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Review

Application of non-invasive central aortic pressure assessment in clinical trials: Clinical experience and value

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Abstract Pressure measured with a cuff and sphygmomanometer in the brachial artery is accepted as an important predictor of future cardiovascular (CV) events. However, recent clinical evidence suggests that central aortic pressure (CAP) provides additional information for assessing CV risk than brachial blood pressure (BrBP). Central hemodynamics can now be non-invasively assessed with a number of devices, however, the methodology employed to measure CAP, in order to better identify the patients at higher CV risk in clinical practice, is still controversial. The purpose of this article is to review the technology behind the non-invasive measurement of CAP via the effects of different classes of antihypertensive drugs on CAP and the data supporting the predictive value of assessing CAP on clinical outcomes, and to foster the transfer of methodological knowledge from clinical trials into routine clinical practice.

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Introduction

Brachial blood pressure (BrBP) is an accepted surrogate marker and major independent risk factor for cardiovascular (CV) disease and decreases in blood pressure have been demonstrated to correlate with reduced incidence of myocardial infarction and stroke.[1] However, the BP profile varies along the arterial tree from its origin to the periphery with mean and diastolic BP being relatively constant while systolic BP is higher in the periphery than in the aorta and elastic central arteries.[2] Thus, systolic BP (SBP) values are dependent on the site of measurement. Central aortic systolic pressure (CASP) appears to be a more relevant measurement than peripheral pressure, as the aortic pressure the target organ beds receives is proportional to the pressure developed by the left ventricle to propel blood against the arterial pressure. The arterial pressure waveform used to calculate CASP is composed of the forward pressure wave created by ventricular contraction and a reflected wave, originating from the primary wave hitting intersections between elastic and more muscular arteries: the overlap between the anterograde and retrograde reflected waves producing the amplification phenomenon of the arterial pressure wave observed in the aorta.[2]

BrBP is thus a composite measure of both the CAP and the degree of amplification of the central pressure. The relationship between CAP and BrBP is not fixed, as it depends on a number of factors including arterial wall distensibility and arterial pressure, and the ratio between the two BPs has been termed the amplification ratio. The relationship between CAP and BrBP, specifically the respective pulse pressures, is also strongly dependent upon heart rate. In some hypertensive patients a reduced amplification ratio may be an indicator of the stiffness of the arterial tree. BrBP is usually higher than CAP due to pressure wave amplification.[2] Systolic pressure amplification is the ratio between brachial and central SBP and pulse pressure amplification (PPA) is the ratio of brachial to central PP. In healthy individuals PPA is approximately 1.5 and varies from 1.7 at $<$20 years of age to 1.2 at $>$80 years of age.[3] PPA is variable between subjects but relatively constant for a given individual reflecting the degree of stiffness of the large arteries and the magnitude of wave reflections.[4]

A number of factors such as age, heart rate and height have differential effects on central and peripheral pressure. In addition, CV risk factors such as hypercholesterolemia, hypertension, smoking and metabolic syndromes, which accelerate aortic stiffening in the large arteries, may have greater effects on CAP.[5] CAP increases with age in part because large arteries become stiffer with age, is reduced by low heart rate and shorter body height (reflecting reducing aortic length and volume), and is reduced with low diastolic pressure. Female gender on average is associated with a lower CAP in comparison with males, although PPA is generally lower in females indicative of a higher central relative to brachial pressure.[6,7]

CAP at the aortic root is regarded as an index of aortic stiffness and represents the true load imposed on heart, brain, kidney and large arteries.[8–10] Recent studies have shown that CAP and CAPP are better predictors of CV events and mortality than BrBP.[11,12] CAP has also demonstrated clinical value in predicting clinical outcomes in selected populations such as patients with end-stage renal disease (ESRD) and patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention.[8,9] CAP measurement is of clinical relevance since it predicts clinical outcomes in both general populations and in patients with CV risk factors.[13] Previous studies have looked at the predictive power of central versus peripheral pressure measurements,[8,12,14,15] and a meta-analysis by Vlachopoulos et al.[11] has shown a trend for CAPP to be more predictive than BrPP ($p = 0.057$), while no difference for SBP was observed.

The 2003 ESC/ESH guidelines for the management of arterial hypertension recommend that the assessment of total CV risk includes an assessment of target organ damage. CAP is dependent on pulse wave velocity (PWV) and augmentation index (AIx) that are linked to the development of target organ damage in patients with hypertension.[16] CAP varies between subjects, and antihypertensive agents (i.e. primarily beta-blockers and heart rate modulating agents) have shown differential effects on CAP despite similar effects on BrBP.[17] A substantial overlap of central and brachial BP among categories of hypertension implies that based simply on the brachial cuff BP, but in reference to the effects of central aortic BP on end-organ damage, there are some individuals who should be treated and who are not and others who are on treatment and perhaps might not require it[5,18]: the paradigm shift that was suggested in the BP Guide study. Measuring CAP in addition to BrBP in patients with CV risk may provide additional information and further characterize blood pressure patterns to improve treatment decisions. The BP GUIDE (value of central Blood Pressure for GUIDing managEment of hypertension) study showed that central BP guidance for hypertension management resulted in a significant reduction in the quantity of antihypertensive medication (across all drug classes) needed to achieve BP control.[19] A recent critical analysis between brachial and central systolic pressure showed that their standard deviations were nearly identical.[20] This is because the population variation caused by PPA is counterbalanced by the larger measurement and model errors embedded in central SBP. The practical implication is that in a comparative study, the sample size needs to be roughly the same whether brachial or central SBP is used as the primary dependent variable.

Until recently, CAP could only be assessed by invasive measurement. Since 2002, several non-invasive techniques, primarily applanation tonometry have been developed to estimate CAP. Cuff BrBP has been commonly used to calibrate peripheral pulse waveforms, the basis for all CAP estimation methods, obtained by tonometry.[21] The widespread use of CAP measurement is hindered by the availability of diverse non-invasive devices and standardization of the method; furthermore, an evidence gap still exists on the predictive value of CAP in prospective studies. The aim of this review is to highlight the clinical relevance of CAP, which can be non-invasively measured in multicenter clinical trials, to assess the effects of antihypertensive treatments on CAP in comparison to BrBP and to better understand their respective predictive value for outcomes.