European Heart Journal (2014) **35**, 1719–1725
doi:10.1093/eurheartj/eht565

REVIEW

Clinical update

Central blood pressure: current evidence and clinical importance

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Received 29 April 2013; revised 27 November 2013; accepted 17 December 2013; online publish-ahead-of-print 23 January 2014

Pressure measured with a cuff and sphygmomanometer in the brachial artery is accepted as an important predictor of future cardiovascular risk. However, systolic pressure varies throughout the arterial tree, such that aortic (central) systolic pressure is actually lower than corresponding brachial values, although this difference is highly variable between individuals. Emerging evidence now suggests that central pressure is better related to future cardiovascular events than is brachial pressure. Moreover, anti-hypertensive drugs can exert differential effects on brachial and central pressure. Therefore, basing treatment decisions on central, rather than brachial pressure, is likely to have important implications for the future diagnosis and management of hypertension. Such a paradigm shift will, however, require further, direct evidence that selectively targeting central pressure, brings added benefit, over and above that already provided by brachial artery pressure.

Keywords Central pressure • Blood pressure • Anti-hypertensive treatment • Cardiovascular risk

Introduction

The brachial cuff sphygmomanometer was introduced into medical practice well over 100 years ago, enabling the routine, non-invasive, measurement of arterial blood pressure. Life insurance companies were among the first to capitalize on the information provided by cuff sphygmomanometry, by observing that blood pressure in largely asymptomatic individuals relates to future cardiovascular risk—observations that are now supported by a wealth of epidemiological data.[1] The most recent Global Burden of Disease report[2] identified hypertension as the leading cause of death and disability worldwide. Moreover, data from over 50 years of randomized controlled trials clearly demonstrate that lowering brachial pressure, in hypertensive individuals, substantially reduces cardiovascular events.[1,3] For these reasons, measurement of brachial blood pressure has become embedded in routine clinical assessment throughout the developed world, and is one of the most widely accepted 'surrogate measures' for regulatory bodies.

The major driving force for the continued use of brachial blood pressure has been its ease of measurement, and the wide variety of devices available for clinical use. However, we have known for over half a century that brachial pressure is a poor surrogate for aortic pressure, which is invariably lower than corresponding brachial values. Recent evidence suggests that central pressure is also more strongly related to future cardiovascular events[4–7] than brachial pressure, and responds differently to certain drugs.[8,9] Appreciating this provides an ideal framework for understanding the much publicized inferiority of atenolol and some other beta-blockers,[10] compared with other drug classes, in the management of essential hypertension. Although central pressure can now be assessed non-invasively with the same ease as brachial pressure, clinicians are unlikely to discard the brachial cuff sphygmomanometer without robust evidence that cardiovascular risk stratification, and monitoring response to therapy, are better when based on central rather than peripheral pressure. Central pressure assessment and accuracy will also have to be standardized, as it has been for brachial pressure assessment with oscillometric devices. This review will discuss our current understanding about central pressure and the evidence required to bring blood pressure measurement, and cardiovascular risk assessment into the modern era.

Physiological concepts

Arterial pressure varies continuously over the cardiac cycle, but in clinical practice only systolic and diastolic pressures are routinely reported. These are invariably measured in the brachial artery using cuff sphygmomanometry—a practice that has changed little over the last century. However, the shape of the pressure waveform

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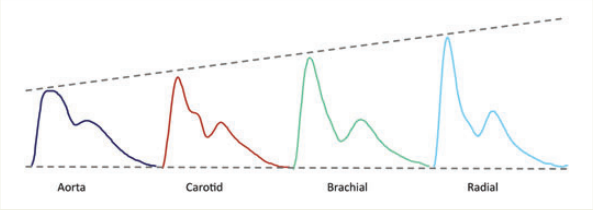

Figure 1 Amplification of the pressure waveform moving from the aorta to the radial artery.

changes continuously throughout the arterial tree. Although diastolic and mean arterial pressures are relatively constant, systolic pressure may be up to 40 mmHg higher in the brachial artery than in the aorta.[11–13] This phenomenon of systolic pressure *amplification* arises principally because of an increase in arterial stiffness moving away from the heart. As the pressure wave travels from the highly elastic central arteries to the stiffer brachial artery, the upper portion of the wave becomes narrower, the systolic peak becomes more prominent, and systolic pressure increases (*Figure 1*).

Historically, two major paradigms have been used in an attempt to understand the changes in waveform morphology observed throughout the arterial system and in response to ageing, vasoactive mediators and drugs. The first, arterial waveform analysis, assumes that the arterial pressure waveform is a composite of a forward travelling wave, generated by left ventricular ejection, and a backward-travelling reflected wave arising from sites of impedance mismatch—i.e. arterial taper and differences in vessel stiffness, which often occur at bifurcations.[14,15] This change in impedance is thought to generate numerous reflected 'wavelets' that sum together to produce a single 'effective' reflected wave, which is thought to *augment*, or increase systolic pressure in the central arteries. The augmentation index, which quantifies the extent of augmented pressure relative to the central pulse pressure, provides information about the amplitude and timing of backward-travelling waves within the central arteries. With an increase in augmented pressure (and augmentation index), the absolute aortic systolic pressure increases, and amplification, defined as the ratio of brachial and aortic pulse pressures, decreases.[14]

The second major paradigm initially viewed the arterial system as a two-element windkessel model (resistance and compliance), where a central reservoir fills during systole and empties during diastole. Although this model is useful for explaining haemodynamic mechanisms during diastole, it predicts the relationship between pressure and flow in systole relatively poorly, and any influence of wave propagation and reflection is effectively ignored.[16] The addition of aortic characteristic impedance (three-element windkessel model) improves the prediction of pressure and flow throughout the entire cardiac cycle, but still does not permit the investigation of wave transmission characteristics. More recently, however, a variation on the windkessel model has been proposed,[17] which incorporates both reservoir- and wave-based approaches into a single model, involving a central reservoir pressure and an excess pressure. The excess pressure is calculated as the difference between the measured pressure and the calculated reservoir component, and relates to wave propagation and reflection. Recent data based on this model dispute the more commonly held view that wave reflections contribute to systolic pressure augmentation, arguing instead that the magnitude of the augmentation pressure is principally determined by the arterial reservoir.[18] Although controversial,[19,20] this new paradigm has generated considerable research interest in recent months.

Irrespective of the precise mechanisms underlying the observed changes in wave shape or the models used to describe them, substantial pressure amplification does exist within the arterial tree. Importantly, the degree of systolic pressure amplification, both within- and between-individuals, is not fixed, and depends on a number of variables including age, gender, height and heart rate,[21–25] as well as systemic diseases affecting the vasculature. Amplification is high in young people, especially men, in whom aortic systolic pressure measured invasively,[11,26] or with the SphygmoCor device[27] can be some 20–30 mmHg lower than that in the brachial artery. Individuals of shorter stature tend to have less amplification, i.e. for a given brachial pressure, central pressure is relatively higher. This is also true for those with lower heart rates, due to the inverse relationship between heart rate and central pressure augmentation. However, only ~70% of the variability in pulse pressure amplification can be explained in multivariable regression models.[21,28] This suggests that central pressure cannot be predicted with sufficient accuracy from brachial pressure by a statistical model but, rather, needs to be assessed directly, using appropriate methods.

The potential clinical relevance of this variability in amplification became evident when we evaluated aortic and brachial pressure in a cohort of 10 000 volunteers.[28] Even in those deemed to be healthy, there was a significant, and highly variable, difference between aortic and brachial systolic pressure at all ages (*Figure 2*). Moreover, when we stratified individuals by brachial artery blood pressure we observed a considerable overlap in aortic systolic pressure, such that over 70% of individuals categorized as having 'high-normal' brachial systolic pressure based on Joint European Cardiology and Hypertension Society guidelines[29] had similar

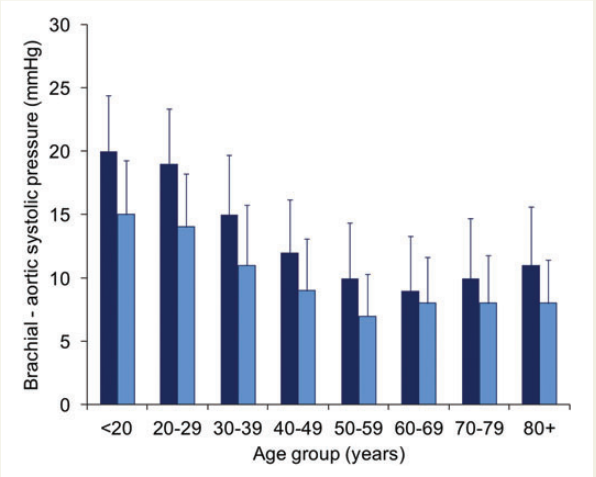

Figure 2 Difference between brachial and aortic systolic blood pressure (SphygmoCor) in healthy men (dark blue bars; $n = 2779$) and women (light blue bars; $n = 2869$). The data represent means ± SD.

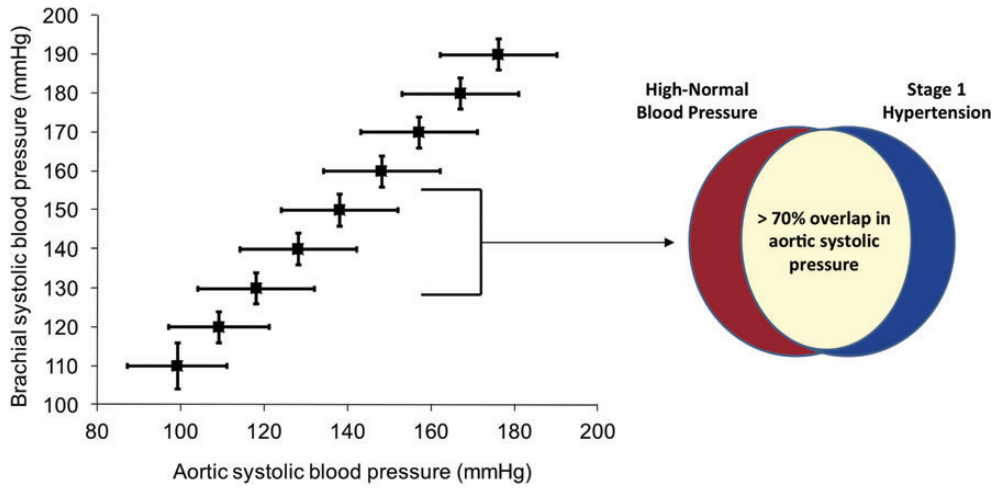

Figure 3 Overlap in aortic systolic blood pressure despite no overlap in brachial systolic pressure, in healthy men and women ($n = 5648$). Over 70% of individuals with high-normal blood pressure had aortic systolic pressures in common with individuals with stage 1 hypertension.[28]

aortic pressures to those with stage 1 hypertension (*Figure 3*). Moreover, >30% of males and 10% of females with normal brachial blood pressure had aortic pressures in common with individuals with stage 1 hypertension. This will have important clinical implications if central pressure turns out to be a better predictor of cardiovascular risk, because it suggests that, currently, we may be treating some subjects with relatively low central pressures, and not treating individuals with elevated central pressures, because they have brachial systolic pressures under current treatment thresholds.

How to measure central pressure

A number of methods are now available for assessing central pressure. The most direct method involves cardiac catheterization and recording of the blood pressure in the ascending aorta using a pressure-sensing catheter (*Figure 4A*). However, this is highly invasive, technically demanding and clearly unsuitable for use in routine screening of large populations. More recently, a number of non-invasive methods have been developed, where pressure waveforms are recorded from sites distal to the aorta, such as the carotid (*Figure 4B*), radial (*Figure 4C*) or brachial (*Figure 4D*) arteries, and calibrated to blood pressure recorded by cuff sphygmomanometry. Each of these approaches has their own strengths and limitations.

Carotid artery pressure is often used as a surrogate for aortic pressure because of the close proximity of these arterial sites. Carotid pressure waveforms are recorded by applanation tonometry and then scaled to the brachial mean and diastolic pressures on the principle that unlike systolic pressure, mean, and diastolic pressure do not vary markedly throughout the arterial tree[11] and are thus suitable for calibrating pressure waveforms recorded from other arterial sites. However, carotid waveforms of sufficient quality can be difficult to obtain in all individuals, especially in obese patients. The technique is highly operator-dependent, making it somewhat unreliable for routine high-throughput screening of central pressure in a non-specialist setting. Moreover, there is also likely to be a small degree of amplification between the carotid artery and aorta,[14,22,30] which may lead to an over-estimation of aortic pressure.

Pulse wave analysis is an alternative method, where pressure waveforms are recorded from peripheral arteries (typically brachial or radial) and corresponding central aortic pressure derived either using a generalized transfer function, identification of the late systolic shoulder of the peripheral pressure waveform, or a proprietary algorithm. A variety of devices are now available which follow one or more of these principles, as summarized in *Table 1*.

A major criticism of these non-invasive devices is that peripheral waveforms are typically calibrated to brachial systolic and diastolic cuff pressures. These tend to under-estimate the 'true' (invasive) brachial artery pressure, leading to falsely low estimates of central pressure. However, brachial cuff pressure is used in the routine diagnosis and treatment of hypertension, and accepted by regulatory authorities as being better validated as a surrogate of outcome than intra-arterial (brachial) pressure.[31] Moreover, recent data demonstrate that errors in the estimation of central pressure are equivalent to errors in brachial cuff sphygmomanometry.[31,32] A second problem arises when *radial* waveforms are calibrated to brachial cuff pressure, because the presence of any brachial-to-radial amplification adds further to the under-estimation of central pressure. Recent data[33,34] indicate that calibration with brachial mean and diastolic pressures may be preferable here. Newer cuff-based devices which scale brachial waveforms obtained with pulse volume plethysmography to the measured brachial cuff pressure, negate any potential influence of brachial-radial amplification. However, they do still tend to be lower than 'true' aortic pressure, due to the inaccurate brachial cuff pressure. Nevertheless, although further validation data are still emerging,[35–37] collectively, these newer devices offer potential advantages in being less operator-dependent than hand-held tonometry methods and are potentially well-suited to use in the primary-care setting.

Central systolic pressure may also be estimated directly from the peripheral pressure waveform without use of a transfer function, as

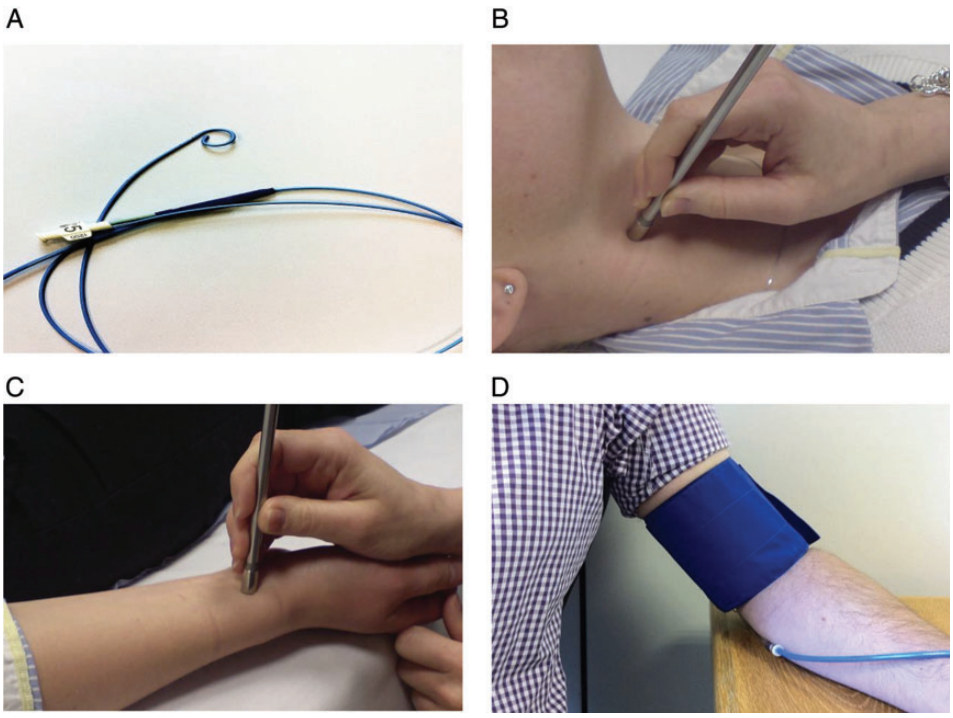

Figure 4 Techniques for assessing central blood pressure. (*A*) Invasive cardiac catheterization; (*B*) direct applanation tonometry of the carotid artery; (*C*) applanation tonometry of the radial artery; (*D*) cuff-based oscillometry at the brachial artery.

Table 1 Indirect, non-invasive methods for estimating central pressure

Method of waveform recording	Device	Company	Method of calibration	Method of estimation	Clinical applicability†
Radial tonometry	BPro[86,87]	HealthSTATS	Brachial–radial cuff BP	GTF (radial-aortic)	++
	SphygmoCor[12,88]	AtCor Medical	Brachial–radial cuff BP	(i) GTF (radial-aortic)	+
				(ii) Late systolic shoulder	+
	HEM9000AI[39,77]	Omron	Brachial cuff BP	(i) Algorithm	++
				(ii) Late systolic shoulder	++
Brachial cuff PVP	*ARCsolver[89,90]		Brachial cuff BP	GTF (brachial-aortic)	+++
	Centron cBP301[35,91]	Centron Diagnostics	Brachial cuff BP	GTF (brachial-aortic)	++++
	Vicorder[92]	Skidmore Medical	Brachial cuff BP	GTF (brachial-aortic)	+++
	XCEL	AtCor Medical	Brachial cuff BP	GTF (brachial-aortic)	+++
	Method of Sung *et al.*[42]		Brachial cuff BP	Algorithm	++
Suprasystolic brachial cuff PVP	Arteriograph[37,93]	TensioMed	Brachial cuff BP	Late systolic wave amplitude	+++
	Cardioscope II[36,94]	Pulsecor	Brachial cuff BP	Algorithm	++++

PVP, pulse volume plethysmography; GTF, generalized transfer function.
*Incorporated in Mobil-O-Graph PWA device (IEM GmbH).
†Personal view based on experience, operator-dependency, need for computer/software interface, with + indicating limited applicability to routine clinical practice and ++++ indicating high applicability.

invasive data show that the late systolic shoulder of the peripheral pressure waveform approximates to aortic systolic pressure.[38–40] However, further validation of this approximation of central pressure is required, since it may be inaccurate in younger individuals (with early, non-augmented peak systolic pressures), or those with low blood pressure.[41] Algorithms may also be applied to the brachial or radial pressure waveforms to obtain estimates of the 'true' aortic pressure, i.e. as would be obtained with invasive measurement.[39,42]

Current evidence regarding the importance of central pressure

The heart, kidneys, and major arteries supplying the brain are exposed to aortic rather than brachial pressure. Therefore, there is a strong rationale to believe that cardiovascular events may ultimately be more closely related to central rather than brachial pressure. Evidence published over the last 12 years concerning the relationship between central pressure and both surrogate markers of risk and hard endpoints strongly support this concept.[43]

Central pressure is more closely correlated with widely accepted surrogate measures of cardiovascular risk such as carotid intima-media thickness (CIMT)[4,44,45] and left ventricular mass (LVM),[45–47] than brachial pressure in cross-sectional studies (see Supplementary material online, *Table S1*). Longitudinal observations provide greater support for the potential value of central pressure measurement. In the REASON Study,[48] regression of LVM was more strongly related to change in central compared with brachial pressure and, after adjustment, only central pressure remained predictive. Similar observations were made in a substudy of ASCOT.[49] Moreover, with anti-hypertensive therapy, the reduction in CIMT relates better to the fall in central pressure.[50]

The predictive value of central pressure has been investigated in a variety of patient cohorts (see Supplementary material online, *Table S2*). Out of 11 published studies, one was based on invasive measurements of central pressure[7] with the rest using tonometry-based techniques. Nine studies reported that central pressure was independently related to future cardiovascular events. Surprisingly, the ANBP2[51] and Framingham Heart Study[52] did not detect any systolic pressure amplification between the carotid and 'brachial' arteries and concluded that there was no advantage in assessing central in addition to brachial pressure. Four of the 11 studies also demonstrate incremental value of central over brachial pressure. Safar *et al.*[5] found that after adjustment for confounders, only central pressure remained predictive in patients with renal failure. In the larger Strong Heart Study, central pressure was more strongly related to future cardiovascular events than brachial pressure, in disease-free individuals.[4] Moreover, after mutual adjustment, brachial pressure ceased to be predictive. Further analyses in this cohort show that individuals with central pulse pressure $\geq$50 mmHg are greatest risk of future cardiovascular events.[53] The Dicomano Study in Italy[6] and a community-based Taiwanese study[45] also observed a stronger association between cardiovascular events and central, rather than brachial pressure. In contrast, Mitchell *et al.*[52] failed to show any additional value of carotid blood pressure in the Framingham Heart Study.

The main issue with the existing studies is that they are relatively underpowered to show convincingly that central pressure is meaningfully superior to brachial values in predicting events, especially given the correlation between the two ($r = 0.6–0.9$). A recent meta-analysis did confirm the independent predictive value of central pressure, and suggested that central pulse pressure may be a better predictor ($P = 0.057$).[54] Unfortunately, not all of the larger studies were included and the findings were based on published summary statistics rather than individual patient data. Clearly, a full evidence synthesis with an individual patient meta-analysis of all existing studies (currently in progress) is required, together with a definitive outcome study, preferably using one of the newer, operator-independent devices which are more suited to the primary-care setting. Only then will we know the true value of central pressure, and whether it adds meaningfully to brachial pressure-based risk prediction.

Pharmacological reduction of central systolic pressure

Until relatively recently, it was widely believed that blood pressure reduction *per se*, matters more than the choice of anti-hypertensive agent.[55] However, the results of two comprehensive meta-analyses,[56,57] together with large comparison studies including the MRC-Elderly,[58] LIFE,[59] and ASCOT[60] trials, all demonstrate that the beta-blocker, atenolol, is inferior to other major anti-hypertensive drug classes in preventing cardiovascular events. Interestingly, there is now convincing evidence that beta-blockers exert differential effects on brachial vs. central pressure. Such evidence may help to explain the adverse findings with atenolol in outcome studies and provides support for the hypothesis that drugs which lower central pressure the most will be more effective.

Numerous studies have now examined the influence of different anti-hypertensive drugs and novel/repurposed agents such as nitrates on brachial vs. central pressure (*Table 2*). However, these studies have typically included small numbers of patients, and have varied in the duration of treatment and methods used to assess central pressure. Moreover, only three studies have directly compared the effect of each of the major anti-hypertensive drug classes on brachial and central pressure.[61–63] Nevertheless, monotherapy studies have universally demonstrated that conventional beta-blockers lower central pressure to a *lesser* extent than brachial pressure. Moreover, the REASON trial,[9] which compared the effects of atenolol with the fixed-dose combination of the ACE inhibitor perindopril and the diuretic, indapamide, showed that, in a subset of patients, combination treatment led to similar reductions in brachial and central pressure, whereas the fall in central pressure with atenolol was only approximately half of that in brachial pressure. The CAFE substudy[8] of the ASCOT trial[60] subsequently reported that individuals randomized to atenolol had a 4.3 mmHg higher central systolic pressure than those given amlodipine, despite identical brachial pressures. Although modest, this differential effect observed with atenolol

Table 2 Comparative effect of anti-hypertensive drugs and nitrates on central systolic pressure

Class	Central systolic pressure
ACE inhibitors[61–63,95–102]	↓
Angiotensin receptor blockers[101,103–105]	↓↔
Beta-blockers[9,61–63,65,95,103,106,107]	↑↑
Calcium channel blockers[61–63,96]	↓↔
Diuretics[61–63,100,102]	↔
Nitrates[68,70,71,74]	↓↓

could explain most of the observed difference in outcome in the ASCOT study.

An important issue is whether atenolol is inferior to all other antihypertensive drugs, or whether the comparator agents are more efficacious than other drugs, including beta-blockers. In the EXPLOR study,[64] the fall in aortic systolic pressure was ~4 mmHg greater in individuals randomized to a valsartan/amlodipine combination vs. atenolol/amlodipine, indicating that even when combined with a calcium channel blocker, atenolol may not effectively protect against cardiovascular events. Moreover, it is important to recognize that not all beta-blockers are identical. The majority of studies has used atenolol, although Deary *et al.*[62] used bisoprolol, with similar results. In contrast, newer, more selective vasodilating agents such as nebivolol[65,66] and celiprolol[50] may have a greater capacity to reduce central systolic pressure, by reducing wave reflections, although further studies are clearly required.[67]

The results of the studies described above lend support to the hypothesis that an inadequate reduction in central pressure may be associated with an adverse outcome. However, further large, randomized and properly powered clinical trials are required in order to provide definitive evidence that for equal reductions in brachial pressure, drugs which lower central pressure most will be better. While non-vasodilating beta-blockers are clearly inappropriate in this regard, nitric oxide donor drugs such as glyceryl trinitrate have the opposite effect of non-vasodilating beta-blockers by substantially reducing wave reflections.[68] Although not a 'classical' or accepted antihypertensive drug, outside of the acute emergency setting, high doses of nitrates do appear to produce sustained reductions in brachial pressure during chronic dosing, despite concerns over tolerance.[69–73] Limited data also suggest that nitrates may reduce central pressure more than brachial pressure; and low doses may reduce central pressure with almost no effect on brachial pressure,[68,74] although concerns regarding development of tolerance and endothelial dysfunction[75,76] remain to be resolved. If these concerns can be resolved, then nitrovasodilators offer a potential strategy with which to preferentially lower central pressure, and thus test the clinical value of assessing central pressure and targeting it therapeutically. However, whether this translates into favourable effects on outcome is yet to be examined.

Outstanding issues

Several methodological issues remain to be addressed before measurement of central pressure is fully integrated into clinical decision-making and of practical benefit for patients. Firstly, although a number of simple-to-use, reliable devices are now on the market, a standard approach to validation of new devices is required: should this be against the current market leaders, or against invasively determined aortic pressure? An analogy can be drawn from oscillometric sphygmomanometers, which are validated against mercury, rather than 'true' invasive brachial pressure. Also, should these devices provide estimates of 'true' central pressure irrespective of brachial cuff pressure? This approach can sometimes produce higher central pressure estimates than the measured brachial cuff pressure,[39,77,78] which may seem unphysiological, but is due to the brachial cuff giving a falsely low estimate of brachial systolic pressure. The alternative approach calculates central pressure *relative* to the measured brachial cuff pressure, which tends to under-estimate the 'true' aortic pressure, but may be more intuitive. Finally, we need to adopt a standard method for calibrating peripheral waveforms, using either systolic/diastolic or mean arterial pressure/diastolic pressure, and to better understand the impact of brachial-radial and aortic-carotid amplification.

Another important issue is defining 'cut-off' values for central pressure. Although definitions and thresholds for brachial pressure are now well established, no such data exist for central pressure. Clearly, defining a 'normal' central pressure is impossible as blood pressure is normally distributed. Although the provision of age- and gender-specific reference ranges might seem attractive, these are never applied to brachial pressure. Moreover, such values are likely to be misleading because they imply that the progressive, age-related increase in blood pressure is without increased risk of cardiovascular disease and is thus physiological, rather than pathological. Nevertheless, it is important to recognize that because of the phenomenon of pressure amplification, one cannot simply apply the current brachial thresholds for diagnosing and treating hypertension to central pressure. An alternative approach might be to determine the usual amount of amplification, and then to 'translate' the current 140/90 brachial cut-off into a corresponding aortic value. Our previous data[28] suggest that this value is ~125/90, although clearly, further data are required. However, there are obvious limitations of this approach, not least the marked effect that age has on amplification. Nevertheless, the Strong Heart Study investigators observed that in over 2400 participants without overt cardiovascular disease, a central pulse pressure of $\geq$50 mmHg predicted an adverse cardiovascular outcome.[53] Thus, for the first time, a clinically useful target for diagnosis and intervention, based on central pressure, has been identified, although these data require confirmation.

As discussed earlier, a full synthesis of the available evidence concerning central pressure and the risk of future cardiovascular events is now required. However, it will also be necessary to determine the clinical relevance of differences between brachial and central pressure for the individual patient, especially given the relatively high correlation between the two. Emerging data support the prognostic superiority of both 24-h ambulatory blood pressure monitoring (ABPM)[79–81] and home monitoring[81] in comparison with office measurements. Interestingly, a recent study[82] demonstrated that 24-h ambulatory cuff pressures were comparable with office *central* pressure measurements in the prediction of risk, although the significance of this study awaits confirmation.[83] As yet, there are no data comparing the predictive value of home monitoring vs. central pressure in the prediction of risk. Ultimately, it will be necessary to evaluate the prognostic value of 24-h ambulatory central pressure. With the recent development of ambulatory central pressure systems,[84,85] this is now possible and it may be reasonable to hypothesize that 24-h central, rather than brachial ABPM would be superior in terms of risk prediction.

Finally, there is now a substantial body of evidence that antihypertensive drugs, and particularly beta-blockers, exert differential effects on brachial and central pressure. As a result, the pharmaceutical industry is becoming increasingly convinced that basing treatment decisions on central, rather than brachial pressure, is likely to have important implications for the future diagnosis and management of

hypertension. However, cuff measurements of brachial systolic and diastolic pressure continue to remain the accepted surrogates by drug regulatory authorities. This means that new therapies will continue to be assessed on the basis of brachial measurements, which may ultimately serve as a potential barrier to novel drug development. Therefore, appropriately powered clinical trials demonstrating that preferential lowering of central pressure improves outcome, will ultimately be required before central pressure becomes an accepted surrogate of cardiovascular risk. Nitrovasodilating drugs may be particularly useful in this respect. Before such trials are completed, smaller studies based on established surrogates for cardiovascular disease, such as carotid IMT and LVM will be important in providing proof of principle that reduction in central rather than brachial pressure is a more effective therapeutic strategy.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

C.M.M. and I.B.W. are supported by the National Institute for Health Research Cambridge Biomedical Research Centre. M.J.R. is supported by the National Institute of Health and I.B.W. is a British Heart Foundation Senior Clinical Fellow.

Conflict of interest: C.M.M., J.R.C., and I.B.W. have received unrestricted educational donations and/or equipment from AtCor Medical, Centron Diagnostics (CMM) and IEM GmbH. MJR and SSF report no conflict of interest.

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