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REVIEW SERIES

Profile of ambulatory blood pressure in resistant hypertension

Alejandro de la Sierra

Resistant hypertension (HT) is a condition that confers a high cardiovascular risk to the patient due to both persistent blood pressure elevation and the high prevalence of comorbidities and organ damage. Ambulatory blood pressure monitoring (ABPM) has become an important tool in the diagnosis and follow-up of the hypertensive patient, and it is even more important in the evaluation of those with resistant HT. Data from the Spanish ABPM Registry have allowed the comparison between large groups of resistant hypertensive patients seen in daily life and those controlled on antihypertensive treatment, as well as in resistant hypertensive patients who are classified based on ambulatory blood pressure values. In comparison with controlled patients, the cohort of resistant hypertensives has a worse circadian profile with a high proportion of nondipping, but also stark differences between office and ambulatory blood pressures. This enhanced white-coat effect was responsible for more than one-third of resistant hypertensive patients having normal 24-h blood pressures. Clinical data, including comorbidities, organ damage and circadian patterns, suggest a lower cardiovascular risk among white-coat resistant hypertensives. This finding was in agreement with longitudinal studies in smaller cohorts, suggesting fewer cardiovascular events and less mortality. In summary, it seems reasonable to routinely use ABPM in the initial evaluation of all resistant hypertensive patients. In a significant number of these patients, ABPM will also be an essential tool in follow-up, especially regarding the possible effects of all therapeutic maneuvers that are devoted to bringing blood pressure into target ranges.
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Keywords: ambulatory blood pressure monitoring; antihypertensive treatment; circadian pattern; resistant hypertension; white-coat hypertension.

INTRODUCTION

Resistant hypertension (HT) is defined as a clinical situation in which blood pressure is not controlled despite optimal antihypertensive treatment, including at least three antihypertensive drugs (one of them preferably being a diuretic) at full doses.[1] Despite significant progress in the treatment of HT, resistant HT is not uncommon and affects 10–15% of all treated hypertensive patients.[2,3] The diagnosis of resistant HT has important implications from diagnostic, prognostic and therapeutic perspectives. Patients with resistant HT more frequently present with secondary causes of HT, more severe target organ damage[4] and a greater risk of cardiovascular complications and death.[5]

Ambulatory blood pressure monitoring (ABPM) has become a very useful (and sometimes essential) tool for the diagnosis and management of hypertensive patients.[6–9] The primary applications of ABPM comprise the diagnosis of white-coat HT, masked HT, hypotension phenomena that occur at any point during a 24-h period, assessment of the circadian and physiological nocturnal decrease patterns and a more precise assessment of the effect and duration of antihypertensive treatment.[10,11] In addition to these known indications, one of the main advantages of ABPM, which involves a large number of blood pressure measurements during everyday activities (including the main causes of variability—activity and rest), is that it is more reliable than a single measurement of an individual's blood pressure. Thus, it is not surprising that the main estimators obtained during ABPM are more closely associated with the presence and evolution of organ damage and have a greater predictive value than office blood pressure measurements. The advantages of ABPM are even greater when a physician is faced with a more difficult clinical situation, as occurs in resistant HT. This chapter reviews the main characteristics of ABPM in patients with resistant HT. Most of the information is derived from various analyses of the Spanish ABPM Registry.

CHARACTERISTICS OF THE SPANISH ABPM REGISTRY

In 2005, the Spanish Society of Hypertension, with the help of the pharmaceutical industry, decided to disseminate both the knowledge and the use of ABPM among health-care professionals involved in caring for patients with cardiovascular risk. The CARDIORISC project involved the distribution of validated ABPM monitors (SpaceLab 90207/Microlife Watch BP 03) to >1000 physicians from various health-care settings, >75% of whom were general practitioners.[12,13] The monitors were accompanied by a training program

Department of Internal Medicine, Hospital Mutua Terrassa, University of Barcelona, Terrassa, Barcelona, Spain
Correspondence: Professor A de la Sierra, Department of Internal Medicine, Hospital Mutua Terrassa, University of Barcelona, Plaza Dr. Robert, 5, Terrassa 08021, Barcelona, Spain.
E-mail: adelasierra@mutuaterrassa.es or asierra@ub.edu
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about correct clinical blood pressure measurements, the utilities of ABPM and how to interpret the main estimators obtained, as well as training and technical support to ensure the correct use of the technique. In addition to the local software, access to a website was provided for downloading monitoring data and clinical data forms for each patient. This approach enabled reports to be obtained in real time. These reports contained the main estimators obtained from monitoring, which consisted of information about their quality and stratification of the absolute cardiovascular risk calculated using the clinical data provided (Figure 1). The clinical and monitoring data were also stored in a server and used for subsequent analyses.

There was a massive response to the initiative, and data immediately started to be recorded, including up to the present day. By January 2013, there were more than 165 000 entries referring to >120 000 patients (www.cardiorisc.com/MP/index_MP.asp accessed on January 16th, 2013). The availability of such a source of information led to the creation of a scientific committee by the Spanish Society of Hypertension, which developed the lines of research that have led to subsequent publications on the registry.

COMPARISON BETWEEN PATIENTS WITH RESISTANT AND CONTROLLED HT

Little information is available about the characteristics of ABPM in patients with resistant HT compared with the general hypertensive population.[14–16] The data in the Spanish ABPM Registry enabled us to assess a group of patients with resistant HT (not controlled with three drugs or being treated with four or more drugs) and to compare them with a group of controlled patients who take three or fewer drugs. With regard to clinical characteristics,[4] the first group was older and had a greater prevalence of obesity and a longer history of HT. The prevalence of diabetes, lipid metabolism disorders and kidney damage defined by either reduced estimated glomerular filtration rate or microalbuminuria, left ventricular hypertrophy on the electrocardiogram or a previous history of cardiovascular disease were all significantly higher in the group of patients with resistant HT (Table 1).

In relation to the differential characteristics of ABPM between resistant and controlled HT patients, the former group clearly presented higher 24-h, daytime and nighttime values in comparison to the latter group. More importantly, resistant HT was associated with a circadian pattern in which the nighttime BP dip was blunted. Thus, night/day ratios for both systolic and diastolic BP (SBP and DBP, respectively) were higher among patients with resistant HT (0.93 ± 0.09 *vs.* 0.92 ± 0.08 for SBP and 0.89 ± 0.10 *vs.* 0.87 ± 0.09 for DBP). Significant differences were also found in the circadian profile distribution between the groups (Figure 2); patients with resistant HT more commonly presented with a riser pattern and less commonly with a dipper pattern.

DIAGNOSIS OF TRUE RESISTANT HT—THE ROLE OF ABPM

The main advantage of ABPM in resistant HT is the diagnosis of white-coat resistant HT. Patients with resistant HT present with a greater white-coat phenomenon than controlled HT patients. In

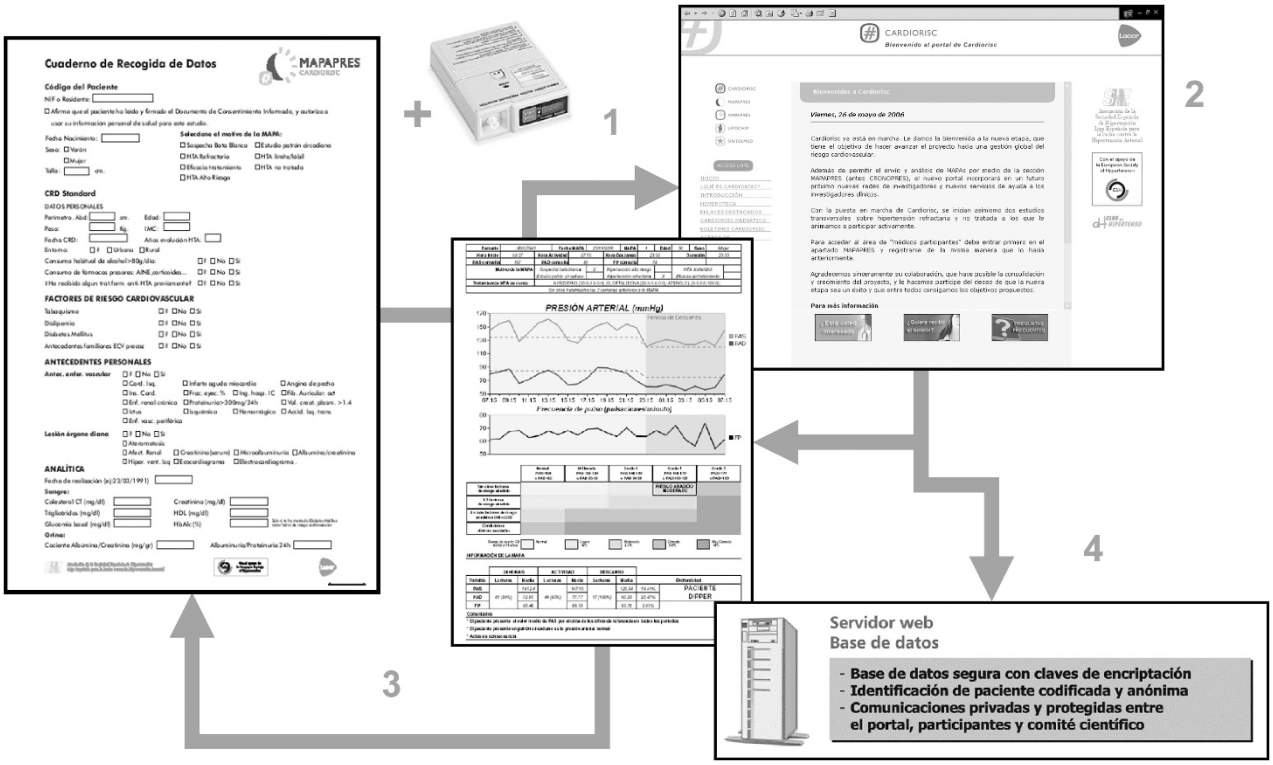

Figure 1 The CARDIORISC Project. How does it work? 1. Clinical forms together with ABPM records are entered into a website through a web platform open to investigators (user and password required). The server returns, in real time, a report containing the main results for the ABPM recording (mean values of 24-h, daytime, nighttime, s.d.s and dipping profile) together with a cardiovascular risk stratification using the 2003 European Society of Hypertension chart. Moreover, data are stored in a server for future analyses. A full color version of this figure is available at the *Hypertension Research* journal online.

Table 1 Clinical characteristics of resistant hypertensives in comparison with those controlled with ⩽3 antihypertensive drugs

	Resistant hypertension	*Controlled patients*	P
Age, years	64.7 ± 11.6	59.7 ± 13.4	<0.001
Gender, % males	52.1	51.5	0.309
Obesity, %	53.4	38.7	<0.001
Abdominal obesity, %	56.1	43.9	<0.001
Duration of hypertension, years	11.1 ± 8.5	6.5 ± 6.7	<0.001
Smokers, %	13.2	15.5	<0.001
Diabetics, %	35.1	18.8	<0.001
Reduced renal function %	24.9	15.9	<0.001
Microalbuminuria, %	27.7	15.4	<0.001
LVH by ECG, %	16.4	7.6	<0.001
Previous CV disease, %	21.1	17.0	<0.001

Abbreviations: CV, cardiovascular; ECG, electrocardiogram; LVH, left ventricular hypertrophy. Values are mean ± s.d. or percentages. Reduced renal function is defined as estimated glomerular filtration rate, using simplified MDRD (Modification of Diet in Renal Disease) formula $<60\,ml\,min^{-1}\,1.73\,m^{-2}$. Microalbuminuria is defined as urinary albumin excretion $\geqslant 30\,mg\,g^{-1}$.

Table 2 Clinical characteristics of true and white-coat resistant hypertensive (RH) patients

	True RH	*White-coat RH*	P
Age, years	64.0 ± 11.7	65.0 ± 10.9	<0.001
Gender, % males	54.6	46.0	<0.001
Obesity, %	50.8	51.6	0.356
Abdominal obesity, %	54.0	54.5	0.712
Duration of hypertension, years	11.4 ± 8.7	10.5 ± 8.2	<0.001
Smokers, %	14.8	10.3	<0.001
Diabetics, %	35.1	27.8	<0.001
Reduced renal function, %	24.4	24.0	0.759
Microalbuminuria, %	30.1	19.6	<0.001
LVH by ECG, %	18.5	14.4	<0.001
Previous CV disease, %	19.1	16.2	0.001

Abbreviations: CV, cardiovascular; ECG, electrocardiogram; LVH, left ventricular hypertrophy. Values are mean ± s.d. or percentages. Reduced renal function is defined as estimated glomerular filtration rate, using simplified MDRD (Modification of Diet in Renal Disease) formula $<60\,ml\,min^{-1}\,1.73\,m^{-2}$. Microalbuminuria is defined as urinary albumin excretion $\geqslant 30\,mg\,g^{-1}$.

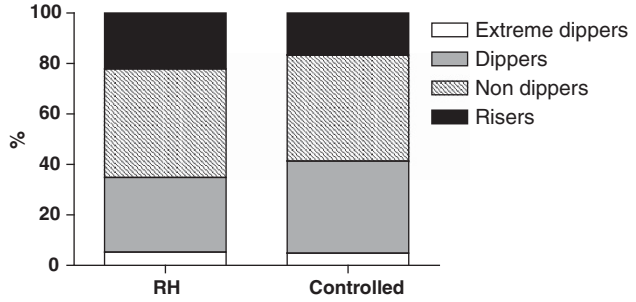

Figure 2 Distribution of circadian blood pressure (BP) patterns in resistant hypertensives (RH) and patients controlled on ⩽3 drugs. Patterns defined based on night systolic BP decrease (extreme dippers >20%; dippers 10–20%, non-dippers 0–10%; risers <0%). RH have a higher proportion of risers and a lower proportion of dippers.

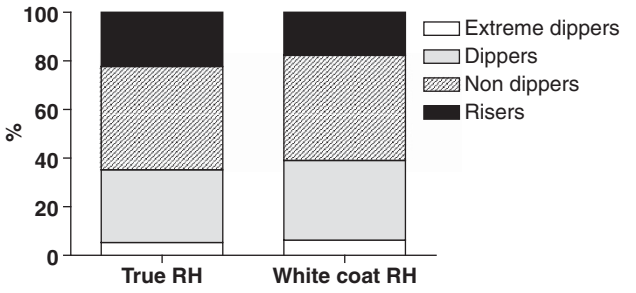

Figure 3 Distribution of circadian blood pressure (BP) patterns in true (24-h BP⩾130 and/or 80 mm Hg) and white-coat (24-h BP<130/80 mm Hg) resistant hypertensives (RH). The proportion of dippers is lower and the proportion of risers is higher in true RH.

comparison between the groups with resistant and controlled HT, the white-coat phenomenon, defined as the differences between clinical BP values and 24-h values, was 24/13 mm Hg for SBP and DBP, respectively, in the group with resistant HT and 5/4 mm Hg in the group of controlled patients.[4]

To evaluate the prevalence of white-coat resistant HT, we only analyzed patients who had not achieved office BP control with three or more drugs. This approach did not include those who, although meeting the definition of resistant HT, presented controlled clinical figures while receiving four or more drugs. The patients in this group totaled 8295, and 37.5% of them presented with 24-h figures of <130/80 mm Hg, 44.1% daytime figures of <135/85 mm Hg and 31.8% nighttime figures of <120/70 mm Hg.[2]

Regarding clinical characteristics, white-coat resistant HT was associated with older age and female gender. Contrasting phenomena were found with HT duration, smoking, diabetes, kidney impairment, left ventricle hypertrophy and previous cardiovascular disease (Table 2).

The distribution of circadian rhythms was also different between true and white-coat resistant HT patients. As Figure 3 shows, the prevalence of the dipper pattern was greater, and the riser pattern lower, in patients with white-coat resistant HT.

CIRCADIAN PATTERN AND ANTIHYPERTENSIVE TREATMENT IN RESISTANT HT PATIENTS

Antihypertensive treatment can indeed affect the BP circadian profile. In a previous analysis of the Spanish ABPM Registry, the clinical factors that were associated with a blunted nocturnal BP dip were similar in both the treated and untreated patients. Advanced age, obesity and advanced disease (silent organ damage or confirmed cardiovascular or kidney disease) were all associated with a non-dipper pattern. Furthermore, in patients under antihypertensive treatment, the number of drugs taken, but not their time of administration, was also associated with this pattern.[17,18]

In the group of resistant HT patients in the Spanish ABPM Registry, a specific analysis was performed on the impact of antihypertensive treatment on BP values obtained by ABPM and on circadian patterns. With regard to the number of drugs, a progressive increase was observed in SBP figures from the group treated with three drugs to the group treated with six or more. This pattern was present for all 24-h, daytime and nighttime SBP but not for DBP (Figure 4). The number of drugs also affected the BP circadian profile, and the night/day ratio progressively increased from three to five drugs, then reached a plateau. From a qualitative perspective, this phenomenon was also found in the proportion of patients with a

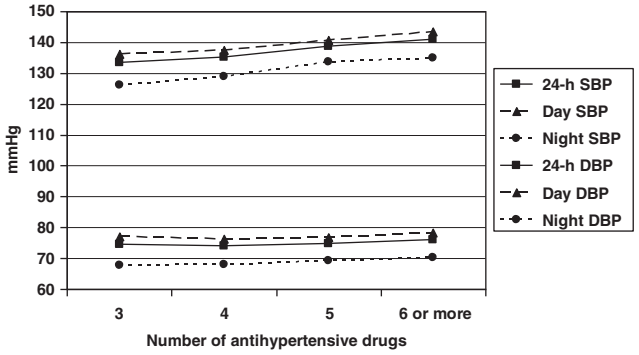

Figure 4 Ambulatory blood pressure (BP) values in resistant hypertensives depending on the number of antihypertensive drugs prescribed. Twenty-four hour, daytime and nighttime systolic BPs (SBPs) significantly increased as the number of drugs increased ($P<0.001$). Diastolic BP (DBP) does not follow the same pattern (*P*:NS).

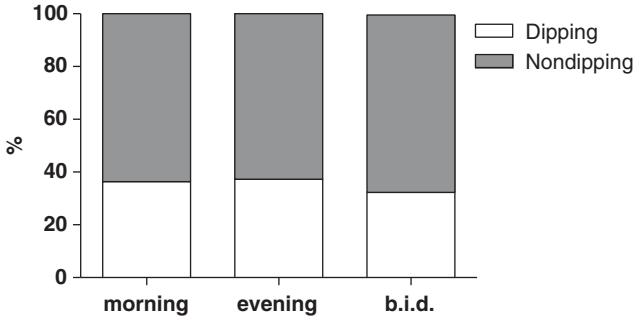

Figure 6 Prevalence of nondipping (non-dippers and risers together) in resistant hypertensives depending on treatment posology. Those on a b.i.d schedule have a higher proportion of nondipping ($P=0.002$).

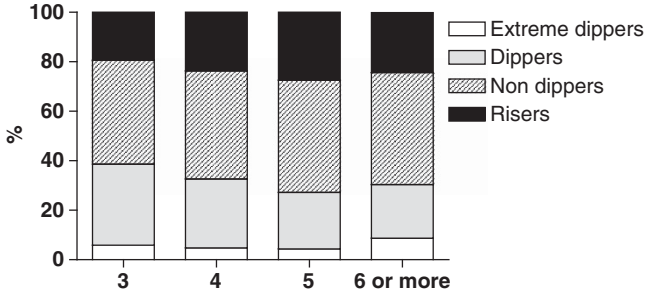

Figure 5 Distribution of circadian blood pressure (BP) patterns in resistant hypertensives depending on the number of drugs received. The proportion of risers increases ($P<0.001$) and the proportion of dippers decreases as the number of drugs increases from 3–5, then reaches a plateau.

dipper profile, which progressively fell as the number of drugs increased, with the opposite phenomenon occurring for the riser profile (Figure 5).

Another possible treatment-related factor that can affect BP values and circadian rhythms is the type of pharmacological combination used. If the joint administration of three drugs is required, the ESH consensus document of 2009 recommended that the most logical option would be a combination of a renin-angiotensin system blocker (an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker), a calcium antagonist and a diuretic.[19] In our series of patients with resistant HT treated with three drugs, we analyzed whether there were differences in ABPM values or the circadian pattern between patients who received this specific pharmacological association ($n=2871$) *vs.* other possible combinations ($n=6201$). Although the 24-h and daytime SBP figures were slightly lower in the former group (by approximately 0.5 mm Hg), neither the DBP figures, the night/day ratio or the proportion of patients with different circadian profiles were significantly different depending on the type of combination used.

Finally, the last therapeutic factor analyzed was the time of administration of antihypertensive drugs. In this respect, a previous study suggested that patients with resistant HT who received three drugs in the morning could improve their BP values and circadian rhythms by taking one of those three drugs at night.[20] When we analyzed the resistant HT patients in the Spanish ABPM Registry, most of them (73%) took all of their medication in the morning, 16% at night and 11% received the administered drugs on a b.i.d. schedule. We found no significant differences in 24-h, daytime or nighttime DBP values between the three treatment posology groups. SBP values were slightly higher in patients who received their medication in a b.i.d. schedule, and the proportion of patients with an insufficient BP reduction at night (non-dipper or riser profiles) was also higher in this group (Figure 6).

These results do not suggest that time of administration of drugs is important in controlling BP or circadian patterns in the resistant HT population. However, these findings should be interpreted with caution, as a more complex posology is also associated with a higher number of drugs and most likely reflects greater BP control difficulties.

ABPM AND CARDIOVASCULAR PROGNOSIS IN RESISTANT HT PATIENTS

In the general population, cardiovascular risk is directly related to BP values. Accordingly, persistently high values despite antihypertensive treatment (the definition of resistant HT) are associated with an increased risk of cardiovascular episodes and death.[5] Regarding the role of ABPM in the prognosis of resistant HT, a study conducted >10 years ago in 86 resistant HT patients suggested that daytime BP according to ABPM was a better predictor of future cardiovascular events than office BP.[21] In a subsequent study, Pierdomenico *et al.*[22] followed up a cohort of patients according to the response to treatment, defining their response through clinical and ambulatory BP figures. More of the patients who presented resistance defined by ambulatory values also presented greater cardiovascular morbidity and mortality than those whose resistance to treatment was only found in clinical BP values. Likewise, Salles *et al.*[23] found greater cardiovascular mortality and morbidity in the follow up of a cohort of resistant HT patients who were classified as being truly resistant (high ambulatory BP values) than in white-coat cases (elevated office BP but normal ambulatory values).

Information about cardiovascular prognosis in resistant HT is not available in the Spanish ABPM Registry patients, as it is a cross-sectional registry. However, two figures indirectly support the greater importance of ambulatory BP values. When patients were divided into true or white-coast resistant HT groups, the former group more commonly presented renal impairment, albuminuria or confirmed cardiovascular disease as compared with the latter group.[2]

Furthermore, in a follow-up analysis of high-risk patients (more than a third of them met resistant HT criteria), nocturnal BP was the parameter that best predicted the onset of cardiovascular disease during follow-up, neglecting the impact of office BP.[24] These findings suggest that, in resistant HT, ABPM is a stratification tool that identifies high-risk patients who require more intensive therapy.

CONCLUSIONS

Discrepancies exist among different clinical guidelines concerning the need for ABPM in the diagnosis and follow-up of HT.[11,25] However, resistant HT is one case in which the use of ABPM would appear to be essential. Confirmation of resistance to treatment with data obtained by ABPM has prognostic and therapeutic implications. Furthermore, the information obtained about the characteristics of the records, both in the absolute values as in BP variability and the circadian profile, is also useful from both prognostic and therapeutic perspectives. Further studies are required to evaluate whether a therapeutic approach based on ambulatory values could be more useful in cardiovascular prevention than the current approach based on clinical BP values.

CONFLICT OF INTEREST

The Spanish ABPM Registry was initiated and is maintained by an unrestricted grant from Lacer Laboratories, Spain and the Spanish Society of Hypertension. Some of the analyses have received a Grant from the Spanish Health Authority (Fondo de Investigación Sanitaria: PI10/01011). AS has participated in educational meetings focused on ABPM. Some of these meetings have been funded by Lacer Laboratories, Spain.

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