

## Clinical features of resistant and refractories hypertensives submitted to 24-hour ABPM

### Características clínicas de pacientes hipertensos resistentes e refratários submetidos à MAPA de 24 horas

### Características clínicas de los pacientes hipertensos resistentes y refractarios sometidos a ABPM 24 horas

DOI:10.34119/bjhrv7n3-052

Submitted: April 08th, 2024

Approved: April 29th, 2024

#### **Ricardo Pereira Silva**

Residency in Cardiology from Instituto Dante Pazzanese, Doctorate in Cardiology from Universidade de São Paulo (USP)  
Institution: Universidade Federal do Ceará  
Address: Fortaleza, Ceará, Brasil  
E-mail: ricardopereirasilva.ufc@gmail.com

#### **Pedro Felipe de Sousa Pinheiro**

Graduating in Medicine  
Institution: Universidade Federal do Ceará  
Address: Fortaleza, Ceará, Brasil  
E-mail: pedrofeliopedu@gmail.com

#### **Haniel Douglas Brito**

Graduating in Medicine  
Institution: Universidade Federal do Ceará  
Address: Fortaleza, Ceará, Brasil  
E-mail: haniel.brito20@gmail.com

#### **Davi Veras Araújo**

Graduating in Medicine  
Institution: Universidade Federal do Ceará  
Address: Fortaleza, Ceará, Brasil  
E-mail: daviveras@alu.ufc.br

#### **Jean Lopes Queiroz**

Graduating in Medicine  
Institution: Universidade Federal do Ceará  
Address: Fortaleza, Ceará, Brasil  
E-mail: jean.lopes@alu.ufc.br

**Thiago Christoferson Costa Firmo**

Graduating in Medicine  
Institution: Universidade Federal do Ceará  
Address: Fortaleza, Ceará, Brasil  
E-mail: thiagomedicina.ufc@gmail.com

**Antônio Brazil Viana**

Master in Clinical Research from Hospital das Clínicas de Porto Alegres - Universidade Federal do Rio Grande do Sul  
Institution: Universidade Federal do Ceará  
Address: Fortaleza, Ceará, Brasil  
E-mail: brazilestatistico@gmail.com

**Elana Couto de Alencar Daniel**

Residency in Cardiology from Hospital de Messejana - Dr. Carlos Alberto Studart Gomes, MSc in Cardiovascular Sciences  
Institution: Universidade Federal do Ceará  
Address: Fortaleza, Ceará, Brasil  
E-mail: elana\_alencar@hotmail.com

**ABSTRACT**

Ten to twenty percent of patients with hypertension are considered resistant to treatment. Resistant hypertension is one in which the patient cannot be controlled with the use of three drugs at maximum doses, including a diuretic, or when blood pressure (BP) is controlled with the use of four or more anti-hypertensive drugs. Refractory hypertension is an extreme phenotype of resistant hypertension, when the BP cannot be controlled despite the usage of four anti-hypertensives. **PURPOSE-** evaluate the clinical profile of resistant and refractory hypertensives by ABPM. **METHODS-** From January of 2019 to June of 2022, a total of 669 ABPMs were performed at Unicordis., in which three or more drugs were used in the therapy. We divided these patients into three groups: I) patients who achieved BP control with three drugs; II) patients with resistant hypertension III) patients with refractory hypertension. **RESULTS-** We observed that 317 had their BP controlled with three drugs (47%), 275 patients (41%) were considered to have resistant hypertension, and 77 patients were in the refractory hypertension group (12%). When we divided the number of patients with refractory hypertension(77) by the sum of patients with resistant and refractory SAH (352), we have that refractory hypertension was present in 21% of the total cases of resistant SAH. **CONCLUSIONS-** Older ages, male gender, and higher BMI were more present in the resistant group than in the control group. Older ages and higher incidence of DM and COPD were more frequent in the refractory group than in the control group.

**Keywords:** resistant, refractories, hypertensives, 24-hour ABPM.

**RESUMO**

Dez a vinte por cento dos pacientes com hipertensão são considerados resistentes ao tratamento. A hipertensão resistente é aquela em que o paciente não pode ser controlado com o uso de três fármacos em doses máximas, incluindo um diurético, ou quando a pressão arterial é controlada com o uso de quatro ou mais fármacos anti-hipertensivos. Hipertensão refratária é um fenótipo extremo de hipertensão resistente, quando a pressão arterial não pode ser controlada apesar do uso de quatro anti-hipertensivos. **PROPÓSITO** - avaliar o perfil clínico de hipertensos resistentes e refratários pela ABPM. **MÉTODOS** - De janeiro de 2019 a junho de

2022, foram realizados 669 ABPMs no Unicordis., nos quais três ou mais fármacos foram utilizados na terapia. Dividimos estes doentes em três grupos: I) doentes que atingiram o controlo da pressão arterial com três fármacos; II) doentes com hipertensão resistente III) doentes com hipertensão refratária . **RESULTADOS-** Observamos que 317 tiveram a PA controlada com três fármacos (47%), 275 pacientes (41%) foram considerados com hipertensão resistente e 77 pacientes estavam no grupo hipertensão refratária (12%). Quando dividimos o número de pacientes com hipertensão refratária(77) pela soma dos pacientes com SAH resistente e refratária (352), temos que a hipertensão refratária estava presente em 21% do total de casos de SAH resistente. **CONCLUSÕES -** Idade avançada, sexo masculino e IMC mais elevado estavam mais presentes no grupo resistente do que no grupo controle. Idades mais velhas e maior incidência de DM e DPOC foram mais frequentes no grupo refratário do que no grupo controle.

**Palavras-chave:** resistentes, refratários, hipertensivos, ABPM 24 horas.

## RESUMEN

Entre el 10 y el 20% de los pacientes con hipertensión se consideran resistentes al tratamiento. La hipertensión resistente es aquella en la que el paciente no puede controlarse con el uso de tres fármacos en dosis máximas, incluyendo un diurético, o cuando la presión arterial se controla con el uso de cuatro o más fármacos antihipertensivos. La hipertensión refractaria es un fenotipo extremo de hipertensión resistente, en la que la presión arterial no puede controlarse a pesar del uso de cuatro antihipertensivos. **OBJETIVO:** evaluar el perfil clínico de los hipertensos resistentes y refractarios por MAPA. **MÉTODOS -** De enero de 2019 a junio de 2022, se realizaron 669 ABPMs en Unicordis, en las que se utilizaron tres o más fármacos en terapia. Los pacientes fueron divididos en tres grupos: I) aquellos que lograron el control de la presión arterial con tres fármacos; II) los pacientes con hipertensión resistente; III) los pacientes con hipertensión refractaria. **RESULTADOS-** Se observó que 317 pacientes tenían PA controlada con tres medicamentos (47%), 275 pacientes (41%) fueron considerados con hipertensión resistente, y 77 pacientes estaban en el grupo de hipertensión refractaria (12%). Al dividir el número de pacientes con hipertensión refractaria (77) por la suma de pacientes con HAS resistente y refractaria (352), se encontró que la hipertensión refractaria estaba presente en el 21% del total de casos de HAS refractaria. **CONCLUSIONES -** La edad avanzada, el sexo masculino y el mayor IMC estuvieron más presentes en el grupo resistente que en el grupo control. Las edades mayores y mayor incidencia de DM y EPOC fueron más frecuentes en el grupo refractario que en el grupo control.

**Palabras clave:** resistente, refractario, hipertenso, ABPM 24 horas.

## 1 INTRODUCTION

Ten to twenty percent of patients with hypertension are considered resistant to treatment. Resistant hypertension is one which the patient cannot be controlled with the use of three drugs at maximum doses, including a diuretic, or when blood pressure (BP) is controlled with the use of four or more anti-hypertensive drugs. The first american and european guidelines that addressed determination and treatment of resistant hypertension date from

2018<sup>1-2</sup>. The finding of resistant hypertension is related to advanced age<sup>17</sup>, obesity, chronic kidney disease and obstructive sleep apnea syndrome (OSAS)<sup>18</sup>. Because these factors are becoming more prevalent with the aging of the population, we can also expect an increase in resistant hypertension incidence<sup>3</sup>. There is controversy on the decision of which is the best method to determine the non-adherence to anti-hypertensive therapy, the main cause of resistant hypertension<sup>4</sup>. Methods to evaluate the adherence to the anti-hypertensive therapeutic can be direct or indirect. Indirect methods are based on self-reported adhesion and can be easily manipulated by the patient. Directly observed and monitored drug-intake are direct methods<sup>5</sup>. Although the classic definition of resistant hypertension is based on PA levels above 140/90 mmHg, some authors believe that 130/80 mmHg levels are the best predictors of uncontrolled BP outside the clinic<sup>6</sup>. Refractory hypertension is an extreme phenotype of resistant hypertension, when the BP cannot be controlled despite the usage of four anti-hypertensives, including a thiazide diuretic and a mineralocorticoid receptor antagonist. Refractory hypertension corresponds to 5-8% of resistant hypertension cases and seems to be influenced by the increase of sympathetic activity. Refractory hypertension appears to be more frequent in women, young and black patients than resistant hypertension. Resistant and refractory hypertension are associated with microalbuminuria, left ventricle hypertrophy, chronic kidney disease, stroke and cardiovascular diseases<sup>7-8</sup>. Patients with refractory hypertension are more likely to have cardiovascular events and have a higher mortality than patients with resistant but not refractory hypertension<sup>9</sup>. 24-hour Ambulatory Blood Pressure Monitoring (ABPM) has a relevant role not only in the diagnosis of resistant and refractory hypertension, but also in the prognosis of diagnosed and apparently uncontrolled resistant hypertension, because this is not a rare entity and it is associated with a higher cardiovascular morbidity and mortality<sup>10-11</sup>.

Target organ damage systematic research is a simple and cheap instrument with high predictive value for resistant hypertension (85%), it can be used to prioritize patients who will need ABPM<sup>12</sup>. Some authors believe that the 24-hour ABPM must be used serially in the management of resistant hypertension<sup>13</sup>. 24-hour ABPM can also be useful to undo the diagnosis of resistant hypertension. When this method is used, 30 to 35% of patients who had a previous diagnosis of resistant hypertension show a well controlled BP in the ambulatory system<sup>14</sup>. A strategy to combine ABPM with therapeutic adherence monitoring and the use of triple anti-hypertensive therapy can normalize the systolic BP in half of the patients with apparent resistant hypertension<sup>15</sup>. Besides ABPM, Home Blood Pressure Monitoring (HBPM) also demonstrates association with cardiovascular outcomes<sup>16</sup>. The objective of this paper is to evaluate the clinical profile of resistant and refractory hypertensives by ABPM.

## 2 METHODS AND MATERIALS

From January of 2019 to June of 2022, a total of 8,382 ABPMs were performed at Unicordis. Of these, 3,812 had the goal of diagnosing SAH and 4,570 were requested for therapeutic evaluation of SAH. Among the latter, in 669 of them, three or more drugs were used in the therapy. We divided these 669 patients into three groups: I) patients who achieved BP control with three drugs; II) patients with resistant SAH (those who did not achieve BP control with three drugs or who achieved control with four drugs), III) patients with refractory SAH (those who did not achieve BP control with four drugs or who achieved control with five or more drugs).

These three groups will be compared regarding: mean age, male/female sex ratio, body mass index (BMI), diagnosis of hypertension (HBP), diabetes mellitus (DM), coronary artery disease (CAD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and obstructive sleep apnea syndrome (OSAS).

The project was approved by Universidade Federal do Ceará Ethics Committee, on 10Mar2023, with number 5.936.349

### 2.1 STATISTICAL ANALYSIS

The quantitative variable age was described as mean and standard deviation. For the categorical variables (all others), data were expressed as frequency and prevalence rate. The groups were compared using the following tests: Kruskal-Wallis, Pearson's chi-square and Fisher's exact test.

## 3 RESULTS

Our study found that among 669 patients who required at least three drugs for BP control, 317 had their BP controlled with three drugs (47%), 275 patients (41%) were considered to have resistant hypertension, and 77 patients were in the refractory hypertension group (12%). When we divided number of patients with refractory SAH (77) by the sum of patients with resistant and refractory SAH (352), we have that refractory hypertension was present in 21% of the total cases of resistant SAH.

Older ages, male gender, and higher BMI were more present in the resistant group than in the control group. Older ages and higher incidence of DM and COPD were more frequent in

the refractory group than in the control group. There was no difference between the groups in the proportion of subjects with dyslipidemia, PAD, arrhythmia, HF, CAD or RF, nor in the proportion of pregnant women, postmenopausal women, smokers, OSAS patients, or patients with a history of stroke (table 1, central figure).

Table 1- comparison among controled, resistant and refractory hipertension patients

	Total	Controlled	Resistant	Refractory	p-value	C x F	C x S	F x S
N	669	317	275	77				
Age	68 ± 14 (69)	68 ± 13 (69)	67 ± 14 (68)	71 ± 14 (73)	<b>0.049</b>	0.070	>0.9	0.064
Sex					<b>&lt;0.001</b>			
F	357 (54%)	191 (61%)	123 (45%)	43 (57%)				
M	304 (46%)	123 (39%)	149 (55%)	32 (43%)				
BMI	28.7 ± 5.0 (28.6)	28.2 ± 5.1 (28.0)	29.2 ± 4.8 (29.2)	28.9 ± 4.8 (28.7)	<b>0.027</b>	0.9	0.023	>0.9
DM	200 (30%)	85 (27%)	76 (28%)	39 (51%)	<b>&lt;0.001</b>			
Dyslipidemia	256 (38%)	128 (40%)	97 (35%)	31 (40%)	0.4			
POAD	44 (6.6%)	23 (7.3%)	17 (6.2%)	4 (5.2%)	0.8			
Arrhythmia	114 (17%)	52 (16%)	50 (18%)	12 (16%)	0.8			
HF	27 (4.0%)	12 (3.8%)	9 (3.3%)	6 (7.8%)	0.2			
Pulmonary disease	25 (3.7%)	11 (3.5%)	7 (2.5%)	7 (9.1%)	<b>0.036</b>			
CAD	52 (7.8%)	23 (7.3%)	22 (8.0%)	7 (9.1%)	0.9			
RF	28 (4.2%)	12 (3.8%)	11 (4.0%)	5 (6.5%)	0.5			
Pregnant	1 (0.1%)	1 (0.3%)	0 (0%)	0 (0%)	>0.9			
Menopause	20 (3.0%)	8 (2.5%)	10 (3.6%)	2 (2.6%)	0.7			
Smoking	19 (2.8%)	8 (2.5%)	9 (3.3%)	2 (2.6%)	0.9			
OSAS	111 (17%)	49 (15%)	48 (17%)	14 (18%)				
Stroke	36 (5.4%)	17 (5.4%)	12 (4.4%)	7 (9.1%)	0.3			

BMI- body mass index; DM- diabetes mellitus; POAD- peripheral arterial occlusive disease;  
HF- heart failure; CAD- coronary artery disease; RF- renal failure  
OSAS- obstructive sleep apnea syndrome  
Source: Prepared by the authors.

#### 4 DISCUSSION AND CONCLUSION

Lazazides states that the prevalence of resistant hypertension in treated hypertensive patients ranges from 8 to 28%<sup>14</sup>, which is lower than the prevalence we found in our casuistic (41%). This happens because Lazarides' statement applies to all treated hypertensive patients, regardless of how many antihypertensive drugs they used, whereas our study population only involved patients using three or more drugs for pressure control.

Muxefeldt mentions that refractory hypertension corresponds to 5 to 8% of the cases of resistant hypertension<sup>7</sup>, while in our series, it corresponds to 21%. The same author states that resistant hypertensives are older and more obese than hypertensives in general, and that resistant hypertension is associated with DM and OSAS. In our series, resistant hypertension was also associated with age, obesity and male gender, but was not associated with DM and OSAS.

While refractory hypertension was associated with advanced age, DM and pulmonary disease in our series, it was associated with female gender, younger age and African-American race in Muxefeldt's work<sup>7</sup>. Modolo reports that the African-American race is more represented in the refractory hypertension group than in the resistant hypertension group<sup>8</sup>. In our series, we did not determine race because of the difficulty of having well-defined races in our country. Among the variables analyzed, we did not find differences between the resistant and refractory groups, probably because the size of our series is too small to demonstrate the difference. Cardoso shows that refractory hypertension is associated with a higher incidence of stroke<sup>9</sup>. In our series, the incidence of stroke in refractory hypertension indeed seems to be much higher than in the resistant and control groups (9.1%, 4.4% and 5.4%, respectively). However, because the absolute number of patients who had strokes in the three groups was low, the difference was not statistically significant. In conclusion, in our paper, advanced age, male gender, and higher BMI were more present in the resistant group than in the control group. Advanced age and higher incidence of DM and COPD were more frequent in the refractory group than in the control group.

## REFERENCES

1. Resistant hypertension: An update. N F Renna . *Hipertens Riesgo Vasc* Jan-Mar 2019;36(1):44-52.
2. Resistant Hypertension Updated Guidelines. Irene Chernova, Namrata Krishnan . *Curr Cardiol Rep* 2019 Aug 30;21(10):117.
3. The Burden of Resistant Hypertension Across the World. Luisa Campos Caldeira Brant 1, Luiz Guilherme Passaglia 2, Marcelo Martins Pinto-Filho 2, Fabio Morato de Castilho 3 2, Antonio Luiz Pinho Ribeiro 3, Bruno Ramos Nascimento . *Curr Hypertens Rep* 2022 Mar;24(3):55-66.
4. Resistant Hypertension: Novel Insights. Guillaume Lamirault 1 2, Mathieu Artifoni 3, Mélanie Daniel 4, Nicolas Barber-Chamoux 5, Nantes University Hospital Working Group On Hypertension . *Curr Hypertens Ver* 2020;16(1):61-72.
5. Adherence to medication and drug monitoring in apparent treatment-resistant hypertension. Per Anders Eskås 1, Sondre Heimark 1, Julian Eek Mariampillai 1, Anne Cecilie K Larstorp 2 3, Fadl Elmula M Fadl Elmula 1 3 4 5, Aud Høiegggen . *Blood Press* 2016 Aug;25(4):199-205.
6. Office blood pressure threshold of 130/80 mmHg better predicts uncontrolled out-of-office blood pressure in apparent treatment-resistant hypertension. Chan Joo Lee 1, Jeong-Ha Ha 2, Jang Young Kim 3, In-Cheol Kim 4, Sung Kee Ryu 5, Moo-Yong Rhee 6 et al. *J Clin Hypertens (Greenwich)* 2021 Mar;23(3):595-605.
7. Resistant and refractory hypertension: two sides of the same disease? Elizabeth Silaid Muxfeldt 1 2, Bernardo Chedier 1 2, Cibele Isaac Saad Rodrigues 3 *J Bras Nefrol* Apr-Jun 2019;41(2):266-274.
8. Resistant or refractory hypertension: are they different? Rodrigo Modolo 1, Ana Paula de Faria, Aurélio Almeida, Heitor Moreno. *Curr Hypertens Rep* 2014 Oct;16(10):485.
9. Refractory Hypertension and Risks of Adverse Cardiovascular Events and Mortality in Patients With Resistant Hypertension: A Prospective Cohort Study. Claudia R L Cardoso , Gil F Salles . *J Am Heart Assoc* 2020 Sep;9(17):e017634.
10. Prognostic value of masked uncontrolled apparent resistant hypertension detected through home blood pressure monitoring. Jessica Barochiner 1 2, Lucas S Aparicio 1, Rocío Martínez 1 2, José Alfie 1, Marcos J Marín . *J Hypertens* 2021 Nov 1;39(11):2141-2146.
11. Prognostic value of non-resistant and resistant masked uncontrolled hypertension detected by ambulatory blood pressure monitoring. Francesca Coccina 1, Anna M Pierdomenico 2, Chiara Cuccurullo 2, Jacopo Pizzicannella 1, Maria T Guagnano 2, Giulia Renda 3, Oriana Trubiani 1, Francesco Cipollone 2, Sante D Pierdomenico . *J Clin Hypertens (Greenwich)* 2022 May;24(5):591-597.
12. The value of ABPM and subclinical target organ damage parameters in diagnosis of resistant hypertension. M Inmaculada Poveda García 1, M Dolores Del Pino Y Pino 2, Raquel



Alarcón Rodriguez 3, Cristian Rodelo-Haad 4, Tesifón Parrón Carreño . Nefrologia (Engl Ed) Jan-Feb 2019;39(1):67-72.

13. Prognostic Importance of On-Treatment Clinic and Ambulatory Blood Pressures in Resistant Hypertension: A Cohort Study. Claudia R L Cardoso 1, Guilherme C Salles 2, Gil F Salles . Hypertension 2020 May;75(5):1184-1194.

14. Ambulatory Blood Pressure Monitoring in the Diagnosis, Prognosis, and Management of Resistant Hypertension: Still a Matter of our Resistance? Antonios A Lazaridis 1, Pantelis A Sarafidis, Luis M Ruilope. Curr Hypertens Rep 2015 Oct;17(10):78.

15. Assessment of a strategy combining ambulatory blood pressure, adherence monitoring and a standardised triple therapy in resistant hypertension. Erietta Polychronopoulou 1, Michel Burnier 1, Georg Ehret 2, Renate Schoenenberger-Berzins 3, Maxime Berney 1, Belen Ponte 4, et al. Blood Press 2021 Dec;30(6):332-340.

16. Association of treatment-resistant hypertension defined by home blood pressure monitoring with cardiovascular outcome. Keisuke Narita 1, Satoshi Hoshida 1, Kazuomi Kario 2 Hypertens Res 2022 Jan;45(1):75-86.

17. Alves, A.P. da P., Botelho, L.E.S., Tsukamoto, A.B., Teixeira, A.L.S., Bon, G.C.B., de Oliveira, M.C., Moreira, L.F. de D., Sales, A.P.P., de Queiroz, E.V., Camini, C.F., da Silva, I.F., Guaraná, K.D., Martins, T.A. dos R. and Ronchi, L.M.M. 2023. Compreensão das características fisiopatológicas da hipertensão arterial sistêmica em relação a senescência: uma revisão de literatura. *Brazilian Journal of Health Review*. 6, 4 (Aug. 2023), 17482–17492.

18. Araujo, B. C. V., Santos, J. V. R. dos, Duarte, J. B., Abreu, E. T., & Rassilan, F. da C. (2024). Abordagens personalizadas no tratamento da hipertensão arterial: otimização da terapia farmacológica com base em fatores individuais. *Brazilian Journal of Health Review*, 7(2), e69226 .