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EDITORIAL

Blood pressure measurement and left ventricular mass: The difficult search for the best fit

Medición de la presión arterial y la masa ventricular izquierda: la difícil búsqueda del mejor ajuste

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Recent Guidelines of the European Society of Hypertension/European Society of Cardiology (ESH/ESC) stick to the clinical relevance of subclinical lesions in different organs, now called asymptomatic ''Hypertension Mediated Organ Damage, HMOD'',[1] as important intermediate markers in the cardiovascular (CV) continuum. All of them share the quality of influencing CV risk stratification in patients with hypertension, independently of traditional risk factors, including blood pressure (BP), thereby adding predictive value to risk tables. They include arterial stiffness, either as pulse pressure $\geq$ 60 mmHg in older people or pulse wave velocity > 10 m/s, left ventricular hypertrophy (LVH) determined by ECG or echocardiography, elevated albumin–creatinine ratio (microalbuminuria), moderate or severe chronic kidney disease (CKD) and ankle–brachial index < 0.9. Of note, compared to the Guidelines of 2013, increased carotid intima-media thickness has been removed from this list of HMOD. Moreover, advanced retinopathy, characterized as hemorrhages, exudates or papilloedema, previously defined as established CV disease, is now located in the list of HMOD, while the presence of significant plaque (i.e. $\geq$50% stenosis) on angiography or ultrasound has been upgraded into the category of established CV disease.

LVH plays an outstanding role among other HMOD in the management of CV diseases. It represents the most frequent HMOD in hypertensive patients from the very beginning of the natural history of hypertension.[2] Besides, although all of them are said to modify CV risk, only hypertensive LVH and CKD do appear unmistakably as direct determinants of high risk, together with a calculated 10-year SCORE of 5–10%, marked elevation of a single risk factor and diabetes mellitus. Nevertheless, while changes in CKD usually occur over a period of years, and mostly toward worsening, regression of LVH is common[3] and can already be observed after only six months. Therefore, management of LVH by choosing the right method to measure BP is nuclear to the treatment of hypertensive patients.

Clinical practice in the last century was based on office brachial BP measurements (OBBP), because this technique is noninvasive, low cost and ease to use. It is therefore not surprising that OBBP is still recommended for screening and diagnosis of hypertension. Nevertheless, there is growing evidence that out-of-office BP has a higher prognostic value of clinical CV outcomes, such as coronary morbid or fatal events and stroke, than OBBP, as shown not only in the general population, in old and young, in women and men, but also in treated and untreated hypertensive patients, in patients at high risk and in patients with CV or renal disease. That's why out-of-office BP measurement is now also recommended to base the diagnosis of hypertension at the

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same level as office BP if it is logistically and economically feasible.

Two different out-of-office methods are nowadays available: home BP monitoring (HBPM) and ambulatory BP monitoring (ABPM). Their prognostic significance is similar and several meta-analyses of prospective studies in the general population, in primary care and in hypertensive patients, indicate that the prediction of CV morbidity and mortality is significantly better with out-of-office BP than with office BP. Head-to-head studies in which both HBPM and ABPM were performed indicate that HBPM is at least as well correlated with HMOD as is ABPM.[4] Furthermore, after adjustment for age and gender the predictive value of both measurements are comparable.[5] HBPM is cheaper than HBPM, more widely available, easy to be repeated and offers measurements over extended period of times. On the other hand, records during day-to-day activities and sleep are outside the range of HBPM, but can be easily provided by ABPM.

Another step forward in improving the measurement of BP was the development in recent years of various techniques that allow estimating aortic BP, also called central BP by means of the analysis of peripheral waveforms using special algorithms. Systolic pressures are lower in central arteries than in the periphery, because of the physiological phenomenon of pulse wave amplification, leading to the so-called ''amplification pressure''. The anatomical proximity of the aorta is expected to better reflect the hemodynamic load on the heart and large arteries than peripheral BP measured at the brachial artery, especially in the younger and middle age range. It is now possible to measure central pressure noninvasively and accurately, as well as to determine normal and reference values.[6] Furthermore, a differential effect of antihypertensive drugs on central compared with brachial BP has been postulated and one meta-analysis has compared the predictive value of central BP versus peripheral BP. In the latter, Vlachopoulos et al.[7] analyzed 11 longitudinal studies that had employed measures of central hemodynamics, including globally 5,648 subjects for a mean follow-up of 45 months. The age- and risk-factor-adjusted pooled relative risk of total CV events was 1.088 (95% CI 1.040–1.139) for a 10 mmHg increase of central systolic pressure, corresponding to a risk increase of 8.8%, and 1.137 (95% CI 1.063–1.215) for a 10 mmHg increase of central pulse pressure with a risk increase of 13.7%. However, when comparing the predictive ability between central and peripheral BP, central pulse pressure was associated with a marginally but not significantly higher relative risk of clinical events than brachial pulse pressure [1.318 (95% CI 1.221–1.423) vs. 1.188 (95% CI 1.104–1.280), respectively, $p = 0.057$], while the risk estimates for central systolic BP and brachial systolic BP were not different [1.236 (95% CI 1.128–1.354) vs. 1.204 (95% CI 1.104–1.313), $p = 0.62$]. To which extent central BP measurement increases the prognostic value of conventional office BP remains unclear.

In this context, we have read with great interest the article by Aparicio et al.[8] included in this issue of Hipertensión y Riesgo Vascular, comparing the association of five methods of BP measurement with left ventricular mass (LVM) in 824 treated and 123 untreated patients who attended a specialized hypertension center. BP was assessed by up to three office-based BP measurements, (1) conventional brachial BP as reported by the referring physicians, (2) central tonometric BP and (3) the standardized BP method taken in the office before the tonometric reading, and also by two other out-of-office methods, (4) home BP (HBPM) and (5) ambulatory monitoring (ABPM). As expected, all of the blood pressure methods were significantly associated with LVM in treated hypertensive patients, although only HBPM and ABPM correlated with LVM in untreated patients. However, the comparison of correlation coefficients between the five methods did not show significant differences in the degree of association with left ventricular mass, with the exception of office versus home systolic blood pressure in the untreated group. In treated hypertensives, the highest correlation coefficient with LVM was obtained with ABPM, while HBPM correlated best with LVM in untreated participants, although the small number of patients strongly limits the validity of this result. It would have been interesting to distinguish between day and night-time ambulatory BP measurements, and no data are given to compare sustained, masked and white-coat hypertension, given the recent data supporting the higher predictive value of masked hypertension versus sustained HTN.[9] Summing up, this study performed in real-life, daily practice adds to the evidence that out-of-office BP measurements represent a better tool to manage hypertensive patients accounting for cardiac target organ damage than office measurements.

One fundamental, technical aspect of central BP measurement deserves special attention. The authors found that office central systolic BP did not perform better than standardized brachial systolic BP. As described in Methods, the transfer function to calculate central BP was calibrated according to the systolic and the diastolic BP components. It is crucial to remember that both, aortic pressure estimation and the absolute systolic pressure amplification expressed as millimeters of mercury (mmHg), depend to a great extent on the calibration either on systolic/diastolic pressures (usually called C1 calibration) or on mean/diastolic BP (C2 calibration). As brachial cuff-measured BP is generally used as the calibration standard, inaccurate peripheral assessment of BP translates into a nuclear problem in central BP estimation. In other words, systematic errors in cuff-measured BP lead unavoidably to under or overestimation of aortic BP. On the contrary, when invasively measured BP is used for calibration, both calibration methods C1 and C2 provide identical results. Beyond academic disputations, differences in calibration methods have been shown to determine associations with clinical outcomes.[10]

Estimation of central BP is therefore intimately connected to the accurate and precise measurement of peripheral BP. And recent research does not endorse common BP measurement methods. On the contrary, accuracy standards for BP devices are poor and should be improved. Sharman et al.[11] meta-analyzed a total of 74 studies that measured intra-arterial aortic BP, intra-arterial brachial BP and cuff BP in globally 3073 participants. Intra-arterial brachial systolic blood pressure (SBP) was higher than aortic values (8.0 mm Hg; 95% CI: 5.9–10.1 mm Hg; $p < 0.0001$) and intra-arterial brachial diastolic BP was lower than aortic values (1.0 mm Hg; 95% CI: 2.0–0.1 mm Hg; $p = 0.038$). Furthermore, cuff BP underestimated intra-arterial brachial SBP (5.7 mm Hg; 95% CI: 8.0–3.5 mm Hg; $p < 0.0001$), but overestimated intra-arterial diastolic BP (5.5 mm Hg; 95%

CI: 3.5–7.5 mm Hg; $p < 0.0001$), resulting in an unexpected similarity between cuff-brachial BP and intra-aortic systolic BP. To add even more confusion to these discrepancies, the authors found that concordance between intra-arterial brachial BP and cuff BP was strongly dependent on the HTN stage, ranging from 50% in prehypertension to 80% in HTN stage 2 (according to the classification of JNC 7).

Should we conclude that the great amount of evidence collected over the last 50 years with easy measurable parameters like systolic and diastolic cuff-brachial BP are a flaw? The answer is a clear ''no''. It is a matter of fact that management of CV diseases has historically been a great success relying on cuff BP measurements, even though systematic errors, a considerable variability and inaccuracy are inherent to this method. Nevertheless, the next question to be answered is which possibilities there are to improve management of hypertension, once its weak points have been recognized.

In the last decade, noninvasive technologies have been developed allowing for estimating central BP on dynamic, ambulatory conditions. Aparicio et al. mention in the Discussion recent advances supporting the hypothesis that 24-h ambulatory aortic is closer associated to LVH than ambulatory brachial BP monitoring. In a multicenter prospective study comprising 289 patients from seven different countries, Weber et al.[12] compared office brachial BP with ambulatory brachial and ambulatory central BP, using an oscillometric cuff-based device and the C2 calibration. The highest correlation coefficients were found for ambulatory central BP, followed by ambulatory brachial and office BP (0.47, 0.41, and 0.29, respectively) as well as larger areas under the curve for the prediction of LVH (0.666, 0.635, and 0.618, respectively). These results are in line with other studies suggesting superiority of aortic systolic BP versus brachial systolic BP to predict subclinical organ damage.[13] Yet, one recent study[14] showed no difference between ambulatory central and ambulatory brachial BP measurements, when defining target organ damage as either the presence or absence of at least one organ (cardiac, renal, or aortic stiffness), a fact that considerably limits the comparability of these studies.

Further evidence is needed to answer this open challenge that could potentially change conventional clinical practice. However, at least three important obstacles lurk on the long run of any process of transition. Firstly, diagnostic and therapeutic inertia exert a deleterious effect on any proposal of improvement if its magnitude remains single-digit. Why should traditional management of hypertension be modified, if the increase in diagnostic accuracy is only small? And central hemodynamics, if any, is not expected to induce astonishingly large improvements. Secondly, even if the postulated changes were true, it would be far from easy to bring about a clear-cut demonstration. A comparison with ABPM clarifies this obstacle. The evidence in favor of ABPM versus office BP is overwhelming, and yet, no single randomized study has scientifically demonstrated its superiority in therapeutic terms, while only one study, to the best of our knowledge, is still being carried out. And thirdly, without a broad, public-health involving strategy, central hemodynamics could remain an isolated isle in a remote world of a few clinicians. Central BP, together with pulse wave velocity, augmentation pressure and augmentation index, represent different aspects of arterial stiffness and central hemodynamics. Arterial stiffness entered the ESH/ESC Guidelines 2007, nevertheless, it remains unknown to the vast majority of physicians in daily clinical practice. And in spite of growing evidence of its usefulness as a biomarker, not even one Autonomous Community in Spain includes the term ''arterial stiffness'' among hypertension-associated damage in the software of the Public Health Administrations.

Fortunately, there is also good news that could help spreading the concept of central hemodynamics. Arterial stiffness could predict progression to hypertension in normotensive young adults[15] and serve as an attractive tool for primordial prevention of hypertension. Besides, community pharmacies in Spain have been involved in measuring central hemodynamics on a large scale showing their capability to screen the population for stiffness and hypertension.[16]

More studies are needed to decide which is the best method to measure BP, to diagnose hypertension, to detect target organ damage and to guide pharmacological treatment. Meanwhile, repeated office BP measurements and/or out-of-office BP measurement with ABPM and/or HBPM remain the golden standard.

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