Clinical Features of 8295 Patients With Resistant Hypertension Classified on the Basis of Ambulatory Blood Pressure Monitoring

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Abstract—We aimed to estimate the prevalence of resistant hypertension through both office and ambulatory blood pressure monitoring in a large cohort of treated hypertensive patients from the Spanish Ambulatory Blood Pressure Monitoring Registry. In addition, we also compared clinical features of patients with true or white-coat–resistant hypertension. In December 2009, we identified 68 045 treated patients with complete information for this analysis. Among them, 8295 (12.2% of the database) had resistant hypertension (office blood pressure ≥140 and/or 90 mm Hg while being treated with ≥3 antihypertensive drugs, 1 of them being a diuretic). After ambulatory blood pressure monitoring, 62.5% of patients were classified as true resistant hypertensives, the remaining 37.5% having white-coat resistance. The former group was younger, more frequently men, with a longer duration of hypertension and a worse cardiovascular risk profile. The group included larger proportions of smokers, diabetics, target organ damage (including left ventricular hypertrophy, impaired renal function, and microalbuminuria), and documented cardiovascular disease. Moreover, true resistant hypertensives exhibited in a greater proportion a riser pattern (22% versus 18%; $P<0.001$). In conclusion, this study first reports the prevalence of resistant hypertension in a large cohort of patients in usual daily practice. Resistant hypertension is present in 12% of the treated hypertensive population, but among them more than one third have normal ambulatory blood pressure. A worse risk profile is associated with true resistant hypertension, but this association is weak, thus making it necessary to assess ambulatory blood pressure monitoring for a correct diagnosis and management. **(*Hypertension*. 2011;57:00-00.) ● Online Data Supplement**

Key Words: resistant hypertension ■ ambulatory blood pressure monitoring ■ circadian pattern ■ cardiovascular risk

Resistant hypertension (RH) is defined as office blood pressure (BP) that remains above goal despite the concurrent use of 3 antihypertensive agents, at full doses, one of them being a diuretic. Although the prevalence of RH largely depends on the setting explored, this condition is of clinical importance, because it is associated with an impaired prognosis.[1]

The definition of RH is based on office measurements. However, the use of ambulatory BP monitoring (ABPM) has allowed for the recognition of the white-coat effect as being responsible for a proportion of resistant hypertensive patients. It is estimated that approximately one third of patients with suspected RH indeed have white-coat or isolated office RH, showing normal daytime or 24-hour ABPM values.[2–4]

Elevated ABPM values in patients with RH are associated with a higher prevalence of target organ damage[4,5] and increased incidence of future cardiovascular events.[6–8] However, these data come from relatively small populations attended in single referral units, whereas there is lack of data coming from large hypertensive populations representing usual clinical care.

In this study, we used a large population of hypertensive subjects included in the Spanish ABPM Registry to specifically identify patients with RH. The aims of the study were to estimate the prevalence of RH and to assess the presence of clinical differences in patients classified on the basis of ABPM as having true or white-coat RH.

Patients and Methods

Study Design

The Spanish ABPM Registry was developed to promote the use of ABPM in clinical practice. The ABPM Registry is based on the

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distribution of >1000 ambulatory BP SpaceLabs 90207 monitors (SpaceLabs Inc, Redmond, WA) for routine use by physicians from primary care centers and specialized units across Spain. Details of physician recruitment and characteristics of the registry have been reported previously.[9–13] Briefly, physicians and nurses received specific training in the technique of ABPM and used the internet-based platform that receives ABPM registries, together with their corresponding medical charts. Physicians then obtained a report in real time, and these registries were stored in the database of an external clinical research organization. The practice guidelines of the European Society of Hypertension for BP measurements were used to establish general indications for ABPM.[14] The registry is continuously growing and has received the data of ≈1500 patients per month since the first patient was recruited in June 2004. The protocol was approved by a series of institutional review boards from the different autonomous communities of Spain, and patients gave informed consent.

In December 2009, we identified 68 045 treated patients who had enough information regarding office BP measurements, ABPM of good quality, and complete clinical information with special attention given to antihypertensive treatment (number, types, and dosing of drugs used). Among them, 10 052 patients (14.8%) fulfilled standard criteria of RH (office BP ≥140 and/or 90 mm Hg despite the use of 3 antihypertensive drugs, 1 of them being a diuretic, or treatment with ≥4 antihypertensive drugs irrespective of office BP values).[1] For the present analysis we selected only those patients with uncontrolled BP values (office BP ≥140 and/or 90 mm Hg) being treated with ≥3 antihypertensive agents at appropriate doses (8295 patients; 12.2%).

BP Measurements

BP was measured at the office with a calibrated mercury sphygmomanometer or a validated oscillometric device, after 5-minute rest in a sitting position. BP values were estimated as the mean of 2 readings. Thereafter, 24-hour ABPM was performed using the SpaceLabs 90207 automated noninvasive oscillometric device, programmed to register BP at 20-minute intervals for the 24-hour period. The majority of registries were performed on working days, and the patients were instructed to maintain their usual activities, return the following morning for device removal, and keep the arm extended and immobile at the time of each cuff inflation. Valid registries had to fulfil a series of pre-established criteria, including ≥80% of systolic BP and diastolic BP successful recordings during the daytime and nighttime periods, 24-hour duration, and ≥1 BP measurement per hour. Daytime and nighttime periods were defined individually according to the patient's self-reported data of going-to-bed and getting-up times. Circadian patterns were defined by calculating the percentage decline in systolic BP or diastolic BP during the night, using the following formula: [(daytime BP−nighttime BP)/daytime BP]×100. According to this, patients were classified as systolic or diastolic extreme dippers (BP decline >20%), dippers (BP decline >10% and <20%), nondippers (BP decline between 0% and 10%), and risers (increase in BP during nighttime).

Study Variables

Variables collected for each patient based on the interviews and physical examination at the time of visit and on data drawn from clinical records were defined and measured in accordance with national and international guidelines.[15,16] These included age, sex, weight, height, body mass index, duration of hypertension, known cardiovascular risk factors (eg, smoking and diabetes mellitus), biochemical values of creatinine and lipid profile, target organ damage including urinary albumin excretion (microalbuminuria defined as values >30 mg/g), ECG (left ventricular hypertrophy defined as a Sokolow-Lyon voltage >38 and/or Cornell duration/voltage index >2440 mm/ms), and clinical cardiovascular disease (coronary heart disease, congestive heart failure, or cerebrovascular disease). Moreover, details about antihypertensive treatment (class of drugs and dosing time in a 3-category scheme, breakfast, lunch, and dinner) were also collected.

Table 1. Clinical Features in Resistant Hypertensives With Normal or Elevated 24-Hour Blood Pressure

Parameter	True RH (N=5182)	White-Coat RH (N=3113)	*P*
Age, y	64.0±11.7	65.0±10.9	<0.001
Sex, % men	54.6	46.0	<0.001
BMI, kg/m^2	30.4±4.7	30.5±5.0	0.228
Duration of hypertension, y	11.4±8.7	10.5±8.2	<0.001
Smokers, %	14.8	10.3	<0.001
Diabetics, %	35.1	27.8	<0.001
Creatinine, μmol/L	75 (62 to 89)	72 (61 to 84)	0.006
Total cholesterol, mmol/L	5.23±1.06	5.21±1.06	0.495
HDL cholesterol, mmol/L	1.33±0.37	1.36±0.37	0.022
Triglycerides, mmol/L	1.64±0.93	1.54±0.72	0.005
UAE, mg/g	11.0 (3.4 to 44.5)	7.0 (2.7 to 20.0)	<0.001
UAE >30 mg/g, %	30.1	19.6	<0.001
LVH by ECG, %	18.5	14.4	<0.001
Previous CV disease, %	19.1	16.2	0.001
Treatment with ≥4 AH drugs, %	38.3	34.4	<0.001
Patients taking part of their medication in the evening, %	24.9	25.8	0.319

Values are mean±SD or median (interquartile range) unless otherwise specified. RH indicates resistant hypertension; BMI, body mass index; UAE, urinary albumin excretion; LVH, left ventricular hypertrophy; ECG, electrocardiogram; CV, cardiovascular; AH, antihypertensive; HDL, high-density lipoprotein.

Statistical Analysis

Data are presented as frequencies and percentages for qualitative variables and as mean±SD (or median [interquartile range]) for quantitative variables. Differences in study variables between groups were assessed with the Pearson χ^2 for qualitative variables and the Student *t* test (or Mann-Whitney test) for quantitative data. A logistic regression analysis was performed to determine the clinical variables associated with true versus white-coat RH. Multiple logistic regression analysis was performed by entering into the model all of the independent variables with a $P<0.05$. The stepwise forward method was used for variable selection. The SPSS for Windows version 15.0 software (SPSS Inc, Chicago, IL) was used for statistical analysis.

Results

A total of 8295 patients were included in the present analysis. They were 4262 (51.4%) men and 4033 (48.6%) women, with a mean age of 64.4±11.4 years. Mean duration of hypertension was 11.1±8.6 years, mean office BP was 161±18/88±13 mm Hg, and mean 24-hour BP was 134±16/75±11 mm Hg. Obesity (body mass index ≥30 kg/m^2) was present in 49.5% of subjects, 13.1% were current smokers, and 32.3% had type 2 diabetes mellitus. A history of previous cardiovascular disease was present in 18.0% with the following features: coronary heart disease 9.8%, cerebrovascular disease 6.3%, and heart failure 3.9%.

After ABPM patients were classified in 2 groups, 5182 patients (62.5%) had ambulatory 24-hour BP values ≥130 and/or 80 mm Hg and were diagnosed as true RH, and 3113 patients (37.5%) showed 24-hour BP values below this limit and were considered as having white-coat RH. Table 1 compares clinical characteristics between patients with true or white-coat RH. As seen, normal ABPM or white-coat RH

Table 2. Differences in Office, Daytime, and Nighttime BP, as Well as Circadian Pattern Distribution, Between RH Patients With Normal or Elevated 24-Hour BP

Parameter	True RH (N=5182)	White-Coat RH (N=3113)	*P*
Office SBP	164±18	157±15	<0.001
Office DBP	90±13	87±12	<0.001
Daytime SBP	145±13	122±8	<0.001
Daytime DBP	81±12	70±8	<0.001
Nighttime SBP	136±17	113±10	<0.001
Nighttime DBP	72±11	61±8	<0.001
Circadian SBP pattern distribution			<0.001
Extreme dippers, %	5.3	6.3	
Dippers, %	29.9	32.7	
Nondippers, %	42.5	43.3	
Risers, %	22.3	17.7	
Circadian DBP pattern distribution			<0.001
Extreme dippers, %	16.1	20.4	
Dippers, %	39.3	43.1	
Nondippers, %	32.5	26.8	
Risers, %	12.1	9.6	

Values are in millimeters of mercury. RH indicates resistant hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure.

was associated with a slightly older age (65 versus 64 years), and a higher proportion of women (54% versus 45%). In comparison with these subjects, those with true RH (elevated ABPM) had a worse cardiovascular risk profile, including higher proportions of smokers (15% versus 10%), diabetics (35% versus 28%), left ventricular hypertrophy as detected by ECG (19% versus 14%), microalbuminuria as defined by an urinary albumin excretion >30 mg/g creatinine (30% versus 20%), and previous cardiovascular disease (19% versus 16%; all comparisons $P<0.001$).

Regarding antihypertensive treatment, the median number of drugs was 3 in both groups, but the proportion of patients treated with ≥4 antihypertensive drugs was also higher in true RH (38% versus 34%). As per definition, all of the patients received a diuretic. The use of other antihypertensive drug classes showed differences between patients with true and white-coat RH. True RH received calcium channel blockers (51.6% versus 52.8%) and β-blockers (41.9% versus 45.6%) less frequently and renin angiotensin system blockers (79.6% versus 67.5%) and α-blockers (23.5% versus 16.6%) more frequently ($P<0.001$ for all comparisons).

In comparison with RH patients with normal ABPM values, those having true RH showed higher BP values, including office, daytime, and night time BPs. Moreover, circadian BP patterns also showed slight differences between groups ($P<0.001$), with a higher proportion of risers, based on either systolic (22.3% versus 17.7%) or diastolic (12.1% versus 9.6%) nocturnal fall, in the group of true RH subjects (Table 2).

Clinical variables showing statistical differences between true and white-coat RH were entered into a multiple logistic regression model. Urinary albumin excretion was excluded from this analysis, as data were lacking in 30% of patients. Table 3 shows the results of this analysis. As can be observed,

Table 3. Multiple Logistic Regression (Stepwise Forward) With Clinical Variables Showing Differences Between True and White-Coat–Resistant Hypertensive Patients

Parameter	MOR	95% CI	*P*
Age, y	0.99	0.98 to 1.00	0.002
Sex, (males vs females)	1.23	1.02 to 1.49	0.031
Duration of hypertension, y	1.02	1.01 to 1.03	0.001
Smokers (yes vs no)	1.25	1.01 to 1.44	0.041
Diabetics (yes vs no)	1.26	1.10 to 1.39	0.002
Creatinine, μmol/L	1.01	1.00 to 1.02	0.028
HDL cholesterol, mmol/L	NS	NS	0.693
Triglycerides, mmol/L	NS	NS	0.113
LVH by ECG (yes vs no)	1.22	1.02 to 1.38	0.033
Previous CV disease (yes vs no)	1.22	1.02 to 1.38	0.034
Treatment with ≥4 AH drugs (≥4 vs 3)	NS	NS	0.460

MOR indicates multivariate odds ratio; LVH, left ventricular hypertrophy; ECG, electrocardiogram; CV, cardiovascular; AH, antihypertensive; HDL, high-density lipoprotein.

a younger age, a male sex, a longer duration of hypertension, current smoking, diabetes mellitus, elevated plasma creatinine, and a history of previous cardiovascular disease were all associated ($P<0.05$) with elevated ABPM values or true RH.

These analyses were repeated by classifying patients in true (≥135 and/or 85 mm Hg; 4637 patients; 55.9%) or white-coat (<135/85 mm Hg; 3658 patients; 44.1%) RH on the basis of daytime BP. Tables S1 and S2 (please see the online Data Supplement at http://hyper.ahajournals.org) show differences between groups. Results using this classification were similar as shown by dividing patients on the basis of 24-hour BP, with the exception of circadian patter distribution, which was not different between groups.

Discussion

The present analysis from the Spanish ABPM Registry shows that prevalence of RH in a large population of treated hypertensives attended in different settings, mostly in primary care, is ≈15%, using the current definition,[1] and ≈12% if we consider only patients with office BP ≥140 and/or 90 mm Hg (excluding patients with normal BP but treated with ≥4 antihypertensive drugs). This is the first time that prevalence of RH was assessed in such a large cohort of patients. Previous reports were carried out in single referral units[3,8,17,18] or indirectly estimated from randomized clinical trials.[19] Mean values of RH prevalence in such situations have been estimated at ≈20%,[1] which is a somewhat higher with respect to the figure presented here. However, the present data reflect more precisely the usual clinical practice, because both primary care physicians and referral units were represented. In any case, it still reflects the inability to bring BP to goal in a significant proportion of hypertensive patients, despite an important therapeutic effort, such as treatment with ≥3 antihypertensive drugs.

ABPM is mandatory in resistant hypertensive patients to define true and white-coat RH, as the latter group has a better prognosis.[6–8] In our database, from >8000 resistant hypertensive patients detected by office BP, only 62.5% had 24-hour values ≥130 and/or 80 mm Hg; the remaining 37.5%

were considered as having white-coat RH. This is also in agreement with previous reports where white-coat hypertension was present in 20% to 40% of patients attended in referral units.[2,4,5,7] Differences in the prevalence of white-coat RH were mainly attributed to the selection of either daytime or 24-hour as the criteria used for definition, as well as the cutoff value (130/80 or 135/85 mm Hg) used. Among different values obtained during ABPM, nocturnal BP is clearly the best prognostic indicator of the cardiovascular outcome,[7,20] so we chose 24-hour BP as the diagnostic criteria of true RH, because it contains both activity and resting BPs. The cutoff of 130/80 mm Hg was selected because it is the normal limit indicated in most ABPM guidelines.[14,16,21]

The second objective of the present analysis was to evaluate possible differences in patients with true or white-coat RH. Differences appeared in both clinical and ABPM parameters. From a clinical point of view, a male sex, a longer duration of hypertension, a worse cardiovascular risk profile (including a higher proportion of smokers, diabetics, and target organ damage, eg, left ventricular hypertrophy, microalbuminuria, or impaired renal function), and a history of a previous cardiovascular event were all more frequent in true RH. Most of these variables remained significant in a multivariate analysis, and they probably reflect the consequences of long-term maintained high BP. However, their discriminating value in clinical practice is probably low, and ABPM must be considered mandatory to clearly distinguish between true and white-coat RH. It is noteworthy that having an older age was not related with true RH in the present study. In fact, these patients were slightly (1 year) but significantly younger, and this difference remained significant even after adjustments were made in the multivariate analysis. All of these features are in agreement with our previous results in treated hypertensive patients (independent of the number of drugs used), where a younger age, a male sex, smoking, diabetes mellitus, and target organ damage were all related to a lack of control of BP both at the office and at ABPM,[10] in contrast to BPs uncontrolled at the office but controlled at ABPM. Moreover, in untreated patients, an older age and a female sex were also related to the presence of white-coat hypertension.[12]

Previous reports of patients with RH classified after ABPM have also observed that true resistant hypertensives more frequently have diabetes mellitus and target organ damage, such as left ventricular hypertrophy and microalbuminuria,[4,5] and the incidence of cardiovascular events was higher during the follow-up of those considered true RH.[6,7] With respect to age, although some authors have reported an older age in white-coat RH,[4,17] others related old age with true resistance.[2]

When examining the circadian pattern of BP, we were able to detect some differences in this pattern distribution. Patients with true RH more frequently showed an abnormal nocturnal dip, essentially because of the higher prevalence of those whose BP increased during nighttime (the riser pattern). This abnormal nocturnal dip has also been related to a worse cardiovascular risk profile in both treated and untreated patients[13] and represents a marker of a poor prognosis in both treated hypertensives[22,23] and in the general population.[24] In RH, an abnormal dip was also related to true resistance in previous studies.[25,26]

In our cohort, most patients (75%) received all antihypertensive medications in the morning, and we did not find differences in such a proportion between those with normal or elevated ABPM values. This is in agreement with a previous report from our group indicating that, in both treated and untreated patients, clinical characteristics of those with a blunted nocturnal BP decline were similar and associated with a worse clinical profile (older age and greater proportions of diabetics and patients with overt cardiovascular disease).[13] These data do not support previous findings indicating that switching a part of the medication from morning to bedtime improves ambulatory BP control.[27] At the present time, the issue regarding the effects of antihypertensive chronotherapy on cardiovascular prognosis is still controversial,[28] although a recent study reported a reduction of cardiovascular events in patients receiving ≥1 antihypertensive drug at bedtime.[29]

The present study is an analysis made on a registry (details have been reported elsewhere)[9–13] and, thus, it has the limitations of the original study not directly focused on RH. We have included only those patients having enough information regarding both BP (office and ABPM) and antihypertensive treatment, excluding those without definite criteria of RH (<3 drugs from different classes and low doses of some of the antihypertensive used). Unfortunately, the characteristics of the registry did not allow for checking medication adherence, and we cannot discard that some patients included as having RH were not adherent to the antihypertensive drug regimen, thus possibly overestimating the true prevalence of RH.

Perspectives

It has been recognized that the estimation of the prevalence of RH was very poor, because studies were not directly addressed on this topic.[1] Previous results were usually obtained in a single referral unit, where patients were derived for specific reasons (one of them probably because of resistance to treatment). This is the first report of a large cohort of patients coming from the Spanish ABPM Registry, which relates more closely with the usual daily practice and the hypertensive population in general. Finally, true resistance is related to baseline risk, including other risk factors, target organ damage, and previous cardiovascular disease. Although some of these characteristics could be helpful in differentiating true from white-coat RH, the intensity of the association is weak, and it must be emphasized that ABPM continues to be needed and must be encouraged for a correct diagnosis and management of all hypertensive patients not controlled on ≥3 antihypertensive drugs.[30]

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Disclosures

Members of the Spanish ABPM Registry, including authors of this article, have participated in educational meetings focused on ABPM.

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CLINICAL FEATURES OF 8295 PATIENTS WITH RESISTANT HYPERTENSION CLASSIFIED ON THE BASIS OF AMBULATORY BLOOD PRESSURE MONITORING. ONLINE SUPPLEMENTAL TABLES

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SHORT TITLE: Ambulatory BP in Resistant Hypertension

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Table S1. Clinical features in resistant hypertensives with normal or elevated daytime blood pressure

Parameter	Elevated daytime BP (N=4637)	Normal daytime BP (N=3658)	P
Age, years	64.3 ± 11.7	65.3 ± 10.8	<0.001
Gender , % males	53.4	45.4	<0.001
BMI, Kg/m^2	30.4 ± 4.8	30.7 ± 5.0	0.190
Duration of hypertension, years	11.5 ± 8.7	10.8 ± 8.3	0.001
Smokers, %	15.4	10.9	<0.001
Diabetics, %	35.3	28.9	<0.001
Creatinine, µmol/L	74 [62-88]	72 [61-84]	0.012
Total cholesterol, mmol/L	5.22 ± 1.04	5.21 ± 1.08	0.655
HDL-Cholesterol, mmol/L	1.32 ± 0.38	1.35 ± 0.38	0.124
Triglycerides, mmol/L	1.61 ± 0.92	1.55 ± 0.70	0.014
UAE, mg/g	10.8 [3.5-42]	7.3 [2.7-22]	<0.001
UAE > 30 mg/g, %	29.1	19.9	<0.001
LVH by EKG, %	18.6	15.8	0.002
Previous CV disease, %	18.6	17.5	0.023
Treatment with 4 or more AH drugs, %	37.8	34.7	<0.001
Patients taking part of their medication in the evening, %	25.1	25.6	0.678

Values are mean ± standard deviation or median [interquartile range]. RH: resistant hypertension, BMI: body mass index, UAE: urinary albumin excretion, LVH: left ventricular hypertrophy, EKG: electrocardiogram, CV: cardiovascular, AH: antihypertensive.

Table S2. Differences in office, 24-hour and nighttime BP, as well as circadian pattern distribution, between RH patients with normal or elevated daytime BP.

Parameter	Elevated daytime BP (N=4637)	Normal daytime BP (N=3658)	P
Office SBP	164 ± 17	157 ±15	<0.001
Office DBP	89 ± 13	87 ± 12	<0.001
24-hour SBP	143 ± 13	119 ± 7	<0.001
24-hour DBP	79 ± 11	68 ± 7	<0.001
Nighttime SBP	127 ± 17	123 ± 10	<0.001
Nighttime DBP	67 ± 11	65 ± 8	<0.001
Circadian SBP pattern distribution			0.213
Extreme dippers, %	5.9	5.1	
Dippers, %	30.5	30.4	
Non dippers, %	43.3	44.8	
Risers, %	20.3	19.7	
Circadian DBP pattern distribution			0.112
Extreme dippers, %	18.2	19.4	
Dippers, %	42.3	42.1	
Non dippers, %	30.5	26.9	
Risers, %	9.0	11.6	

Values in mmHg, RH: resistant hypertension, SBP: systolic blood pressure, DBP: diastolic blood pressure.