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Does it matter where we measure blood pressure?

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Although blood pressure measured at the brachial artery plays a central role in our understanding and management of cardiovascular risk, in recent years great emphasis has been placed on the importance of central blood pressure. It seems straightforward that knowledge of the blood pressure directly affecting the major organs is important for understanding the pathophysiology and treatment of cardiovascular risk. However, the field has been troubled by controversies over measurement techniques and difficulty in designing therapies to modify central but not peripheral blood pressure. In this review, we consider the physiology underlying the change in blood pressure through the arterial tree and how central blood pressure can be measured. In addition, we review the evidence regarding the relationship of central BP to cardiovascular disease and the effects of treatment. New measurement techniques and evidence regarding the specific benefits of therapies in modulating central haemodynamics mean that this is a rapidly developing area, and understanding the concept of central blood pressure will be vital in the future.

Introduction

It is over 100 years since Dr Nikolai Korotkoff, a Russian physician, first described his auscultatory technique for the measurement of blood pressure (BP). Since then, BP assessed at the brachial artery has been a mainstay of epidemiological studies, drug trials, risk stratification and management of individual patients. There is compelling evidence from huge observational studies that brachial artery BP is a strong risk factor for heart disease and strokes [1], and that its reduction with antihypertensive medication is associated with improvement in prognosis [2].

In recent years, however, awareness has grown that brachial artery BP is only a surrogate marker for the pressure experienced by the brain, heart and kidneys, which is closer to 'central' or aortic BP. New techniques for simple measurement of central BP have been developed. These, combined with growing evidence that central BP is more closely associated with cardiovascular outcome and may be affected differently by different antihypertensive drugs, have led to growing interest in the pathophysiology and treatment of central rather than brachial BP.

In this review, we consider why BP varies depending upon where it is assessed in the arterial tree and how it can be measured. In addition, we cover the evidence regarding the relationship of central BP to cardiovascular disease and the effects of treatment.

Why are aortic and brachial blood pressures different?

In order to understand the factors determining central BP and how it changes through the arterial tree, the underlying vascular physiology must first be considered. Arteries are not merely conduits through which blood is pumped from the heart to organs but have an additional smoothing function where large changes in BP and flow resulting from intermittent ventricular ejection are integrated into steady flow within peripheral tissues. This predominantly occurs in elastic arteries, such as the aorta, where arterial walls contain a predominance of elastin fibres, permitting significant distension during systole. During diastole the artery recoils, pushing blood forwards through the arterial tree. Muscular arteries, such as the radial, have a higher

proportion of collagen fibres, making them less distensible. Changes in arterial structure can be quantified in terms of vessel stiffness, which is the pressure required to provide a unit change in volume. In healthy young people, arterial stiffness is lowest in the elastic ascending and thoracic aorta and highest in distal lower limb arteries, such as the tibial. However, arterial stiffness in central elastic arteries increases progressively with age and is a major factor responsible for the increased pulse pressure (PP; the difference between systolic and diastolic blood pressure) observed with age [3]. Loss of vessel elasticity may be due to progressive medial elastin fatigue, fracture and degradation, with a consequent increased loading on stiffer collagen fibres [4] or increased vascular calcification [5]. Aortic stiffness has been independently associated with cardiovascular events and mortality across many different populations [6].

A second factor that alters the shape of the arterial waveform and the absolute values of central BP is reflected pressure waves. When the left ventricle ejects blood into the aorta in systole, a wave that initially travels from the heart through the arterial tree is generated. At arterial branch points, the wave is reflected back towards the heart and summates with the forward-travelling wave. In young healthy individuals, in whom aortic stiffness is low, this reflected wave travels slowly and summates with the forward wave during late systole or diastole, increasing coronary blood flow during diastole. However, where central arterial stiffness is increased, rapid transmission of the forward and backward waves leads to summation during systole, causing a second systolic peak in the central waveform and an increase in systolic pressure, hence pulse pressure. The second systolic peak has been shown to be a major contributor to the systolic hypertension that commonly occurs with ageing [7].

Having considered the changes that occur in vascular structure with ageing and how these affect central BP, we should now consider why this differs from that measured at the brachial artery. This is due to the 'amplification phenomenon', where the amplitude of a pressure wave is higher in peripheral than central arteries. The physiology underlying this is complex and not completely understood. Arterial stiffness of the arm vessels rapidly increases with distance from the heart. This amplifies the early harmonics of the pressure waveforms and leads to a narrower wave with higher systolic BP. Thus, brachial systolic and pulse pressure are significantly higher than central pressures in young individuals, whereas diastolic blood pressure is roughly constant [4]. The contribution of reflected waves is uncertain, but as the pressure wave moves from the heart towards the brachial artery the effect of reflected waves may increase due to reduced distance to sites of wave reflection, further augmenting the increase in systolic BP. With ageing, the difference in arterial stiffness between central and peripheral arteries falls and even reverses, leading to a progressive fall in pressure amplification [8]. In addition, hypertension, raised lipids and smoking impact upon pressure amplification so that central systolic and pulse pressures are relatively higher in people with these cardiovascular risk factors [8].

Measurement of central blood pressure

The most accurate assessment of central aortic pressure is obtained invasively by passing a high-fidelity pressure transducer connected to an angiographic catheter directly into the ascending aorta. However, this technique is clearly not suitable for large population or clinical studies, which have only been possible since the development of non-invasive methods. These involve applanation tonometry, where transcutaneous pressure transducers at the end of a probe are held so as to slightly flatten but not compress an artery in order to equalize circumferential pressures. Pressure waveforms can then be obtained which are almost identical to those obtained by intra-arterial measurements [9]. The technique is most suitable for use where a large artery can be supported by a lean or bony structure and runs close to the skin, such as at the radial, carotid or femoral arteries.

From these waveforms, two main methods have been developed for non-invasively determining estimates of central BP. The first approach is to use the carotid waveform as a surrogate for that of the aorta, calibrating the wave to brachial diastolic and mean pressure, which are nearly constant throughout the arterial tree [9].

The second method is to use a generalized transfer function (a mathematical description of the change from the input to output signals of a system) to derive an aortic waveform from measurements made at the radial artery. Ease of use and high repeatability has made this the main technique used in clinical studies. The transfer function has been well validated against invasive measurements of central pressures during cardiac catherization [10], but ethical constraints mean that such comparisons are limited in populations unlikely to undergo these procedures. Therefore, the validity of using a single transfer function to estimate central BP parameters across ages and comorbidities remains the subject of much debate and controversy [11]. In addition, inaccuracy may arise through calibration of the radial artery pressure wave with brachial artery pressures, thereby omitting the brachial-to-radial pressure amplification, which can lead to significant underestimation of aortic pressure.

Concern about the use of a universal transfer function has led to development of novel methods to derive information about central pressures from the radial artery waveform. For example, the late systolic 'shoulder' of the peripheral pulse approximates central systolic pressure, and the relationship is maintained despite changes in heart rate and nitrate-induced vasodilatation [12]. Further

development of these techniques, as well as novel brachial artery-based measurements, are likely to lead to rapid expansion of the evidence base over the next few years.

Relationship between central blood pressure and cardiovascular disease

Central, rather than brachial, BP is the pressure 'experienced' by the large vessels and heart. Increasing evidence is emerging that central BP is more closely related to surrogate markers of cardiovascular disease in these areas than brachial BP.

In a study of healthy subjects and never-treated hypertensives, carotid internal diameter and intima–media thickness was strongly related to carotid PP but not to mean PP or brachial PP [13]. Among patients with end-stage kidney disease undergoing dialysis, echocardiographic left ventricular mass is more closely related to aortic than brachial systolic BP [14]. In the Strong Heart Study, a population-based study of 3520 American Indians where central pressure parameters were estimated at baseline using radial applanation tonometry, central PP was more strongly related to carotid artery vascular mass, intima–media thickness and carotid atherosclerotic plaque score than was brachial PP [15].

Recent evidence also suggests that raised large artery pressure may have a deleterious effect on the distant microvasculature. Raised central pressure is associated with age-related macular degeneration [16] and progression of renal disease [17].

The first evidence that measures of aortic BP could provide prognostic information beyond intermediate surrogate markers of risk came in 2002 with a study of patients with end-stage renal disease. Safar and colleagues showed that central PP, measured at the carotid artery, was a significant predictor of all-cause mortality, whereas brachial blood pressures, including PP, had no predictive value for mortality after adjustment [18]. Subsequent data to support the prognostic importance of central BP come from analysis of 2403 participants from the Strong Heart Study who were free of cardiovascular disease at baseline. Of these, 319 suffered cardiovascular events during a mean follow-up of 4.8 years, and in Cox regression analysis, after full adjustment for traditional risk factors, central PP predicted cardiovascular events more strongly than brachial PP [15]. Most recently, a study of normotensive and untreated hypertensive elderly individuals confirmed that higher carotid PP, but not brachial PP, independently predicted cardiovascular events and mortality [19].

This growing body of evidence has led an expert consensus group to call for the wider use of central haemodynamics in clinical practice and research studies [20]. However, a recent meta-analysis of all published data demonstrated that while central PP has a significant predictive value for cardiovascular events and mortality, this is marginally but not significantly better compared with brachial PP [21]. Nonetheless, the strong physiological basis and current data suggesting the importance of central pressure means that a number of large observational and outcome studies including measurements of central BP are underway, which will provide much more information over the next few years.

Implications for treatment of hypertension

The range of central blood pressure for any level of brachial blood pressure is wide, so that a proportion of individuals classified as being normotensive from brachial BP based on current guidelines may in fact be at increased risk according to their central BP [8]. As central BP is associated with a number of surrogate markers of cardiovascular disease and may be a better predictor of future cardiovascular risk than brachial pressure, it is likely that in the future the assessment of central pressure will improve the identification and management of patients with elevated cardiovascular risk.

For many years, clinical trials of antihypertensives have focused on reduction of brachial BP. The consensus opinion was that the degree of BP reduction was more important than the class of antihypertensive drug used. However, recent evidence has suggested that β-blockers are less effective than other classes of drugs, and this led to them being removed from guidelines as a first-line choice of antihypertensive [22]. The apparent paradox of why β-blockers are less effective, despite lowering brachial BP to a similar degree compared with other antihypertensives, may be resolved by considering the effects on central BP.

In double-blind crossover studies, β-blockers are less effective at reducing central arterial systolic BP compared with calcium channel blockers, diuretics and angiotensin-converting enzyme inhibitors [23]. In patients with isolated systolic hypertension, this increased central pressure has been associated with a rise in wave reflection from the arterial tree and an increase in plasma brain natriuretic peptide, suggesting an increase in left ventricular afterload [24].

The largest clinical study that has assessed central haemodynamics to date is the Conduit Artery Function Evaluation (CAFÉ) study [25], a substudy of the main Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study [26]. Cardiovascular event rates were compared between treatment with an atenolol and bendroflumethiazide combination and treatment with an amlodipine- and perindopril-based antihypertensive regimen. Although the trial was stopped early, event rates were lower in the amlodipine–perindopril arm, despite only a 2.7/1.9 mmHg difference in brachial BP between the arms. Among the subset of 2199 patients recruited into CAFÉ, despite extremely similar

brachial systolic BP (mean difference in area under the curve 0.7 mmHg; 95% CI 0.4–1.7) central systolic BP was 4.3 mmHg lower in the amlodipine–perindopril arm. This differential effect on central and peripheral pressures has been used to explain the difference in outcome despite similar brachial BP in the main ASCOT study.

Although the evidence that β-blockers as a class are less effective than other antihypertensives in lowering central BP is compelling, there are also suggestions that individual β-blockers vary widely in their impact on central haemodynamics. Drugs such as dilevalol and nebivolol have a vasodilatory effect on peripheral conduit arteries and result in reduced wave reflection compared with atenolol [27, 28]. Most recently, a randomized, double-blind study of 80 treatment-naive hypertensive patients compared the effects of nebivolol and metoprolol on several haemodynamic parameters. Both drugs reduced heart rate and brachial BP to the same extent, but there was a fall in brachial PP and central BP only in the nebivolol group. In addition, the results suggested that the fall in central BP translated to a reduction in target organ damage, with an improvement in echocardiographic markers of left ventricular wall thickness observed only in the nebivolol arm [29].

A further class of drugs that, while not conventionally used as antihypertensives, have been shown potentially to have a beneficial effect on central blood pressure are nitric oxide donors, such as glyceryl trinitrate. At doses associated with minimal change in brachial BP, central BP and wave reflections are significantly reduced by administration of a glyceryl trinitrate patch [30], while oral isosorbide mononitrate reduced brachial and central BP in elderly patients with refractory systolic hypertension [31]. Therefore, nitrovasodilators may offer a new treatment option for patients with hypertension associated with stiff arteries and enhanced wave reflection.

Conclusion

Understanding of the importance of central BP has grown rapidly over recent years, and this is likely to be significantly strengthened by the outcome data of currently ongoing observational studies. Consideration of the impact of therapies on central as well as brachial BP has helped our understanding of the results of recent clinical trials and focused attention on the importance of treatments for underlying pathophysiology. However, clear proof that assessment of central BP in routine clinical practice is useful will only come if clinical trials demonstrate that selective reduction in central pressure reduces cardiovascular events. Such a trial is challenging to conduct, because to be meaningful the study arms must be matched for brachial but not central BP reduction. However, attempts to conduct these clinical trials are underway and, if successful, have the potential to alter our understanding and management of blood pressure for the next century.

Competing Interests

There are no competing interests to declare.

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