Prevalence and Clinical Characteristics of Refractory Hypertension

Pedro Armario, MD, PhD; David A. Calhoun, MD; Anna Oliveras, MD, PhD; Pedro Blanch, MD, PhD; Ernest Vinyoles, MD, PhD; Jose R. Banegas, MD, PhD; Manuel Gorostidi, MD; Julián Segura, MD, PhD; Luis M. Ruilope, MD; Tanja Dudenbostel, MD; Alejandro de la Sierra, MD, PhD

Background—We aimed to estimate the prevalence of refractory hypertension (RfH) and to determine the clinical differences between these patients and resistant hypertensives (RH). Secondly, we assessed the prevalence of white-coat RfH and clinical differences between true- and white-coat RfH patients.

Methods and Results—The present analysis was conducted on the Spanish Ambulatory Blood Pressure Monitoring Registry database containing 70,997 treated hypertensive patients. RH and RfH were defined by the presence of elevated office blood pressure (≥140 and/or ≥90 mm Hg) in patients treated with at least 3 (RH) and 5 (RfH) antihypertensive drugs. White-coat RH was defined by RH with normal (<130/80 mm Hg) 24-hour blood pressure. A total of 11,972 (16.9%) patients fulfilled the standard criteria of RH, and 955 (1.4%) were considered as having RfH. Compared with RH patients, those with RfH were younger, more frequently male, and after adjusting for age and sex, had increased prevalence of target organ damage, and previous cardiovascular disease. The prevalence of white coat RfH was lower than white-coat RH (26.7% versus 37.1%, P<0.001). White-coat RfH, in comparison with those with true RfH, showed a lower prevalence of both left ventricular hypertrophy (22% versus 29.7%; P=0.018) and microalbuminuria (28.3% versus 42.9%; P=0.047).

Conclusions—The prevalence of RH was low and these patients had a greater cardiovascular risk profile compared with RH. One out of 4 patients with RfH have normal 24-hour blood pressure and less target organ damage, thus indicating the important role of ambulatory blood pressure monitoring in guiding antihypertensive therapy in difficult-to-treat patients. (J Am Heart Assoc. 2017;6:e007365. DOI: 10.1161/JAHA.117.007365.)

Key Words: refractory hypertension • resistant hypertension • target organ damage • white coat refractory hypertension
Clinical Perspective

What Is New?

- The prevalence of the white-coat effect is reported for the first time in a wide sample of refractory hypertensive patients.

What Are the Clinical Implications?

- One out of 4 patients with refractory hypertension have normal 24-hour blood pressure measurements and they also have less target organ damage.
- Ambulatory blood pressure monitoring should be encouraged for all subjects not achieving office blood pressure control, as it can help identify patients who will require additional therapies.

RFH. A recent report has suggested the white-coat effect was very uncommon in RFH patients, although results were based on a small group of patients attending a highly specialized hypertension clinic. This situation could be different when examining a broader spectrum of clinical care, which includes primary care centers.

In the present study, we aimed to assess the prevalence of RFH and white-coat RFH. Furthermore, we compared clinical characteristics between RFH and RH patients, as well as between true and white-coat RFH in a large sample of treated hypertensive patients seen in real-world (primary care and specialized hypertension units) clinical practice.

Patients and Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design

The Spanish Ambulatory BP Monitoring (ABPM) Registry was initiated in 2004 to promote the use of ABPM in clinical practice. Details of physician recruitment and characteristics of the registry have been reported elsewhere.11,12 Briefly, physicians and nurses received specific training in the technique of ABPM and used the internet-based platform that receives ABPM records, 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.13,14

The present analysis was conducted on the Spanish ABPM Registry database containing 70,997 treated patients who had enough information regarding office BP measurements, ABPM of good quality, and complete clinical information.

Clinical resistant hypertension was considered as an office systolic and diastolic BP ≥140 and/or 90 mm Hg, respectively, despite a prescribed therapeutic schedule with an appropriate combination of ≥3 antihypertensive drugs, including a diuretic. Clinical RFH was considered as an office systolic and diastolic BP ≥140 and/or 90 mm Hg, respectively, despite a prescribed therapeutic schedule with an appropriate combination of ≥5 antihypertensive drugs, including a diuretic. Patients with suspected poor adherence to antihypertensive therapy were excluded, and secondary causes of hypertension were evaluated according the clinical criteria.

The local Institutional Ethic Committees approved the study protocol. Written informed consent was obtained from all participants. The investigation conforms to the principles outlined in the declaration of Helsinki.

BP Measurements

The methodology of office BP measurements and 24-hour ABPM has been previously described by our group.2,4,11,12 Briefly, BP was measured at the office with a calibrated mercury sphygmomanometer or a validated oscillometric device, after 5 minutes rest in a sitting position. BP values were estimated as the mean of 2 readings. Thereafter, 24-hour ABPM was performed using Spacelabs 90207 automated noninvasive oscillometric device, programmed to register BP at 20-minute intervals for the 24-hour period. Valid registries had to fulfill a series of pre-established criteria, including ≥80% of systolic 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 patients’ self-reported data of going-to-bed and getting-up times. Circadian patterns were defined by calculating night-to-day ratios for systolic and diastolic BP. According to this, patients were classified as systolic or diastolic extreme dippers (night-to-day ratio <0.8), dippers (night-to-day ratio 0.8–0.9), nondippers (night-to-day ratio 0.9–1), and risers (night-to-day ratio >1).

Study Variables

Variables of each patient collected from the interview and physical examination obtained at the routine visit and from clinical records were defined and measured in accordance with international guidelines. These included age, sex, weight, body mass index, duration of hypertension, known cardiovascular risk factors, biochemical values of creatinine, and lipid profile, target organ damage including urinary albumin excretion (microalbuminuria defined as values >30 mg/g of creatinine), ECG (left ventricular hypertrophy defined as a
Sokolow-Lyon voltage >38 mm and/or Cornell duration/voltage index >2440 mm/ms, and clinical cardiovascular disease: coronary heart disease, congestive heart failure, or cerebrovascular disease. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease-Epidemiology Collaborative equation. Diabetes mellitus was diagnosed using the medical history if the patient was under antidiabetic treatment or by 2 or more fasting plasma glucose determinations ≥7.0 mmol/L (126 mg/dL). Dyslipidemia was considered to be present if patients were being treated with lipid-lowering drugs and/or total cholesterol was >5 mmol/L (190 mg/dL), low-density lipoprotein cholesterol was >3.0 mmol/L (115 mg/dL), high-density lipoprotein cholesterol was <1.0 mmol/L (40 mg/dL) in men or <1.2 mmol/L (46 mg/dL) in women, or triglycerides were >1.7 mmol/L (150 mg/dL). Moreover, details about antihypertensive treatment (including number and types of drugs) were also collected.

Statistical Analysis

Data are presented as absolute 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 χ² test for qualitative variables and the Student t test (or Mann–Whitney test) for quantitative data. In addition, general linear models for quantitative variables and multiple logistic regression for qualitative variables were used for the assessment of differences after adjusting for age and sex. The SPSS Windows version 19.0 software (SPSS Inc, Chicago, IL) was used for statistical analysis.

Results

A total of 11,972 (16.9%) patients fulfilled the standard criteria of RH (office systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mm Hg despite the use of ≥3 antihypertensive drugs), and 955 (7.9% of RH; 1.4% of the entire treated group) were considered as having RfH (elevated office BP despite the simultaneous use of 5 or more antihypertensive agents).

Compared with RH, patients with RfH were younger, more frequently males, had a longer duration of hypertension, and higher prevalence of obesity, diabetes mellitus, and dyslipidemia. The prevalence of chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m²) was also higher in RfH patients. Regarding organ damage, after adjusting for age and sex, microalbuminuria, ECG-based left ventricular hypertrophy and previous history of a cardiovascular event were also significantly higher in RfH, compared with RH patients (Table 1).

All groups of antihypertensive drugs were more commonly used in RfH versus RH patients, including mineralocorticoid receptor antagonists, which amounted to 11.5% of RfH (n = 111; 88 with spironolactone and 22 with eplerenone), and to 1.4% in RH (P < 0.001 for the comparison between groups) (Table 2).

Table 1. Clinical Features in RfHs in Comparison With RH Subjects

<table>
<thead>
<tr>
<th></th>
<th>RH (n=955)</th>
<th>RH (n=11 017)</th>
<th>P Value</th>
<th>P Adjusted for Age and Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.9 (11.0)</td>
<td>64.9 (11.6)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Sex, % men</td>
<td>56.3</td>
<td>51.3</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Duration hypertension, y</td>
<td>13.3 (9.2)</td>
<td>10.9 (8.5)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31.6 (4.8)</td>
<td>30.7 (4.8)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity (BMI ≥30), %</td>
<td>59.6</td>
<td>51.4</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>48.1</td>
<td>33.5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>15.1</td>
<td>12.9</td>
<td>0.056</td>
<td>0.290</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>61.9</td>
<td>51.7</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVH by ECG, %</td>
<td>27.6</td>
<td>14.9</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.20 (0.69)</td>
<td>1.02 (0.42)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min per 1.73 m², %</td>
<td>32.1</td>
<td>23.6</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UAE, mg/g</td>
<td>14.2 [4–58.5]</td>
<td>8.9 [3.3–28]</td>
<td>&lt;0.005</td>
<td>0.101</td>
</tr>
<tr>
<td>UAE ≥30 mg/g, %</td>
<td>38.3</td>
<td>24.5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous cardiovascular disease, %</td>
<td>20.5</td>
<td>14.7</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean (SD) or median [interquartile range]. BMI indicates body mass index; eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy; RfH, refractory hypertension; RH, resistant hypertension; UAE, urinary albumin excretion.
Table 3 shows office and ambulatory BP values in patients with RH and RH. After adjusting for age and sex, the former group had significantly higher values for office, 24-hour, daytime and nighttime systolic BP, and for nighttime diastolic BP. RH was also associated with higher night-to-day ratios for both systolic and diastolic BP. As a consequence, the proportion of reduced dippers/risers was increased in RH, compared with RH patients (P<0.001 for both comparisons) (Figure).

A total of 255 patients among 955 with RH (26.7%) had normal 24-hour BP (<130/80 mm Hg). The prevalence of white-coat RH was significantly lower when compared with RH (37.1% with normal 24-hour BP; P<0.001). When comparing patients with true, versus white-coat RH (Table 4), the former group were more frequently males, with a longer duration of hypertension, and more frequently had left ventricular hypertrophy on ECG or microalbuminuria.

Discussion
The main findings of the present study were, firstly, that the prevalence of this particular phenotype of RH was low (1.4% of treated hypertensive) but still accounts for a significant part of the population of RH (7.9%). Secondly, cardiovascular risk was higher in the group of RH in comparison to RH. Thirdly, the prevalence of white-coat RH was significantly lower when compared with RH (37.1% with normal 24-hour BP; P<0.001). When comparing patients with true, versus white-coat RH (Table 4), the former group were more frequently males, with a longer duration of hypertension, and more frequently had left ventricular hypertrophy on ECG or microalbuminuria.

In the present study, only 1.4% of treated hypertensive patients had RH. The prevalence of RH observed in the participants in the REGARD (Reasons for Geographic And Racial Differences in Stroke) Study was even lower (0.5%). In the present study, 7.9% of RH had RH. Dudenbostel et al9,17 reported that the prevalence of RH in a referral hypertension

Table 2. Antihypertensive Drug Classes in Patients With RH or RH

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>RH (n=955)</th>
<th>RH (n=11 017)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics*</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>RAS blockers</td>
<td>99.4%</td>
<td>95.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CCB</td>
<td>84.9%</td>
<td>58.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>77.2%</td>
<td>43.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>α-Blockers</td>
<td>62.4%</td>
<td>17.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Central blocking agents</td>
<td>12.1%</td>
<td>1.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aldosterone antagonents</td>
<td>11.5%</td>
<td>1.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>2.2%</td>
<td>0.2%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Central blocking agents include clonidine, moxonidine, reserpine, and α-methyldopa. Vasodilators include hydralazine and minoxidil. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; RAS, renin–angiotensin system; RH, refractory hypertension; RH, resistant hypertension. *Required for definition. RAS blockers include ACE inhibitors, ARB, and aliskiren.

Figure. Distribution of circadian patterns in refractory and resistant hypertensive patients. The former group has a higher proportion of reduced dippers and risers for both systolic and diastolic BP (P<0.001 for both comparisons). BP indicates blood pressure.

Can you provide a summary of the main findings of the present study? The main findings of the present study were:

1. The prevalence of a particular phenotype of RH was low (1.4% of treated hypertensive) but still accounts for a significant part of the population of RH (7.9%).
2. Cardiovascular risk was higher in the group of RH compared to RH.
3. The prevalence of white-coat RH was significantly lower when compared to RH (37.1% with normal 24-hour BP; P<0.001).
4. When comparing patients with true, versus white-coat RH, the former group were more frequently males, with a longer duration of hypertension, and more frequently had left ventricular hypertrophy on ECG or microalbuminuria.

What is the prevalence of RH observed in the REGARD (Reasons for Geographic And Racial Differences in Stroke) Study? The prevalence of RH observed in the REGARD study was even lower at 0.5%.

In the present study, only 1.4% of treated hypertensive patients had RH. The prevalence of RH observed in the participants in the REGARD study was even lower (0.5%). In the present study, 7.9% of RH had RH. Dudenbostel et al. reported that the prevalence of RH in a referral hypertension setting was lower than expected.
unit was ≥5%, and Calhoun et al estimated a prevalence of Rhf of 3.6% of subjects with controlled or uncontrolled RH. The slightly higher prevalence observed in our study could be explained by 2 reasons: first, because low BP control is one of the main indications for ABPM, it is possible that the Spanish Registry was selecting more subjects with difficult-to-treat hypertension than other population-based studies. Secondly, the prevalence of Rhf depends critically on the definition we did not specify. Differences between Rhf and Rh go in the same direction as those observed when comparing RH versus controlled patients, thus suggesting that, when markedly present, the same characteristics leading to RH would be responsible for treatment failure and development of Rhf, as an extreme phenotype.

Another important novel feature in Rhf patients is the worse circadian profile in comparison to RH. Not only are office and ambulatory systolic blood pressure higher, but also differences are more important in nighttime BP, and the nocturnal decline in BP is lower. Both nocturnal BP elevation and reduced nocturnal dipping have been associated with increased prevalence of target organ damage and a worse cardiovascular outcome in patients with Rhf.

We have also reported here that 1 out of 4 Rhf patients in the present study show normal 24-hour BP, suggesting that the white-coat effect accounts for a quite high rate of patients with apparent treatment failure. Although its prevalence was considerably lower than that of RH, it is surprising that those patients were still receiving 5 or more drugs based only on clinic BP, without considering ABPM in earlier steps of management. A recent report has found that normal ABPM of Rhf was present only in 2 out of 31 patients with Rhf. Wees therefore that perhaps a previous normal ABPM has prevented an increase in antihypertensive treatment in patients attending a specialized hypertension clinic, thus selecting only those with a true resistance to 5 drugs. In addition, the report from Siddiqi et al used automated office BP monitoring, which has been claimed to result in lower values than daytime BP obtained through ABPM. In contrast, our data derive from the implementation of ABPM in clinical settings where this tool was not available.

Table 4. Clinical Features in Rhfs With or Without Elevated 24-H BP

<table>
<thead>
<tr>
<th></th>
<th>True Rhf (n=700)</th>
<th>White-Coat Rhf (n=255)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.9 (11.0)</td>
<td>63.9 (10.7)</td>
<td>0.984</td>
</tr>
<tr>
<td>Sex, % men</td>
<td>58.4</td>
<td>50.6</td>
<td>0.033</td>
</tr>
<tr>
<td>Duration hypertension, y</td>
<td>13.7 (9.2)</td>
<td>12.3 (9.3)</td>
<td>0.040</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31.6 (4.9)</td>
<td>31.5 (4.8)</td>
<td>0.703</td>
</tr>
<tr>
<td>Obesity (BMI ≥30), %</td>
<td>60.1</td>
<td>58.0</td>
<td>0.602</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>48.9</td>
<td>45.9</td>
<td>0.422</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>16.3</td>
<td>11.8</td>
<td>0.102</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>63.7</td>
<td>56.9</td>
<td>0.060</td>
</tr>
<tr>
<td>LVH by ECG, %</td>
<td>29.7</td>
<td>22.0</td>
<td>0.018</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min per 1.73 m², %</td>
<td>32.0</td>
<td>32.2</td>
<td>0.962</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.21 (0.69)</td>
<td>1.16 (0.66)</td>
<td>0.475</td>
</tr>
<tr>
<td>UAE, mg/g</td>
<td>16.8 [5.0–99.0]</td>
<td>8.0 [3.1–32]</td>
<td>0.010</td>
</tr>
<tr>
<td>UAE ≥30 mg/g, %</td>
<td>42.9</td>
<td>28.3</td>
<td>0.047</td>
</tr>
<tr>
<td>Previous cardiovascular disease, %</td>
<td>20.6</td>
<td>20.4</td>
<td>0.952</td>
</tr>
</tbody>
</table>

Values are mean (SD) or median [interquartile range]. BMI indicates body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy; Rhf, refractory hypertension; UAE, urinary albumin excretion.
Characteristics of Refractory Hypertension  Armario et al

Previously unavailable. We can also speculate that most patients were uptitrated to 5 or more antihypertensive drugs without considering ABPM.

Differences in ambulatory in RfH were associated with differences in the cardiovascular risk profile, as left ventricular hypertrophy and microalbuminuria were more common in true- versus white-coat RfH patients. It seems reasonable to advocate for ABPM to guide therapeutic decisions, at least in those patients not achieving BP control with 3 antihypertensive drugs.

Our study has some limitations. First, it is a cross-sectional study that allows only descriptive associations, but this was the main objective of the present report; secondly, like other registries, the Spanish registry was not directly focused on RfH.

Another limitation we must mention is that the diagnosis of RH or RfH is probable, but not absolutely confirmed, since we cannot ensure that all secondary causes of hypertension have been discarded in such a large database, not just the suboptimal adherence. We must remark that according to the study-accepted definition, the criterion used to define refractory hypertension required the use of a diuretic, but not necessarily a mineralocorticoid receptor antagonist. Most patients were included in this database before the publication of the results of the PATHWAY-2 Study.19 Certainly, in the light of recent evidence, the percentage of patients with noncontrolled BP that receive a mineralocorticoid receptor antagonist in our cohort is low. In addition, only whites have been included in the present study, and our results cannot be extrapolated to other populations; other previous studies have shown that RfH was more common among patients of black ancestry.8

In conclusion, 1.4% of treated hypertensive patients are not controlled even they are treated with 5 or more antihypertensive drugs. These RH patients, in comparison to RH, have some distinctive clinical features of a worse cardiovascular risk profile and more target organ damage, probably associated with higher ambulatory BP and more pronounced circadian alterations. One in 4 RfH patients have normal 24-hour BP (white-coat RfH) also exhibiting less organ damage than those with true RfH. Our findings are relevant for clinical practice because given the magnitude of white-coat RfH, physicians should be aware of avoiding overdiagnosing and overtreating these patients, based only on clinic BP if the decisions rely exclusively on clinic BP. Standardized repeated BP measurement obtained by patients at home during several days has also been recommended in clinical practice, but in patients with RH and RfH 24-hour ABPM is more reliable and also provides relevant information about nighttime BP and circadian pattern. Moreover, given the low use of the effective-proven mineralocorticoid antagonist receptor drugs in RfH, a large room for improvement in BP control remains as a simple, reasonable perspective.

Acknowledgments

We thank all of the participants of the Spanish ABPM Registry.

Sources of Funding

The Spanish ABPM Registry was initiated and is maintained by an unrestricted grant from Lacer Laboratories, Spain, and receives support by the Spanish Society of Hypertension.

Disclosures

None.

References


Prevalence and Clinical Characteristics of Refractory Hypertension
Pedro Armario, David A. Calhoun, Anna Oliveras, Pedro Blanch, Ernest Vinyoles, Jose R. Banegas, Manuel Gorostidi, Julián Segura, Luis M. Ruilope, Tanja Dudenbostel and Alejandro de la Sierra

*J Am Heart Assoc.* 2017;6:e007365; originally published December 7, 2017;
doi: 10.1161/JAHA.117.007365

The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://jaha.ahajournals.org/content/6/12/e007365