First Brazilian Position on Resistant Hypertension

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Definition and epidemiology

Definition

Resistant Hypertension (RH) is defined as blood pressure (BP) that remains above the recommended target in spite of the use of three antihypertensive drugs with synergistic actions at maximum recommended and tolerated doses, one of which should preferably be a diuretic, or when four or more different antihypertensive drugs are used, even when BP is controlled[1].

True RH must be differentiated from pseudo-resistance, which occurs due to non-adherence to treatment, inadequate blood pressure measurements, use of inadequate doses or therapeutic regimens, or the occurrence of white-coat effect[2].

Control of hypertension in Brazil and worldwide

An average of 30% of the adult population has high blood pressure (HBP), about 1.2 billion people in the world[3]. In Brazil, 14 population-based studies (1994-2009) revealed low levels of BP control (19.6%)[4].

The fact that hypertension control doubled in the U.S. from 1988 to 2008 (27.3% vs. 53.5%)[5], and increased fivefold in Canada from 1992 to 2009 (13.2% vs. 64.6%)[6], reflects important advances in HBP detection and treatment in these countries.

Incidence and prevalence of resistant hypertension

Daugherty et al. found an RH incidence of 1.9% in an 18-month follow-up of hypertensive patients who started treatment. This study involved a large cohort of ethnically diverse patients and took treatment adherence into account, therefore excluding pseudo-resistance[7].

Although the exact RH prevalence has not been established yet, it is estimated that the condition affects 12-15% of individuals with high blood pressure[8]. Data from the National Health and Nutrition Examination Survey (NHANES) in the period of 2003 to 2008 showed that 12.8% of hypertensive patients taking antihypertensive drugs in the United States had RH[9]. Egan et al.[10] noted that these percentages have increased in the United States.

Factors contributing to resistant hypertension

Both systolic and diastolic hypertension may be resistant, the former being more prevalent[1]. Causal factors include increased sensitivity to salt, fluid overload (due to increased sodium intake, chronic nephropathy, or inadequate diuretic therapy), exogenous substances (non-hormonal anti-inflammatory drugs, corticosteroids, oral contraceptives, sympathomimetics, chemotherapy drugs, antidepressants, immunosuppressants, decongestants, anorectics, alcohol, and cocaine), and secondary causes of hypertension (emphasizing primary aldosteronism, obstructive sleep apnea, chronic nephropathy, and renal artery stenosis)[11,12].

The following characteristics are predominant in patients with resistant hypertension: older age, African descent, obesity, left ventricular hypertrophy, diabetes mellitus, chronic kidney disease, metabolic syndrome, increased salt intake, and reduced physical activity. It should be noted that the white-coat effect is present in about 30% of RH patients[1,13].

Prognostic aspects

RH is a condition with difficult clinical management and high cardiovascular risk. Most epidemiological studies evaluating the prognosis of resistant hypertension have limitations such as lack of uniformity in definitions and information on drugs used, inclusion of cases of pseudo-hypertension, as well as insufficient follow-up time and exclusion of young patients[1,14].

The prognosis is especially associated with the following factors: prolonged exposure to high blood pressure, increased blood pressure, target organ damage and mineralocorticoid (aldosterone) excess, and high rates of sodium intake[15-17]. Several studies show that aldosterone is an important marker of cardiovascular disease severity[18].

Ambulatory Blood Pressure Monitoring (ABPM) is an important prognostic marker, especially nocturnal blood pressure and 24-hour pulse pressure[14,19,20].

Assessment flowchart

The first step in the investigation of resistant hypertension is the exclusion of causes of pseudo-resistance, such as inadequate blood pressure measurement technique, poor adherence to treatment, pseudo-hypertension, and white-coat effect[1] (Figure 1). ABPM is the method of choice for confirmation of inadequate blood pressure control, but if this

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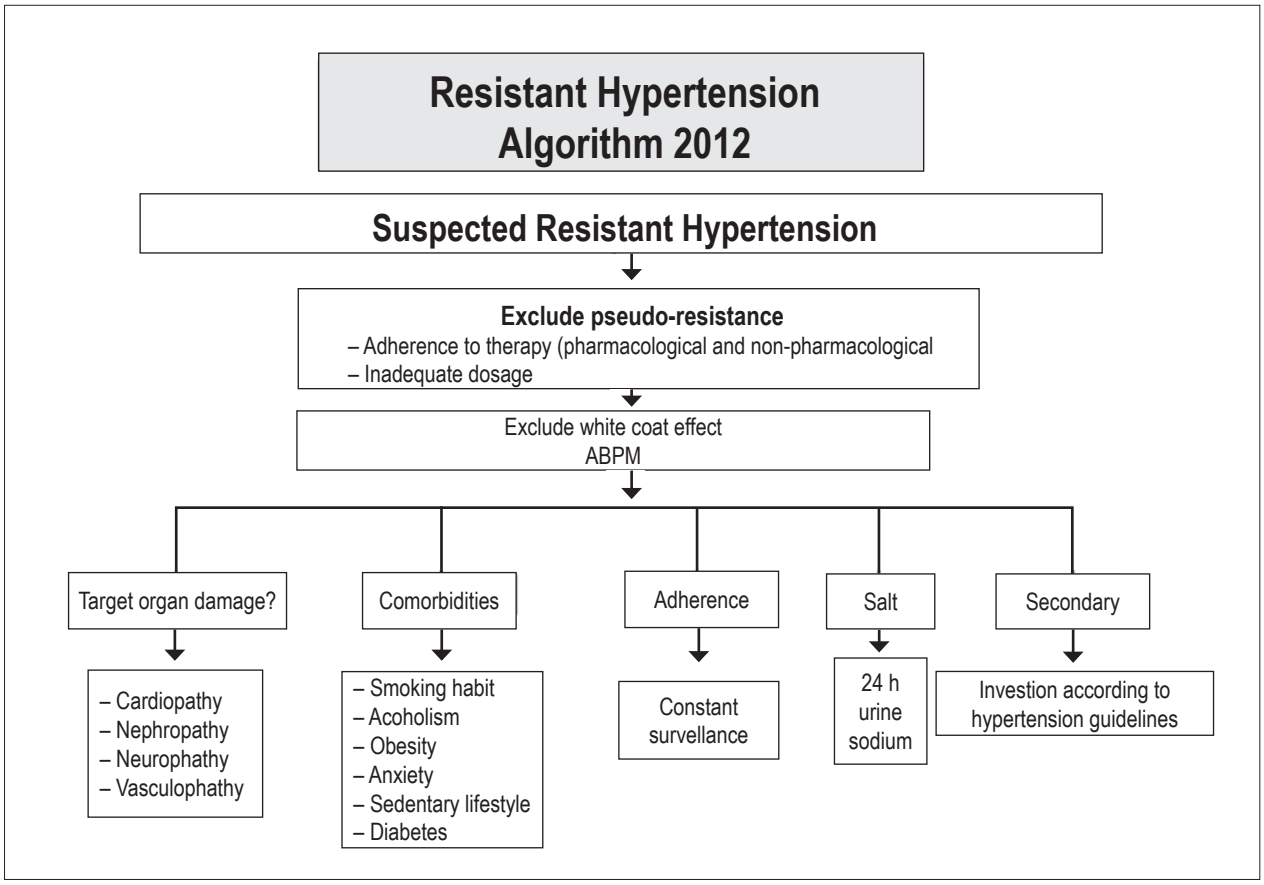

Figure 1 – *Resistant Hypertension Assessment Flowchart*

is not available, Home Blood Pressure Monitoring (HMBP) or Self-Monitoring Blood Pressure (SMBP) are useful[13, 21].

Target organ damage and associated comorbidities should be investigated with specialized tests, because they influence the stratification of cardiovascular risk, and are prognostic markers[22,23].

Among the causes of pseudo-resistance, poor adherence is the major challenge. Therapeutic inertia, prescription of insufficient doses or non-synergistic medications, and poor doctor-patient relationship should be observed, as well as the search for agents that can interfere with blood pressure control. If the goal to be achieved is not reached within six months, a short period hospitalization should be considered[24].

Approximately 30% to 50% of patients underestimate their sodium intake. The impact of sodium restriction on resistant hypertension is well established, and the determination of 24-hour urinary sodium excretion should be performed as control[16]. The diagnosis of secondary hypertension should be thoroughly searched for in resistant hypertension.

Blood pressure measurement

The use of an accurate technique for BP measurement is essential for the accurate diagnosis of resistant hypertension. The patient should be quietly seated for five minutes before the measurement, with the back supported and the arm at heart level. A cuff suitable for the arm circumference should be used (width/length proportion 1:2, and width and length of rubber cuff corresponding to 40% and 80% of arm circumference, respectively)[25]. A minimum of three readings should be taken at intervals of at least one minute, and the average of the last two measurements should be used if the difference between them is less than or equal to 4 mm Hg. BP should be measured in both arms, and the arm with the higher pressures should be used in future measurements. If the difference between the arms is greater than 15 mmHg for systolic blood pressure and/or 10 mmHg for diastolic blood pressure, atherosclerotic[26] vascular disease should be investigated. BP measurements in supine and upright positions should be taken in the follow-up evaluations to assess orthostatic hypotension.

ABPM

ABPM is an important tool in the diagnosis of a major cause of pseudo-resistance, in which individuals with a BP supposedly higher than the goal in the clinician's office have a normal ABPM. This difference between office and awake ABPM blood pressure measurements is called white-coat effect. Very high pressure levels may be a limitation to the test, because of patient discomfort. In these situations, HMBP and SMBP are alternative options.

HMBP

HMBP is an indirect method of recording the blood pressure, with three measurements in the morning and three at night for five days[4]. HMBP indications are basically the same as for ABPM, but HMBP may be better tolerated in patients with very high blood pressure. HMBP can also identify the white-coat effect, therefore excluding or confirming RH.

SMBP

SMBP is a measurement method usually performed at home by patients or family members. The main advantage of SMBP is the possibility of obtaining a more accurate estimate of the actual blood pressure values, because they are obtained in the environment where the patients live, provided that validated and calibrated equipment is used. Table 1 shows a list of pressure values considered normal for hypertension and for white-coat effect in Office, ABPM, HMBP, and SMBP measurements.

Target organ lesions

Vascular and brain disorders

Vascular abnormalities may be present in the early stages of hypertensive disease. RH is associated with more severe vascular dysfunction, as assessed by endothelium-dependent vasodilation and serum biomarkers, which may explain an absence of nocturnal blood pressure decline and a higher pulse pressure during ABPM[27,28]. There is a close relationship between high levels of BP, endothelial dysfunction and increased vascular stiffness in patients with resistant hypertension, demonstrated by a reduction in flow-mediated vasodilatation and in a high pulse wave velocity. In this population, higher levels of aldosterone are also observed[29,30].

The nervous system may be affected early in RH and it is mostly benefited from adequate BP control. Vascular changes are universal, and cerebral vessels are affected relatively early in the hypertensive process. Retinal microvascular abnormalities reflect what happens in the brain. A retinal exam may show microaneurysms, hemorrhages, hard and soft exudates, pathological arteriovenous crossings, and arterial wall thickening.

Carotid stenosis, intracranial and aortic arch atherosclerosis, and cardiac lesions may be responsible for ischemic or thromboembolic phenomena. The uncontrolled hypertension can lead, over time, to small brain aneurysms that may rupture, causing large subarachnoid or intracerebral hemorrhage.[31] Lacunar infarcts are small, generally less than 2.0 cm in diameter, and they result from obstruction of small perforating vessels, and may be responsible for progressive dementia.

Cardiac disorders

The main cardiac damage in patients with resistant hypertension is left ventricular hypertrophy (LVH). In Brazil, the prevalence of LVH, diagnosed by echocardiography, in patients with resistant hypertension is 83.3%[32]. In these patients, ECG changes with T wave inversion and ST segment depression in leads V5 and V6 indicate a worse prognostic[33,34]. LVH is an important independent risk factor for cardiovascular morbidity and mortality, increasing the risk by 1.5 times in individuals with this lesion[35]. This condition predisposes the development of heart failure, ventricular tachyarrhythmias, ischemic or embolic stroke, and atrial fibrillation. In LVH, decreased coronary flow reserve, arterial wall stiffening, and endothelial dysfunction lead to a significant myocardial ischemia. In these individuals, since they present macrovascular and microvascular endothelial dysfunction, chest pain symptoms should be taken seriously, even when angiography shows no evidence of relevant coronary disease[36].

Kidney disorders

Renal lesions are common and occur early, with hemodynamic changes secondary to glomerular mass loss, but which determine hypertrophy and hyperfiltration of residual normal nephrons.

The so-called "benign" hypertensive nephrosclerosis is characterized by arteriosclerosis and arteriolosclerosis, hyalinosis, tubular-interstitial lesions, and focal segmental or global glomerulosclerosis[37]. On the other hand, myointimal hyperplasia and fibrinoid necrosis are described as abnormalities that may eventually lead to the lesions caused by malignant hypertension[37].

There are several risk factors that may contribute to the development and progression of hypertensive nephrosclerosis: age (over 50), male gender, genetic predisposition and ethnicity (African descent), duration and severity of hypertension, low socioeconomic status, severity of proteinuria, severity of renal dysfunction, dyslipidemia; and other aggressors: smoking habit, excessive salt and protein intake in the diet, use of anti-inflammatory drugs, antibiotics and other nephrotoxic agents[38].

Phenotype of resistant hypertensive patients

Advanced age is a major factor related to the difficulty in achieving systolic BP goals. Alongside, the Framingham study found a correlation between difficulty of BP control and the presence of a higher baseline systolic blood pressure[39]. LVH and obesity are also strong predictors of failure to control hypertension, the latter being more related to difficulties

Table 1 - Office, ABPM, HMBP, and SMBP blood pressure values in mmHg, characterizing normal and white-coat effect values

	Office	ABPM (awake average)	HMBP	SMBP
Normal	< 140/90	≤ 130/85	≤ 130/85	≤ 130/85
Hypertension	≥ 140/90	> 130/85	> 130/85	> 130/85
White-coat effect	Difference between office and awake ABPM (or HMBP) measurements			

in controlling the diastolic blood pressure. High rates of sodium intake[18], chronic kidney disease (glomerular filtration rate ≤60 mL/min), diabetes, and African descent complete the list of clinical characteristics associated with difficulty of BP control[1]. Other conditions have been associated, such as: a) presence of silent and early damage in target organs such as microalbuminuria[23,40,41], LVH[42,43], obstructive sleep apnea syndrome[46-44], and metabolic syndrome[47]. Although a cause and effect relationship with resistant hypertension has not been fully defined yet for the last two conditions, some studies have indicated the existence of common mechanisms for obesity, metabolic syndrome, diabetes, sleep disorders and inflammatory activity in hypertensive patients, in general[48,49]. There is a common association among positive screening test for hypercortisolism and diabetes, advanced age and a non-dipper pattern in a resistant hypertensive population[50]. Furthermore, RH patients with type 2 diabetes have a more severe autonomic dysfunction associated with higher levels of body mass index and reduced plasma levels of adiponectin[51]. The presence of elevated plasma levels of aldosterone has been identified as relevant to the failure of BP control[52].

Secondary hypertension

There is no evidence to suggest the true prevalence of secondary causes among subjects with resistant hypertension. However, the likelihood of secondary causes among patients with severe and/or difficult-to-control hypertension is notably greater. Obstructive Sleep Apnea (OSA), Primary Aldosteronism (PA), Chronic Renal Parenchymal Disease (CRPD), Renovascular Hypertension (RVH), Pheochromocytoma (PHEO), Cushing's syndrome (CS), Coarctation of the Aorta (CoA), thyroid disorders and the use of some drugs that affect the blood pressure, illicit drugs and alcohol abuse are the most common secondary forms of resistant hypertension. OSA is highly prevalent; in our country, it was found in 64% of patients with resistant hypertension[53]. There was a prevalence of 20% of PA in the resistant hypertensive population[54]. Atherosclerotic RVH is present in 12.5% of resistant hypertensive patients aged over 50 years[55]. PHEO is associated with paroxysmal (30% of cases) or resistant hypertension with or without paroxysms in 50% to 60% of the cases[56]. The possibility of a secondary cause is one of the key points of the evaluation of hypertensive patients. In RH, however, greater emphasis should be put on the investigation of secondary causes, and specific exams and tests should be conducted in suspected cases. Table 2 shows the main causes of secondary hypertension, suggestive symptoms and the main diagnostic methods for the investigation of these conditions.

Nonpharmacological measures

The use of nonpharmacological measures is of great importance in the treatment of RH[1]. Despite the small number of studies evaluating the effectiveness of these measures, they have proven to be effective in the treatment of hypertensive patients in general, and this benefit seems to be higher in severe hypertensive patients than in those with mild/moderate hypertension. Therefore, patients with resistant hypertension should be counseled about the importance of reducing salt in the diet, losing weight, exercising regularly and practicing moderation in consumption of alcohol[1,4].

Salt restriction: a high intake of dietary sodium demonstrably contributes to resistance to antihypertensive therapy. Elderly patients of African descent or with impaired renal function are especially sensitive to salt. Despite a low sodium diet moderately lower (3.7 to 7.0/0.9 to 2.5 mmHg) blood pressure in hypertensive patients in general[57-60], those with resistant hypertension are particularly salt-sensitive. A study comparing the effects of a low sodium diet in patients with resistant hypertension showed that a diet containing approximately 2.5 g salt/day can reduce BP by 23.0/9.0 mmHg. This study demonstrates that the reduction in salt intake (3.0-4.0 g salt/day) is essential in managing patients with resistant hypertension. It is important to emphasize how difficult it is to reduce dietary salt intake to the recommended values[61].

Alcohol consumption: There is a direct relationship between the amount of alcohol consumed and blood pressure levels, so that excessive consumption of alcohol contributes significantly to the difficulty in controlling BP. Men who consume excessive amounts of alcohol (≥ 4 doses/day) are 50% more likely to have BP above goal[63]. Aguilera et al.[64] evaluated the effect of abstinence from alcohol on blood pressure in deep-rooted drinkers, and found an average reduction of 7.2 and 6.6 mmHg, respectively, in systolic and diastolic BP over 24 hours[64]. In the same study, the prevalence of hypertension among participants decreased from 42% to 12%. Moderate consumption of alcohol (≤ 20 g of ethanol or two doses per day) or total abstinence is recommended for deep-rooted drinkers.

Weight loss: obesity is associated with stimulation of the sympathetic nervous system, retention of salt and sleep apnea[1,4]. Therefore, obesity is associated with elevated blood pressure and resistance to antihypertensive treatment, and weight loss significantly reduces blood pressure. Patients with Body Mass Index (BMI) ≥30 kg/m^2 have 50% higher chance of presenting uncontrolled BP than those with normal BMI (<25 kg/m^2)[65]. A cross-sectional study with 45,125 patients revealed that, compared to those with normal BMI, patients with BMI >40 kg/m^2 were three times more likely to require the use of three anti-hypertensive and five times more likely to need four drugs to achieve adequate control of BP[66]. Therefore, weight loss must always be sought in RH patients who present overweight or obesity.

Physical activity: the available data point to a clear beneficial effect of regular physical activity in reducing BP[1,67]. The practice of aerobic exercises has a direct effect on lowering blood pressure and improves the metabolic profile. Resistance exercises also seem to have a beneficial effect on blood pressure, and should complement aerobic activity[4,67]. Therefore, patients with resistant hypertension should be encouraged to perform light to moderate physical activity after medical evaluation. The training program should not be started if the systolic and diastolic pressures are above 160 and/ or 105 mmHg, respectively.

Table 2 - Main causes of secondary hypertension, symptoms and signs, initial screening tests and diagnostic confirmation exams

Cause	Suggestive clinica findings	Screening tests	Advanced diagnostic exams
OSA	Snoring, episodes of apnea during sleep, daytime sleepiness, obesity, short neck	Berlin Questionnaire, Epworth sleepiness scale	Polysomnography (apnea-hypopnea index > 5 events/hour)
Primary aldosteronism	Hypokalemia (spontaneous or induced by diuretics), paresthesias	Aldosterone/renin > 30 (Renin < 1 and Aldo > 12)	Computed tomography (nodule or hyperplasia), fludrocortisone test, saline infusion test, measurement of aldosterone by adrenal vein catheterization
Chronic Kidney Disease	facial edema, uremic breath, anemia, diabetes or family history of nephropathy	serum creatinine, glomerular filtration rate estimated by formulas (< 60 mL/min), microalbuminuria, proteinuria	Renal ultrasound (signs of renal parenchymal disease)
Renovascular hypertension	Abdominal bruit, >30% increase in serum creatinine with the use of ACEI, ARB or DRI; hypertension in young or elderly patients	Renal artery Doppler (peak velocity ≥ 150 cm/s; renal-aortic velocity ratio ≥ 3); tomoangiography/MRI of renal arteries	Renal arteriography (lesion over 60% / translesional gradient > 20 mmHg)
Cushing's syndrome	moon facies, hump, purple striae, central obesity, hirsutism	24-hour urinary cortisol, plasma cortisol suppression test after low dose of dexamethasone (overnight), nocturnal salivary cortisol	Computed tomography of the adrenals and/or MRI of the hypophysis
Pheochromocytoma	headache, palpitations, sweating, tachycardia, orthostatic hypotension, syncope	Serum metanephrines, urinary metanephrines, plasma catecholamines	MRI of the adrenals, MIBG scintigraphy, PET scan
Coarctation of the aorta	Reduction of pulses in the legs, the pressure difference greater than 20 mmHg between arms and legs, blow on the back.	Magnetic resonance angiography of the aorta, echocardiography	Aortography
Hyperthyroidism and hypothyroidism	Tachy/bradycardia, increased sensitivity to heat/cold, myxedema, diarrhea or constipation, menstrual abnormalities	TSH, free T4	Thyroid ultrasound
Substances that can raise blood pressure elevation		Investigate the use of: non-narcotic analgesics, anti-inflammatory non-steroid, corticosteroids, sympathomimetic agents (decongestants, appetite suppressants, cocaine), stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine, methamphetamine, modafinil), alcohol, oral contraceptives, cyclosporine, erythropoietin, licorice, herbs (ephedra, Mahuang)	

OSA: obstructive sleep apnea syndrome; ACE: converting enzyme inhibitor; ARB: angiotensin receptor blocker; DRI: direct renin inhibitor; TSH: thyroid-stimulating hormone.

Pharmacological treatment

The purpose of the pharmacological treatment of resistant hypertension is the reduction of cardiovascular risk. For this it is recommended to achieve the following BP goal: Office BP of 130/80 mmHg; 24-hour ABPM of 125/75 (ideal), 130/80 mmHg may be tolerable; and HMBP of 130/80 mmHg[13,19].

Verification of the antihypertensive regimen, assessing the combination, dosage and proper optimization of medications, correcting sub-doses or lack of adherence, and investigating the use of other classes of drugs that may interfere with the antihypertensive efficacy, should always be conducted to confirm the diagnosis of RH[1].

The rationale in choosing a regimen of antihypertensive drugs is to block all the possible mechanisms involved in blood pressure elevation. The combination of a drug that blocks the Renin-Angiotensin-Aldosterone System (RAAS), which may be an Angiotensin Converting Enzyme Inhibitor (ACEI) or an Angiotensin II AT1 Receptor Blocker (ARB), associated with a prolonged action dihydropiridine Calcium Channel Antagonist (CCA) and a thiazide diuretic, is often very effective and well tolerated clinically. This is considered the best triple combination, the more effective and synergistic one in achieving the recommended BP goal[68,69]. The use of a renin inhibitor as a drug that blocks the RAAS is less evident in terms of cardiovascular protection.

Fluid overload seems to be the most frequent pathophysiological mechanism in this population. Thiazide diuretics with prolonged action are recommended. Chlorthalidone, having greater antihypertensive efficacy than hydrochlorothiazide, and a plasma half-life estimated between 45 and 60 hours, is preferably recommended for RH patients with preserved renal function.[1] Loop diuretics are indicated if creatinine clearance is below 30 mL/min. Due to its short duration of action (3 to 6 hours), it is recommended that they are used twice a day.

Several classes of antihypertensive drugs compete to the position of a fourth drug, but so far no comparative study has been conducted with them to demonstrate superiority in terms of anti-hypertensive efficacy or cardiovascular protection. The addition of mineralocorticoid receptor blockers to the treatment with conventional drugs is the four-drug regimen with greater visibility and it significantly reduces blood pressure in patients with resistant hypertension. In an ASCOT sub-study, the participants who completed the study and did not have a controlled BP with three antihypertensive agents received spironolactone (mean 25 mg) as a fourth drug. After a mean follow up of 1.3 years, the systolic and the diastolic BP decreased 21.9 and 9.5 mmHg, respectively. The reduction in blood pressure with spironolactone occurs regardless of the aldosterone/plasma renin activity ratio[70].

The choice of additional drugs to the four-drug combination is empirical and should be individualized[4,71] (Figure 2). Hospitalization is not recommended for the investigation of secondary hypertension or therapy optimization, but this is a strategy that can be used when available, if after six months of therapy optimization the recommended BP goal is not achieved, being an alternative verification of adherence and sodium restriction.

Although there is no evidence of reduction of cardiovascular risk, chronotherapy is an adjuvant strategy in patients on three drugs and with the goal BP not reached prior to the combination of a fourth agent; in these cases an ACC may be used in the night period[72]. This strategy has proven effective in the implementation of sleep blood pressure reduction and decrease.

Adherence can be implemented by simplifying the treatment regimen with the use of fixed drug combinations. Even if the BP goal is not achieved, pressure values should be as close as possible to the recommended goal.

New treatments

The lack of evidence about the best therapy in RH led to the development of new treatments which are being prioritarily tested in patients with poor response to the initial pharmacological treatment.

Direct stimulation of the carotid sinus

The increased sympathetic tone and decreased parasympathetic tone increase peripheral vascular resistance to sodium retention, reduce renal blood flow and glucose metabolism, and contribute negatively to myocardial remodeling[73]. The chronic stimulation of baroreceptors may exert beneficial effects on blood pressure.

The Rheos Baroreflex Activation Therapy System is a programmable device that resembles a surgically implanted pacemaker and consists of a pulse generator. The Rheos Pivotal Trial found no significant benefits with this system, and further studies are expected to show the benefits of this device[74].

Renal sympathetic denervation

Renal sympathetic nerves contribute to the development and maintenance of hypertension, and renal sympathetic activity is exacerbated in hypertensive patients. Endovascular renal sympathetic ablation was evaluated in a case series of patients

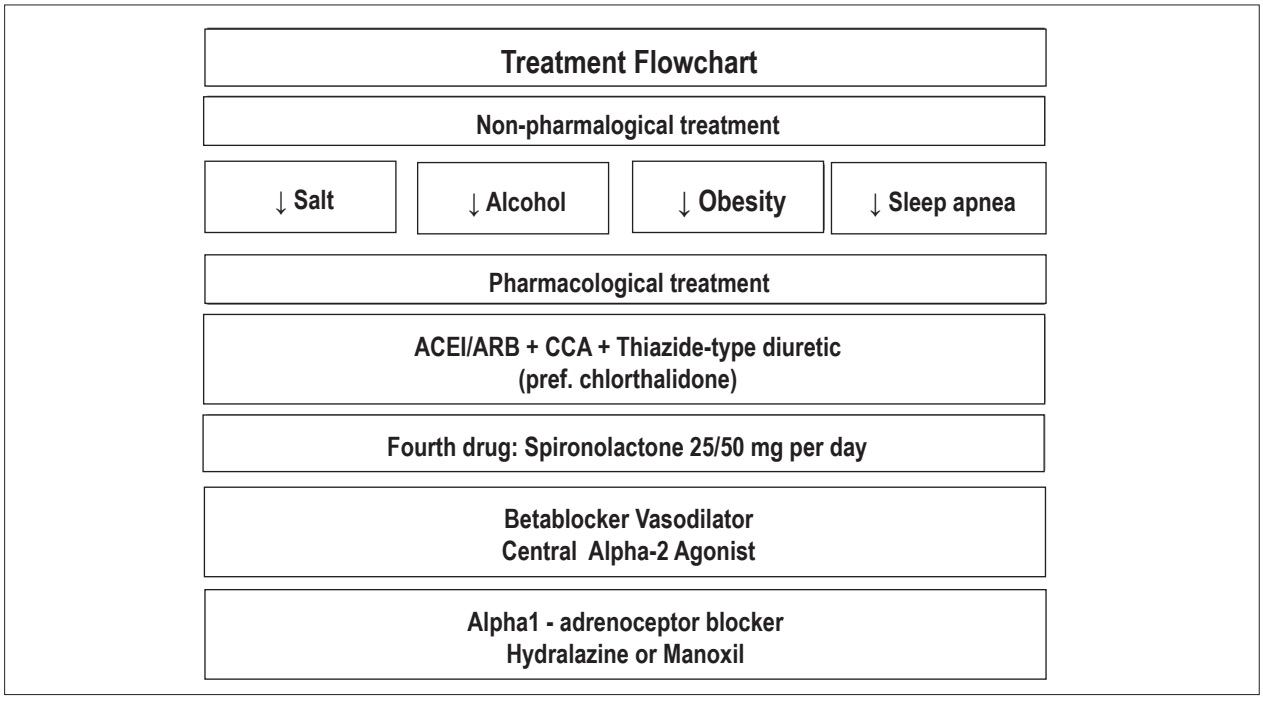

Figure 2 – *Flowchart of the treatment of resistant hypertension.*

with resistant hypertension. Over two years, there was a decrease of 32 mmHg and 14 mmHg in the SBP and DBP, respectively, with a very low rate of complications.[75] In the study Symplicity-2, in six months, the difference in pressure drop between the groups was 33 mmHg and 11 mmHg in SBP and DBP, respectively. In the intervention group, 84% of patients had a reduction of at least 10 mmHg, whereas in the control group, this proportion was 35%. There were no major complications related to the described procedure. These findings show that endovascular ablation of the renal artery is a promising procedure in the context of RH, but further studies are necessary to show the possibility of reproducible results and better dissemination of the technique.

Use of Continuous Positive Airway Pressure (CPAP)

The effects of CPAP on RH were tested in a clinical trial with 75 patients who had their RH condition confirmed by ABPM and who had an apnea-hypopnea index (AHI) ≥ 15/h[76]. After a three-month follow-up, only 24h-DBP reduced significantly in the group treated with CPAP (4.9 ± 6.4 mmHg vs. 0.1 ± 7.3 mmHg in control). The antihypertensive effect was more pronounced in those who tolerated the use of CPAP for more than 5.8 h/day. All the evidence concerning the antihypertensive effect of CPAP and the results of this trial in resistant hypertension indicate that this option can be tried as an adjunctive treatment in patients with AHI greater than 15/h, especially those who tolerate their use for more than 5 h/day.

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