kidney disease (CKD) is common and effects approximately 15% of adults in the USA (37 million people). Kidney disease is the ninth leading cause of death. CKD increases the risk for cardiac disease, stroke, and death, and leads to multiple significant additional diseases.
- Hypertension and diabetes are the leading causes of CKD in adults and also represent the most treatable targets to prevent CKD and to reduce CKD progression. Hypertension is responsible for continued morbidity, mortality and high socioeconomic costs despite the widespread availability and use of cuff brachial artery measurements for diagnosis and monitoring.
- 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 is predictive of end-organ damage including impaired renal function. Brachial and central aortic pressures provide complimentary information for risk prediction and management decisions.
- The risk of cardiovascular events 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.
- 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.
- Prescription of anti-hypertension medications has the potential of significant benefit but as with all medications, may be associated with adverse consequences (hypotension and drug specific adverse effects) and should always be judicious and carefully considered, particularly in patients with CKD. Assessment of central pressures provides relevant information that informs prescription medication needs.
- 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.

- 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 should be a part of the care of all patients with chronic kidney disease.

Background

Chronic Kidney Disease

Chronic kidney disease (CKD) encompasses mild through severe impairment of renal function. The definition of CKD is kidney damage or a decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for at least 3 months.[1]

CKD is classified according to GFR as follows:[1]

Stage 1: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m^2)

Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m^2)

Stage 3a: Moderate reduction in GFR (45-59 mL/min/1.73 m^2)

Stage 3b: Moderate reduction in GFR (30-44 mL/min/1.73 m^2)

Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m^2)

Stage 5: Kidney failure (GFR < 15 mL/min/1.73 m^2 or dialysis)

Stage 5 CKD is most often referred to as end-stage renal disease (ESRD).

Chronic kidney disease (CKD) is common and effects approximately 15% of adults in the USA (37 million people).[2] Most adults (90%) are unaware that they have CKD as it is generally slowly progressive. According to the Centers for Disease Control and Prevention (CDC), CKD occurs in 38% of adults at least 65 years old, 12% of those between 45 and 64 years, and 6% of people between 18 and 44 years. The following statistics are from the USA.[2]

- Kidney disease is the ninth leading cause of death
- 350 people begin dialysis each day due to ESRD
- 131,600 people start treatment for ESRD in a year
- 786,000 people are living with ESRD with 71% receiving dialysis and 29% with a kidney transplant.

The cost of treating CKD in Medicare recipients has been estimated to be $82 billion (2018), with an additional $36.6 billion of cost for treating those with ESRD.[2] A 2017 study included 106,050 patients with CKD and 56,761 controls without CKD.[3] Average all-cause annual costs increased exponentially with increase CKD stage [(a) commercial group – from $7,537 (no CKD) to $76,969 (CKD stages 4-5), (b) Medicare group – $8,091 (no CKD) to $46,178 (CKD stages 4-5)]. Average annual costs for ESRD patients were $121,948 (commercial group) and $87,339 (Medicare group).[3]

Approximately 15% of US adults (37 million people) have CKD. The cost for treating CKD in Medicare recipients has been estimated to be $82 billion, with an additional $36.6 billion for treating ESRD.

CKD increases the risk for cardiac disease, stroke, and death. A substantial list of symptoms and diseases are a consequence of CKD and include anemia, anorexia, cardiac dysfunction (including arrhythmias), diminished immune responses, electrolyte alteration, encephalopathy, erectile dysfunction, fatigue, fluid retention (peripheral and pulmonary edema), hypertension, impaired cognition, metabolic bone disease, nausea, pericarditis, peripheral neuropathy, platelet dysfunction (bleeding, ecchymosis), and sleep disorders (restless leg syndrome).

Hypertension and diabetes are the leading causes of CKD in adults. Other etiologic factors include cardiovascular disease, family history of CKD including inherited kidney disorders, immune mediated diseases, past damage to the kidneys, and older age. It is readily apparent therefore that hypertension and diabetes represent the most treatable targets to prevent CKD. The objective of this document is to describe the role of central aortic blood pressure monitoring as an important part of hypertension management with the goal of reducing the adverse downstream consequences on renal function.

Hypertension and diabetes are the leading causes of CKD in adults and represent the most treatable targets to prevent CKD and CKD progression.

Hypertension

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, significant variability exists such that central pressures cannot be reliably inferred from brachial pressures.[5] Additionally, brachial systolic pressures are generally higher than central (aortic) pressures although diastolic pressures are similar. The difference between the peripheral and central pulse pressure is referred to as pulse pressure amplification.

Cuff brachial blood pressure might be viewed as a surrogate for central (i.e., aortic) blood pressures; however, aortic pressure, which differs from brachial pressure, represents the actual pressure that is transmitted to organs effected by hypertension (e.g., heart, brain, kidney) due to the closer proximity of the ascending aorta to these vital organs.

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 SphygmoCor XCEL system is a dual arterial pressure monitoring medical device for the measurement of brachial and central aortic pressures, which can be obtained in the clinic in the same visit.

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The Need for Evaluation of Central Aortic Pressures

Compelling examples of the need for central aortic pressure monitoring in addition to brachial pressure monitoring include the more accurate assessment of systemic alterations in blood pressure, the issue 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 (e.g., symptoms that lead to medication discontinuation, morbidity such as hypotension, metabolic effects, and organ adverse effects) and the need to optimize preventive strategies (e.g., prevent end-organ damage, morbidity and mortality). 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 Renal Impairment

End-organ damage associated with hypertension is physiologically a result of elevated central aortic pressures as such pressures are the pressures that 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 0.9.6-8 Despite the high 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.[5] The study by McEniery reinforces the issue that both central and peripheral pressures are closely related but not interchangeable.

Central aortic pressure is predictive of end-organ damage including impaired renal function. Wang and colleagues evaluated the relationship of central and peripheral pressures to end-organ damage in 1,272 subjects.[9] Glomerular filtration rate and carotid intima-media thickness 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).[9]

Glomerular filtration rate and carotid intima-media were more strongly related to central pressures than peripheral pressures.[9]

Booysen et al sought to determine the relationship of BP to target organ damage in a cohort of 1,169 participants. The investigators used an upper threshold for cSBP of 112 mm Hg in a study of 1,169 participants.[10] In patients with a normal/high-normal BP (120/80 to <140/90 mm Hg) with cSBP values < 112

mm Hg, no target organ changes were noted. In patients with a normal/high-normal BP with cSBP values > 112 mm Hg (i.e., exceeded optimal threshold value), estimated glomerular filtration rate was decreased and left ventricular mass index was increased. The report demonstrated that central pressure provided additional information regarding the propensity to end-organ damage (including renal damage) related to hypertension.

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Yu et al investigated the prevalence of central hypertension and its association with end-organ damage in 1,983 elderly people.[11] 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 compared to isolated brachial hypertension or isolated central hypertension as follows:[11]

- 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% confidence interval)

The study results demonstrate 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.[11] 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.

Central Aortic Pressures as a Predictive Measure of Adverse Cardiovascular Events

Multiple studies, including meta-analyses, have evaluated central BP 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 central BP is at least as predictive as peripheral blood pressure.[9,12-16] A meta-analysis conducted by Wang et al indicated that central blood pressure appears to have a higher predictive value for end-organ damage.[17]

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.[18] 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).[18]

A more recent meta-analysis assessed 24 prospective studies with 146,986 individuals.[19] 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.[19]

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.[20] 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.

The most recently published meta-analysis used the International Database of Central Arterial Properties for Risk Stratification.[21] The database included 5,576 subjects (mean age 54.2 years) with 56% men and 54% being women. The objective was to examine thresholds for central aortic systolic BP (cSBP) that would be associated with clinical outcomes and whether cSBP, either alone or in combination with brachial systolic BP (bSBP) improved risk stratification. The CV outcome was the composite of CV mortality and nonfatal end points (specifically death from ischemic heart disease, sudden death, nonfatal myocardial, infarction, coronary revascularization, heart failure and fatal and nonfatal cerebrovascular end points). SphygmoCor technology was used to determine cSBP and a multivariate bootstrap analysis was performed. cSBP thresholds (mmHg (95% CI)) of 110.5 (109.1–111.8), 120.2 (119.4–121.0), 130.0 (129.6–130.3), and 149.5 (148.4–150.5) generated 5-year cardiovascular (CV) risks that equated to bSBP thresholds of 120, 130, 140, and 160. Using thresholds of 120 mm Hg for cSBP and 130 mmHg for bSBP thresholds, concordant central and brachial normotension was present in 43.1%, concordant hypertension in 48.2%, isolated brachial hypertension in 5.0%, and isolated central hypertension in 3.7%. The hazard ratios (95% CI) for the CV endpoint relative to concordant normotension were: (a) 1.30 (0.58–2.94) for isolated brachial hypertension, (b) 2.28 (1.21–4.30) for isolated central hypertension, and (c) 2.02 (1.41–2.91) for concordant hypertension. For isolated central and concordant hypertension, the hazard ratios (95% CI) for cerebrovascular events was 3.71 (1.37–10.06) and 2.60 (1.35–5.00), respectively (Table 1). The authors concluded that "Irrespective of the brachial blood pressure status, central hypertension increased cardiovascular and cerebrovascular risk indicating the importance of controlling central hypertension." The data clearly demonstrate the additional and independent risk information provided by central aortic BP monitoring.

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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 higher than peripheral systolic BP in several studies and is uniformly at least as high 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

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.

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.[22]

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

	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

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:[22]

- 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).[22] 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.[7] 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.[7] 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.[23] While slightly more stringent than the value noted above, it is still similar to what was proposed by the other investigators.

Lamarche and colleagues recently reported a prospective study that examined the predictive value of central systolic blood pressure for cardiovascular events.[20] 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.[20] 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.

Threshold values for management decisions are supported by the aforementioned reports. Target goals are desirable for the practical application and widespread adoption 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 as have documented what can be proposed as optimal central aortic pressures, which can be incorporated as target goals and thresholds for management decisions. The studies referred to in the previous section (Booysen et al[10] and Yu et al[11]) provide clinically relevant data defining threshold values that include evaluations of renal function.

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.

Incorporating Central Aortic Pressure Monitoring into the Care of Patients with Impaired Renal Function: Optimization of Pharmacotherapy for Hypertension

Other than lifestyle modification, pharmacotherapy is the primary treatment modality for hypertension and therefore one of the most important approaches to the prevention and management of CKD. 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)

Previous sections in this document highlight the issues of confirmation of hypertension using both peripheral and central pressures for treatment decisions. 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.[24] 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.[24] 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.

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.

The measurement of central aortic pressures in addition to brachial pressures provides clinically important patient care information.

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.[25] 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.[25] Several studies have noted an increased mortality in elderly patients related to lower treated blood pressure.[26,27] Older hypertensive patient have an increased risk of postural hypotension, balance and gait impairment, confusion, and dizziness.[28] Finally, an increased risk for injuries related to falls may result from overly aggressive treatment of hypertension.[28]

Cushman et al performed a randomized trial of intensive BP control (systolic BP <120 mm Hg) compared to standard therapy (systolic BO < 140 mm Hg) in 4,733 subjects with type 2 diabetes. The mean follow-up was 4.7 years.[29] Intensive therapy did not reduce the rate of the composite of fatal and non-fatal cardiovascular events. However, intensive therapy vs. standard therapy was associated with a higher proportion of subjects with serious adverse events (3.3% vs. 1.3%, p<0.001), elevated creatinine (23.8% vs. 15.5%, p<0.001), and reduced eGFR (4.2% vs. 2.2%, p<0.001). The study highlights the need to ensure that decisions for hypertension management consider any propensity to medication induced episodes of hypotension, which may impact renal function. The addition of central pressure monitoring can assist in this objective (e.g., normal to high normal brachial pressure and low-normal to low central aortic pressure).

A study examining 651,749 US veterans with CKD sought to assess the association of blood pressure with mortality in CKD patients.[26] The lowest mortality was observed with blood pressure of 130–159/70–89 mmHg. Patients with systolic and diastolic BP concomitantly very high or very low had the highest mortality. Results were consistent in subgroups of patients with normal and elevated levels of urine microalbumin-creatinine ratio. Depending on the model used, the hazard ratio for mortality with systolic BP < 120 mm Hg and diastolic BP < 80 mm Hg ranged from 1.42 to 1.62 (i.e., 42% to 62% increased risk). As with the previous study, avoiding hypotension should have a significant clinical impact. Again, the addition of central pressure monitoring in patients with CKD can assist in this objective.

The addition of central aortic pressure monitoring can assist in hypertension management decisions that consider any propensity towards medication induced episodes of hypotension, which may negatively impact renal function.

In summary, prescription of anti-hypertension medications has the potential of significant benefit but as with all medications, may be associated with adverse consequences such as reduced renal function and should always be judicious and carefully considered, particularly in patients with CKD. 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 may be 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:

- Chronic kidney disease (CKD) is common and effects approximately 15% of adults in the USA (37 million people). Kidney disease is the ninth leading cause of death. CKD increases the risk for cardiac disease, stroke, and death, and leads to multiple significant additional diseases.
- Hypertension and diabetes are the leading causes of CKD in adults and also represent the most treatable targets to prevent CKD and to reduce CKD progression. Hypertension is responsible for continued morbidity, mortality and high socioeconomic costs despite the widespread availability and use of cuff brachial artery measurements for diagnosis and monitoring.
- 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 is predictive of end-organ damage including impaired renal function. Brachial and central aortic pressures provide complimentary information for risk prediction and management decisions.

- The risk of cardiovascular events 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.
- 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.
- Prescription of anti-hypertension medications has the potential of significant benefit but as with all medications, may be associated with adverse consequences (hypotension and drug specific adverse effects) and should always be judicious and carefully considered, particularly in patients with CKD. Assessment of central pressures provides relevant information that informs prescription medication needs.
- 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:
    - 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
    - Avoiding initiation of medication when white coat hypertension is suspected.
      Scenario: Elevated brachial pressure and normal central pressures
    - Confirmation that increased treatment may not be needed.
      Scenario: Borderline high peripheral pressures and normal central pressures
    - 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, which is complementary to continued reliance on brachial pressure monitoring should be a part of the care of all patients with chronic kidney disease.

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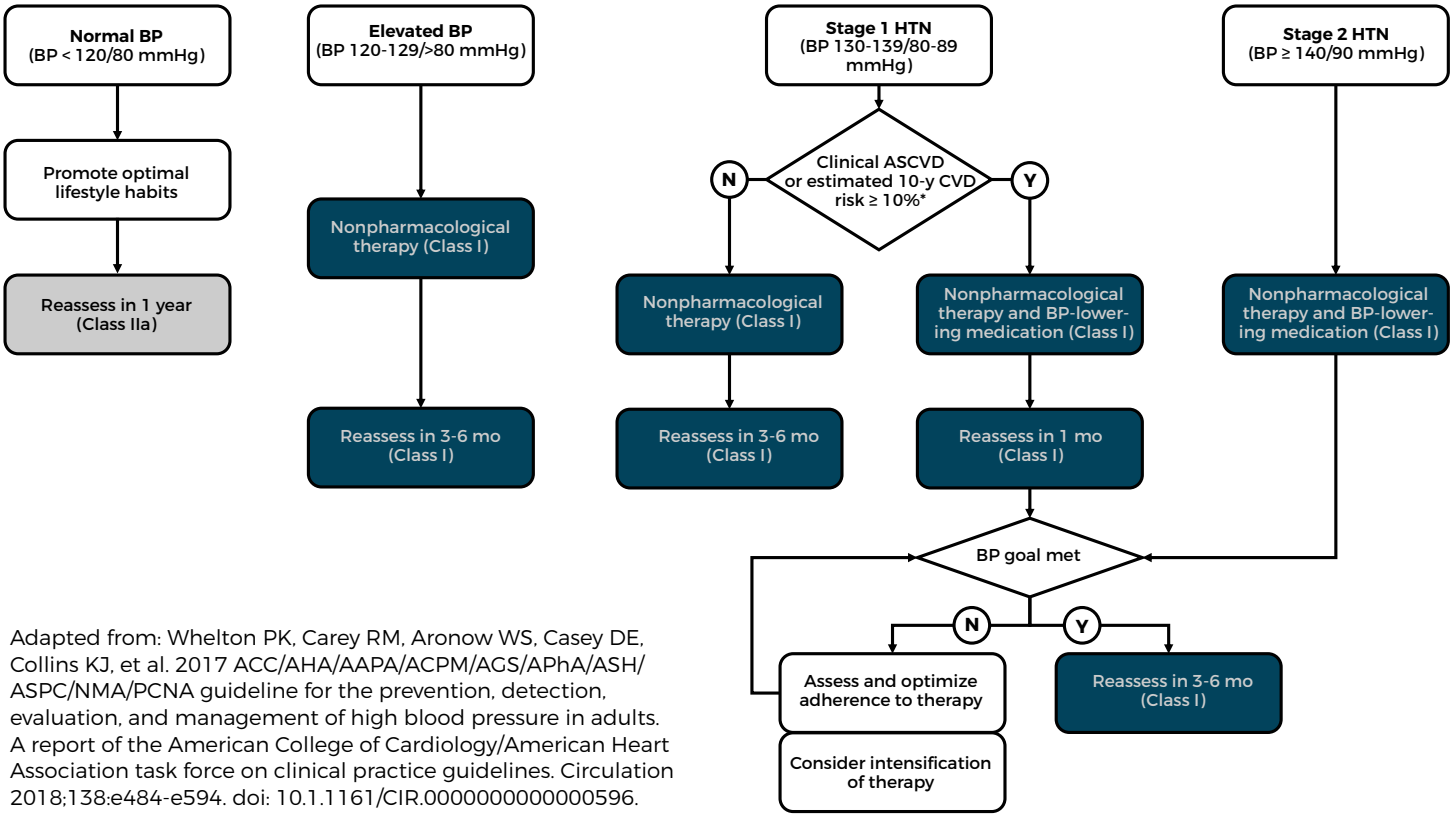
Appendix A

Blood Pressure Thresholds and Recommendations for Treatment and Follow-Up



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