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EDITORIAL COMMENT

What to Anticipate From Pulse Pressure Amplification*

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The blood pressure (BP) wave is gradually distorted in terms of shape as it travels from the central elastic arteries to the muscular conduit arteries (1). This is a physiological phenomenon, associated with the fact that BP is a periodic oscillating wave that is transmitted and reflected within a nonuniform visco-elastic arterial bed. As a consequence, in healthy subjects, the amplitude (pulse pressure [PP]) of the pressure wave increases gradually from the aorta/carotid arteries to the brachial/radial arteries yet without any additional energy input in the arterial system, because the mean arterial pressure (MAP) as well as the diastolic blood pressure remain almost unchanged between these sites. Therefore, this phenomenon, known as "PP amplification," is attributed mainly to the gradual increase of the systolic blood pressure (SBP). Several clinical implications regarding optimal cardiovascular (CV) risk stratification and treatment might arise due to the disparity of brachial and central PP (1).

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The assessment of PP amplification requires measurement/estimation of both peripheral and central PP. In the current issue of the *Journal*, Benetos et al. (2) generated a statistical model to predict central PP from peripheral PP and classical CV risk factors. This model was based on data derived from a population (n = 834) referred to a specialized center for the management of CV disease, who underwent carotid BP estimation by using a validated noninvasive methodology (direct carotid tonometry) (3). This model was then applied in a large population of 125,151 subjects who underwent a health check-up, to estimate central PP and PP amplification and to investigate their association with mortality after 10 years of follow up. The authors showed that PP amplification is an independent predictor of mortality, at least as good as brachial and central PP or even better.

Herein, we will comment on the mechanics and pathophysiology of PP amplification, its clinical relevance, the novelty of the present outcome, as well as the strengths and weaknesses of this study (2).

Definition and Clinical Relevance of PP Amplification

Pulse pressure amplification has been expressed by several formulas in the past. Most commonly, it is defined by the ratio PP_2/PP_1 between the distal site (PP_2) (e.g., radial artery) and the proximal site (PP_1) (e.g., aorta) (1). Alternatively, it can be expressed as the difference (in mm Hg) $PP_2 - PP_1$ (1) or the ratio of $(PP_2 - PP_1)/PP_1$ (4). All these formulas might provide equivalent principal results (1,4,5); however, whether they are identical on the basis of clinical impact has to be further evaluated.

From a physiological point of view, for a given brachial PP, the lower the central PP the more beneficial the effect on the CV system, because the heart and the aorta confront lower pulsatile load (i.e., the higher the absolute difference [mm Hg] of PP amplification the better). Additionally, the absolute value of PP amplification decreases with age (1,4,5). Therefore, it seems more appropriate to express PP amplification as PP_2/PP_1 (e.g., 80/60 mm Hg = 1.33) (1) rather than PP_1/PP_2 (e.g., 60/80 mm Hg = 0.75) (2), because the former formula integrates the 2 aforementioned features. Herein, PP amplification will be defined as the ratio PP_2/PP_1.

Given the mounting evidence from studies showing that central, more than peripheral BP, is associated with target organ damage and potentially with CV risk (6), the disparity between central and peripheral PP (usually ranging from 5 to 20 mm Hg) has important clinical implications regarding optimal BP-associated CV risk stratification and treatment. The BP-associated CV risk might be substantially over- or under-estimated when classified according to conventional brachial BP measurements based on international guidelines classification due to a considerable overlap in aortic SBP between the discrete categories (5). Second, it is proven that not all classes of antihypertensive drugs have similar effect on PP amplification (7). Drugs with vasodilating effects increase PP amplification when compared with beta-blockers (7).

Supporting evidence on the clinical relevance of PP amplification has been so far provided by 2 small prospective studies. In end-stage renal disease, low PP amplification but not brachial PP was an independent predictor of all cause and CV mortality (8), superior to carotid PP. In another study evaluating untreated subjects with essential hypertension (9), regression of left ventricular mass index after treatment was independently associated with the increase of

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PP amplification but not with the reduction in brachial PP. Benetos et al. (2) showed for the first time in a large epidemiological study that PP amplification is a predictor of all-cause as well as CV mortality, independently from classical CV risk factors.

Mechanics and Pathophysiology of PP Amplification

Cross-sectional observational data in healthy subjects from the ACCT (Anglo-Cardiff Collaborative Trial) (5) and the Asklepios Study (4) have shown that PP amplification is modulated by vascular properties (large artery stiffness, peripheral resistance, and mainly pressure wave reflections) as well as by heart rate. The mechanism by which these parameters affect the PP amplification is largely related to the "timing–synchronization" of the forward and backward (reflected) pressure waves. The closer the BP is measured to the reflections sites (i.e., further in the periphery), the earlier the forward (ejected from the left ventricle) and the backward (reflected at the peripheral reflection sites) travelling waves will be coupled, enhancing the peak SBP (4). Classical nonmodifiable (i.e., age, sex) and modifiable (i.e., hypertension, diabetes mellitus, hypercholesterolemia, smoking) CV risk factors or established CV disease are also associated with reduced PP amplification in observational studies (1,5). These factors act by accelerating "normal vascular aging," which is per se the main modulator of large artery stiffness and wave reflections.

From this point of view, PP amplification could be considered as a mechanical biomarker of CV disease and risk, as suggested by Benetos et al. (2), integrating CV risk factors as well as global arterial properties. The available data imply that PP amplification is not just a mathematical expression but "carries" additional physiological information, potentially above that of central and peripheral PP alone. However, any new efficient biomarker should be easy in application, useful for detection and prognosis as well as for guiding treatment, but also it should provide complementary and independent information compared with existing biomarkers. In this respect, the current data on PP amplification are very limited.

Epidemiology Versus Daily Clinical Practice

There is important intraindividual and interindividual variation of PP amplification (1,5). Invasive and noninvasive studies have shown that the gradient between central and peripheral PP might change significantly under the acute or chronic effect of vasoactive substances, drugs, or common daily consumed beverages (1) and of course due to vascular aging (4,5). Therefore, a statistical approach for the assessment of central hemodynamic status is of limited value in clinical practice yet important for the understanding of arterial mechanics from large epidemiological studies.

Moreover, the generalized application of any regression model is limited by the unavoidable differences between the studied population and the "targeted" population. In the present study the target population was younger with lower burden of CV risk factors than the one used to generate the statistical model. The model generated in this study explained 86% of the variability of central PP. However, classical CV risk factors explained only up to 3% of central PP variance, whereas glucose was the only modifiable CV risk factor in the model. Therefore, it could be speculated that direct instead of statistical assessment of PP amplification might generate different results with a potential greater prognostic significance.

Finally, it is important to clarify the effect of the steady component of BP (i.e., MAP) in order to assess the independent net effect of PP amplification on CV disease; ideally this requires direct assessment of MAP and PP amplification.

Perspectives

Pulse pressure amplification is a physiological phenomenon with clinical implications. The need to noninvasively assess central PP is the major drawback. The available methods have several limitations (3); the cardinal one concerns the need for calibrating central pressure waveforms with noninvasively acquired peripheral BP or/and the use of mathematical transformation models. The expression of PP amplification as a ratio of peripheral to central PP is potentially less dependent on calibration errors due to inaccuracies in the measurement of diastolic blood pressure, as suggested by the authors, which might be considered as an advantage of this "biomarker." Most importantly, the additional effort and cost to assess central hemodynamic parameters in selected populations must be justified by clear data derived from clinical trials, currently lacking, demonstrating the superiority of these parameters over the conventional brachial cuff BPs. The anticipation of optimal BP-associated CV risk stratification and treatment, on the basis of central hemodynamic status is physiologically relevant; yet, it might turn into "Great Expectations" if further biomedical innovation is not achieved in order to increase accuracy and facilitate its application in clinical practice.

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REFERENCES

1. Avolio A, Van Bortel L, Boutouyrie P, et al. The role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the Data. Hypertension 2009;54:375–83.
2. Benetos A, Thomas F, Joly L. Pulse pressure amplification: a mechanical biomarker of cardiovascular risk. J Am Coll Cardiol 2010;55:1032–7.
3. Papaioannou TG, Protogerou AD, Stamatelopoulos KS, Vavuranakis M, Stefanadis C. Non-invasive methods and techniques for central

blood pressure estimation: procedures, validation, reproducibility and limitations. Curr Pharm Des 2009;15:245–53.
4. Segers P, Mahieu D, Kips J, et al., for the Aslepios Investigators. Amplification of the pressure pulse in the upper limb in healthy, middle-aged men and women. Hypertension 2009;54:414–20.
5. McEniery CM, Yasmin, McDonnell B, et al. Central pressure: variability and impact of cardiovascular risk factors: the Anglo-Cardiff Collaborative Trial II. Hypertension 2008;51:1476–82.
6. Protogerou AD, Papaioannou TG, Blacher J, Papamichael C, Lekakis J, Safar M. Central blood pressure: do we need them in the management of cardiovascular disease? Is it a feasible therapeutic target? J Hypertens 2007;25:265–72.
7. Protogerou AD, Stergiou GS, Vlachopoulos C, Blacher J, Achimastos A. The effect of antihypertensive drugs on central blood pressure beyond peripheral blood pressure. Part II: evidence for specific class-effects of antihypertensive drugs on pressure amplification. Curr Pharm Des 2009;15:272–89.
8. Safar ME, Blacher J, Pannier B, et al. Central pulse pressure and mortality in end-stage renal disease. Hypertension 2002;39:735–8.
9. Hashimoto J, Imai Y, O'Rourke MF. Monitoring of antihypertensive therapy for reduction in left ventricular mass. Am J Hypertens 2007; 20:1229–33.

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