Chapter 13 - Resistant Arterial Hypertension

Definition and epidemiology

Resistant AH (RAH) is defined as uncontrolled office BP despite the use of at least three antihypertensive drugs at appropriate doses, including preferably one DIU, or as controlled BP using at least four drugs.[1-3] Because it does not include the systematic assessment of therapy and adherence, that situation is better defined as apparent RAH (pseudoresistance). Identification of true RAH is fundamental to establish specific approaches.[2] Population-based studies have estimated a 12% prevalence in the hypertensive population.[2] In Brazil, the ReHOT study assesses prevalence and therapeutic choice.[4] Refractory hypertension is defined as uncontrolled BP using at least five antihypertensive drugs,[5] and corresponds to 3.6% of resistant hypertensive individuals. To diagnose RAH, ABPM is required, as well as systematic assessment of adherence. (GR: I; LE: C).

Associated factors

Causative factors are as follows: higher salt sensitivity, increased blood volume (higher sodium intake, CKD or inappropriate diuretic therapy), exogenous substances that raise BP, and secondary causes (OSAHS, primary aldosteronism, CKD, and renal artery stenosis).[1,3,6] The characteristics of RAH are: more advanced age, African ancestry, obesity, MS, DM, sedentary lifestyle, chronic nephropathy, and LVH.[1,3]

The pathophysiological aspects related to resistance are as follows: (i) sympathetic and RAAS hyperactivity; (ii) vascular smooth muscle proliferation; (iii) sodium retention; and (iv) activation of proinflammatory factors.[1,7] Greater endothelial dysfunction and arterial stiffness are present.[8] In ABPM, there is high prevalence (30%) of WCE and attenuation of nocturnal BP dipping.[9] The prevalence of black ethnicity, DM and albuminuria is higher among refractory hypertensive individuals.[5]

Diagnostic investigation

Pseudoresistance

Pseudoresistance is due to poor BP measurement technique, low adherence to treatment and inappropriate therapeutic regimen.[1,2,10] Studies have shown that 50-80% of the patients fail to adhere to treatment completely or partially.[10-12] The diagnosis of RAH should only be established after inclusion of an appropriate DIU[13] and adjustment of the antihypertensive regimen.[12]

Complementary tests

Blood biochemistry, urinalysis and ECG should be requested at the time of diagnosis, and repeated at least once a year.[1,12] Echocardiogram and retinal exam, when available, should be repeated every 2 to 3 years.

Secondary causes

Secondary causes are common in RAH,[6] OSAHS being the most prevalent (80%, and 50% with moderate-severe apnea),[14] followed by hyperaldosteronism (20%, mainly adrenal hyperplasia)[15] and renal artery stenosis (2.5%).[6] Other secondary causes should only be investigated in the presence of suggestive clinical findings.[6]

ABPM and HBPM

Although the diagnosis of RAH is based on office BP measurement,[1] BP assessment by using ABPM or HBPM is mandatory for the initial diagnosis and clinical follow-up.[1,9,16,17] It is estimated that 30-50% of resistant hypertensive individuals have normal outside-the-office BP levels.[9,12,16] The diagnosis obtained on ABPM defines diagnostic and therapeutic management (Chart 1).[1,12,16]

In true or masked RAH, the medication should be progressively adjusted[16] with the introduction of nocturnal doses of antihypertensive drugs.[18] Patients with controlled BP on ABPM should have their therapy maintained, regardless of the office BP levels. In white-coat RAH, confirmatory ABPM needs to be performed after 3 months, and repeated every six months (if wakefulness SBP ≥ 115 mm Hg) or annually (if wakefulness SBP < 115 mm Hg).[19]

When ABPM is not available, HBPM is a good complementary method. Although it does not assess the nocturnal period and overestimates BP levels, HBPM reaches moderate agreement on the diagnosis,[20] with high specificity and low sensitivity (Chart 2).[17]

Treatment

Non-pharmacological treatment

The NPT is aimed at:

Encouraging lifestyle changes: reduction in salt intake (up to 2.0 g of sodium/day); DASH diet; body weight loss (BMI < 25 kg/m²); physical activity; smoking cessation; and moderate alcohol intake;[1,3,21,22]

Suspending substances that raise BP.[1,3]

Chart 1 – Classification of RAH based on ABPM

Office BP	ABPM	
	Wakefulness BP ≥ 135/85 and/or Sleep BP ≥ 120/70 mm Hg	Wakefulness BP < 135/85 and Sleep BP < 120/70 mm Hg
≥ 140/90 mm Hg	True RAH	White-coat RAH
< 140/90 mm Hg	Masked RAH	Controlled RAH

Chart 2 – Diagnostic investigation of RAH

	Grade of recommendation	Level of evidence
To rule pseudoresistance out		
Adherence to therapy	I	C
Adjustment of the antihypertensive regimen	I	C
Complementary exams		
Blood biochemistry: glucose, creatinine, potassium and lipid panel Urine assessment: albuminuria and proteinuria ECG	I	C
Investigation of secondary causes		
OSAHS Hyperaldosteronism Renal artery stenosis	I	A
ABPM or HBPM		
Assessment of BP control	IIa	C

Pharmacological treatment

The basic principle of the pharmacological treatment is the association of antihypertensive drugs that block most pathophysiological mechanisms of BP elevation. Ideally, the following should be prescribed at full-tolerated dose and at proper intervals: a DIU, a RAAS inhibitor, and a dihydropyridine CCB. In certain situations, such as CAD, CHF and tachyarrhythmias, a BB can replace a CCB in the initial therapeutic regimen with 3 medications.

The correct use of DIUs to ensure control of volemic expansion is essential, and more than half of the patients can meet the BP target with DIU optimization.[13] Chlorthalidone is superior to hydrochlorothiazide.[23] For stage 4 or 5 CKD patients, loop DIUs should be used and administered at least twice a day. Spironolactone, an aldosterone antagonist, is the choice for the fourth drug in patients with true RAH, enabling a mean reduction of 15-20 mm Hg in SBP, and of 7-10 mm Hg in DBP, at doses of 25-50 mg/day.[24] However, up to 20-30% of the patients might not tolerate its use, because of renal function worsening, hyperpotassemia, gynecomastia or mastalgia. In such cases, amiloride can be used (5-10 mg/day), but with an apparently lower BP response.[25] The use of clonidine as the fourth drug is being assessed in the Brazilian ReHOT study, considering the sympathetic and RAAS activity measurements as possible predictors of the best therapeutic response to clonidine and spironolactone, respectively.[4]

In patients not reaching BP control on ABPM after the addition of spironolactone, BBs (mainly those with vasodilating effect) are the fifth drugs, if not contraindicated. Central alpha-agonists (clonidine and alpha methyldopa), direct vasodilators (hydralazine and minoxidil), or central agonists of imidazoline receptors are usually used as the sixth and seventh drugs. In addition, associations of multiple DIUs (thiazide DIUs, loop DIUs and spironolactone), especially in the presence of edema, or dihydropyridine and non-dihydropyridine CCBs can be used in the most critically ill patients.

Chronotherapy guided by ABPM, with the nocturnal administration of at least one antihypertensive drug, could improve BP control and reverse the unfavorable non-dipping pattern in those patients, in addition to reducing CV morbidity and mortality (Chart 3).[18]

New therapeutic strategies

New strategies are being developed, but are still experimental. Although safe, they are not better than the conventional treatment, and should only be used in truly resistant patients (Chart 4).

Direct and chronic stimulation of carotid sinus baroreceptors

The Rheos system is a programable device, like a pacemaker, surgically implanted, consisting in a generator of impulses that activate the carotid baroreceptors via radiofrequency. The Rheos Pivotal Trial has not detected significant long-term benefits.[26]

Renal sympathetic denervation

Percutaneous transluminal renal sympathetic denervation through a catheter has been mainly assessed in the SYMPLICITY studies conducted in RAH patients. Recent meta-analyses[27,28] have not confirmed the initially promising results.

Use of CPAP

The antihypertensive effect of CPAP is controversial. However, as an auxiliary treatment in patients with OSAHS, mainly those who tolerate its use for more than 4 hours/night, there is evidence that it can help to reestablish the dipping pattern.[29]

Chart 3 – Treatment of resistant arterial hypertension

Intervention	Grade of recommendation	Level of evidence
Adopt lifestyle changes	I	B
Optimize treatment with 3 drugs: chlorthalidone*, ACEI or ARB, and CCB†	I	B
Add spironolactone as the 4th drug	IIa	B
Add BB as the 5th drug†	IIb	C
In sequence, add centrally acting sympatholytic drugs or direct vasodilators	IIb	C
Prescribe the night administration of one or more drugs	IIb	B
Check and improve adherence to treatment	I	C

Chart 4 – New therapeutic strategies for resistant arterial hypertension

Intervention	Grade of recommendation	Level of evidence
Stimulation of carotid sinus baroreceptors (Rheos device)[26]	IIb	B
Renal sympathetic denervation[27,28]	IIb	B
Use of CPAP[29]	IIb	B
Central arteriovenous anastomosis (coupler device)[30]	IIb	B

Central iliac arteriovenous anastomosis

The ROX Control HTN study[30] has shown promising results with significant reductions in BP levels and in hypertensive complications of patients with central iliac arteriovenous anastomosis with the coupler device.

Prognosis

A retrospective cohort study performed from a North American registry indicates that, after beginning the antihypertensive treatment, the apparent RAH incidence (uncontrolled BP with 3 medications) is 0.7/100/patients-year, and those patients' relative risk for CV events is 1.47 (95% confidence interval: 1.33-1.62).[31] A prospective study with 556 resistant hypertensives (follow-up of 4.8 years) has shown that uncontrolled ABPM and lack of nocturnal dipping are important markers of CV risk.[32] The apparent RAH condition is considered of independent risk for the occurrence of CV events. (GR: IIa; LE: C). Performing ABPM is recommended to establish the prognosis of hypertensives with true RAH. (GR: IIa; LE: C).

References

1. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension. 2008;51(6):1403-19.
2. Judd E, Calhoun DA. Apparent and true resistant hypertension: definition, prevalence and outcomes. J Hum Hypertens. 2014;28(8):463-8.
3. Alessi A, Brandão AA, Coca A, Cordeiro AC, Nogueira AR, Diógenes de Magalhães F, et al. First Brazilian position on resistant hypertension. Arq Bras Cardiol. 2012;99(1):576-85. Erratum in: Arq Bras Cardiol. 2013;100(3):304.
4. Krieger EM, Drager LF, Giorgi DM, Krieger JE, Pereira AC, Barreto-Filho JA, et al; ReHOT Investigators. Resistant hypertension optimal treatment trial: a randomized controlled trial. Clin Cardiol. 2014;37(1):1-6. Erratum in: Clin Cardiol. 2014;37(6):388.
5. Calhoun DA, Booth JN 3rd, Oparil S, Irvin MR, Shimbo D, Lackland DT, et al. Refractory hypertension: determination of prevalence, risk factors, and comorbidities in a large, population-based cohort. Hypertension. 2014;63(3):451-8.
6. Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, de Paula LK, Amaro AC, et al. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. Hypertension. 2011;58(5):811-7.
7. de Faria AP, Modolo R, Fontana V, Moreno H. Adipokines: novel players in resistant hypertension. J Clin Hypertens (Greenwich). 2014;16(10):754-9.
8. Figueiredo VN, Yugar-Toledo JC, Martins LC, Martins LB, de Faria AP, de Haro Moraes C, et al. Vascular stiffness and endothelial dysfunction: correlations at different levels of blood pressure. Blood Press. 2012;21(1):31-8.
9. de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension. 2011;57(5):898-902.
10. Egan BM, Zhao Y, Li J, Brzezinski WA, Todoran TM, Brook RD, et al. Prevalence of optimal treatment regimens in patients with apparent treatment-resistant hypertension based on office blood pressure in a community-based practice network. Hypertension. 2013;62(4):691-7.

11. Burnier M, Wuerzner G, Struijker-Boudier H, Urquhart J. Measuring, analyzing, and managing drug adherence in resistant hypertension. Hypertension. 2013;62(2):218-25.

12. Muxfeldt ES, de Souza F, Salles GF. Resistant hypertension: a practical clinical approach. J Hum Hypertens. 2013;27(11):657-62.

13. Garg JP, Elliott WJ, Folker A, Izhar M, Black HR; RUSH University Hypertension Service. Resistant hypertension revisited: a comparison of two university based cohorts. Am J Hypertens. 2005;18(5 Pt 1):619-26.

14. Muxfeldt ES, Margallo VS, Guimarães GM, Salles GF. Prevalence and associated factors of obstructive sleep apnea in patients with resistant hypertension. Am J Hypertens. 2014;27(8):1069-78.

15. Calhoun DA. Hyperaldosteronism as a common cause of resistant hypertension. Annu Rev Med. 2013;64:233-47.

16. Muxfeldt ES; Salles GF. How to use ambulatory blood pressure monitoring in resistant hypertension. Hypertens Res. 2013;36(5):385-9.

17. Muxfeldt ES, Barros GS, Viegas BB, Carlos FO, Salles GF. Is home blood pressure monitoring useful in the management of patients with resistant hypertension? Am J Hypertens. 2015;28(2):190-9.

18. Hermida RC, Ayala DE, Fernández JR, Calvo C. Chronotherapy improves blood pressure control and reverts the nondipper pattern in patients with resistant hypertension. Hypertension. 2008;51(1):69-76.

19. Muxfeldt ES, Fiszman R, de Souza F, Viegas B, Oliveira FC, Salles GF. Appropriate time interval to repeat ambulatory blood pressure monitoring in patients with white-coat resistant hypertension. Hypertension. 2012;59(2):384-9.

20. Nasothimiou EG, Tzamouranis D, Roussias LG, Stergiou GS. Home versus ambulatory blood pressure monitoring in the diagnosis of clinic resistant and true resistant hypertension. J Hum Hypertens. 2012;26(12):696-700.

21. Pimenta E, Gaddam KK, Oparil S, Aban I, Husain S, Dell'Italia LJ, et al. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. Hypertension. 2009;54(3):475-81.

22. Guimaraes GV, de Barros Cruz LG, Fernandes-Silva MM, Dorea EL, Bocchi EA. Heated water-based exercise training reduces 24-hour ambulatory blood pressure levels in resistant hypertensive patients: a randomized controlled trial (HEx trial). Int J Cardiol. 2014;172(2):434-41.

23. Ernst ME, Carter BL, Zheng S, Grimm RH Jr. Meta-analysis of dose-response characteristics of hydrochlorothiazide and chlorthalidone: effects on systolic blood pressure and potassium. Am J Hypertens. 2010;23(4):440-6.

24. Liu G, Zheng XX, Xu YL, Lu J, Hui RT, Huang XH. Effect of aldosterone antagonists on blood pressure in patients with resistant hypertension: a meta-analysis. J Hum Hypertens. 2015;29(3):159-66.

25. Lane DA, Beevers DG. Amiloride 10 mg is less effective than spironolactone 25 mg in patients with hypertension resistant to a multidrug regime including an angiotensin-blocking agent. J Hypertens. 2007;25(12):2515-6.

26. Bakris GL, Nadim MK, Haller H, Lovett EG, Schafer JE, Bisognano JD. Baroreflex activation therapy provides durable benefit in patients with resistant hypertension: results of long-term follow-up in the Rheos Pivotal Trial. J Am Soc Hypertens. 2012;6(2):152-8.

27. Fadl Elmula F, Jin Y, Larstorp AC, Persu A, Kjeldsen SE, Staessen JA. Meta-analysis of five prospective and randomized trials of renal sympathetic denervation on office and ambulatory systolic blood pressure in treatment resistant hypertension. J Hypertens. 2015;33 Suppl1:e107.

28. Fadl Elmula FE, Jin Y, Yang WY, Thijs L, Lu YC, Larstorp AC, et al; European Network Coordinating Research On Renal Denervation (ENCOReD) Consortium. Meta-analysis of randomized controlled trials on renal denervation in treatment –resistant hypertension. Blood Press. 2015;24(5):263-74.

29. Martinez-Garcia MA, Capote F, Campos-Rodriguez F, Lloberes P, Díaz de Atauri MJ, Somoza M, et al; Spanish Sleep Network. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. JAMA. 2013;310(22):2407-15.

30. Lobo MD, Sobotka PA, Stanton A, Cockcroft JR, Sulke N, Dolan E, et al; ROX CONTROL HTN Investigators. Central arteriouvenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN Study): a randomised controlled trial. Lancet. 2015;385(9978):1634-41.

31. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation. 2012;125(13):1635-42.

32. de Souza F, Muxfeldt ES, Salles GF. Prognostic factors in resistant hypertension: implications for cardiovascular risk stratification and therapeutic management. Expert Rev Cardiovasc Ther. 2012;10(6):735-45.