Ambulatory Blood Pressure Monitoring Is Ready to Replace Clinic Blood Pressure in the Diagnosis of Hypertension

Con Side of the Argument

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The San Francisco experience with Perloff and Sokolow was the starting point for the clinical application of ambulatory blood pressure (ABP) measurement. Using a semiautomatic device, the superiority of ABP to office measurement was demonstrated in the relationship with hypertension-induced organ damage[1] and in the risk for cardiovascular events.[2] This seminal study impelled an issue with the largest production and impact in the field of hypertension in recent decades, boosting research and having an enormous influence on daily clinical practice. Initially restricted to specialized clinics, ABP monitoring (ABPM) has largely expanded to primary care in many countries. Similarly, scientific production has increased extraordinarily. The number of articles that include 24-hour ABPM in the title or abstract has grown exponentially from the beginning of the 1990s to ≈600 articles per year.

Fifty years on from the pioneering work, ABPM is now considered a keystone in hypertension management. Several guidelines and consensus have been published with recommendations for the monitoring process, reference values, and clinical and research use.[3–6] Recently, the ESH-ESC 2013 guidelines[7] upgraded the importance of out-of-office BP measurement for hypertension management, and the NICE guidelines[8] recommend that, "If the clinic BP is 140/90 mm Hg or higher, offer ABPM to confirm the diagnosis of HTN." Likewise, the Canadian Education Program in Hypertension[9] recommended, "At visit 2 for the assessment of hypertension, patients without macrovascular target organ damage, diabetes mellitus, or CKD but with BP lower than 180/110 mm Hg, should undergo further evaluation using repeated office BP, ABPM or home monitoring." Moreover, a recent full document[10] and a summary[11] from the European Working Group on BP Monitoring updated the information available and emphasized fundamentals and recommendations. More recent guidelines in hypertension management from the American Heart Association[12] and from the Joint National Committee 8[13] did not include comments on ABPM, although the American Heart Association[14] and the American Society of Hypertension[15] had previously released specific documents about ABP.

Despite the advances and the extensive literature on the issue, as well as the widespread clinical use, the solution to relevant questions is still pending before ABP can replace office BP for the diagnosis and management of hypertension. Likewise, self-BP measurement allows for a wider use of out-of-office BP values at the time of diagnosis and even more for the follow-up of patients. The use of self-BP measurement, however, has the same shortage of relevant information as ABPM. In this article, we point out the limitations of ABP values and derived parameters in prognostic studies, the uncertainties in the classification of patients, and the relevant unmet needs. A final comment about the availability is also included.

Con 1: Limitation of ABP Values in Prognostic Studies

The average of 24-hour, awake or nocturnal BP measured with ABPM has a better relationship with the presence of hypertension-induced organ damage, left ventricular hypertrophy,[16,17] urinary albumin excretion,[17–19] estimated glomerular filtration rate,[20] and signs of cerebral small vessel disease[21] when compared with the office BP counterparts. Superiority

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of these ABPM to office BP values is largely reduced or even disappears with automated/prolonged BP measurements. The superiority of ambulatory to office BP in assessing the risk to develop cardiovascular and renal events has been studied in a wide spectrum of conditions and populations. In the general population,[22] hypertension,[23–25] isolated systolic hypertension,[26] resistant hypertension,[27] diabetes mellitus,[28] chronic kidney disease,[29] hemodialysis,[30] and post-transplant,[31] a large number of studies are in agreement with the superiority of ABP.[32,33] Likewise, a better prognostic value has been claimed for nocturnal BP in comparison with the active BP period or for 24 hours, with nocturnal BP being the value that best fits with the risk of cardiovascular and renal events. The better relationship with organ damage and the prognostic superiority of ABP is often inferred from the fact that mean BP values have a steeper relationship with cardiovascular events than BP values measured in the clinical setting, but this is in part a result of the narrower distribution of ambulatory values when compared with clinical BP values,[34] even lower for nocturnal than for diurnal. Whether or not the reason for this apparent superiority can be explained by mathematical reasoning is a controversial issue.

All of these studies have obtained positive results with only 1 monitoring at the beginning of the study period, whereas the outcomes considered—total or cardiovascular mortality, myocardial infarction, stroke, end-stage renal disease—occur years later. No information on the BP values during the study period has been given. It is an important limitation to confirming that ambulatory BP is superior to its office counterpart, principally when the necessity for antihypertensive treatment and BP goals are guided by office BP values. Furthermore, the changes in office and ambulatory BP are not parallel and differ greatly.[35]

Few studies have focused on the development of organ damage or on the occurrence of events that have been published with >1 monitoring. In all of them, BP goals were established for office BP and not for ambulatory. Mancia et al[36] published the first evidence that ABP may be clinically superior to traditional BP measurements in 206 hypertensive subjects with left ventricular hypertrophy treated during 12 months in the Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation (SAMPLE) study. The left ventricular mass index reduction was not related to the reduction in clinic BP, but it was to the reduction in the average of 24-hour BP. Treatment-induced reduction in average daytime and night-time BPs correlated with left ventricular mass index changes as strongly as 24-hour BP. Lurbe et al,[37] in patients with type 1 diabetes mellitus, used ABPM to assess BP at the initial evaluation and about 2 years later, at which time all subjects had normal urinary albumin excretion. A persistent increase in systolic BP during sleep preceded the development of microalbuminuria. In those subjects whose BP during sleep decreased normally, the progression from normal albumin excretion to microalbuminuria appeared to be less likely. Zanchetti et al,[38] in the European Lacidipine Study on Atherosclerosis, a randomized, double-blind 4-year trial of the effect of lacidipine or atenolol on echographic carotid intima-media thickness, performed ABPM yearly. In a multivariable linear regression model, mean on-treatment of both clinic and 24-hour systolic BP was associated with end-of-treatment carotid intima-media thickness and with cardiovascular outcomes, although it was unpowered.[39]

Con 2: Derived Parameters Other Than the BP Averages Have Limited Value

In clinical practice, the average of 24-hour, diurnal, or nocturnal BPs is today the recommended parameter for defining hypertension status and for monitoring the BP-lowering effect of antihypertensive agents. Apart from the average of BP values, other derived parameters from ABPM have been considered to be relevant such as variability,[40] day/night ratio,[41] and early morning surge.[42]

Increased short-term and long-term BP variability are associated with the development, progression, and severity of cardiac, vascular, and renal damage and with an increased risk of cardiovascular events and mortality.[43] The potential clinical value of these derived parameters, however, are still to be confirmed because the value of stratifying risk has not been proven[44] and are considered a matter for research until more evidence is obtained.[7]

Abnormalities in the circadian profile, the so-called nondipping pattern, have been described as being associated with different clinical conditions and produced by different mechanisms, which include barroreflex or autonomic dysfunction, relative nocturnal volume overload, and abnormal sodium handling.[45] A blunted decline of the physiological BP reduction has been associated with the presence of organ damage[46,47] and with a worse prognosis for cardiovascular[48] and renal disease.[49] A particular period of circadian variability is the early morning surge. This has also been linked to vascular damage throughout the circulation, which may involve the myocardium, large arteries, and other target organs.[50] An increased risk for cardiovascular events, such as myocardial infarction and stroke, especially in the presence of the comorbidities of diabetes mellitus, as well as cardiac and renal disease, has also been described.[51] The major drawbacks for these parameters, circadian variability and early morning surge, are the poor reproducibility[52] and the fact that the day/night ratio and the early morning surge per se depend on both awake and sleep BP values. There is not enough evidence to support giving excessive relevance to the fact that changes in the patterns can influence the success of the antihypertensive treatment.[7]

Besides the BP-derived parameters, monitors added modules to capture signals at the same time as BP. The beat-to-beat ECG,[53] the assessment of pulse wave velocity, augmentation index, and central BP are some examples of this. The ECG signal[53] allows for the assessment of the relationship between BP changes and myocardial ischemia or arrhythmia. The Qkd index[54] to estimate pulse wave velocity, the augmentation index to estimate the reflecting wave, central BP, and pulse wave velocity[55–57] are measured intermittently during 24 hours. Although it was claimed that these parameters correlate better with organ damage when measured for 24 hours, compared with office measurements,[57,58] the potential clinical utility has not been tested yet.

Con 3: Uncertainties in Classification of Patients

It is worthy to mention here the discrepancies between office and ambulatory BP at the time to diagnose or to assess BP control in a given patient, the so-called white-coat or masked hypertension. Measurements of BP during regular living

conditions and during nocturnal rest, out of the clinical environment, avoid the alarm reaction, or the white-coat reaction.[59,60] Persistent alarm reaction introduces a bias at the time of diagnosing hypertension and stratifying risk. The true meaning of the alarm reaction has been discussed since it was first described, but the increased diagnosis of white-coat hypertension can consider normal subjects who can get benefit from early antihypertensive treatment. More recently recognized is the opposite phenomenon, masked hypertension, elevated daytime, or awake ambulatory BP with normal office BP.[61] In this case, a higher reactivity during the regular activities of daily life seems to be a frontrunner of progression to hypertension and is usually associated with early signs of organ damage.[62,63]

Stratification of patients based on these discrepancies between office and ambulatory BP values, however, depends largely on the criteria used to define hypertension in ambulatory BP and on the day-to-day intraindividual differences. First, classifying patients can differ not only if the criteria for defining hypertension in ambulatory BP use the average of 24-hour or the awake period, but also when different BP thresholds are used. The absence of grounded values for defining hypertension (see below) introduces uncertainties and potential bias when it comes to classifying subjects.

Con 4: Relevant Unmet Needs

Despite all the advances in ambulatory BP that have been made during the past 50 years, pivotal information not only remains unanswered but also, to our knowledge, a plan of action to obtain it is lacking. This is in sharp contrast with the large number of trials in which office BP provides evidence about a threshold to define hypertension as well as a goal to be achieved during antihypertensive treatment in the general hypertensive population as well as in specific conditions.[7] The absence of a definition of hypertension, the lack of information about the appropriate goals, and, as a result, the lack of evidence that ambulatory BP-guided therapy can obtain greater reductions in morbidity and mortality than office BP-guided treatment are unmet needs in ambulatory BP.

Con 4a: Absence of Grounded BP Reference Values to Define Hypertension

Sir Geoffrey Rose defined hypertension in 1971 as "that BP level above which detection and treatment do more good than harm."[64] In agreement with this, thresholds to define hypertension have been reduced until the values that are accepted today, thanks to studies that support the new thresholds. In contrast, the definition of hypertension using ambulatory BP values has been made using different approaches, but never the gold standard defined by Rose. In fact, the thresholds for defining hypertension have been derived from the percentiles of the general population and from correspondence with the office BP counterpart defined by the generally accepted 140/90 mm Hg or by the values obtained in population-based studies. A clever approach to defining the threshold was made by the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes Investigators research cooperation. From this database, ambulatory BP thresholds were determined as those that yielded a 10-year cardiovascular risk similar to those associated with optimal, normal, and hypertension in office measurements.[65] That notwithstanding, it is important to remember that the BP values were measured only at the beginning of the studies and not during the follow-up.

If we assume that a definition using ambulatory BP gives a better risk stratification, this was not the case in the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. The fitting of individual data to a Cox proportional hazard model used to quantify the 11-year risk of cardiovascular mortality was equally good for ambulatory and office systolic BP; there was no superiority of the ambulatory over the office values.[66] Receiver operating curves for the prediction of cardiovascular events or all-cause mortality were largely superimposable for clinic and ambulatory BPs with only a small and not invariably significant increase in the area under the curve when office BP was used along with ABP.[67] The PAMELA study does not support the contention that ABP adds substantially to the predictive value of clinic BP. Similar approaches to the PAMELA study to estimate the potential superiority of ambulatory values over the office values have not been made in other long-term outcome studies, although they should be encouraged. Other methods of statistical analysis, including net reclassification improvement and the integrative discrimination index, can better define the discriminative power of ambulatory BP as a diagnostic tool and should be applied in the future.[68]

Con 4b: Absence of Grounded BP Goals

Likewise, the out-of-office BP goals during antihypertensive treatment have not been established up to now, because only 2 studies using them as a target have been conducted. The first one, Antihypertensive Treatment Based on Conventional or Ambulatory Blood Pressure measurement,[69] which searched for differences in left ventricular mass, was conducted >15 years ago in 419 subjects who were followed up for 6 months. The study reported that the adjustment of antihypertensive treatment based on ambulatory monitoring and the average of daytime BP instead of conventional BP measurement at the physician's office led to less intensive drug treatment with preservation of BP control, general well-being, and an inhibition of left ventricular enlargement, but it did not reduce the cost of antihypertensive treatment. An analysis of cost-effectiveness using a theoretical model concluded that the overall cost of treatment and years of drug treatment would be reduced.[70]

The Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients trial[71] examined the efficacy of intensified BP control in delaying the progression of renal disease among children with various types of underlying kidney disorders. In the trial, the BP goals were set by an average of 24-hour ABPM assessed at 6-month intervals. Subjects were randomly assigned to either a reduction in conventional BP, between 50th to 90th percentiles, or to an intensified target below the 50th percentile. In the intensified BP control, with target 24-hour BP values in the low range of normal, the mean BP decreased 3 mm Hg more than those for the conventional group, which conferred a substantial benefit with respect to

renal function. When the differences in office BP were analyzed, the differences between the intensified and the conventional group were 2 mm Hg for systolic and 1 mm Hg for diastolic BP.

With the scarce information available now, it is impossible to make decisions or release recommendations other than that of reducing BP below the consensus-defined thresholds of hypertension.

Con 4c: Absence of Grounded Evidences of the Superiority to Target ABPM on Cardiovascular or Renal Outcomes

Whether or not ambulatory BP-guided therapy can obtain greater reductions in morbidity and mortality than office BP-guided treatment remains to be assessed. The studies that compared target ambulatory or office BP addressed the need for antihypertensive drugs and the achieved BP values, but not the impact on outcomes.[72,73]

Con 5: ABPM Is not Available Widespread

Finally, availability for routine use of ABPM has important constraints. From the initial semiautomatic monitors, which were operated by the patient, automatic devices were developed to measure BP in ambulatory conditions.[74] Innovations reduced monitor size and noise, aiding portability and tolerability. In parallel, better algorithms in oscillometric devices[75,76] contributed to improving the accuracy and reliability of BP readings. Validation protocols from the British Hypertension Society, Association for the Advancement of Medical Instrumentation, International Standards Organization, and European Society for Hypertension International Protocol (Version 2)[77] facilitated the selection of the monitors with the best algorithms. Likewise, validation protocols identified differences in the degree of accuracy when used in adults, elderly, pregnant women, and children because of differences in vascular elasticity and pulse amplitude. Recommendations based on the results of the validation process were given to minimize erroneous BP values.[78]

Despite the existence of multiple validated monitors, their cost is still high, requiring computer assistance to preset the monitoring and to retrieve the information. In addition, the procedure is time-consuming and requires some level of expertise to analyze the report, despite there now being computer-generated reports that reduce the time needed for interpretation and allow for availability to a wider public even in pharmacies.[79] Although the availability is increasing in developed countries, it is still low when compared with the high prevalence of hypertension mainly in developing countries, in which high BP accounts for a high burden of cardiovascular disease.

Conclusions

In conclusion, knowledge on ambulatory BP has provided a large weight of experience that seems to support the superiority of ambulatory to office BP. The real impact of this superiority, however, should be tested in the coming years. The combined efforts of health authorities and scientific organizations are required to plan studies that answer the following key question: Is time to replace office BP with ABP? The answer in our opinion is not yet, but it may be.

Disclosures

None.

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Response to Ambulatory Blood Pressure Monitoring Is Ready to Replace Clinic Blood Pressure in the Diagnosis of Hypertension: Con Side of the Argument

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The superiority of ambulatory blood pressure measurements (ABPM) over clinic BP is undisputed and acknowledged by both articles in the debate. The criticism raised that outcome studies only obtained measurements at the beginning of the study is true but not actually relevant in a head-to-head comparison with techniques (Con 1). The value of ABPM is not only higher resolution from multiple measurements but also the inclusion of nocturnal period, which cannot be replicated in the clinic. Indeed, the recent study of Niiranen et al[1] found that neither clinic nor home measurements came close to matching APBM for prognostic value and really ends this particular debate. The alleged limitations of derived ABPM parameters are not relevant to the discussion (Con 2). The uncertainty of patient classification (Con 3) actually lies in the poor ability of clinic BP to diagnose a large portion of the population correctly. This is largely eliminated by ABPM. There is widespread agreement on the definition of hypertension by ABPM (Con 4) as detailed in Table 2 of the Pro argument. These were defined by calculated equivalence to clinic BP[2] and confirmed in large outcome studies.[3] The clear benefits of guiding treatment with ABPM have been outlined in both articles as is the reduction in cost of treatment. This is not a negative (Con 4). Far more comprehensive cost benefit analysis now clearly favors ABPM. Finally, the availability of ABPM (Con 5) is rapidly increasing, costs are diminishing, and less training is required because of technological advances. Given the overwhelming evidence in favor of ABPM, we may well be negligent in not recommending it now for diagnosis and management of hypertension.

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