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## Brief report

## Misdiagnosis of resistant hypertension: Real frequency of true resistant hypertension in patients with suspected resistance to treatment<sup>☆</sup>

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## ABSTRACT

**Introduction:** Resistant hypertension (RH) has been defined as failure to control office blood pressure (BP) despite the use of  $\geq 3$  different antihypertensive agents at optimal doses, including, ideally, a diuretic. Apparent RH, defines patients with an incorrect diagnosis of RH due to different causes. The objective was to determine whether most patients with RH in fact have apparent but not true RH.

**Patients and methods:** Observational study involving 93 patients with suspected RH, being 60 patients finally included. Screening for secondary causes of hypertension was performed. True RH was defined as office BP  $> 140/90$  mmHg despite full doses of 3 antihypertensive drugs including a diuretic.

**Results:** Mean age  $63.7 \pm 9.8$  years, 68.3% were male. Office BP  $154.3 \pm 14.4/84.4 \pm 13.7$  mmHg. Of the 60 patients, 23.3% had white coat effect, 3.3% did not have a diuretic and 8.3% were non-adherent-to-treatment. Accordingly, 58.3% were classified as true RH. Spironolactone was added in 62.5% of patients of whom 78.4% achieved ambulatory BP control.

**Discussion:** Almost half of the patients with suspected RH were not really true RH. We provide more evidence of excess of fluid retention as an underlying cause of lack of BP control in patients with RH, reinforce the relevant paper of spironolactone for the management in those patients.

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### Diagnóstico erróneo de la hipertensión resistente: frecuencia real de la hipertensión resistente en los pacientes con sospecha de resistencia al tratamiento

## RESUMEN

**Introducción:** La hipertensión resistente (HR) se ha definido como la falta de control de la presión arterial (PA) a pesar de la administración de  $\geq 3$  fármacos antihipertensivos a dosis óptimas, incluyendo, idealmente, un diurético. La HR aparente se define por un diagnóstico incorrecto de HR, debido a diferentes causas. El objetivo fue determinar si la mayoría de los pacientes con sospecha de HR tienen HR verdadera o HR aparente.

**Pacientes y métodos:** Estudio observacional que incluyó a 93 pacientes con sospecha de HR, siendo finalmente incluidos 60. Se realizó el cribado de causas secundarias de hipertensión. La HR verdadera se definió como PA  $> 140/90$  mmHg a pesar del tratamiento con dosis completas de 3 fármacos antihipertensivos incluyendo un diurético tiazídico.

## Palabras clave:

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**Resultados:** Edad media  $63,7 \pm 9,8$  años, el 68,3% varones. PA clínica  $154,3 \pm 14,4/84,4 \pm 13,7$  mmHg. De los 60 pacientes, el 23,3% tenía efecto bata blanca, el 3,3% no recibía diurético y el 8,3% no era adherente al tratamiento. El 58,3% de los pacientes se clasificaron como HR verdadera. Se añadió espironolactona en el 62,5% de los pacientes, alcanzando el 78,4% el control ambulatorio de la PA.

**Discusión:** Casi la mitad de los pacientes con sospecha de HR, realmente no lo son. El estudio proporciona mayor evidencia sobre el exceso de retención de líquido como causa subyacente de la falta de control de la PA en pacientes con HR, reforzando el relevante papel de la espironolactona en el manejo de estos pacientes.

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The term *resistant hypertension* (RH) has been used since the early 1960s to identify patients with difficult-to-treat hypertension. In the 5 decades since then, RH has consistently been defined as failure to control office blood pressure (BP)  $\leq 140/90$  mmHg despite the use of  $\geq 3$  antihypertensive agents at optimal doses, ideally, including a diuretic.<sup>1</sup> In 2008, the American Heart Association extended the definition to include patients with well controlled BP, although requiring  $\geq 4$  antihypertensive medications. This clinical situation is also known as controlled resistant hypertension.<sup>2</sup> The term *refractory hypertension* should be restricted to a small group of patients who are truly refractory to pharmacological treatment, with normalization of BP  $\leq 140/90$  mmHg not being possible even with maximum antihypertensive therapy. Longitudinal studies indicate that patients with true RH have a worse prognosis than general hypertensive cohorts, both in terms of cardiovascular events and total mortality, and therefore correct identification of these patients is necessary to reduce their cardiovascular risk.<sup>1</sup>

The prevalence of RH has been derived from post hoc analyses of large prevention of morbidity and mortality clinical trials, population-based studies and hypertension registries,<sup>3</sup> and is estimated to be 10–12% of all hypertensive patients. However, more important than the prevalence of suspected RH, is clarification of how many of these patients have true RH and how many have refractory hypertension and are candidates for interventional therapies. Many patients with suspected RH have the so-called *apparent RH*, which defines patients with an incorrect diagnosis of RH due to inadequate drug doses or inadequate combinations, non-adherence to treatment, or inaccurate office BP measurement in subjects with a white-coat effect (WCE),<sup>4</sup> or incorrect diagnosis of identifiable causes of secondary HT. These clinical situations are common and may represent more than 50% of all patients with suspected RH. The cardiovascular prognosis of patients with apparent RH is similar to that of all hypertensive patients and clearly better than that of patients with true RH. Therefore, an earlier and accurate diagnosis of true RH is necessary in order to reduce their cardiovascular risk and optimize treatment.<sup>5</sup>

The objective of our study was to determine whether most patients with RH in fact have apparent but not true RH, and to identify the underlying causes related to the misdiagnosis of RH and determine the real frequency of true RH and refractory hypertension in our population.

We conducted an observational study involving 93 consecutively potential patients referred to our Hypertension Unit (Hospital Clinic, Barcelona) for suspected RH by general practitioners (2014–2015). Of them, 6 patients refused to participate into the study and 27 not meet inclusion criteria for RH definition (12 patients received  $\leq 2$  antihypertensive drugs and 15 patients had office BP  $< 140/90$  mmHg). Finally, 60 patients were included into the study. At baseline, clinical and ambulatory BP (ABPM) values were collected. Screening for secondary causes of hypertension included a clinical history, laboratory analyses and imaging. Noninvasive thoracic electrical bioimpedance (TEB) was used to evaluate hemodynamic modulators and the hemodynamic status. We followed them at 3 months according to usual clinical practice.

True RH was defined as office BP  $\geq 140/90$  mmHg (and 24-h ABPM  $\geq 130/80$  mmHg) despite treatment with full doses of 3 antihypertensive drugs including a thiazide diuretic, and after exclusion of nonadherence to treatment, white-coat effect (WCE), pseudohypertension, and secondary causes of HT. Refractory hypertension was defined as the uncontrolled BP despite treatment with  $\geq 4$  drugs including spironolactone.

Baseline characteristics are summarized in [Table 1s \(available in on-line supplementary material\)](#). Mean age was  $63.7 \pm 9.8$  years, 68.3% were male and mean office BP values were  $154.3 \pm 14.4/84.4 \pm 13.7$  mmHg. Only 2 patients received 4 antihypertensive drugs with controlled office BP. Sixty-five per cent of patients presented dyslipidemia, 58.3% obesity and 50% diabetes mellitus. The main causes of RH found are shown in [Fig. 1](#). Of the 60 patients studied, 23.3% had WCE, 3.3% did not have a diuretic in the therapeutic regimen, 8.3% were non-adherent to the prescribed medication, 5% had obstructive sleep apnoea syndrome, and 1.7% had significant renal artery stenosis. Accordingly, 35 (58.3%) of patients were classified as true RH. These results are similar to those of other studies that clearly showed that apparent RH occurs in a large proportion of patients who are undertreated or misdiagnosed.<sup>4,5</sup>

[Table 1](#) shows the characteristics of patients with true RH and apparent RH. Patients with true RH had a higher prevalence of diabetes, metabolic syndrome, and target organ damage, and significant higher ABPM values than patients with apparent RH, reinforcing the idea that these patients tends to be at higher cardiovascular risk and have a worse prognosis. Surely, the small sample size may contribute not to reach statistical significance. No other significance differences were observed for gender, age or renal disease.

Although RH has multifactorial causes, evidence suggests that excess fluid retention plays an important pathogenic role.<sup>5</sup> This hypothesis has been sustained by studies that reported better BP control with the intensification of diuretic therapy using different diuretics (clorthalidone or spironolactone)<sup>6</sup> added to a standard thiazide diuretic in RH patients. In our study, the assessment of the hemodynamic profile at baseline, showed that patients with true RH had greater hypervolemia than patients with apparent RH (94.4% vs 70.8%,  $p = 0.023$ ) and a greater prevalence of a hypoinotropic pattern (72.2% vs 45.8%;  $p = 0.028$ , respectively).

After therapeutic adjustment based on the hemodynamic pattern, 63.3% of true RH patients achieved ambulatory BP control (mean 24-h  $< 130/80$  mmHg) vs 80% of apparent RH patients. Mean number of antihypertensive drugs at the end of the study was  $4.15 \pm 0.79$ . Spironolactone was added in 62.5% of patients of whom 78.4% achieved ABPM control. Only 3 patients (5%) were truly cases of refractory hypertension.

Our results emphasize that almost half of the patients with suspected RH were not really true RH. Notice that, the most frequent causes of apparent HR are WCE, under treatment, nonadherence, and other causes of the misdiagnosis of secondary hypertension. Furthermore, we provide more evidence about excess fluid retention as a relevant underlying causes of RH supported by a great

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