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ORIGINAL ARTICLE

Stroke Is Associated with Refractory Hypertension among Resistant and Refractory Patients in a Cross-Sectional Study

Guilherme de Andrade Costa,[1] Jamary Oliveira Filho,[1] Luana Ferreira-Campos,[1] Alex Cleber Improta-Caria,[1,2,3] Cristiano Macedo,[2] Marcelo Vincenzo Sarno Filho,[1] Leonardo Silva Roever Borges,[4] Roque Aras Júnior[1]

Universidade Federal da Bahia,[1] Salvador, BA – Brazil
Hospital Universitário Professor Edgard Santos,[2] Salvador, BA – Brazil
Laboratório de Bioquímica e Biologia Molecular do Exercício, Universidade de São Paulo,[3] São Paulo, SP – Brazil
Universidade Federal de Uberlândia,[4] Uberlândia, MG – Brazil

Abstract

Background: Refractory hypertension (RfH) is a severe phenotype of resistant hypertension (RH) linked to higher risk of stroke and other adverse cardiovascular events, but knowledge about it is still lacking.

Objectives: To evaluate the association between RfH and stroke.

Methods: We conducted a cross-sectional study in a referral clinic for patients with severe hypertension in the period from 2018 to 2020. RH was defined as uncontrolled blood pressure (BP) despite the use of 3 antihypertensive agents, including a diuretic, or the use of ≥ 4 agents regardless of BP control. RfH was defined as lack of BP control despite use of ≥ 5 antihypertensive agents. Individuals were classified as RfH or RH, and multivariate logistic regression models were constructed to examine the association between RfH and stroke.

Results: We evaluated a total of 137 patients; 81% were female, and 93,3% were Black or multiracial. The mean age was 64.4 years. Stroke was more prevalent in the RfH group (35.7%), in comparison to the RH group (12.8%) (p value = 0.01). Unadjusted odds ratio (OR) and 95% confidence interval (CI) for factors associated with stroke were RfH (OR 3.77; 95% CI 1.45 to 9.80), systolic BP (OR 1.02; 95% CI 1.002 to 1.04) and diastolic BP (OR 1.03; 95% CI 1.001 to 1.06). Adjusted OR for factors associated with stroke were RfH (OR 3.55; 95% CI 1.02 to 12.42), systolic BP (OR 1.02; 95% CI 0.99 to 1.05) and diastolic BP (OR 1.01; 95% CI 0.96 to 1.06).

Conclusion: RfH was associated with higher prevalence of stroke. Efforts are required to better understand this association to prevent adverse cardiovascular outcomes in these patients.

Keywords: Hypertension; Stroke; Heart Disease Risk Factors.

Introduction

Hypertension is an important risk factor for adverse cardiovascular events, including stroke. Achieving blood pressure (BP) control, therefore, is an essential step to reduce the impact the condition has on patients' health. However, it is estimated that only 10% of patients with hypertension reach their BP goal. Resistant hypertension (RH) is a phenotype of hypertension characterized by high risk and difficulty in achieving BP goal.[1] It is defined as uncontrolled BP despite the use of 3 or more antihypertensive drugs in adequate doses, including a diuretic, a calcium channel blocker, and a renin-angiotensin system blocker, or controlled BP with the use of 4 or more medications.[2,3] This classification allows the identification of patients who share clinical and epidemiological characteristics and who can benefit from specific strategies.[4,5] It is estimated that 11.7% to 13.7% of all patients with hypertension have RH.[6–8]

Refractory hypertension (RfH) is a severe subtype of RH and is defined as uncontrolled BP despite the use of 5 or more antihypertensive drugs, including spironolactone and a thiazide-like diuretic.[2,3] The prevalence of RfH

Mailing Address: Guilherme de Andrade Costa
Universidade Federal da Bahia, Faculdade de Medicina de Bahia. Av. Reitor Miguel Calmon, S/N. Postal code: 40110-100. Salvador, BA – Brazil
E-mail: guilhermeand.costa@yahoo.com

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Central Illustration: Stroke Is Associated with Refractory Hypertension among Resistant and Refractory Patients in a Cross-Sectional Study

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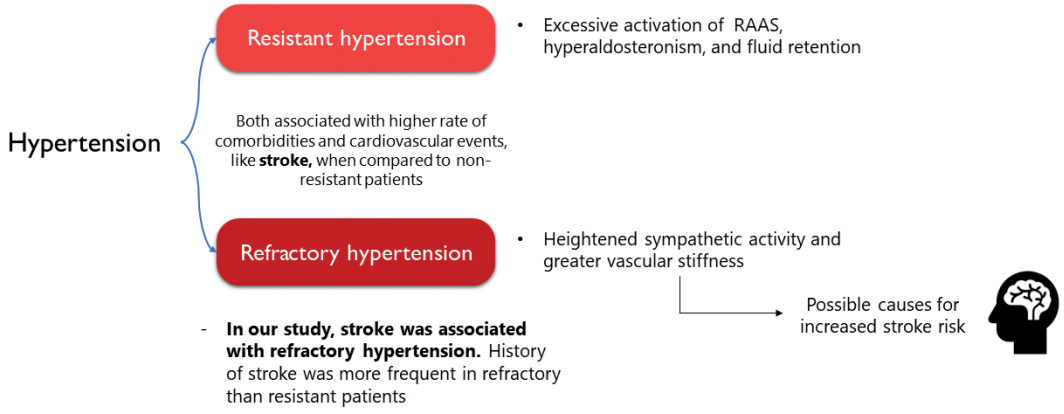

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among the population with RH is estimated to be between 3% and 15%.[5,9–12] The high variance is mainly due to differences between methodologies. The prognosis of refractory patients has been described as worse than those of resistant patients, with a higher frequency of target organ damage secondary to adverse cardiovascular events, such as stroke.[5,10,12] The aim of this study is to evaluate RfH as a factor associated with stroke in a population of patients with RfH and RH.

Methods

This is an observational cross-sectional study conducted in an outpatient referral center for severe hypertension. The study was approved by the Federal University of Bahia (UFBA) – Hospital Universitário Prof. Edgar Santos Ethics Committee, under approval number 81701717.6.0000.0049.

Study population

The sample was selected by convenience among patients with RH and RfH, followed at the reference clinic between June 2018 and March 2020. RH was defined as uncontrolled BP (systolic blood pressure [SBP] ≥ 140 mmHg or diastolic blood pressure [DBP] ≥ 90 mmHg) despite the use of 3 antihypertensive agents of different classes, including a thiazide diuretic, a calcium channel blocker, and a renin-angiotensin system blocker, if tolerated, given at maximal or maximally tolerated doses or as controlled BP with the use of 4 antihypertensive agents of different classes given at maximal or maximally tolerated doses, including a thiazide diuretic, a calcium channel blocker, and a renin-angiotensin system blocker, if tolerated. RfH was defined as uncontrolled BP despite the use of 5 or more antihypertensive drugs, including spironolactone and a thiazide-like diuretic, if tolerated.[2,3]

Data were collected through interviews and medical records review. The presence of history cardiovascular events and comorbidities (stroke, coronary artery disease, heart failure, dyslipidemia, diabetes, chronic kidney disease) was defined by a positive history reported by the participant and/or noted in the medical record. Stroke was defined according to the World Health Organization definition,[13] and the diagnosis of stroke was confirmed with head computed tomography records. BP was measured during the routine medical consultation, after a five-minute rest, with the back supported in a sitting position, legs uncrossed, and arm resting at heart level. A measurement was taken in each arm in sequence, and the average of both measurements was used as a reference value for the patient's BP. The measurements were performed with an automatic oscillometric sphygmomanometer (Omron HEM 711 DLX), validated by the British Hypertension Society (BHS) and by the Association for Advancement of Medical Instrumentation (AAMI).[14] To assess adherence to drug therapy, the Morisky questionnaire (MMAS-8) was applied.[15]

Statistical analysis

The RH and RfH groups were compared in relation to the collected variables. Categorical variables were described as percentages and compared using the chi-square test or Fisher's exact test. Continuous variables were described as means and standard deviations or median and interquartile range, according to the Kolmogorov-Smirnov normality test. Continuous variables were compared using the Mann-Whitney U test or Student's T test for independent samples. Factors associated with stroke were assessed using univariate and multivariable logistic regression. A multivariate logistic regression was performed with presence of history of stroke as dependent variable and presence of RfH, SBP, DPB, obesity, chronic kidney disease, and total cholesterol as independent variables. In this model, variable selection was based on data from bivariate analyses; variables of interest with p value < 0.250 were selected. In all cases, statistical significance was considered at two-tailed $p < 0.05$, with a 95% CI. The collected data were stored in a specific database of the Statistical Package for Social Sciences program (SPSS, Chicago, Illinois, USA), version 21.0. The study was approved by the local ethics committee, and all participants gave written informed consent to participate.

Results

A total of 137 patients were evaluated, of which 81% were women, and 93.3% were Black or multiracial. The mean age was 64.4 ± 10.9 years. Of the 137 patients, 79.6% had RH, and 20.4% had RfH (Figure 1). On average, the time since hypertension diagnosis was 24.9 ± 11.5 years. The use of the recommended combination of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker + calcium channel blocker + thiazide-type diuretic was present in 70.6% of patients. The groups had similar results in the medication adherence questionnaire.

Overall, the patients presented with high BP levels, 154.6 ± 24.4 mmHg of SBP and 86.4 ± 14.1 mmHg of DBP. SBP levels were higher in the RfH group (164.7 ± 20.3 mmHg) than in the RH group (152.0 ± 24.8 mmHg) ($p = 0.008$), as were DPB levels, which were 96.7 ± 13.7 mmHg in the RfH group and 84.5 ± 13.6 mmHg in the RH group ($p = 0.002$).

The study population presented with high levels of comorbidities: 49.6% were diabetic; 75.0% had dyslipidemia, and 30.7% reported a history of smoking. Obesity and metabolic syndrome were present in 40.6% and 71.9% of patients, respectively. No statistical difference was observed between the groups. Cholesterol, fasting plasma glucose, and A1c levels of both groups were also compared, without showing statistical differences (Table 1).

The analysis of target organ damage showed a significant difference in the prevalence of previous stroke between the groups: 35.7% of patients with RfH had a history of stroke, in contrast to 12.8% of patients with RH ($p = 0.01$).

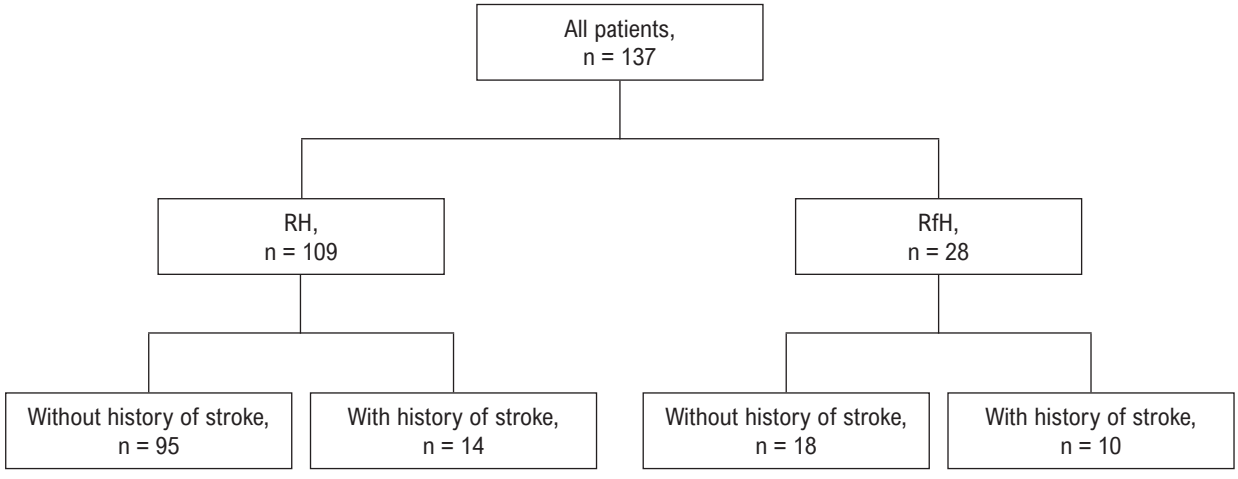

Figure 1 – Distribution of the study population.
RfH: refractory hypertension; RH: resistant hypertension.

Table 1 – Comparison of demographic and clinical features of patients with RH and RfH

	RH n = 109 (79.6%)	RfH n = 28 (20.4%)	All patients n = 137	P value
Demographic characteristics				
Age (years)	64.6 (±11.1)	63.7 (±9.9)	64.4 (±10.9)	0.680
Female	87(79.8%)	24(85.7%)	111(81.0%)	0.478
Black or multiracial	98 (91.6%)	28 (100%)	126 (93.3%)	**0.203***
Years since diagnosis of hypertension	24.6 (±11.9)	26.1 (9.9±)	24.9 (±11.5)	0.481
Years of follow-up at the clinic	14.6 (8.9±)	16.1 (8.1±)	14.9 (±8.8)	0.430
Comorbidities and cardiovascular history				
Diabetes mellitus	52 (47.7%)	16 (57.1%)	68 (49.6%)	0.373
Dyslipidemia	80 (74.1%)	22 (78.6%)	102 (75.0%)	0.624
Obesity	43 (40.6%)	11 (40.7%)	54 (40.6%)	0.987
Metabolic syndrome	77 (71.3%)	20 (74.1%)	97 (71.9%)	0.774
History of or current smoking	33 (30.3%)	9 (32.1%)	42 (30.7%)	0.848
Stroke	14 (12.8%)	10 (35.7%)	24 (17.5%)	**0.010**
Coronary artery disease	25 (22.9%)	11 (39.3%)	36 (26.3%)	0.080
Chronic kidney disease	21 (22.1%)	5 (20.0%)	26 (21.7%)	0.820
Congestive heart failure	17 (15.9%)	5 (17.9%)	22 (16.3%)	0.779
Laboratory test values				
Total cholesterol	188.2 (±48.5)	189.3 (±49.8)	188.4 (±48.4)	0.930
LDL	109.3 (±40.5)	112.9 (±46.0)	110.0 (±41.4)	0.720
HDL	53.1 (±16.0)	52.2 (±12.2)	52.9 (±15.3)	0.813
Triglycerides	129.5 (±64.2)	134.0 (±80.0)	130.3 (±66.9)	0.797
Glucose	126.8 (±61.5)	114.3 (±26.3)	124.3 (±56.3)	0.352
BP and heart rate measurements				
SBP	152.0 (±24.8)	164.7 (±20.3)	154.6 (±24.4)	**0.008**
DBP	84.5 (±13.6)	96.7 (±13.7)	86.4 (±14.1)	**0.002**
Pulse pressure	67.5 (±21.0)	71.0 (±18.4)	77.2 (±20.5)	0.419
Heart rate	77.4 (±13.9)	76.5 (±16.9)	68.2 (±14.5)	0.782

Hypertension and other treatments				
Number of BP medications in use[a]	4 (3 – 4)	5 (5 – 5.75)	4 (3 – 4.5)	**0.0001**
ACEi/ARB + CCB + thiazide-type diuretic	76 (69.7%)	20 (74.1%)	96 (70.6%)	0.657
Thiazide-like diuretic	93 (85.3%)	24 (85.7%)	117 (85.4%)	0.613
ACEi	25 (22.9%)	7 (25.0%)	32 (23.4%)	0.497
ARB	83 (76.1%)	21 (75.0%)	104 (75.9%)	0.548
CCB	90 (82.6%)	21 (75.0%)	111 (81.0%)	0.255
Spironolactone	42 (38.5%)	21 (75.0%)	63 (46.0%)	**0.001**
Beta-blocker	26 (23.9%)	8 (28.6%)	34 (24.8%)	0.385
Alfa-blocker	8 (7.3%)	14 (50.0%)	22 (16.1%)	**0.0001**
Statins	83 (76.1%)	20 (71.4%)	103 (75.2%)	0.385
Aspirin	35 (32.1%)	17 (60.7%)	52 (38.0%)	**0.005**
Treatment adherence (MMAS-8) †	7 (7 – 8)	7 (6 – 8)	7 (6 – 8)	0.626

ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptors blockers; BP: blood pressure; CCB: calcium channel blockers; DBP: diastolic blood pressure; MMAS-8: Morisky Medication Adherence Scale; RfH: refractory hypertension; RH: resistant hypertension; SBP: systolic blood pressure; LDL: low-density lipoprotein ; HDL: high-density lipoprotein. Values are mean (standard deviation) or number of individuals (valid %). P values are comparisons between RH patients and RfH patients. *P value for comparison between Black and multiracial patients with RH and RfH. † Values expressed as median (interquartile range).

In univariate analysis, patients with a history of stroke were associated with a higher prevalence of RfH (OR 3.770, 1.450 to 9.798) and higher levels of SBP (OR 1.020, 1.002 to 1,039) and DBP (OR 1.033, 1.001 to 1.065). Stroke history was also associated with a higher number of BP medications. Aspirin use was more frequent in patients with stroke history, as expected (Table 2).

In a multivariate model, the only factor independently associated with stroke history was RfH (adjusted OR 3.551 [1.015 to 12.420]) (Table 3).

Discussion

We observed a high prevalence of RfH among patients with RH in our study (20.4%), above the values found in other studies, which varied between 10.6% and 13.9%.[11,12] These differences can be explained by the clinical profile of the population, as the study was carried out in an outpatient referral clinic for severe hypertension, in addition to the large number of Black and multiracial patients, which have been reported as associated with severe hypertension phenotypes.[16,17] Divergences between studies commonly arise due to methodological differences, which reflect the challenges in excluding patients with pseudo-resistance. An important point of interest is to exclude pseudo-resistance due to white coat effect. Recent studies, however, have shown a low prevalence of pseudo-resistance due to the white coat effect among patients with apparent RfH, with rates lower than 10% [18,19]

In our assessment, patients reported satisfactory levels of medication adherence. Nonetheless, the methods commonly available for evaluating medication adherence have their limitations and often overestimate patients' adherence.[20] Studies using mass spectrometry revealed that half of the patients diagnosed with RH were partially or totally non-adherent.[20,21] Siddiqui et al. investigated the prevalence of true RfH in a population of patients with apparent RfH, and, after excluding patients with white coat effect and non-adherent patients, the researchers found that 60% of the patients were partially (45%) or totally (15%) non-adherent.[18]

Table 2 – Variables in relation to stroke history

	Total sample (n = 137)	Without stroke history (n = 113, 82.5%)	With stroke history (n = 24, 17.5%)	OR (95% CI)	P value
RfH	28 (20.4%)	18 (15.9%)	10 (41.7%)	3.770 (1.450 - 9.798) *	**0.005*†**
SBP	154.6 (±24.4)	152.5 (±24.8)	164.7 (20.3)	1.020 (1.002 - 1.039) *	**0.029 *†**
DBP	86.4 (±14.1)	85.3 (±13.2)	91.8 (17.1)	1.033 (1.001 - 1.065) *	**0.043 *†**
Age	64.4 (±10.9)	64.1 (±11.1)	66.1 (±9.9)	1.018 (0.976 – 1.062)	0.402
Age ≥ 65	72 (52.6%)	59 (52.2%)	13 (54.2%)	1.082 (0.447 - 2.618)	0.862
Female	111(81.0%)	93 (82.3%)	18 (75.0%)	0.645 (0.227 - 1.830)	0.407
Number of BP medications	4 (3 - 4.5)	4 (3-4)	4 (4-5)	1.715 (1.113 - 2.643) *	**0.015 ***
ACEi/ARB + CCB+ thiazide-type diuretic	96 (70.6%)	81 (72.3%)	15 (62.5%)	0.638 (0.253 - 1.607)	0.338
Aspirin use	52 (38.0%)	32 (28.3%)	20 (83.3%)	12.656 (4.012 - 39.926) *	**>0.001***
MMAS-8 ‡	7 (6 - 8)	7 (6-8)	7 (6-8)	0.937 (0.701 - 1.252)	0.658
Diabetes	68 (49.6%)	54 (47.8%)	14 (58.3%)	1.530 (0.627 - 3.730)	0.348
Dyslipidemia	102 (75.0%)	85 (75.9%)	17 (29.2%)	0.771 (0.289 - 2.057)	0.603
Obesity	54 (40.6%)	47 (41.6%)	7 (29.1%)	0.543 (0.208 - 1.416)	**0.208†**
Metabolic syndrome	97 (71.9%)	80 (72.1%)	17 (70.8%)	0.941 (0.356 - 2.490)	0.903
CKD	26 (21.7%)	19 (19.4%)	7 (31.8%)	1.940 (0.694 - 5.421)	**0.201†**
History of or current smoking	42 (30.7%)	36 (31.9%)	6 (25.0%)	0.713 (0.261 - 1.948)	0.508
Diabetes	68 (49.6%)	54 (47.8%)	14 (58.3%)	1.530 (0.627 - 3.730)	0.348
Dyslipidemia	102 (75.0%)	85 (75.9%)	17 (29.2%)	0.771 (0.289 - 2.057)	0.603
Total cholesterol	188.4 (±48.4)	191.4 (±48.0)	171.2 (48.8)	0.990 (0.978 - 1.003)	**0.124†**
HDL	52.9 (±15.3)	53.2 (±15.9)	50.8 (11.5)	0.989 (0.952 - 1.027)	0.567
LDL	110.0 (±41.4)	111.3 (±42.4)	102.9 (35.7)	0.995 (0.982 - 1.008)	0.439
Triglycerides	130.3 (±66.9)	129.4 (±60.3)	136.5 (103.6)	1.002 (0.993 - 1.010)	0.721
Glucose	124.3 (±56.3)	126.9 (±60.2)	110.9 (26.9)	0.993 (0.979 - 1.006)	0.286

*ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptors blockers; BP: blood pressure; CCB, calcium channel blockers; CI: confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; MMAS-8: Morisky Medication Adherence Scale; OR: odds ratio; RfH, refractory hypertension; SBP, systolic blood pressure; LDL: low-density lipoprotein ; HDL: high-density lipoprotein. Values are mean (standard deviation) or number of individuals (valid %). P values are comparisons between RH patients and RfH patients. *P value for comparison between Black and multiracial patients with RH and RfH. † Variables included in multivariate regression model. ‡ Values expressed as median (interquartile range).*

Table 3 – Risk factors for stroke history among patients with resistant and RfH

	Adjusted OR (95% CI)	P value
RfH	3.551 (1.015 – 12.420)	0.047
SBP	1.019 (0.988 – 1.050)	0.231
DBP	1.009 (0.962 – 1.058)	0.716
Obesity	0.788 (0.235 – 2.635)	0.698
CKD	1.790 (0.509 – 6.296)	0.364
Total cholesterol	0.988 (0.974 – 1.003)	0.106

CI: confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; OR: odds ratio; RfH, refractory hypertension; SBP, systolic blood pressure. Results from multivariate logistic regression model.

Patients with RfH and RH had similar demographic, clinical features, and risk factor profiles, differing only in BP levels. Use of aspirin was also higher in the RfH group, which can be explained by the higher prevalence of previous major adverse cardiovascular events. A high prevalence of comorbidities was found in both groups, corroborating the high-risk cardiovascular profile featured in the literature.[5,10,12] Similar findings were reported in the ALLHAT trial.[22]

In our study, stroke history was independently associated with RfH when compared to RH, after adjusting for BP levels and other factors (Central Figure). In agreement with our findings, an association between stroke and RfH has been reported in a prospective cohort with a hazard ratio of 2.03 (1.15 to 3.60) compared to patients with RH; [12] other cross-sectional studies also demonstrate this association.[11,16] A higher prevalence of RfH among stroke survivors has also been reported in a cross-sectional study, which found an association between RfH and stroke subtypes that arise from small arteries disease, such as intracerebral hemorrhages and lacunar infarcts.[23]

The association between these events and RfH may reflect pathophysiological differences between these severe hypertension phenotypes. The principal mechanism of resistance to treatment in RH is related to changes in volume status, exacerbated water retention, sensitivity to sodium, and hyperaldosteronism secondary to the activation of the renin-angiotensin-aldosterone system.[24,25] In contrast, studies indicate that unresponsiveness to treatment among patients with RfH is linked to an elevation of sympathetic activity, as evidenced by higher heart rates, greater vascular stiffness, increased systemic vascular resistance, and higher levels of urinary metanephrines among that population.[9,26,27] An important factor of the refractory phenotype yet to be studied is its circadian BP behavior and, notably, its nocturnal BP pattern. Studies have found a higher prevalence of nocturnal hypertension and nondipping BP pattern among patients with RH.[12,19,28,29] These findings, like RfH, have been linked to sympathetic overactivation and increased cardiovascular risks. [30–33] However, research that studies circadian BP behavior differences between resistant and refractory populations is still needed.

Limitations

The findings in this report are subject to limitations. First, our study did not benefit from the exclusion of patients with pseudo-RH by use of ambulatory BP monitoring. However, the population sample was characterized by long periods, with over 10 years, on average, of treatment for RH in our clinic. Our patients have frequent visits and have previously been assessed for the white coat effect. These factors help minimize the occurrence of pseudo-resistance in our population. The current study is cross-sectional and does not intend to establish a causal relationship in our findings. The ethnic profile present in our study may raise issues of generalizability, but it is representative of the local population, which may have contributed to the risk profile found in the study, given the previously reported associations between Black individuals and severe hypertension. [16] The large majority of women in our study may also affect generalizability, and it is a reflection of the study's sample being selected by convenience in our outpatient center, which is predominantly attended by women. It is also important to note that the classification of each individual ethnicity was self-reported, as recommended by Brazilian institutions. This, however, could lead to bias, due to high prevalence of multiple ethnicities in our population.

Future directions

Our findings would benefit from being confirmed by more studies in larger populations. In addition,

further research is warranted to solidify knowledge concerning RfH and its impact on stroke incidence and other cardiovascular outcomes. Potential areas of research include differences in pathophysiology mechanisms between RH and RfH, how they may impact cardiovascular health in distinct manners, and possible divergencies in their therapies to target these differences.

Conclusion

In summary, we found an association of RfH with stroke, in a population of patients with RfH and RH. These findings suggest that RfH may be associated with higher risk of stroke, possibly due to differences in pathophysiologic mechanisms between these two entities.

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Author Contributions

Conception and design of the research: Costa GA, Macedo C, Aras-Júnior R. Acquisition of data: Costa GA, Sarno Filho MV. Analysis and interpretation of the data: Costa GA, Ferreira-Campos L, Aras-Júnior R. Statistical analysis: Costa GA, Sarno-Filho MV. Writing of the manuscript: Costa GA. Critical revision of the manuscript for intellectual content: Improta-Caria AC, Ferreira-Campos L, Borges LSR, Oliveira-Filho J, Aras-Júnior R.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the UFBA - Hospital Universitário Prof. Edgar Santos under the protocol number 81701717.6.0000.0049. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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