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The Role of Central Pressure Monitoring in the Management of Patients with Diabetes Mellitus and Elevated Blood Pressure

Executive Summary

- Diabetes mellitus is a common chronic disease that effects approximately 10.5% of the population in the USA (2018). In 2016, a total of 7.8 million hospital discharges were reported with diabetes as any listed diagnosis among US adults aged 18 years or older, with 1.7 million of the discharges including major cardiovascular diseases (75.3 per 1,000 adults with diabetes).
- According to the 2020 National Diabetes Statistics Report, 68.4% of diabetics had a systolic blood pressure of 140 mmHg or higher, or diastolic blood pressure of 90 mmHg or higher, or were on prescription medication for their high blood pressure. Diabetes with associated 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 (heart, brain, kidneys). 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.
- 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 diabetes. Assessment of central pressures provides relevant information that informs prescription medication needs in diabetic patients.
- 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.

- Independent data have confirmed the reliability of non-invasively obtained central aortic pressures utilizing SphygmoCor technology in numerous patient populations including patients with diabetes.
- 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 diabetes and associated hypertension.

Background

Burden of Diabetes

Diabetes and hypertension are both common chronic diseases. People with diabetes commonly have hypertension. Both diseases have long-term negative consequences on vascular health, morbidity, and mortality. The prevalence of diabetes in the United States in 2018 was estimated to be 34.2 million (10.5% of the population),1 with the prevalence in adults increasing with age. In 2018, diabetes was diagnosed in 26.8% of adults who were at least 65 years old. Based on data from 1999–2016, the prevalence of diabetes had increased from 9.5% (1999–2002) to 12.0 (2013–2016).[1]

Diabetes is a well-documented significant risk factor for macro and microvascular disease including cardiovascular disease (e.g., ischemic heart disease and heart failure), peripheral vascular disease, cerebrovascular disease (e.g., transient ischemic attacks and stroke), chronic renal disease, and retinopathy.[2,3] People with diabetes commonly have additional risk factors for vascular disease, which include smoking, obesity, physical inactivity, hypercholesterolemia, and hypertension. According to the 2020 National Diabetes Statistics Report, 68.4% of diabetics had a systolic blood pressure of 140 mmHg or higher (Stage 2 hypertension), or diastolic blood pressure of 90 mmHg or higher, or were on prescription medication for their high blood pressure.[1] In addition to glycemic control, it is critical to address risk factors, particularly hypertension, in order to reduce the vascular complications of diabetes.

The burden of diabetes on an individual is enormous in terms of lifelong monitoring, drug administration, and management of complications with associated disability. The burden on the health care system is substantial. In 2016, a total of 7.8 million hospital discharges were reported with diabetes as any listed diagnosis among US adults aged 18 years or older (339.0 per 1,000 adults with diabetes); the discharges included:[1]

- 1.7 million for major cardiovascular diseases (75.3 per 1,000 adults with diabetes)
    - 438,000 for ischemic heart disease (18.9 per 1,000 adults with diabetes)
    - 313,000 for stroke (13.6 per 1,000 adults with diabetes)
- 130,000 for a lower-extremity amputation (5.6 per 1,000 adults with diabetes)

The total direct and indirect estimated costs of diagnosed diabetes in the United States in 2017 was $327 billion. Total direct estimated costs of diagnosed diabetes increased from $188 billion in 2012 to $237 billion in 2017 (2017 dollars); total indirect costs increased from $73 billion to $90 billion in the same period (2017 dollars). Between 2012 and 2017, excess medical costs per person associated with diabetes increased from $8,417 to $9,601 (2017 dollars). Control of risk factors contributing to the morbidity of diabetes has a meaningful impact on the overall socioeconomic impact of diabetes.

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Targeting Hypertension Monitoring in Patients with Diabetes

Vascular complications are the leading cause of morbidity and mortality for individuals with diabetes and are the largest contributor to the direct and indirect costs of diabetes.[2,3] Studies have consistently shown that patients with diabetes commonly have hypertension and that the presence of both diseases result in a higher risk of vascular and renal disease compared to either disease alone.[4,5] It is therefore critical to improve diagnosis, monitoring, and treatment of blood pressure in diabetic patients with hypertension. Numerous studies have shown that antihypertensive therapy reduces vascular complications associated with diabetes.[6-10]

In a 2017 position statement of diabetes and hypertension[3], the American Diabetes Association (ADA) recommended the following:

Blood pressure should be measured at every routine clinical care visit. Patients with an elevated blood pressure (>140/90 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, within 1 month, to confirm the diagnosis of hypertension.

All hypertensive patients with diabetes should have home blood pressure monitored to identify white-coat hypertension.

Orthostatic measurement of blood pressure (lying/sitting to standing changes) should be performed during initial evaluation of hypertension and periodically at follow-up, or when symptoms of orthostatic hypotension are present, and regularly if orthostatic hypotension has been diagnosed.

Therapeutic options and recommendations are outlined in the 2017 position statement[3] and will not be discussed within this document.

Monitoring of 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."[11] 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.[12] 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.

The SphygmoCor XCEL is the only FDA cleared medical device for non-invasive central arterial pressure waveform measurement and analysis for all adults.

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)).

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 appears to be value in monitoring both variables.

Incorporating Central Blood Pressure Monitoring in Diabetic Patients with Hypertension

The American Diabetes Association in their recommendations highlight several clinically relevant issues where the addition of central aortic blood pressure monitoring would be useful.[3] These issues are particularly important in patients with diabetes given how common vascular complications are and the need to carefully manage medications for both beneficial (reduce vascular complications) and harmful effects (morbidity and end-organ damage associated with low blood pressure). The issues highlighted included confirmation of hypertension, white coat hypertension, masked hypertension, and orthostatic hypotension (which is associated with autonomic dysfunction due to diabetes).[3]

Masked hypertension is defined as a normal office measured BP (<140/90 mmHg) but an elevated home BP (>135/85 mmHg). White-coat hypertension is defined by an elevated office measured BP (>140/90 mmHg) and normal home blood pressure (<135/85 mmHg). Diagnosing white-coat hypertension is important so as to avoid medication overtreatment, which is particularly relevant in diabetes. For the opposite condition, masked hypertension, undertreatment may occur. Central aortic BP measurements in the office may assist in identifying both of these conditions and therefore should improve the suspicion of the diagnosis and confirm both diagnoses.

Orthostatic hypotension in diabetes is due to autonomic neuropathy (a complication of diabetes), and by decreased intravascular volume (a consequence of hyperglycemia). Given the primary action, antihypertensive medications will exacerbate the magnitude, symptoms and consequences of hypotension. Orthostatic hypotension is defined by a systolic BP decrease > 20 mmHg or diastolic BP decrease > 10 mmHg within 3 min of standing relative to lying or sitting.[13] Orthostatic hypotension is common in people with type 2 diabetes and hypotension and is associated with an increased risk of mortality and heart failure.[14]

Although complications such as hypotension may occur, it is clear through meta-analyses of clinical trials that antihypertensive treatment of patients with diabetes and baseline Stage 2 hypertension reduce the risks of vascular disease (including ischemic heart disease, heart failure, retinopathy, and renal dysfunction (as indicated by decreased albuminuria and therefore must be utilized appropriately.6-10,15

The importance of monitoring for blood pressure control, both for elevated and for low blood pressure is highlighted by the results of the ACCORD Study reported by Cushman and colleagues.[16] The study investigated whether therapy targeting intensive blood pressure control (i.e., systolic <120 mm Hg) reduces major cardiovascular events in participants with type 2 diabetes at high risk for cardiovascular events. A total of 4,733 subjects were randomized to intensive management or standard management (i.e., target systolic <140 mm Hg). Mean follow-up was 4.7 years. The primary endpoint (composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) was not significantly different between the two groups. However, other data demonstrated adverse consequences such as increased serious adverse events, reduced renal function, and possibly a higher risk of renal failure when targeting intensive therapy (Table 1).

Table 1: Results from the ACCORD Trial of intensive vs. standard BP management in patients with type II diabetes.

	Therapy		
	Intensive	**Standard**	**p-value**
Primary Endpoint	1.9%	2.1%	0.2
Death[1]	1.3%	1.2%	0.55
Serious Adverse Event[2]	3.3%	1.3%	<0.001
Elevated creatinine	23.8%	15.5%	<0.001
eGFR[3]	4.2%	2.2%	<0.001
Renal Failure[4]	0.2%	0.04%	0.12

1annual rate, 2attributed to antihypertensive medications, 3estimated glomerular filtration rate <30 ml/min/1.73 m2, 4represents 5 vs. 1 patient

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).

Clinical Studies of Central Aortic Pressure Monitoring in Diabetes

Numerous studies have been published that provide rationale for incorporated central aortic pressure monitoring into the care of patients with hypertension. The key publications have been discussed in previous summary documents produced by Atcor Medical, some of which, but not all, will be repeated here.[15-17] Peer-reviewed publications have demonstrated the consistent associations of elevated central aortic pressures with an increased risk of end-organ damage (cardiac, renal, brain) and of adverse clinical vascular outcomes.[17-19] Furthermore, specific central aortic systolic blood pressure thresholds that define increased risk and can therefore be considered as management targets have been defined using similar methodology that defined current brachial BP thresholds. The literature and threshold values are described in the aforementioned Atcor Medical summary documents.[17-19] The data indicate that central aortic pressure monitoring may provide additional, complementary, and independent information to that obtained by brachial BP monitoring. The publications are generic to hypertension and the data apply equally and perhaps more so to patients with both diabetes and hypertension given the additional risk of both diseases combined compared to either alone.

Nevertheless, there are specific publications that describe patients with diabetes and hypertension that provide further data regarding the utility of incorporating central aortic BP monitoring into the care of these patients.

Yang and colleagues investigated the association of central blood pressure (cBP) and cardiovascular disease (CVD) in diabetic patients with hypertension in a cross-sectional study of 360 subjects.[18] Central aortic BP variables were central systolic and diastolic BP (cSBP and cDBP), and augmentation index adjusted for 75 beats per minute of heart rate (AIx75). Subjects were divided into two groups based on the presence or absence of CVD groups. Coronary heart disease diagnosis was based on computer tomography coronary artery with contrast or coronary artery angiography, and ischemic stroke was based on clinical symptoms and computer tomography evidence, and composite CVD was comprised of coronary heart disease and ischemic stroke. The mean age of subjects was 50.6 years with 58% of subjects being male. Coronary heart disease and ischemic stroke were diagnosed in 35 and 43 subjects respectively. Those with CVD had significantly higher central cSBP and AIx75 compared with those without CVD. Increased age, male gender, and presence of coronary heart disease and ischemic stroke were associated with increased AIx75, whereas renin–angiotensin–axis inhibitor was associated with reduced AIx75. After adjusted for traditional risk factors including brachial SBP, both cSBP, and AIx75 remained significantly associated with CVD (odds ratio (95% confidence interval) = 1.09 (1.08–1.31) and 1.20 (1.15–1.42), respectively). Diabetic patients with hypertension, ageing, male gender, and presence of CVD are independent risk factors of central BP increase; and increased cSBP and AIx75 are significantly associated with CVD.

The association between cSBP and AIx75 with composite CVD was evaluated and found to be significant with a stepwise adjusted model. The unadjusted model showed an elevated odds ratio (95% confidence interval) for cSBP of 1.69 (1.45-1.87) and for AIx75 of 1.82 (1.61-2.03). Overall, in model 3, after adjusted for age, male gender, smoking, body mass index, glycated hemoglobin, total cholesterol, renin–angiotensin–axis inhibitor, and brachial SBP, both cSBP and AIx75 remained significantly associated with the prevalence of CVD, with odds ratio (95% confidence interval) of 1.09 (1.08–1.31) and 1.20 (1.15–1.42), respectively.20 The data are displayed in Table 2

Table 2: Odds ratio (95% confidence interval) using logistic regression analysis for the risk of cardiovascular disease.20

	Unadjusted	Model 1	Model 2	Model 3
cSBP	1.69 (1.45-1.87)	1.42 (1.23-1.70)	1.30 (1.20-1.54)	1.09 (1.08-1.31)
AIx75	1.82 (1.61-2.03)	1.71 (1.54-1.93)	1.56 (1.42-1.77)	1.20 (1.15-1.42)`

Model 1: adjusted for age and male gender; Model 2: further adjusted for smoking, body mass index, glycated hemoglobin, and total cholesterol; Model 2: further adjusted for ACE/ARB and brachial systolic blood pressure

The study demonstrated that patients with diabetes, hypertension and CVD have significantly higher cSBP and AIx75 that is independent of brachial BP. Therefore, increased cSBP and AIx75 are associated with the prevalence of CVD that provides additional risk information relative to brachial BP. The study also provided interesting data regarding therapeutic choices in that renin–angiotensin–axis inhibitors appeared to reduce AIx75, suggesting that angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) may preferentially reduce central BP compared to other antihypertensive medication classes.

The Finnish Diabetic Nephropathy Study is a prospective study of type 1 diabetics who have been followed

since 1997.[21] PWA was measured in 906 individuals to determine if central pressures including AIx and cSBP would be associated with all-cause mortality as well as a composite of cardiovascular and/or diabetes-related mortality using multivariable Cox regression models. The 67 patients who died during follow-up had higher baseline AIx compared with those alive (median 28% vs. 19%; p<0.001). The increased risk (hazard ratio (HR) 1.71 [95% CI 1.10–2.65]; p=0.017) was independent of risk factors (age, sex, body mass index, HbA1c, estimated glomerular filtration rate, and previous cardiovascular event) Similarly, higher AIx was associated with the composite secondary end point of cardiovascular and diabetes-related death (n=53) after similar adjustments (HR 2.30 [1.38–3.83]; p=0.001). In addition, those who died had higher baseline cSBP (138 vs.119 mm Hg; p<0.001) and central pulse pressure (61 vs. 41 mm Hg, p<0.001). The differences for brachial sBP and peripheral pulse pressure were 151 vs. 134 mm Hg (p<0.001) and 76 vs 55 mm Hg (p<0.001). The data indicate that elevated AIx and cSBP are associated with all-cause mortality as well as a composite cardiovascular and/or diabetes-related cause of death in individuals with type 1 diabetes.

In an earlier study from the same cohort of type 1 diabetics, patients without signs of diabetic nephropathy had a high AIx than age-matched control subjects (17.3% + 0.6% versus 10.0% + 1.2%; p<0.001) indicating arterial stiffening as an early measurable physiologic consequence.[22] AIx (OR 1.08; 95% CI 1.03 – 1.13; p=0.002) was associated with diabetic laser-treated retinopathy in patients with normoalbuminuria in a multivariate logistic regression analysis, which included adjustments from multiple risk factors including brachial sBP. The same was true for AIx and diabetic nephropathy (1.04 (1.01 – 1.08); p=0.004) as well as AIx and CVD (1.06 (1.00 – 1.12); p=0.01). The data demonstrate the association of elevated PWA variables, particularly AIx, with microvascular and macrovascular complications in patients with type 1 diabetes. The implication from both reports is that monitoring of cSBP and AIx can help identify at-risk patients who may be targeted for more intensive management of blood pressure.

Monitoring of cSBP and AIx can help identify at-risk patients for end-organ damage and mortality who may be targeted for more intensive management of blood pressure.

Confidence in measurement devices (incorporating both hardware, software, and algorithms) often is assessed in broad populations of healthy individuals or specific disease states with relatively narrow inclusion/exclusion criteria. Following device approval and acceptance by health care professionals, such medical devices are commonly used in patient populations that have not specifically been evaluated, although the disease states may have been encompassed in smaller numbers in the broader population of subjects studied. Nevertheless, post-approval data within specific disease states is important to provide reassurance that the medical device has appropriate data for therapeutic decisions. For diabetic patients, because the extent and distribution of arterial stiffness differs from normal healthy subjects, one could question whether the generalized transfer function developed for non-invasive evaluation of central aortic pressures applies equally to subjects with diabetes. Data specific to diabetic patients would therefore be helpful in providing reassurance regarding therapeutic decisions based on the technology within the SphygmoCor device. Several studies have been published that demonstrate that information from the SphygmoCor technology is similar to and can be used with confidence in patients with diabetes.

Three studies are relevant to the validation of non-invasively obtained central aortic pressure measurements in diabetic patients using the SphygmoCor technology.[21-23] Laugesen et al assessed the intra-and inter-observer reproducibility of pulse wave analysis (PWA) variables in patients with type 2 diabetes using the SphygmoCor device.[23] Two trained observers performed two PWA standardized measurements in random order in 20

patients with type 2 diabetes. The mean intra-observer differences (± 2 SD) for the two observers were 0.0 ± 2.8 mmHg and 0.3 ± 3.2 mmHg for cSBP, 0.0 ± 1.2 mmHg and 0.1 ± 1.0 mmHg for cDBP, -1.1 ± 3.2% and 1.1 ± 9.6% for AIx, and -1.6 ± 6.6% and 0.1 ± 9.0% for AIx75. The mean inter-observer differences (± 2 SD) were-2.6 ± 13.0 mmHg (cSBP), -2.1 ± 7.4 mmHg (cDBP), -0.8 ± 8.4% (AIx), and -1.5 ± 7.4% (AIx75). These values show the degree of precision and low variability for central aortic blood pressure values. Despite the relatively small numbers of subjects, the investigators data demonstrated the reproducibility of PWA using the SphygmoCor device in patients with type 2 diabetes. The same center published additional data in 34 patients with type 2 diabetes estimating cSBP and cDBP using the SphygmoCor device and comparing these data with invasively recorded data.[24] The difference between non-invasive and invasively measured central aortic SBP and DBP was -2.3±5.6 and 1.0±0.9mm Hg respectively. When calibrating with oscillometric brachial systolic and diastolic BPs, the differences were -9.6±8.1 and 14.1±6.2mm Hg respectively. Calibration with the average of 3 brachial BPs did not improve accuracy. The investigators concluded that the SphygmoCor transfer function appears to be valid in patients with type 2 diabetes. Wilkinson et al sought to determine the reproducibility of AIx measured using PWA via the SphygmoCor device.[25] Subjects with and without a range of recognized cardiovascular risk factors were studied to provide a wide range of values. Two different observers used PWA to determine AIx in 33 subjects, each on two randomly determined occasions. AIx ranged from -15.0 to +45.0%, with a group mean of +19.6+/-12.0%. The within-observer difference was 0.49+/-5.37% and between-observer difference 0.23+/-3.80%. The authors demonstrated further substantiated the reproducibility of PWA using the SphygmoCor system. In summary, independent investigations, albeit in relatively small sample sizes, have shown that central aortic blood pressure values using SphygmoCor technology is reliable and reproducible in patients with diabetes. The clinical data for central aortic blood pressure monitoring in broader populations should therefore be applicable to patients with diabetes.

Central aortic pressure information from the SphygmoCor technology has been documented to be reliable and can be used in patients with diabetes.

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.[15] 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).[11] 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.[11]

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.[11]

Takase and colleagues evaluated the distribution of central blood pressure values in a population study of Japanese subjects.[26] 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.[26] 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.[11]

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.[27,28]

Booysen et al reported an upper threshold for cSBP of 112 mm Hg in a study of 1,169 participants.[27] 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.[27] Lamarche and colleagues recently reported a prospective study that examined the predictive value of central systolic blood pressure for cardiovascular events.[29] 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.[29] 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.[30] 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.[30] 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.

Threshold values for central aortic systolic pressure that represent decision points for therapeutic decisions can be determined based on published data from multiple studies.

Incorporating Central Aortic Pressure Monitoring into the Care of Patients with Diabetes and Hypertension: 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 management of diabetic patients with hypertension. Treatment with combined (i.e., fixed dose combination) medications are often the mainstay of treatment. Nevertheless, despite the availability of multiple medications and multiple classes of medications, suboptimal treatment and the consequences thereof are readily recognized as ongoing societal problems in terms of morbidity and socioeconomic costs. Specific issues related to prescription hypertension medications include undertreatment, overtreatment, compliance, drug cost, adverse events, and interactions with concomitant medications, all of which impact a patient's adherence behavior to prescribed treatment and the burden of hypertension. Optimizing prescription medication and the self-administration of therapy is critical to controlling hypertension.

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

1. Confirmation of hypertension so that initiation of medication is more likely to be the correct decision for a patient.
   Scenario: Concurrent elevation in brachial and central pressures

2. Avoiding initiation of medication when white coat hypertension is suspected.
   Scenario: Elevated brachial pressure and normal central pressures, provided that an elevated heart rate does not confound the results.

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

4. Targeting when to consider reduction of medication.
   Scenario: Normal peripheral and low central pressures, or extended period of normal peripheral and normal central pressures (particularly in the setting of medication tolerance issues)

As stated, a critical rationale for incorporating central aortic pressure monitoring is the confirmation of hypertension that is suspected based on peripheral pressures that are then utilized 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.

The publications and data described in this and the aforementioned Atcor documents[15-17] 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.

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:

- Diabetes mellitus is a common chronic disease that effects approximately 10.5% of the population in the USA according to data from 2018 (34 million people). In 2016, a total of 7.8 million hospital discharges were reported with diabetes as any listed diagnosis among US adults aged 18 years or older, with 1.7 million documented for major cardiovascular diseases (75.3 per 1,000 adults with diabetes).
- According to the 2020 National Diabetes Statistics Report, 68.4% of diabetics had a systolic blood pressure of 140 mmHg or higher, or diastolic blood pressure of 90 mmHg or higher, or were on prescription medication for their high blood pressure. Diabetes with associated 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 (heart, brain, kidneys). 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.
- 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 diabetes. Assessment of central pressures provides relevant information that informs hypertension prescription medication needs in diabetic patients.
- 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.
- Independent data have confirmed the reliability of non-invasively obtained central aortic pressures utilizing SphygmoCor technology in numerous populations including patients with diabetes.
- 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 should be a part of the care of all patients with diabetes and associated hypertension.

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