Twenty-four hour ambulatory central blood pressure in adolescents and young adults: methodological issues

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The large number of studies involving paediatric and young populations confirms the increasing interest in methods to obtain reliable blood pressure (BP) values in youth. Awareness of the differences in the pathophysiology of BP regulation between young and adults is growing among physician involved in patients care and not only among researchers or hypertension specialists. A precise knowledge of these differences is essential for an accurate diagnostic approach and appropriate treatment. The elastic behaviour of the aorta and large arteries may cause a relevant difference between SBP in the peripheral muscular arteries compared with that in the ascending aorta. This phenomenon, known as BP amplification, is particularly prominent in the early life, characterized by high distensibility of the arterial wall.

The amplification phenomenon mainly depends on the relationship between forward and backward BP waves [1]. The earlier the return of the reflected waves into the ascending aorta and the superimposition between forward and backward BP waves, the lower the difference between the central and peripheral BP values. The amplification phenomenon is thus inversely related to arterial stiffness, which can be expressed as aortic pulse wave velocity (PWV). A high BP amplification can be found in isolated systolic hypertension, characterized by high SBP at the brachial artery level, with normal central (aortic) BP values. This condition is rather prevalent in males, in the first three decades of life, where it can reach up to 15% of patients [2]. Despite advances in knowledge, it is still uncertain whether knowing the degree of BP amplification and values of central BP in young people may be useful to refine the cardiovascular risk assessment, as it is in adults and in the elderly [3].

The differences in the pathophysiology of BP in young and in adults requires a different methodological approach in the measurement of BP in young patients. The selection of the most appropriate methodology in adolescents can be crucial, given the difficulties in defining a correct classification of BP with the only measurement of the office BP [4], and the considerable variability of short and long-term BP in this population [5]. Guidelines currently recommend the use of ambulatory BP monitoring in children and adolescents, considered its key role to exclude white coat or masked hypertension [3]. The clinical value of central BP measurement is still controversial. This is not surprising considered the wide range of tools claiming to measure central BP and the still unresolved issues in the methodology of central BP assessing. Some arterial tonometers record pulse wave directly at the common carotid artery level, as surrogate for central aortic pressure. Other devices estimate central BP by means of a transfer function, starting from the morphological analysis of the peripheral pulse waveform, recorded at the radial or brachial artery level. In these cases, the peripheral pressure curve is acquired by applanation tonometry or mechanotransducers. More recently, some automated oscillometric devices that provide an estimate of central BP have been proposed on the market. Central BP is obtained by transfer function, starting from the analysis of the waveform of the brachial volume impulse, obtained by holding cuff pressure at subdiastolic or suprasystolic levels for a few seconds, as for the Mobil-O-Graph device (IEM GmbH, Stolberg, Germany).

However, all the above methods, which estimate central BP through the analysis of carotid or peripheral pulse pressure (PP) curves, always require a calibration of pulse wave, starting from the pressure values recorded at brachial artery level by means of traditional validated sphygmomanometers. The calibration method strongly affects the accuracy of central BP measurement. Two calibration methods are generally used to calibrate the pulse waveform: the first uses brachial SBP and DBP, whereas the second calibrates to brachial mean and diastolic pressures. Calibrating with either of these two methods can produce significantly different estimations of central BP and provide different prognostic value for outcomes or association with organ damage [6]. Anyway, methodological issues of calibration were evaluated and discussed by analysing data on adult or elderly patients or with specific comorbidities, as chronic kidney disease. The evidence in young individuals

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of the additional value provided by central BP is limited and confined to office measurements.

In this context, the study by Ntineri *et al.* [7] in this issue of the *Journal of Hypertension*, addresses the issue of reliability of 24-h ambulatory central BP monitoring and related calibration methods in adolescents and young adults. A series of interesting considerations emerge from this study, which enrolled 136 young untreated patients, followed for suspected arterial hypertension, who were assessed for subclinical organ damage with evaluation of the left ventricular (LV) mass by echocardiography, intima–media thickness by carotid ultrasound and estimation of aortic stiffness by measuring the PWV. The primary stated objective of this study was to investigate the association of central ambulatory BP with organ damage. Central BP was estimated using Mobil-O-Graph device by calibrating the pulse wave using both SBP and DBP values (c1 method) or mean arterial pressure and DBP (c2 method).

A high difference in 24-h central SBP mean values was present between the two calibration methods (109 ± 9 mmHg in c1 vs. 130 ± 14 mmHg in c2). Similarly, using the same Mobil-O-Graph system, in KidCoreBP Study, involving 69 children aged 9.0 ± 4.4 years, undergoing clinically indicated aortic catheterization, Mynard *et al.* [8] found significant differences in central SBP between the two calibration methods (87 ± 14 mmHg in c1 vs. 101 ± 17 mmHg in c2). Analogous results were obtained by Weber *et al.* [9] on an adult population (118 ± 15 mmHg in c1 vs. 132 ± 19 mmHg in c2). All these studies confirm that the calibration method is a determining factor in the noninvasive estimate of central pressure.

Closely related to the systolic central BP values, the phenomenon of arterial pressure amplification also varies according to the calibration used. The study of Ntineri *et al.* [7] showed a positive SBP amplification of 14.2 mmHg in c1 (corresponding to a PP amplification of +43.2%), and a negative SBP amplification of −6.4 mmHg in c2 (corresponding to a PP amplification of −7.9%). These results agree with the study of Weber *et al.* [9] (PP amplification in c1 and c2 = +34 and −5%, respectively) and Mynard *et al.* [8] (PP amplification in c1 and c2 = +30 and −4%, respectively). However, the negative amplification provided by c2 method seems to be nonphysiological and seriously questions the methods involving a transfer function approach for central pressure waveform estimation starting from the analysis of the waveform of the brachial volume impulse generated by oscillometric devices. On the other hand, the KidCoreBP study [8], recently showed that these devices provide unreliable central BP values in children and adolescents. Thus, Mobil-O-Graph device significantly overestimate the central SBP in the comparison with invasive measurement, and this overestimation seems to be related to overestimation of brachial SBP by these devices.

As the estimate of the central BP provided by the Mobil-O-Graph is based on the analysis of the morphology of the PP curve, it is also interesting to evaluate the relationship between the form factor defined by the two calibration methods. The evaluation of the form factor represents a useful index relating to the pressure waveform. Form factor is defined by the ratio (mean BP − DBP)/PP, and is generally expressed as percentage. Considering the mean arterial pressure as constant throughout the arterial system, in the Ntineri's study [7] the mean value of the form factor was 61% in c1 and 39% in c2. However, a form factor value in ascending aorta of 61% is really unlikely. We have calculated the form factor on the integral of pressure waves invasively recorded in the ascending aorta on 64 consecutive patients (aged 65 ± 12 years) undergoing cardiac catheterization at our haemodynamic centre. The average of the form factor values ± SD was 39.6 ± 7.7%. In a large paediatric population (490 children aged 11.9 ± 3.2 years) in whom central BP was estimated by arterial tonometry, we found a central form factor of 43.6 ± 5.1% (data being published).

The crucial effect of calibration in the present study of Ntineri *et al.* [7] is evident in the stratification relating to organ damage, where central 24-h BP assessed by Mobil-O-Graph with c2 calibration provided better results than c1 or than peripheral, brachial BP. C2-calibrated central BP showed a good association with LV mass index and intima–media thickness. This association was stronger than peripheral SBP in adolescents but not in young adults. However, considering the relevant methodological concerns listed above, justified doubts arise as to the reliability of these results, which need to be confirmed with further studies.

These methodological issues are even more evident when we analyse the results concerning the relationship between central BP and PWV derived from the Mobil-O-Graph. A number of studies [10–13] have recently clearly shown how the aortic PWV estimated by the Mobil-O-Graph is not advisable in epidemiological study and in the evaluation of cardiovascular risk, as it is almost exclusively related to age and BP values. Indeed, also the Ntineri's study [7] shows an abnormal and amazing relationship between PWV and peripheral SBP ($r = 0.94$). In the presence of a limited age range, the SBP value assumes a decisive role in defining the value of the aortic PWV estimated by the Mobil-O-Graph. These results are similar to what highlighted in our recent study, involving 103 young adults (aged 38 ± 15 years), where we found that 98% of the aortic PWV values provided by the Mobil-O-Graph was justified by age and systolic pressure alone, according to the equation: PWV = age-squared/1000 + 0.038 × brachial SBP [12]. Based on these evidences, the results concerning the relationship between central BP and PWV should be ignored.

One of the most relevant suggestions from the present study proposed by Ntineri *et al.* [7] was to highlight how a 'one-fits-all' methodology for estimating central BP may not be appropriate. A personalized approach could be necessary to refine methodologies for central BP assessment. What has been observed in certain categories of patients may not be appropriate for selected subgroups of population, such as children, adolescents and young adults. Moreover, this study highlights the need to seriously address the problem of calibrating the peripheral pressure curve for the estimation of central BP. The use of indirect methods, deriving central BP from peripheral arteries by transfer function may be more subject to systematic errors, while local derivation of carotid BP by applanation tonometry with appropriate waveform calibration could adapt better to the single patient. On the contrary, these methods are difficult to propose in 24-h central BP monitoring. At

present, the use of central BP evaluation combined with ambulatory 24-h monitoring is a promising tool, but still confined to clinical research, due to lack of standardization, methodological issues and heterogeneous results regarding the real superiority compared with traditional peripheral BP measurements in the evaluation of cardiovascular risk [14,15]. Further studies aimed at solving these methodological issues could provide a more reliable BP measurement in every individual and define the clinical usefulness of central 24-h BP measurement.

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Conflicts of interest

There are no conflicts of interest.

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