ATCOR

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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.
- 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 adverse CV outcomes with elevated central pressure is at least as high and possibly higher than with brachial pressure.
- 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.
- Independent data have confirmed the reliability of non-invasively obtained central aortic pressures utilizing SphygmoCor® technology in numerous patient populations including patients with diabetes.
- incorporation of central aortic pressure monitoring should be considered for 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.

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. Of note, brachial and central pressure measurements correlate but cannot reliably be predicted from each other in a given individual.[12]

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
Death1	1.3%	1.2%	0.55
Serious Adverse Event2	3.3%	1.3%	<0.001
Elevated creatinine	23.8%	15.5%	<0.001
eGFR3	4.2%	2.2%	<0.001
Renal Failure4	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.

Incorporating Central Aortic Pressure Monitoring into the Care of Patients with Diabetes and Hypertension: Optimization of Pharmacotherapy for Hypertension

Hypertension management through the addition of non-invasive measurements of central aortic pressures has the potential to improve care through: (a) refining requirements for BP monitoring, (b) decreasing over-treatment, (c) early identification for earlier or more aggressive treatment, and (d) decreasing the overall cost of care (e.g., use of tools such as ambulatory blood pressure monitoring (ABPM), drug costs).

Identifying the requirements and amount of medication is critical to controlling gestational hypertension.

The following table provides examples where central aortic blood pressure monitoring may positively impact the treatment of gestational hypertension:

Table 3: Examples of clinical utility of measuring both brachial and central aortic blood pressure.

CLINICAL USE	BRACHIAL BP	CENTRAL BP
Confirming hypertension (drug prescription is optimized)	Elevated	Elevated
Suspicion of white coat hypertension	Elevated	Normal or Low
Avoidance of increased drug prescription	Borderline high	Normal or Low
Consideration of reducing drug prescription (patients receiving at least one anti-hypertensive medication	Normal (particularly when there is suspected medication adverse effects)	Low (or extended period of normal)

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.

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.

- 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.
- 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 hypertensive disorders of pregnancy as the dual arterial pressure SphygmoCor® XCEL device 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.

In conclusion, incorporation of central aortic pressure monitoring should be considered for all patients with diabetes and associated hypertension.

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