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COMMENTARY

Is validation of non-invasive hemodynamic measurement devices actually required?

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In the last decades, evidence has suggested that antihypertensive drug classes have differential effects on central blood pressure and indices of arterial function and structure independent of their peripheral blood pressure-lowering effects.[1] The effects of the angiotensin receptor blocker losartan and of the beta-blocker carvedilol on central blood pressure, aortic pulse wave velocity and augmentation index were compared in the open-label trial by Kim *et al.*[2] published in the current issue of *Hypertension Research*. Although this study is original, well conducted, and could have provided further and interesting data for a better understanding of the effects of hypertension treatment on vascular hemodynamics, it is characterized by serious methodological limitations related to the method used for hemodynamic assessment.

Indeed, the Gaon 21A Pulse Wave Analysis System (Hanbyul Meditech, Jeonju, Korea) employed in this study has not been formally validated to assess central blood pressure. The only evidence on the feasibility of Gaon 21A System comes from a study conducted by Kang *et al.*[3] This cannot be considered as a study of validation, only a comparative study exploring the ability to measure central blood pressure and indices of arterial function against a reference tonometric device (SphygmoCor, AtCor Medical, Sydney, NSW, Australia). Both devices, SphygmoCor and the Gaon 21A System, use a transfer function from radial artery waveform to evaluate aortic pressure waveform. However, the results of the cited article are questionable. Indeed, while the values of central systolic blood pressure provided by the Gaon 21A System and SphygmoCor were consistent, only a weak correlation was observed for parameters obtained from pulse waveform analysis (that is, augmentation index, subendocardial viability ratio and ejection duration). The waveforms provided by both these systems as well as the algorithms employed for transfer function were significantly different (up to the point that they were not interchangeable).

Although the discussion about the questionable reliability of transfer function from radial artery waveform to evaluate aortic pressure is not the subject of this commentary, it should be noted that no formal validation study of the transfer function algorithm used by this system has been conducted and that no assumptions on the accuracy of the transfer function of the Gaon 21A System in estimating central blood pressure from peripheral pulse waveform can be drawn from the study by Kang *et al.*[3] The transfer function used by SphygmoCor was supported by scientific literature, whereas no literature appears to support the algorithm used by the Gaon 21A System to determine the central pressure using the radial pressure waveform. The validation of SphygmoCor cannot be automatically transferred to all devices using a transfer function to assess central blood pressure from peripheral pulse waveform. Consequently, the use of unvalidated devices makes the results of the research unreliable. How can a multicenter study that utilizes unvalidated devices be conceived and carried out? How can a scientific instrument without adequate scientific validation be put on the market?

Another questionable aspect of the study by Kim *et al.* is with regard to the method employed for the calculation of distance in the estimation of pulse wave velocity. The authors followed the indications of the PP-1000 (Hanbyul Meditech, Jeonju, Korea) manufacturer to calculate traveling distance. However, these recommendations are not supported by previous validation studies. Moreover, no formal validation study has been conducted to determine the accuracy of the algorithm employed by the PP-1000 by Hanbyul Meditech in the estimation of pulse wave velocity. Recently, international guidelines were issued in an attempt to delineate standards of measurement of arterial stiffness, not only in research studies but also in daily clinical practice.[4,5] They have been based on the evidence provided by clinical studies over the past decades and on the consensus of experts in the field. Nonetheless, the authors disregarded this evidence and followed the manufacturer recommendations for the calculation of distance, which are not supported by the currently available evidence.

… BUT WHICH VALIDATION?

Over the last decade, several devices for the non-invasive assessment of central blood pressure and indices of arterial function derived from peripheral pulse wave analysis have become commercially available. Although most of these devices have been celebrated for their ability to provide automated measurements of different hemodynamic parameters in a relatively fast and operator-independent manner, the evidence supporting their ability to properly acquire aortic waveform and accurately calculate central aortic pressure is less clear. Issues related to the algorithms used for transfer function that have been implemented in some of these devices—which in some instances have raised important questions

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regarding their accuracy and validity in estimating central aortic pressure based on the analysis of brachial or radial pulse waveforms—are also unclear. Moreover, the ability of validation studies to determine the actual accuracy of devices for the non-invasive assessment of central aortic pressure (reconstructing central blood pressure from peripheral blood pressure measurements) against invasive standard procedures should be questioned.

From a mathematical perspective, the average difference between systolic blood pressure values acquired at the brachial artery level by means of a standard sphygmomanometer and central systolic blood pressure values is approximately 10 mm Hg. This difference may significantly change due to heart rate values and as a consequence of the blood pressure measurement technique employed. Moreover, the degree of variability between peripheral and central blood pressure levels may be significantly affected by age: although in elderly patients the blood pressure amplification phenomenon is almost absent, in youths the difference between central and peripheral blood pressure levels may exceed 25 mm Hg. However, when assessed in a general population including subjects of different ages, the average inter-individual difference between central and peripheral blood pressure levels may be significantly reduced to a few mmHg. If we account for this difference in an algorithm for transfer function (regardless of its complexity), it might be accurate for the estimation of central blood pressure levels from peripheral blood pressure measurements in the context of a validation study.

An example of this is illustrated by the analysis of our data from more than 2000 subjects. The central blood pressure levels of these subjects were assessed with a validated and reliable device, and their peripheral blood pressure levels were simultaneously recorded with a standard validated sphygmomanometer at the level of the brachial artery.[6] To assess central systolic blood pressure from peripheral blood pressure levels, 10 mm Hg was subtracted from the brachial systolic blood pressure values. When correlation analyses were performed, there was a strong and significant linear relationship between central blood pressure levels determined by the two methods ($r^2 = 0.94$; $r = 0.97$), with a mean difference of 0.30 ± 4.74 mm Hg (mean $+2$ s.d. $=$ 9.78 mm Hg; mean -2 s.d. $= -9.17$ mm Hg) in the Bland–Altman analysis (Figure 1). The correlation between central blood pressure levels obtained by tonometry and central blood pressure levels derived from peripheral blood pressure measures was further improved ($R^2 = 0.97$) when also considering heart rate values. Starting from 75 b.p.m., adding or subtracting 1 mm Hg to peripheral blood pressure for each 10 b.p.m. increase or decrease in heart rate, respectively, the difference between the two methods in estimating central systolic blood pressure was 0.75 ± 4.47 mm Hg (mean $+2$ s.d. $=$ 9.69 mm Hg; mean -2 s.d. $= -8.17$ Hg) in the Bland–Altman analysis.

In addition, when central systolic blood pressure values estimated by subtracting 10 mm Hg from the brachial systolic blood pressure were compared with the central systolic blood pressure directly measured in the ascending aorta with a standard invasive method, a significant and close correlation was observed between the two methods (Figure 2).

These data indicate that even the application of a simple mathematical formula to estimate central blood pressure values from peripheral measurements might be sufficient to obtain a good correlation with non-invasive (that is, obtained with a reference tonometric method) and invasive measures of central blood pressure.

VALIDATION OF DEVICE OR VALIDATION OF METHOD?

The example illustrated above clearly shows that any device for assessing central blood pressure put on the market can easily obtain a formal validation. Also instruments with no scientific basis may be validated, even if it has undergone to a rigorous protocol in an important and authoritative research center. Consequently, validation studies concerning instruments for assessing central blood pressure considering the outcome alone (that is, central systolic blood pressure value) risk either providing misleading results or certifying devices without any scientific basis.

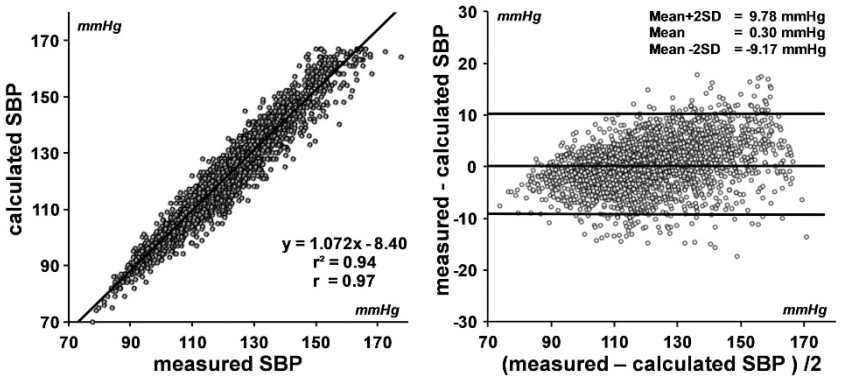

Figure 1 Correlation between central systolic blood pressure values calculated according to a mathematical formula using brachial pressure values and central systolic blood pressure values measured directly with a non-invasive validated method. Left panel: linear regression; right panel: Bland–Altman analysis. SBP, systolic blood pressure.

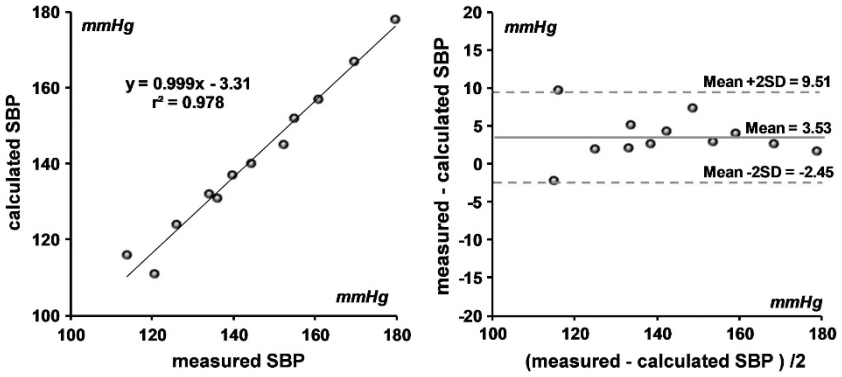

Figure 2 Correlations between central systolic blood pressure values were calculated according to a mathematical formula using brachial pressure values and central systolic blood pressure values in the ascending aorta recorded invasively. Left panel: linear regression; right panel: Bland–Altman analysis. SBP, systolic blood pressure.

Thus, validation studies should concentrate on validation of the method employed for non-invasive hemodynamic assessment rather than only consider quantitative variables (that is, central blood pressure levels). In brief, validation studies should consider important issues regarding the physical and physiological validity of the method employed by devices to record central blood pressure and central pressure waveforms.

Only after such an assessment, which must be accurate and without a shadow of doubt, of the reliability of the method we can finally validate the non-invasive device against a reference gold-standard invasive method, comparing the blood pressure values and the first harmonics of the waveforms recorded both invasively and non-invasively.

WHY WE NEED RELIABLE INSTRUMENTS

Pulse wave analysis and evaluation of central blood pressure values are currently considered as complementary diagnostic tests for hypertensive patients. Pulse wave analysis may also provide useful information for an indirect study of the myocardial function and cardiac work. Moreover, assessment of central blood pressure waveform, aortic distensibility and central blood pressure values may provide significant insight into the pathophysiological mechanisms involved in the pathogenesis of hypertension and other cardiovascular diseases. This knowledge might lead to a more personalized diagnostic and therapeutic approach to hypertensive and cardiovascular patients, increasing blood pressure control rates, preventing unnecessary treatment and drug side effects, and improving patient compliance to therapy.

Therefore, it is very important that central blood pressure waveform, aortic distensibility and central blood pressure values recorded non-invasively are reliable and that the parameters relative to the central arterial pressure waveform accurately reproduce those recorded in the ascending aorta.

CONFLICT OF INTEREST

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