

Review Article

Ambulatory Blood Pressure Monitoring in Resistant Hypertension

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ABPM constitutes a valuable tool in the diagnosis of RH. The identification of white coat RH and masked hypertension (which may fulfill or not the definition of RH) is of great importance in the clinical management of such patients. Moreover, the various ABPM components such as average BP values, circadian BP variability patterns, and ambulatory BP-derived indices, such as ambulatory arterial stiffness index (AASI), add significantly to the risk stratification of RH. Lastly, ABPM may indicate the need for implementation of specific therapeutic strategies, such as chronotherapy, that is, administration-time dependent therapy, and the evaluation of their efficacy.

1. Introduction

Ambulatory blood pressure monitoring (ABPM) is the method of obtaining automated brachial blood pressure (BP) measurements at fixed time intervals, during a 24-hour period away from a medical environment. This represents a more “realistic” approach to BP assessment since it involves BP measurement during the usual daily activities and sleep. In this sense, the overall haemodynamic load and BP variability is more accurately estimated. Numerous studies have shown that ambulatory BP compared to office BP is more reproducible and superior in predicting target organ damage and incidence of cardiovascular events in both the general hypertensive population and in subjects with chronic kidney disease [1, 2]. All these advantages of ambulatory BP in comparison to office BP, along with the ability to identify the white coat phenomenon, that is, the combination of increased office BP with normal ambulatory BP, and masked hypertension, that is, the combination of normal office BP with increased ambulatory BP, resulted in the transition of ABPM from a research tool to a clinical modality.

The indications for ABPM in the clinical management of hypertensives include among others the resistance to

treatment [3]. This has been defined as BP above goal despite the use of three agents of different classes in optimal doses, ideally including a diuretic. More recently hypertension controlled with four or more agents has been proposed to be included in the spectrum of resistant hypertension [4]. Although the prognosis of resistant hypertension (RH) is inadequately substantiated in the literature due to lack of sufficiently powered studies, there is plenty of evidence relating target organ damage and cardiovascular outcomes to BP levels. Uncontrolled BP along with a clustering of other risk factors is a harbinger of poor outcome in RH. Consequently, ABPM has implications in both the diagnosis and management of RH.

2. ABPM As a Tool for the Diagnosis of Resistant Hypertension

One of the crucial points in the identification of RH as a unique hypertension-related phenomenon that warrants special management is the distinction of true RH from “pseudoresistance” [3]. The latter term is used to describe clinical situations with increased BP readings because of

improper BP measurement technique, heavily calcified arteries, white coat effect, and lack of compliance to the prescribed medication. White coat RH, a phenomenon that is characterized by elevated office BP but normal ambulatory and home BP [2] ranges from 25 to over 50% in subjects with apparent resistance to treatment [5–7].

Muxfeldt et al., in a cohort of 286 hypertensive subjects with uncontrolled BP, found that 43.7% had white coat RH, (office BP > 140/90 mmHg and daytime BP < 135/85 mmHg) and less target organ damage compared to the true resistant hypertensives [6]. In support, Pierdomenico et al. [7] in a cohort of 742 treated hypertensive subjects, 426 apparently responders and 276 apparently resistant, found that 126 subjects (29.5% of the apparently responders) had masked hypertension and 146 (52.8% of the apparent resistant) had white coat RH. In the same study, in the follow-up period cardiovascular risk was higher in masked hypertensives (masked versus responder hypertensives, relative risk (RR) 2.28, 95% confidence interval (CI) 1.1–4.7, $P < .05$) and in true resistant hypertensives (true resistant versus responder hypertensives, RR 2.94, 95% CI 1.02–8.41, $P < .05$) [7]. According to the above, a significant proportion of treated subjects with apparently controlled hypertension may actually “mask” their poor response to treatment and some of them could possibly be classified as subjects with resistant hypertension. Therefore, ABPM identifies patients with white coat RH or masked hypertension contributing to avoiding overtreatment in the first case and achieving optimal management in the second one.

Regarding BP measurement at home and at the office, the established guidelines are not always followed resulting in false BP readings [8]. This cause of pseudoresistance could be identified with ABPM usage.

Consequently, the physician having confirmed the adherence to the prescribed therapy that includes three antihypertensive agents at full doses, including a diuretic, should use ABPM in order to label the patient as truly resistant hypertensive [9].

3. ABPM Characteristics of Resistant Hypertensives

Since ABPM is a fundamental tool to differentiate true RH from white-coat RH, it has been widely used in the identification of the BP pattern that characterizes patients with RH. Muxfeldt et al. demonstrated that subjects with true RH compared to white coat RH had lower nocturnal systolic BP reductions (6.4 ± 8.8 versus 9.8 ± 7.5 mmHg, $P = .0004$), lower nocturnal diastolic BP (10.4 ± 9.6 versus 13.6 ± 9.2 mmHg, $P = .001$), and a higher percentage of nondippers (i.e., subjects nighttime BP fall <10% of the corresponding daytime BP values) (68.7% versus 49.6%, $P = .001$) [6]. Similarly Friedman and Logan showed that the prevalence of nondipping among normotensive, controlled hypertensive, and resistant hypertensive subjects was 25.0%, 42.3%, and 61.5%, respectively, ($P = .006$) [10]. It should be emphasized that in terms of pathophysiology, both RH

and nondipping status have been linked to sympathetic overactivity, subclinical inflammation, and volume overload [11–14]. Furthermore, the failure of the once daily administration of antihypertensive drugs to provide 24-hour coverage has been identified as a cause of high nighttime BP, nondipping pattern and true RH [15].

By definition, subjects with true RH compared to those with white-coat effect present significantly higher ambulatory BP. Apart from this, certain studies demonstrate that patients with true RH have also increased ambulatory pulse pressure in comparison with those with white coat RH [6, 16]. Interestingly ambulatory 24-hour, daytime, and nighttime heart rate is higher in true resistant hypertensives, supporting the notion that increased sympathetic activation may be present in true RH [16].

4. ABPM and Cardiovascular Prognosis in RH

Although it is well known that the risk for cardiovascular hard end points in hypertension disease rises as the BP levels rise [17], there is a lack of evidence on the cardiovascular prognosis of RH. There is one study demonstrating the higher risk of patients with true RH compared to those with white-coat RH for fatal and nonfatal cardiovascular events [7]. On the other hand, there are studies evaluating the prognostic role of ABPM and its indices in patients with RH, highlighting its significance in the clinical management. In particular, Salles et al. in a cohort of 556 subjects with resistant hypertension demonstrated that 24-hour (HR: 1.32; 95% CI: 1.08–1.60; $P < .01$), daytime (HR: 1.26; 95% CI: 1.04–1.53; $P < .005$), and nighttime systolic BP (HR: 1.38; 95% CI: 1.13–1.68; $P < .01$), 24-hour (HR: 1.33; 95% CI: 1.06–1.66; $P < .01$), daytime (HR: 1.31; 95% CI: 1.05–1.63; $P < .01$), and nighttime (HR: 1.36; 95% CI: 1.10–1.69; $P < .05$) diastolic BP, and 24-hour (HR: 1.22; 95% CI: 1.00–1.48; $P < .01$) and nighttime (HR: 1.27; 95% CI: 1.04–1.55; $P < .01$) pulse pressure were independent predictors of fatal and nonfatal cardiovascular events and of cardiovascular and total mortality irrespectively of the office BP values [18]. Of note, there was no difference between systolic and diastolic BP, while pulse pressure was a weaker predictor and nighttime BP was superior to daytime BP [18].

Similarly Redon et al. exhibited that in 86 subjects with RH daytime diastolic BP predicted cardiovascular events (lower tertile versus higher tertile of daytime diastolic BP; RR: 6.42; 95% CI: 1.39–29.7; $P = .017$), while office BP had no prognostic significance [19].

Concerning the prognostic information of nondipping pattern in RH, Muxfeldt et al. demonstrated that, in a cohort of 556 subjects with RH, BP nondipping predicted a composite end point of fatal and nonfatal cardiovascular events, cardiovascular and total mortality (HR: 1.74; 95% CI: 1.12–2.71, HR: 2.31; 95% CI: 1.09–4.92, HR: 1.67; 95% CI: 0.95–2.94, resp.) above and beyond other traditional cardiovascular risk factors and mean ambulatory BP levels [20]. However, these results were not confirmed in other studies [21].

Although there are scarce data on the comparative value of the aforementioned indices derived from ABPM as

potential prognostic markers in RH, in a study of Magnanini et al. in women with RH, uncontrolled daytime BP was the stronger independent risk factor (RR: 1.67; 95% CI 1.00–2.78) [21].

Adding to the cluster of components of ABPM that carry valuable prognostic information, ambulatory arterial stiffness index (AASI), which has been defined as the regression slope of diastolic on systolic BP [22], emerges as a potential predictor of cardiovascular morbidity and mortality in RH (HR: 1.46; 95% CI: 1.12–1.92), after adjustment for traditional risk factors and other ABPM parameters [23].

5. Association of ABPM Components with Target Organ Damage in RH

ABPM can be useful as the components derived from it have been associated with target organ damage surrogates in hypertension. More specifically, high-pulse pressure and nondipping status in resistant hypertensives have been associated with a high-cardiovascular risk profile including greater age, higher prevalence of cerebrovascular disease and nephropathy, increased serum creatinine and microalbuminuria, and higher left ventricular mass index [24]. Moreover, a blunted nocturnal reduction in BP, a widened 24-hour pulse pressure and AASI have been independently associated with increased aortic stiffness in resistant hypertensive patients [21, 24]. Finally, according to some studies 24-hour pulse pressure presents a closer correlation to target organ damage compared to the other ABPM indices [23, 25].

6. ABPM Implications in the RH Treatment

ABPM emerges nowadays as a useful tool in the evaluation of the efficacy of antihypertensive treatment in clinical trials [26]. The contribution of ABPM in the assessment of treatment effectiveness, could be more prominent in the setting of RH, where it has been shown to possess a pivotal role in haemodynamic load evaluation [27]. Additionally, apart from just testing the efficacy of different drugs, ABPM has been used in the evaluation of the implementation of certain therapeutic strategies in resistant hypertensives by evaluating patients' compliance [28].

Furthermore, as ABPM reveals the unfavorable circadian BP pattern of patients with RH, namely, the nondipping profile, ABPM has been used in the investigation of the efficacy of therapeutic strategies aiming at administration-time-dependent effects (chronotherapy) on the circadian BP pattern and on the degree of 24-hour BP control in RH [29]. Because a possible cause of the unfavorable BP pattern in RH is the short-acting antihypertensive treatment that is based on a single morning dosage, administration of one of the three drugs at bedtime may result in better clinic and ambulatory BP control as well as in lower prevalence of nondipping pattern [30, 31].

Some of the disadvantages of ABPM such as cuff discomfort or procedure-related disturbed sleep may be overcome with the use of home BP as a means of out of

office assessment of BP. However, evidence of the superiority of home BP over office BP, for the assessment of RH, is scarce while there are no data regarding any comparisons with ABPM, which for the present represents the most reliable tool in this setting.

References

- [1] T. G. Pickering, D. Shimbo, and D. Haas, "Ambulatory blood-pressure monitoring," *The New England Journal of Medicine*, vol. 354, no. 22, pp. 2316–2374, 2006.
- [2] V. Pogue, M. Rahman, M. Lipkowitz et al., "Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease," *Hypertension*, vol. 53, no. 1, pp. 20–27, 2009.
- [3] P. A. Sarafidis and G. L. Bakris, "Resistant hypertension. An overview of evaluation and treatment," *Journal of the American College of Cardiology*, vol. 52, no. 22, pp. 1749–1757, 2008.
- [4] D. A. Calhoun, D. Jones, S. Textor et al., "Resistant hypertension: diagnosis, evaluation, and treatment a scientific statement from the american heart association professional education committee of the council for high blood pressure research," *Hypertension*, vol. 51, no. 6, pp. 1403–1419, 2008.
- [5] M. A. Brown, M. L. Buddle, and A. Martin, "Is resistant hypertension really resistant?" *American Journal of Hypertension*, vol. 14, no. 12, pp. 1263–1269, 2001.
- [6] E. S. Muxfeldt, K. V. Bloch, A. R. Nogueira, and G. F. Salles, "Twenty-four hour ambulatory blood pressure monitoring pattern of resistant hypertension," *Blood Pressure Monitoring*, vol. 8, no. 5, pp. 181–185, 2003.
- [7] S. D. Pierdomenico, D. Lapenna, A. Bucci et al., "Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension," *American Journal of Hypertension*, vol. 18, no. 11, pp. 1422–1428, 2005.
- [8] S. W. Tobe and R. Lewanczuk, "Resistant hypertension," *The Canadian Journal of Cardiology*, vol. 25, no. 5, pp. 315–317, 2009.
- [9] W. B. White, "Ambulatory blood pressure monitoring as an investigative tool for characterizing resistant hypertension and its rational treatment," *Journal of Clinical Hypertension*, vol. 9, supplement 1, pp. 25–30, 2007.
- [10] O. Friedman and A. G. Logan, "Nocturnal blood pressure profiles among normotensive, controlled hypertensive and refractory hypertensive subjects," *The Canadian Journal of Cardiology*, vol. 25, no. 9, pp. e312–e316, 2009.
- [11] F. Sayk, C. Becker, C. Teckentrup et al., "To dip or not to dip: on the physiology of blood pressure decrease during nocturnal sleep in healthy humans," *Hypertension*, vol. 49, no. 5, pp. 1070–1076, 2007.
- [12] J. W. Graves, R. L. Bloomfield, and V. M. Buckalew Jr., "Plasma volume in resistant hypertension: guide to pathophysiology and therapy," *The American Journal of the Medical Sciences*, vol. 298, no. 6, pp. 361–365, 1989.
- [13] T. Uzu, K. Ishikawa, T. Fujii, S. Nakamura, T. Inenaga, and G. Kimura, "Sodium restriction shifts circadian rhythm of blood pressure from nondipper to dipper in essential hypertension," *Circulation*, vol. 96, no. 6, pp. 1859–1862, 1997.
- [14] C. Tsioufis, D. Syrseloudis, K. Dimitriadis et al., "Disturbed circadian blood pressure rhythm and C-reactive protein in essential hypertension," *Journal of Human Hypertension*, vol. 22, no. 7, pp. 501–508, 2008.

- [15] R. C. Hermida, D. E. Ayala, C. Calvo et al., "Effects of time of day of treatment on ambulatory blood pressure pattern of patients with resistant hypertension," *Hypertension*, vol. 46, no. 4, pp. 1053–1059, 2005.
- [16] F. Veglio, F. Rabbia, P. Riva et al., "Ambulatory blood pressure monitoring and clinical characteristics of the true and white-coat resistant hypertension," *Clinical and Experimental Hypertension*, vol. 23, no. 3, pp. 203–211, 2001.
- [17] S. Lewington, R. Clarke, N. Qizilbash, R. Peto, and R. Collins, "Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies," *The Lancet*, vol. 360, no. 9349, pp. 1903–1913, 2002.
- [18] G. F. Salles, C. R. L. Cardoso, and E. S. Muxfeldt, "Prognostic influence of office and ambulatory blood pressures in resistant hypertension," *Archives of Internal Medicine*, vol. 168, no. 21, pp. 2340–2346, 2008.
- [19] J. Redon, C. Campos, M. L. Narciso, J. L. Rodicio, J. M. Pascual, and L. M. Ruilope, "Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: a prospective study," *Hypertension*, vol. 31, no. 2, pp. 712–718, 1998.
- [20] E. S. Muxfeldt, C. R. L. Cardoso, and G. F. Salles, "Prognostic value of nocturnal blood pressure reduction in resistant hypertension," *Archives of Internal Medicine*, vol. 169, no. 9, pp. 874–880, 2009.
- [21] M. M. F. Magnanini, A. D. R. Nogueira, M. S. Carvalho, and K. V. Bloch, "Ambulatory blood pressure monitoring and cardiovascular risk in resistant hypertensive women," *Arquivos Brasileiros de Cardiologia*, vol. 92, no. 6, pp. 448–489, 2009.
- [22] E. Dolan, L. Thijs, Y. Li et al., "Ambulatory arterial stiffness index as a predictor of cardiovascular mortality in the dublin outcome study," *Hypertension*, vol. 47, no. 3, pp. 365–370, 2006.
- [23] E. S. Muxfeldt, C. R. L. Cardoso, V. B. Dias, A. C. M. Nascimento, and G. F. Salles, "Prognostic impact of the ambulatory arterial stiffness index in resistant hypertension," *Journal of Hypertension*, vol. 28, no. 7, pp. 1547–1553, 2010.
- [24] C. H. Castelpoggi, V. S. Pereira, R. Fiszman, C. R. L. Cardoso, E. S. Muxfeldt, and G. F. Salles, "A blunted decrease in nocturnal blood pressure is independently associated with increased aortic stiffness in patients with resistant hypertension," *Hypertension Research*, vol. 32, no. 7, pp. 591–596, 2009.
- [25] E. S. Muxfeldt and G. F. Salles, "Pulse pressure or dipping pattern: which one is a better cardiovascular risk marker in resistant hypertension?" *Journal of Hypertension*, vol. 26, no. 5, pp. 878–884, 2008.
- [26] A. J. S. Coats, "Benefits of ambulatory blood pressure monitoring in the design of antihypertensive drug trials," *Blood Pressure Monitoring*, vol. 1, no. 2, pp. 157–160, 1996.
- [27] A. Dees, T. K. K. Hovinga, J. G. S. Breed, V. M. C. Verstappen, S. M. T. Puister, and L. Meems, "Calcium antagonists, a useful additional therapy in treatment resistant hypertension: comparison of felodipine ER and nifedipine Retard by 24-h ambulatory blood pressure monitoring," *Netherlands Journal of Medicine*, vol. 50, no. 1, pp. 2–12, 1997.
- [28] M. S. de Castro, F. D. Fuchs, M. C. Santos et al., "Pharmaceutical care program for patients with uncontrolled hypertension. Report of a double-blind clinical trial with ambulatory blood pressure monitoring," *American Journal of Hypertension*, vol. 19, no. 5, pp. 528–533, 2006.
- [29] R. C. Hermida, D. E. Ayala, C. Calvo et al., "Effects of time of day of treatment on ambulatory blood pressure pattern of patients with resistant hypertension," *Hypertension*, vol. 46, no. 4, pp. 1053–1059, 2005.
- [30] R. C. Hermida, D. E. Ayala, J. R. Fernández, and C. Calvo, "Chronotherapy improves blood pressure control and reverts the nondipper pattern in patients with resistant hypertension," *Hypertension*, vol. 51, no. 1, pp. 69–76, 2008.
- [31] R. C. Hermida, D. E. Ayala, A. Mojón, and J. R. Fernández, "Effects of time of antihypertensive treatment on ambulatory blood pressure and clinical characteristics of subjects with resistant hypertension," *American Journal of Hypertension*, vol. 23, no. 4, pp. 432–439, 2010.