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REVIEW

Central blood pressure in the management of hypertension: soon reaching the goal?

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Blood pressure (BP) is conventionally measured by cuff at the brachial artery as an indication of pressure experienced by the organs. However, individual variation in pulse pressure amplification means that brachial cuff BP may be a poor representation of true central BP. Estimation of central BP is now possible using non-invasive methods that are amenable for widespread use. This paper reviews the evidence regarding the potential value of central BP in hypertension management. The major lines of evidence that support the use of central BP as a clinical tool include the: (1) major discrepancies in central BP among people with similar brachial BP; (2) independent relationship of central BP with end-organ damage; (3) independent relationship of central BP with cardiovascular (CV) events and mortality; (4) differential central and brachial BP responses to antihypertensive medications and; (5) improvements in end-organ damage after therapy more strongly relate to central than brachial BP. Despite all this, important evidence gaps relating to clinical use of central BP need fulfilling. These include the lack of central BP reference values and randomized, controlled studies to determine if: (1) central BP can help with diagnostic/therapeutic decisions and; (2) CV outcome is improved by targeting therapy towards lowering central BP levels. Additional challenges such as standardization of central BP methods, and understanding which patients are most likely to benefit from central BP monitoring also need to be determined. Overall, the future for central BP as a worthwhile clinical instrument appears positive, but there is much to be done.

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With every cardiac contraction, a pressure waveform is transmitted to the peripheral circulation via large arteries that become progressively smaller in diameter, as well as stiffer in wall tension, with distance from the heart. Owing to these changed vascular properties and the nature of arterial pressure wave travel within a relatively 'closed-end' vascular system, systolic blood pressure (SBP) in the distal vasculature (that is, brachial/radial arteries) is generally higher than in the central arteries (that is, aorta/carotid artery).[1] Conventional upper arm (brachial) cuff BP measurement is an indirect analysis of the pressure pulsations within the brachial artery, and the BP values are used to estimate the pressure load experienced by the organs, especially the heart, brain, kidneys and eyes. Whereas diastolic BP is roughly similar between the aorta and brachial arteries (for example, within $\sim$3 mm Hg), SBP (and, therefore, pulse pressure; PP) may differ substantially (for example, 2 to $>$30 mm Hg).[2] The consequence of these central-to-peripheral SBP and PP differences (termed amplification) is that conventional brachial BP readings can only be regarded as a proxy of the true BP experienced by organs.

A variety of commercial techniques to non-invasively estimate central (proximal aortic) BP have been available for some years. The basic operating principal of a commonly used method is that radial artery pressure waveforms are recorded by applanation tonometry, and a central BP waveform is synthesized using a generalized mathematical transfer function. Such a transfer function is possible owing to a consistent relationship between radial and aortic pressure waveforms under different conditions.[1] Individual transfer functions between the pressure pulsations at the different arterial sites are determined in the frequency domain by relating the modulus and phase of corresponding harmonic components. A generalized representation of a transfer function is then constructed by pooling individual transfer functions from the subjects being studied.[3,4] This process has been subject to criticism owing to the perception that error is introduced into central BP estimations by using a transfer function. In fact, independent researchers have shown the algorithms to be robust for accurately measuring central BP even during haemodynamic perturbations induced by exercise,[5] Valsalva manoeuvre or nitroglycerin,[3] and the error from transformation is insignificant. Caution may, however, be warranted regarding the possibility of underestimating central systolic blood pressure (SBP) at higher heart rates (for example, $\sim$100 bpm or greater),[6] and major error can be created by using inaccurate upper arm cuff BP values to calibrate the pressure waveforms.[6,7] Careful attention to correctly measuring brachial cuff BP can help alleviate, but not entirely deal with this problem, particularly, as there may be additional SBP amplification from the brachial to radial arterial beds.[8] In any case, estimation of central BP without a transfer function is possible from the carotid artery (usually by applanation tonometry) as a surrogate of aortic BP, or from the second systolic peak on the radial waveform. However, the latter technique underestimates central SBP at low pressures,[9] and both methods still rely on accurate calibration using brachial cuff BP.

Although heavily used in the research domain, there has been negligible clinical uptake of central BP methods. In order for new tests to be considered for routine clinical use, they must satisfy

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several criteria including simplicity and acceptability to both patients and doctors. As brachial cuff BP fulfils these requirements, commercial efforts have been directed towards developing devices to measure central BP by this mode of operation. In recent years, several devices, which are virtually identical in appearance to standard automated brachial BP machines, have been developed to measure central BP via pressure or volumetric waveform analysis at subdiastolic or suprasystolic pressures. These advancements offer a practical and feasible means for integration of central BP into clinical practice for hypertension management. The purpose of this review is to provide an overview of the evidence with respect to whether central BP could be of value in hypertension management. Deficits in the literature, as well as future requirements and some challenges in the field are also discussed. Although more data are needed, we contend that there are five lines of evidence that generally support the notion that central BP should be useful in hypertension management (see Table 1).

EVIDENCE LINE 1: MAJOR DISCREPANCIES IN CENTRAL BP AMONG PEOPLE WITH SIMILAR BRACHIAL BP

Kroeker and Wood[10] were among the first to simultaneously record invasive arterial pressure in the aortic arch, as well as multiple peripheral sites in healthy men while resting and during exercise. Under resting conditions, brachial SBP was amplified an average 9% higher than aortic SBP and, in this small group ($n = 12$), the range was a sizeable 1–18%. In 1968, focusing on exercise, Rowell *et al*.[11] made similar observations and concluded that BP amplification 'has major clinical implications' because peripheral BP recordings are not representative of central artery pressures. Almost 40 years later, and after development of non-invasive central BP using radial tonometry, the first large-scale ($n = 4001$) population-based assessment of brachial and central BP reported sizeable age- and gender-related differences in BP amplification.[12] On average, SBP amplification was 20 mm Hg (men) and 15 mm Hg (women) at age <20 years, but this difference was markedly lower for men and women aged 40–49 years (12 and 9 mm Hg, respectively).[12] Age-related PP discrepancies were also evident, with central PP increasing linearly through the life course, whereas brachial PP declined in the period from <20 to 50–59 years of age, before increasing thereafter.[12] Relatively wide confidence limits were observed in central BP variables across all age groups, with the data altogether implying that it was possible for large variability in central BP among people with similar brachial BP, irrespective of age.

The degree of central BP variability in healthy individuals, as well as those with cardiovascular (CV) risk factors or diseases, was examined in two independent reports.[2,13] Central BP relative to brachial BP was significantly higher in people with risk factors or diseases compared with healthy people.[2,13] When study participants were stratified according to the European Society of Hypertension (ESH) brachial BP classifications (for example, optimal, normal, high-normal, stage 1, 2, 3 hypertension), there was massive overlap of central SBP between distinctive brachial BP classification groups. For example, $>70\%$ overlap in central SBP occurred between the normal and the high-normal brachial BP categories.[13] Figure 1 provides an example of the magnitude of central BP incongruity potentially occurring between individuals with the same brachial BP, whereas Figure 2 shows the overlap in central SBP and systolic-BP amplification between brachial BP categories. Overall, there is indisputable evidence that central BP is not the same as peripheral BP, and cannot be reliably estimated using standard brachial cuff BP.

EVIDENCE LINE 2: INDEPENDENT RELATIONSHIP OF CENTRAL BP WITH END-ORGAN DAMAGE

CV disease is amplified when arteries and organs are chronically exposed to high BP. The haemodynamic mechanisms leading to end-organ damage are complex, probably organ-specific and not fully understood; however, as central BP more closely approximates the pressure experienced by organs, it is reasonable to expect that evidence of end-organ damage should be more strongly related to central BP than to brachial BP. Indeed, there is persuasive data to this effect, some of which was recently reviewed.[14,15] Cardiac hypertrophy,[16,17] as well as left ventricular systolic and diastolic dysfunction, are related to elevated central augmentation index, SBP and PP, independent of the standard cuff BP.[18,19] In the same way, adverse effects on the structure (for example, carotid wall hypertrophy, intima-media thickness and plaque score) and function (for example, compliance) of large central arteries is more contingent on central arterial pressure rather than conventional brachial BP.[20,21] There is also very good evidence that central (carotid) artery lumen size, function and PP separately relate to kidney function, in terms of glomerular filtration rate, albuminuria and progression of chronic kidney disease.[22–25] Brain atrophy, silent subcortical infarcts and cognitive impairment all independently correlate with central haemodynamic factors.[26] Whether this is the transmission of excessive pressure or flow pulsatility into the carotid circulation that can trigger brain microvascular damage and remodelling is unknown.

Table 1. Evidence that central blood pressure (BP) has incremental value above and beyond brachial BP in the diagnosis and management of patients with hypertension

		Current strength (+ to + + +)
Present evidence		
1	Major discrepancies in central BP among people with similar brachial BP	+ + +
2	Independent relationship of central BP with end-organ damage	+ +
3	Central BP predicts cardiovascular events and mortality independent of brachial BP	+
4	Differential central and brachial BP responses to antihypertensive medications	+ +
5	End-organ changes after antihypertensive therapy are more strongly related to central BP than brachial BP	+ +
Needed evidence		
1	Available population-based reference values	
2	RCTs for demonstrating the usefulness of central BP in the management of hypertension	
3	RCTs for demonstrating that the reduction in central BP has a better predictive value for cardiovascular events than the reduction in brachial BP (that is, central BP is a surrogate end point)	

Abbreviation: RCT, randomized controlled trial. The strength of the current evidence is graded from one + to three + + +.

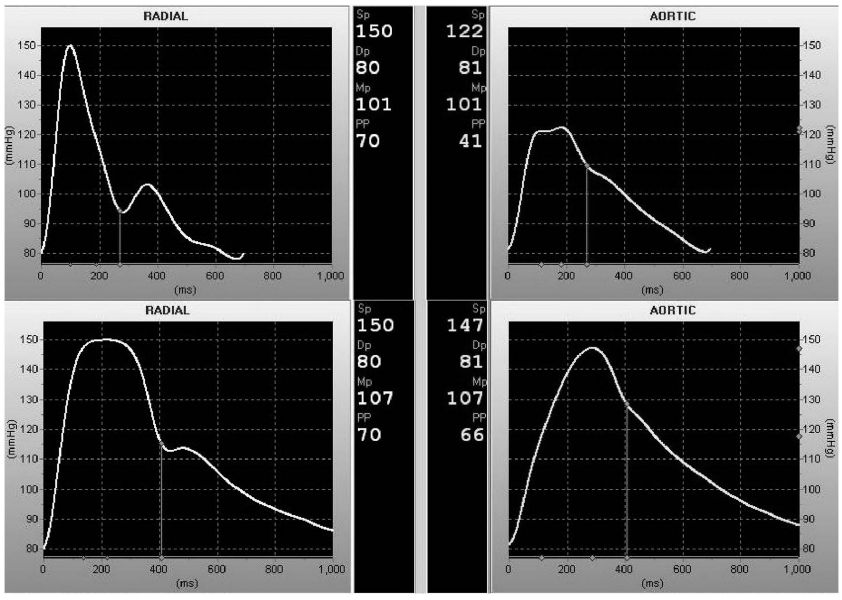

Figure 1. Example of radial (left graphs) and central (aortic; right graphs) pressure waveforms from two male subjects with the same brachial BP (150/80 mm Hg), but significantly different central systolic BP (122/81 and 147/81 mm Hg, respectively). The waveforms in the upper panels represent high systolic BP amplification (28 mm Hg), whereas the lower panel waveforms represent low systolic BP amplification (3 mm Hg). Adapted from Sharman *et al.*[2]

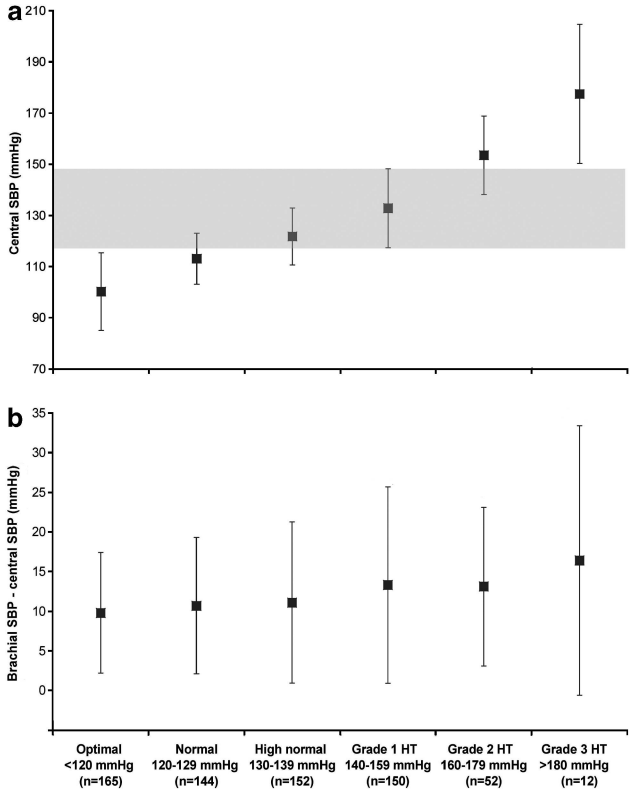

Figure 2. Central systolic BP (**a**), and brachial–aortic systolic BP difference (**b**) in 675 participants classified into European Society of Hypertension BP levels. The shaded area represents the range of central systolic BP in patients with grade 1 hypertension (HT). Data represent mean ± 2 s.d., and has been corrected for age, gender, heart rate and use of medications. Central systolic BP was significantly different between all brachial BP levels ($P<0.001$ for all). Adapted from Sharman *et al.*[2]

A low carotid augmentation index at 1 week after ischaemic stroke predicts excellent functional outcome 90 days later.[27] A natural extension of these studies that consistently show a relation between end-organ risk burden and central BP variables is to determine, in longitudinal studies,[23,27,28] whether central haemodynamics could provide more accurate prognostic information on the progression of target-organ damage beyond cuff BP.

EVIDENCE LINE 3: CENTRAL BP PREDICTS CV EVENTS AND MORTALITY INDEPENDENT OF BRACHIAL BP

The first study to demonstrate an independent relationship between central BP and survival was in 180 patients with end-stage renal disease.[29] Elevated carotid augmentation index and aortic-pulse wave velocity (stiffness), but low brachial diastolic BP, were associated with increased all-cause and CV death, whereas the relation to brachial PP was nonsignificant.[29] In subsequent years, several similar studies in different patient populations (including healthy individuals) were undertaken, and in 2010, a systematic review and meta-analysis on the prognostic value of central haemodynamic indices was published.[30] Data were analysed from 11 longitudinal studies involving 5648 subjects followed for an average of 45 months. After correcting for CV risk factors that included brachial BP or history of hypertension in five studies, an absolute increase of 10% in central augmentation index (recorded invasively, or with carotid or radial tonometry) corresponded to 31.8 and 38.4% relative risk increase for CV and all-cause mortality, respectively.[30] When the comparative predictive ability of central compared with brachial PP was assessed, central PP was the stronger determinant of clinical events, but this was only of borderline significance (relative risk increase 31.8% (95% confidence interval: 22.1–42.3%) versus 18.8% (95% confidence interval: 10.4–28.0%); $P=0.057$).[30] This important work clearly identified a pattern of favorability towards central BP indices being better than brachial BP in terms of risk prediction, but meta-analysis on pooled data has limitations, and

the findings fall short of being conclusive. Meta-analysis on individual patient data is keenly awaited.

Only one study has sought to interrogate the crucial matter of whether central BP could have prognostic utility exceeding that of 'gold standard' 24-h-ambulatory BP monitoring.[31] Whereas definitive superiority of either method could not be established, both central SBP and 24-h SBP independently predicted CV mortality after correction for common risk factors.[31] Building on this, another report from the community-based Framingham Heart Study cohort assessed the relative prognostic importance of aortic-pulse wave velocity (itself an independent marker of CV mortality),[32] compared with central BP.[33] In multivariable models, aortic stiffness emerged as the predominant haemodynamic predictor of major CV events and, when added to a model comprising a full set of standard risk factors, significantly improved risk discrimination and reclassification.[33] Several aspects of the study received criticism, not least of which being the technical (and quality control) shortcoming of using brachial tonometry to estimate central BP; but even so, the study was yet another to endorse central artery stiffness as a possible CV risk biomarker—this hypothesis is soon to be tested for the first time in a large, prospective, randomized trial of targeted reduction in aortic stiffness.[34]

Such randomized studies with the aim of targeted central BP reduction are needed because a consistent limitation of all the above mentioned central BP prognostic studies is that they are observational, and causality between elevated central BP and CV risk cannot be inferred. The only randomized intervention trial with recording of central BP and CV events was the Conduit Artery Function Evaluation study in 2199 patients with hypertension and multiple CV risk factors.[35] This was a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial and was impressive in terms of proving differential effects of antihypertensive medications on central BP estimated by radial tonometry compared with brachial BP. However, the relation between central BP and CV-related outcomes was only a secondary aim, and central BP measures were not recorded until 1 year after baseline examination, thus it was not possible to calculate the change in central BP. In the end, even though central PP was shown to independently predict CV events and incident renal impairment (by *post-hoc* analysis), the study was not appropriately designed to test whether central BP as a target for therapy was superior to brachial BP. On balance, the available evidence suggests that central BP should be the more favourable method, but this still remains to be tested.

EVIDENCE LINE 4: DIFFERENTIAL CENTRAL AND BRACHIAL BP RESPONSES TO ANTIHYPERTENSIVE MEDICATIONS

The cause of individual differences in central-to-brachial BP amplification is yet to be fully understood, but is known to be influenced by a multitude of physiological factors, including large artery compliance, vascular resistance, stroke volume and heart rate, to name a few. Antihypertensive agents have various modes of action (both within- and between-drug class/es) that influence the above named CV parameters to varying degrees, thereby potentially resulting in different changes on central BP compared with brachial BP. In 1990, the dramatic disparity in central versus peripheral BP responses to vasoactive drugs was reported by Kelly *et al.*[36] in the setting of acute sublingual administration of 300 mg glyceryl trinitrate to 14 patients undergoing cardiac catheterization. Invasively recorded ascending aortic and brachial artery pressure waveforms showed larger falls in aortic SBP after medication. Most importantly, the individual responses to the medication were highly variable and in three people, brachial SBP was relatively unchanged, whereas there were significant central SBP decreases. This result is exemplified in Figure 3 and underscores the rationale as to why the effects of antihypertensive

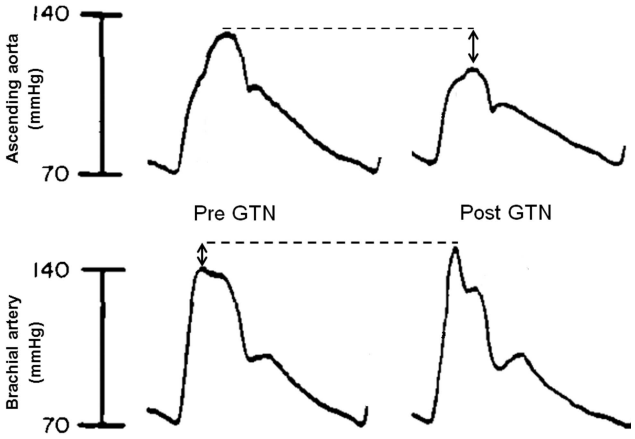

Figure 3. Ascending aortic (central) BP waveforms (upper panel) and brachial artery BP waveforms (lower panel) pre- and post administration of 300 mg sublingual glyceryl trinitrate (GTN). Note that there is a large fall in central systolic BP (peak of the pressure waveform) post GTN, but at the same time, brachial systolic BP is relatively unchanged (slight rise). Adapted from Kelly *et al.*[36] with permission.

therapy may be best assessed by the central BP. Many studies have now examined the disparate central and peripheral haemodynamic responses to antihypertensive medications, and summary data on between-class effects were recently published.[37]

Broadly speaking, the drug classes that increase SBP amplification (that is, larger decrease in central SBP relative to brachial SBP) are angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, dihydropyridine calcium channel blockers and nitrates, whereas diuretics and beta blockers are less efficacious.[37,38] Indeed, there are 'compelling evidence' that atenolol exerts adverse effects by reducing BP amplification,[37] as shown in the Conduit Artery Function Evaluation study.[35] Knowledge of an individual's central BP response to antihypertensive drugs could assist doctors in making more informed decisions regarding titration of therapy. For example, in Figure 1, despite the same brachial BP between individuals (150/80 mm Hg), and taking into account absolute CV risk, uptitration of antihypertensive medication may be strongly justified in the patient with relatively high central SBP (147 mm Hg; lower panel), whereas this approach may be inappropriate and over treating the other patient with relatively low central SBP (122 mm Hg; upper panel). This type of management process could also be of value in hypertension diagnosis, and may be helpful in specific populations where drug titration decisions are difficult or at risk of potentiating harm, such as in the elderly, although there is little data in these areas.

EVIDENCE LINE 5: END-ORGAN CHANGES AFTER ANTIHYPERTENSIVE THERAPY ARE MORE STRONGLY RELATED TO CENTRAL BP THAN BRACHIAL BP

If central BP is to be considered appropriate for hypertension management, it is necessary for improvement in end-organ characteristics through therapy to be more strongly influenced by the changes in central BP (for example, relief of 'central hypertension'), rather than the changes in brachial BP. At least four studies have reported such findings. In the REASON study, a randomized, double-blind study, comparing the low-dose combination of perindopril/indapamide to atenolol, de Luca *et al.*[39] showed that perindopril/indapamide was more effective than atenolol in reducing left ventricular mass through a higher reduction in central PP. Second, in the randomized, double-blind study of Kampus *et al.*,[40] comparison of the peripherally vasodilating beta blocker nebivolol (5 mg per day) was made

with metroprolol (50 mg per day) over 1 year in 80 patients with hypertension. Regression of left ventricular mass was only evident after nebivolol, and on multiple regression analysis, the change in septal wall thickness was only related to changes in central SBP.[40] Third, in an observational study following patients over 1 year after initiation of antihypertensive therapy, PP amplification (expressed as the ratio of brachial to central PP) predicted the change in left ventricular mass, independent of home BP.[41] Using data from this study, these authors presented power calculations to determine the sample size needed for a clinical trial, in which a significant change in left ventricular mass index was the primary outcome. Remarkably, only 25 subjects would be required on the basis of PP amplification, but more than 1000 subjects would be needed if relying on measurement of home BP,[41] thus indicating superior precision of central BP. Finally, in a blinded trial of 98 patients with hypertension, randomized to celiprolol (200 mg per day) or enalapril (10 mg per day) over 9 months, reduction in carotid intima-media thickness was principally determined by the reduction in carotid PP.[42]

DEFICITS IN THE LITERATURE REGARDING CENTRAL BP: WHAT IS NEEDED?

When the five evidence lines presented above are considered in total, the logical conclusion is that central BP should offer benefits in hypertension management that are incremental to traditional brachial BP. However, there remain several major evidence gaps which, in the absence of fulfilling, will probably continue to relegate cuff brachial BP as the clinical standard. The evidence needed is as follows:

1. Population-based-reference central BP values.
2. Randomized, controlled studies to determine if central BP could help with the management of hypertension, including diagnosis and treatment.
3. Randomized, controlled studies to determine if CV risk/CV outcome is improved by targeting therapy towards lowering central BP levels.

Population-based-reference central BP values

Before the routine assessment of central BP can be considered, an understanding of 'normal values' (that is, in healthy subjects with no CV risk factors) and 'reference values' (that is, in patients with some CV risk factors) must be determined. These reference values, published as an abstract,[43] obtained in 91 588 individuals (including 27 658 healthy individuals) by applanation tonometry or related methods, and originating from 54 research centres worldwide, are currently under analysis.

Usefulness of central BP for the management of hypertension

This issue will be partly answered with the BP GUIDE study, of which the principal findings should be published in 2013.[44] This prospective, randomized, open-label, blinded end point trial in 286 patients with hypertension followed over 1 year, aims to determine if central BP can assist doctors with therapeutic decisions beyond the highest standard usual care approach. The end points are left ventricular mass (using three-dimensional echocardiography), medication use and quality of life. It is hypothesized that cardiac mass will not differ between treatment groups, but guidance using central BP will result in less medication due to knowledge of appropriately controlled central BP, as well as improved quality of life due to less use of medication, or more appropriate choices.[44] If positive, this study should provide extra impetus for the conduct of large, multinational, randomized studies with therapy aimed at specific reduction of central BP, and with hard clinical end points.

Central BP as a surrogate end point

Indeed, randomized, controlled studies are needed to determine if CV outcome is improved by targeting therapy towards lowering central BP levels. One of the reasons why these studies have not already been undertaken is the difficulty of designing an intervention that preferentially lowers central BP, because modern antihypertensive agents will lower both central and peripheral BP,[37] and this could make it problematic to equivocally determine whether end point effects are due to central or peripheral BP changes, or a combination of both. In any case, this may be an academic argument if outcomes are improved with respect to clinical decisions, patient health and behaviour.[34] Ironically, these evidence requirements are yet to be entirely satisfied for the out-of-office brachial BP methods of home BP and 24-h-ambulatory BP, yet it is commonly accepted that these tests are superior to in-office brachial BP and guidelines, which suggest their preferential use when available. This begs the question—why should a higher level of evidence be required for central BP integration to clinical practice than for out-of-office brachial BP?

PRACTICAL CONSIDERATIONS: CHALLENGES AND FUTURE DIRECTIONS

As always, advances in technology precede the evidence base to justify integration of the technology into clinical practice. Recently for central BP, the technology–evidence gap has widened owing to an extensive variety of commercially available central BP-recording devices. With this comes quality control issues around appropriate level of validity and inter-device variability, and as such there is a need for consensus on standardisation of central BP-assessment methods. This problem also relates to the potential difficulty of convincing the broader medical community that non-invasive central BP is an appropriate surrogate marker of invasive aortic BP, even after appropriate calibration. Accordingly, more data comparing the validity of commercial device central parameters with state-of-the-art invasive catheters are required. Of course, the most convincing evidence for valid measurements with novel apparatus is the demonstration that central BP, measured using one of these novel apparatus, has predictive value for CV events. A less convincing demonstration, but still useful, would be to show differential effects of drugs on central BP. In that respect, technologies used in pioneering studies (analysed in[30]) demonstrating the predictive value of central BP for CV events (Millar Instruments;[29] Sphygmocor/AtCor[17–19,21] and Cardiovascular Engineering[33]) should be privileged for routine clinical use.

There is now capacity to measure 24-h-ambulatory central BP from brachial oscillometric pulse wave analysis.[45] This development theoretically represents the highest-level determination of BP control, but there is no data on the clinical relevance of this method, and it would be valuable for future pharmacological and epidemiologic studies to incorporate this type of technology. As with other methods, further evaluation of the working principles and algorithms used to estimate central BP by this technology is needed.

Another impediment to clinical uptake of central BP is the absence of health-care rebating to cover costs of the service delivery in most countries. This may change once there is a greater understanding on the health economic effectiveness of delivering health care guided by central BP but, again, this is yet to be established. As already discussed above, biomarker measurement can improve health outcome through several mechanisms: better patient understanding of the disease, healthier patient behaviours and better clinical decisions.

Finally, an important issue is which patient groups are most likely to benefit from central BP monitoring. Patients with optimal BP control at the brachial level (for example, SBP <120 mm Hg) may not be good targets, unless they experience symptoms

related to hypotension. By contrast, patients with grade I or II hypertension and considered as at low or moderate CV risk (that is, two or less CV risk factors) may largely benefit from central BP monitoring if values are high. Although central BP is not yet accepted by international guidelines (and particularly the ESH-ESC Guidelines for the Management of Hypertension) as a routine measurement, abnormally high central BP may urge the physician to detect organ damage, which by itself means a higher level of risk, and is an incentive to start treatment or adjust antihypertensive therapy. This raises the issue of reference values, as seen above.

SUMMARY AND CONCLUSIONS

On balance, the evidence indicates that central BP will have incremental value above and beyond brachial BP in diagnosis and management of patients with hypertension. The stethoscope and cuff sphygmomanometer have been the trademark apparatus of doctors for many decades, and it is not unnatural for there to be resistance to change. There is no suggestion that traditional brachial BP should be abandoned fully in favour of central BP, but instead added consideration of central BP in some patient groups is expected to yield important information that is additional to conventional brachial BP. Unquestionably, further evidence of a randomized and controlled nature is required before general acceptance, and widespread use of central BP is undertaken beyond the research domain.

CONFLICT OF INTEREST

Both authors have received equipment or grants from companies that manufacture central blood pressure devices. These include; AtCor Medical, PulseCor, Alam Medical, EIM, Hemo Sapiens, and OMRON.

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