State of the Art Central Blood Pressure Measurement
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INTRODUCTION

The clinical consequences of hypertension - cardiovascular events such as stroke, heart attack and kidney disease - are, combined, the number one killer in the developed world.

Central blood pressure is the pressure in the ascending aorta, which is to say it is the pressure measured at the point at which blood is ejected from the heart. It is the pressure that the target organs (the brain and kidneys, and the heart itself) are directly exposed to. Due to arterial pressure amplification, central blood pressure is lower than at peripheral locations such as the brachial artery, where blood pressure is traditionally measured. Importantly, it is not possible to estimate the central blood pressure from the brachial BP.

Central pressure has been shown to correlate with target organ damage in a manner superior to brachial blood pressure. Additionally, central blood pressure waveform analysis via AtCor's SphygmoCor technology allows a practitioner to better understand the drivers of hypertension, including arterial stiffness (typically treated with vasoactive agents) and excess fluid volume (most commonly treated with diuretics). As a result, assessment of central blood pressure allows for enhanced understanding of cardiovascular risk and individualization of intervention, whether via drugs or lifestyle modification.

BLOOD PRESSURE MEASUREMENT

For over 100 years, physicians have relied on the systolic and diastolic pressures measured with a brachial cuff sphygmomanometer to manage their patients. This is true because (a) this has been the only practical noninvasive BP measurement technique available, and (b) brachial BP tracks risk in populations. Importantly, this is why brachial BP is of interest to insurance companies, who view the world in risk pools rather than as individuals.

CARDIOVASCULAR RISK AND BLOOD PRESSURE MEASUREMENT

In "The heart, kidney, and brain as target organs in hypertension", Mensah et al state:

> "The heart, kidney, brain, and arterial blood vessels are prime targets of hypertensive damage. Uncontrolled hypertension accelerates the damage to these organs and results in eventual organ failure and cardiovascular death and disability. Current guidelines for

> the appropriate treatment and control of hypertension requires an assessment of the presence of target organ damage. When present, evidence of target organ damage determines the urgency and intensity of drug treatment and may also dictate the choice of initial antihypertensive drug class."

The fact that central BP more closely reflects CV risk than brachial BP is not controversial and is stated consistently in the literature. The predictive superiority of central blood pressure over brachial blood pressure is primarily due to the closer proximity of the ascending aorta to the target organs.

> In "2019 Consensus of the Taiwan Hypertension Society and Taiwan Society of Cardiology on the Clinical Application of Central Blood Pressure in the Management of Hypertension", Cheng et al state:
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> > "Noninvasive central BP is better than conventional brachial BP to assess target organ damage and long-term cardiovascular outcomes"
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> In "Association of Central Versus Brachial Blood Pressure With Target-Organ Damage: Systematic Review and Meta-Analysis", Kollias et al state:
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> > "In conclusion, central compared with brachial BP seems to be more strongly associated with most of the investigated indices of preclinical organ damage."

Given the above, knowing an individual's brachial BP gives a sense of cardiovascular risk, but only a 'gross estimate' if brachial BP does not accurately predict the central aortic BP (the pressure at the heart), which is the pressure that the target organs directly experience. The degree of unpredictability of CBP from BBP dictates how much of a shortcoming one faces when working with brachial BP on its own. The evidence shows that central systolic blood pressure cannot be estimated from the brachial systolic value.

In "Central Pressure: Variability and Impact of Cardiovascular Risk Factors", McEniery et al. analyzed a central and brachial pressure dataset of over 10,000 adults aged 18 to 101 years whose individual brachial systolic pressures ranged from 100 to 200 mmHg. They documented individual variability between brachial and central systolic pressures ranging from as few as 2-3 mmHg to approximately 30 mmHg. Because of such individual variability, central pressure cannot be reliably inferred from brachial pressure measurement. A key conclusion from this 2008 publication was:

> "These data demonstrate that cardiovascular risk factors affect the pulse pressure ratio, and that central pressure cannot be reliably inferred from peripheral pressure. However, assessment of central pressure may improve the identification and management of patients with elevated cardiovascular risk."

CENTRAL BLOOD PRESSURE AND BRAIN HEALTH

A 2019 publication from Columbia University and the University of Miami, "Association Between Central Blood Pressure and Subclinical Cerebrovascular Disease in Older Adults", showed that both brachial and central blood pressure were independently associated with silent brain infarction, but only higher central systolic pressure and central pulse pressure were significantly associated with white matter hyperintensity volume.

In Blood Pressure and Cognitive Function :The Role of Central Aortic and Brachial Pressures higher central systolic and pulse pressures, and lower pulse pressure amplification (see below) were significantly associated with poorer performance on several tests of cognition. The authors conclude:

> "In summary, central pressures and amplification were sensitive indicators of cognitive aging, predicting aspects of cognitive performance not predicted by brachial blood pressure. "

Two publications from 2018, Aortic Stiffness is Associated with Increased Risk of Incident Dementia in Older Adults and Pulse Wave Velocity Is Associated With Greater Risk of Dementia in Mild Cognitive Impairment Patients, both showed PWV predicted progression to dementia in those free of dementia at baseline as well as in those with mild cognitive impairment, respectively. These results further emphasize that increased central pressure pulsatility, as a consequence of increased large artery stiffness, is an independent driver of cognitive decline.

CENTRAL TO BRACHIAL BLOOD PRESSURE AMPLIFICATION

The difference between central and brachial blood pressure is commonly referred to as 'amplification' because blood pressure increases as the measurement site moves away from the heart. This means that brachial systolic BP is almost always greater than central systolic BP. We also know:

- Diastolic and mean pressures are quite consistent (i.e., virtually equal) throughout the large arteries, so the variability that is of interest is in systolic pressure. [In examples below, consider a patient with BBP of 140/80 and CBP of 125/80]
- Amplification can be measured as a percentage referred to as pulse pressure amplification (or 'ratio' in the quote immediately above), in which case it is calculated as brachial pulse pressure divided by central pulse pressure [if BPP=60 mmHg and CPP=45 mmHg then PP amplification = 60/45=133%]
- Amplification can also be represented in mmHg, and is simply the difference between BPP and CPP [60-45=15 mmHg]

Across any given population, amplification will tend to be approximately 10-12 mmHg *on average,* decreasing in old age. McEniery stated:

> "Current guidelines for the diagnosis and treatment of hypertension are based solely on brachial BP. However, brachial and central BPs are not the same, even in older individuals, as demonstrated by the current data where differences of 8 to 10 mm Hg between brachial and aortic systolic BP are standard. Increased central BP is associated with a number of pathophysiological mechanisms, such as left ventricular hypertrophy, altered myocardial perfusion, and carotid artery remodeling, all of which increase the risk of cardiovascular events. Moreover, central pressure may be a better predictor of future cardiovascular risk in selected patient groups than brachial pressure. Therefore, it seems likely that the assessment of central pressure will improve the identification and management of patients with elevated cardiovascular risk."

The term 'amplification' provides nomenclature for discussion of the relative under- or -over-estimation of risk. For example, a high normal patient with amplification of 2 mmHg (under-estimation) vs one with amplification of 20 mmHg (over-estimation).

Studies in both healthy and diseased subjects have consistently demonstrated that elevated central aortic blood pressure is independently associated with increased cardiovascular events and is superior to brachial pressure as a predictor of those events.

In "High Central Pulse Pressure Is Independently Associated With Adverse Cardiovascular Outcome - The Strong Heart Study", Roman et al. reported that *central* pulse pressures were more strongly predictive of cardiovascular events, independent of brachial pressures. Specifically, when the central pulse pressure equals or exceeds 50mmHg, the risk of cardiovascular disease increases by nearly 70%; brachial pressure did not demonstrate any such threshold. The authors stated:

> "This and other recent studies provide strong evidence for the superiority of central BP, particularly PP, to brachial BP in correlation with subclinical vascular disease and association with CVD events. Furthermore, preliminary evidence suggests that achievement of a lower central BP for a given level of brachial BP may be more effective in reducing CVD target organ damage and morbidity and mortality."

In "Aortic, but not brachial blood pressure category enhances the ability to identify target organ changes in normotensives", Booysen et al found that, even in normotensive subjects, those with a CSP above 112 mmHg had systematically greater target organ damage than those below that threshold, regardless of brachial systolic pressure. The authors stated:

> "In conclusion, in contrast to the lack of ability of normal or high-normal [brachial] BP categories to identify normotensives with target organ changes, in the present study we show that in normotensives, 'optimal' central aortic BP values clearly identify the presence of target organ changes. Thus, the use of aortic BP measurements may enhance the ability to risk stratify those with a normal/high-normal brachial BP."

Roman and Devereux reviewed numerous longitudinal studies demonstrating that changes in central aortic blood pressure are more significant than decreases in brachial blood pressure with respect to target organ damage in hypertensives, stating:

> "In conclusion, numerous studies have documented a superior relation of central over brachial BP to intermediate cardiovascular phenotypes or cardiovascular target organ damage. In general, PP has been more strongly related to vascular disease, whereas systolic pressure seems to be a more important determinant of LVH. The similarity of findings in a wide variety of patient-based and population-based studies as well as a broad range of ethnicities supports the robust nature of this phenomenon."

Zou et al investigated, in 675 patients aged >60 years, central pressure and arterial stiffness indices and their prediction of CV events or death. They found that *CBP improved prediction of these events, as compared to brachial pressure, within the relatively short follow-up period of two years*.

Summarizing the key points above:

- **Central blood pressure is superior to brachial blood pressure in assessing CV risk (keep in mind that 'assessing CV risk' is why we measure brachial BP)**
- **Individual variability in the difference between central and brachial pressures can be significant and clinically important.**
- **Central aortic pressures and arterial stiffness indices cannot be reliably inferred from brachial pressures, so must be measured.**

ARTERIAL STIFFNESS, HYPERTENSION AND CENTRAL PRESSURE WAVEFORM ANALYSIS

While blood pressure is most often characterized in terms of simply a maximum (systolic) and a minimum (diastolic) pressure, it is actually a continuous wave made up of the summation of pressure waves generated by the heart's contraction and the pressure reflected back toward the heart from the peripheral arterial tree. The interaction of these two waves is strongly affected by the speed of the transmitted and reflected waves – the faster the wave travels, the

less separation there is between the two. The primary determinant of the wave speed is arterial stiffness (stiffer arteries = faster wave reflection). The central arterial pressure waveform, especially during systole, differs in various parts of the arterial tree if, for example, the reflected wave occurs earlier or later in the cardiac cycle

A key driver of variability of BP amplification between individuals is variability of degree of arterial stiffness. Young, healthy people typically have a compliant arterial system. This compliance results in minimization of arterial pressure wave reflections, which occur as the pressure wave generated by the heart's contraction reach arterial bifurcations, points of vessel narrowing and other sources of impedance mismatch. Each such point generates a single reflected wave, but these sum to a single reflected wave when measured at the ascending aorta. The degree of wave reflection is a function of age and arterial health, which is in turn driven by disease processes (hypertension, diabetes, etc.) and aging itself.

The primary drivers of CV risk that result from increased wave reflection are:

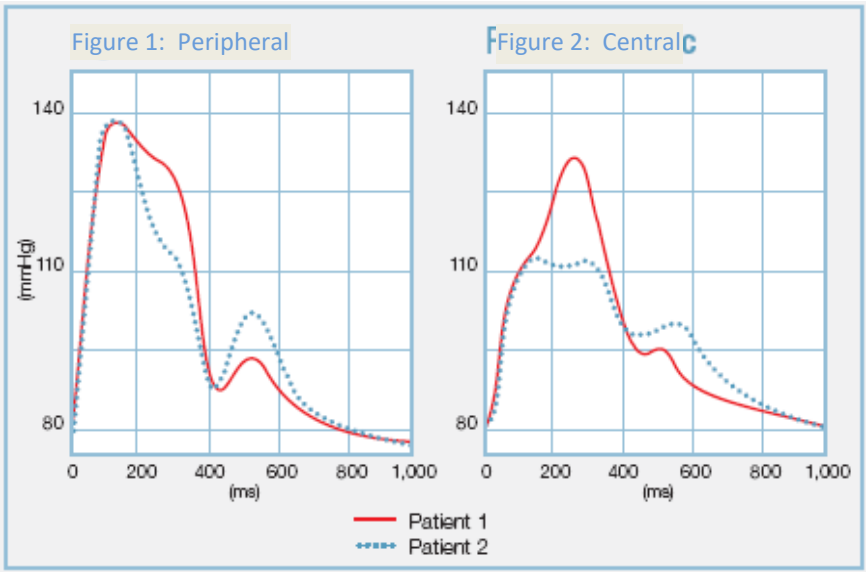
- Increased central pulse pressure, which correlates with stroke risk as the brain is directly exposed to this increased pulsatility
- Increased left ventricular load, which serves to drive increase in LV mass as the heart muscle works harder to overcome this resistance
- Reduced coronary artery perfusion pressure, which increases risk of myocardial ischemia

In central pressure waveform analysis, the Augmentation Index, which is the ratio of the central pressure augmentation (typically peak central pressure minus the pressure at which the inflection point for wave reflection can be detected in the upstroke of the waveform) to central pulse pressure, is largely a function of systemic arterial stiffness.

Arterial stiffness and hypertension have been viewed as 'chicken and egg' phenomena over the years, but Kaess et al performed a longitudinal study of ~1,800 participants from the Framingham Offspring study, investigating the relationship between arterial stiffness and blood pressure progression over seven years.

- Higher baseline arterial stiffness predicted the later development of incident hypertension
- Importantly, higher brachial baseline BP was not predictive of an increase in arterial stiffness

ILLUSTRATION OF DIFFERENTIAL CBP WITH EQUIVALENT BBP



Above: Two patients with equivalent brachial pressures (Figure 1) but with significantly different central arterial pressure waveforms (Figure 2). The difference in waveform shapes, due to differences in arterial stiffness and the effects of wave reflections, affect the aortic but not the brachial systolic and pulse pressures.

CENTRAL BLOOD PRESSURE AND DRUG EFFECTS

Different classes of anti-hypertensive medications can have differential effects on the central hemodynamics and on central vs. brachial pressure. In general, vasoactive medications have a more beneficial impact on central aortic waveforms than non-vasoactive drugs. Arterial vasodilators promote relaxation of vascular smooth muscle cells, delaying the return of the reflected wave and reducing systolic pressure augmentation. The effect on central aortic waveform indices of different classes of vasoactive drugs varies by class. In addition, an individual's response can vary, even within the same class of drugs.

Numerous studies have shown that analysis of the central arterial pressure waveform explains the effects of anti-hypertensive drugs and predicts clinical outcomes significantly better than brachial pressure.

> The Conduit Artery Function Evaluation (CAFE) Study employed a classic anti-hypertensive study design, randomizing patients to one of two treatment groups (calcium channel blocker vs beta blocker), with all patients managed to the same target brachial pressure, and then monitored to determine if there were differential clinical outcomes. SphygmoCor was also used to measure subjects' central pressure. Despite achieving virtually identical brachial blood pressures in both treatment arms the calcium channel blocker group experienced significantly LESS cardiovascular events. The study showed a 4 mmHg lower central systolic pressure in the calcium channel blocker treatment group, thus demonstrating that elevated central systolic and pulse pressure are associated with a higher risk of cardiovascular events and renal impairment, even though brachial pressures were the same in the different study cohorts. The authors (Williams, et. al.) stated:
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> > "BP-lowering drugs can have substantially different effects on central aortic pressures and hemodynamics despite a similar impact on brachial BP. Moreover, central aortic pulse pressure may be a determinant of clinical outcomes."
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> Kampus et al. showed that individuals treated to the same target brachial pressure had different central systolic and pulse pressures and different left ventricular mass effects, echoing the work by Booysen et. al. above, stating:
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> > "Our study expands earlier observations of BB [beta blockers] and shows that, despite the similar effect of both drugs on brachial BP and arterial stiffness, NEB [nebivolol, a vasoactive beta-blocker] has a more significant impact on central BP and left ventricular wall thickness than MET [metoprolol].

Since augmentation index is a measure of the contribution of the reflected wave to central systolic pressure, it provides an indication of the efficacy of vasoactive drugs intended to

reduce wave reflection. In patients with elevated augmentation pressure and/or augmentation index, vasodilating/vasoactive drugs may have a greater efficacy than non-vasodilating drugs. Patients with a lower augmentation pressure and/or augmentation index indicate hypertension due to factors other than arterial stiffness (e.g., high cardiac output).

To summarize, medications may have significantly different effects on the central arterial pressure waveform than on brachial blood pressure. For this reason, it is important to utilize the central waveform to select drugs in hypertension management, and to measure central pressure post-treatment to understand those effects, since it is the central effects that will be a stronger determinant of drug effectiveness and patient outcomes.

CENTRAL BLOOD PRESSURE WAVEFORM ANALYSIS IN PATIENT MANAGEMENT

As previously discussed, central arterial pressure waveform analysis provides clinicians with better prognostic and diagnostic information to determine the need for and type of interventions. There is growing consensus that the time is right to move to adoption of central pressure waveform analysis to individualize blood pressure management and improve care and outcomes.

In 2013, the BP Guide Study was published. The study investigated the usefulness of central BP to guide hypertension management. This was a prospective study in 286 hypertensive patients, randomized to treatment decisions guided by best-practice usual care (n=142; using office, home, and 24-hour ambulatory BP) or, in addition, by central BP assessment (n=144; using SphygmoCor).

KEY FINDINGS

- This study showed that when central arterial pressure waveform information is incorporated into brachial blood pressure management, significantly different treatment decisions are made (vs. no central pressure waveform information)
- Patients who had their brachial pressures managed with central arterial pressure waveform information had a significant reduction in the amount of medication they required
- 16% of patients whose treatment decisions included information from their central arterial pressure waveform completely ceased all medication and still maintained brachial blood pressure control
- In patients receiving the standard of care, only 2% completely ceased taking medication

KEY TALKING POINTS

- Incorporation of central arterial waveform information into hypertension management has a significant impact on treatment decisions

- A significant number of patients may be over-medicated when only their brachial blood pressures are considered

In 2015, a panel of researchers and clinicians was convened by the North American Artery Society to discuss recommendations for the use of noninvasive central arterial pressure waveforms in clinical practice. The panel concluded that analysis of the central pressure waveform provided valuable information when added to traditional brachial blood pressure measurement. Central arterial pressure waveform analysis, in addition to brachial blood pressure measurement, allows physicians to assess the effects of arterial stiffening and pressure wave reflection.

The panel focused their recommendations on three areas where pulse wave analysis can make a significant difference in patient care:

- Deciding whether to initiate, intensify or change therapy in younger patients.
- Deciding which anti-hypertensive medication to prescribe and when to add additional medications.
- Determining whether drug therapy or lifestyle changes that have reduced brachial pressure have equally reduced central blood pressure.

In 2016 The Lancet Commission on Hypertension issued "A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations". This document encouraged pursuit of central pressure assessment as a part of this goal:

> "One approach to haemodynamic characterization of patients with hypertension involves the assessment of central systolic blood pressure, which variably differs from the conventionally measured brachial systolic blood pressure. There are conflicting observations regarding the incremental prognostic value of central compared with brachial blood pressure. However, it should be emphasised that considerable differences in central systolic blood pressure can occur among people with similar brachial systolic blood pressure, and that antihypertensive therapy can affect central and brachial systolic blood pressures differently. Because central blood pressure (and how it changes in response to drug therapy) seems to relate more strongly to end-organ damage than brachial blood pressure, precise estimation of central blood pressure is expected to improve management decisions in hypertension, as suggested by findings from a randomised trial [the BP Guide study]. Methods to measure central blood pressure might be particularly useful in elderly people with high prevalence of white-coat hypertension, and among young individuals with isolated systolic hypertension."

In a 2017 review of nebivolol's utility in managing central BP in hypertensive patients, Borghi et al stated:

> "[B]rachial systolic BP does not represent actual systolic BP in the central arteries which encounter cardiac load directly. Due to wave amplification from central to peripheral arteries, a significant difference exists between the two. Central BP measurements also account for arterial stiffness, vessel branching and vascular mechanics, unlike brachial BP. Emerging data suggests that hypertension can be diagnosed more accurately by central pressure indices as compared to brachial BP ... Central BP indices offer better estimation of BP in central arteries and should be considered in routine clinical practice."

CENTRAL PRESSURE TARGETS

Importantly, three papers discussed here have posited targets for central systolic pressure.

- The Booysen group identified 112 mmHg as an 'optimal' CSP, above which there is measurable increase in target organ damage.
- The Taiwanese consensus statement proposed <110 mmHg as optimal CSP, with 110-129 defined as prehypertension and ≥130 defined as hypertension.
- The North American Artery Proceedings paper proposed 124 mmHg as an upper limit of normal for CSP.

SUMMARY

- **Analysis of the central aortic waveform provides important and valuable information related to wave reflection and central hemodynamics that is not available from standard brachial cuff measurements.**
- **Central pressure waveform analysis provides the ability to noninvasively obtain central arterial pressure waveforms in the office without the risks associated with invasive procedures.**
- **The target populations for whom the strongest data are available are (1) high normal/prehypertensive patients, for whom central blood pressure can provide much greater insight (via understanding of amplification) than brachial pressure alone, and (2) hypertensive patients as per the NAA Clinical Use of PWA paper.**
- **In patients with elevated augmentation pressure and/or augmentation index, vasodilating drugs (e.g., ACEIs, ARBs, CCBs, vasoactive beta blockers) may have a greater efficacy than non-vasodilating drugs (e.g., beta blockers, thiazide diuretics). The converse is true for hypertensives with low wave reflection indices.**

- **Central arterial pressure waveform analysis can aid in individualizing care. By reducing the harmful effects of the early return of the reflected wave, central arterial pressure waveform analysis can help prevent or reduce target organ damage and cardiovascular events.**

- **A target for normal CSP is in the range of 124-129 mmHg, while an optimal value is 110-112 mmHg. This is a practical parameter and measure for a consumer to use to monitor their own arterial health and CV risk.**