

Resistant hypertension: a dangerous and challenging clinical situation

Abstract

High blood pressure is a very important risk factor for the development of Cardiovascular Diseases (CVD), which are among the main causes of death globally. In particular, Resistant Hypertension (RH) predisposes individuals to a higher risk of CVD. RH is defined as the absence of blood pressure control despite the use of at least three classes of antihypertensive agents, one of them being a diuretic, in optimal dosage. To identify true RH, it is essential to exclude specific clinic conditions, such as pseudo-resistance and causes of Secondary Hypertension (SR), since these situations can also be related to poorly controlled hypertension. A large number of factors may be investigated to exclude pseudo-resistance, which includes: non-adherence to the antihypertensive therapy, white coat hypertension, inaccurate blood pressure measurement, non-optimized therapeutic scheme, low acceptance of the need for life-style modifications. In this review we will address the aspects of the pathophysiology, diagnosis and treatment of HR.

Keywords: resistant hypertension, blood pressure, secondary arterial hypertension, cardiovascular disease

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Abbreviations: CVD, cardiovascular diseases; CCB, calcium channel blocker; SR, secondary hypertension; ABPM, ambulatory blood pressure monitoring; PA, primary aldosteronism, OSA, Obstructive sleep apnea; RD, renovascular disease; RPD, renal parenchymal disease

Introduction

High blood pressure is a very important risk factor for the development of Cardiovascular Diseases (CVD), which are among the main causes of death globally.¹ In particular, Resistant Hypertension (RH) predisposes individuals to a higher risk of CVD. RH is defined as the absence of blood pressure control despite the use of at least three classes of antihypertensive agents, one of them being a diuretic (when tolerated), in optimal dosage. The higher vulnerability presented by this group of patients is due to the prolonged period of uncontrolled hypertension and to the coexistence of other risk factors, such as obesity, diabetes and dyslipidemia.² It is valid to emphasize that this definition of RH also extends to those patients which require at least four classes of antihypertensive drugs to maintain normal blood pressure levels.³⁻⁵

Frequently, the term “refractory hypertension” is used as a synonym of RH, however it corresponds to a clinical condition with worse prognosis when compared to RH and therefore is related to even greater complications. It is defined as failure to control blood pressure despite the use of at least 5 different classes of antihypertensive agents, including a long-acting thiazide-type diuretic and a mineralocorticoid receptor antagonist.^{5,6}

Ideally, the triple therapeutic scheme is composed of a renin-angiotensin system blocker (an angiotensin-converting enzyme inhibitor–ACE inhibitor; or an angiotensin receptor blocker–ARB),

a calcium channel blocker (CCB) and a diuretic.³⁻⁵ In patients with preserved or slightly diminished renal function, it is preferable to use chlorthalidone or indapamide rather than hydrochlorothiazide, since they're more potent agents, in part due to its longer action time.^{7,8}

To identify true RH, it is essential to exclude specific clinic conditions, such as pseudo-resistance and causes of Secondary Hypertension (SR), since these situations can also be related to poorly controlled hypertension.⁹ A large number of factors may be investigated to exclude pseudo-resistance, which includes: non-adherence to the antihypertensive therapy, white coat hypertension, inaccurate blood pressure measurement, non-optimized therapeutic scheme, low acceptance of life-style modifications (physical activity, smoking and alcoholism cessation, and low sodium ingestion).^{4,6}

In relation to SH, it is fundamental to investigate the disorders that are more commonly associated with this condition: Obstructive Sleep Apnea; Renovascular Disease; Primary Aldosteronism and Renal Parenchymal Disease. However, it should be noted that other more uncommon causes must be remembered when facing antihypertensive drug resistance, such as Pheochromocytoma, Cushing's syndrome, Thyroid Diseases and Hyperparathyroidism. There are also medications that can contribute to an increase in arterial blood pressure and to the development of RH, but the manifestation of these effects is individual to each patient, and some of them may not present blood pressure alterations when using them.¹⁰

The aim of this review is to describe the complexity of RH and its peculiarities, and to determine the main tools that should be used to the adequate diagnosis and to establish an effective therapy, not only to improve the patient condition, but also to prevent future complications which these individuals are predisposed to.

Methods

Literature search strategy

We undertook a systematic search of EMBASE (<http://www.embase.com>) and Pub Med (<http://www.ncbi.nlm.nih.gov/pubmed>) through August 2019 for studies related to RH and CVD. The following search terms were entered in the database searches: resistant hypertension, diagnosis, evaluation, and treatment. In addition, Reference lists of all relevant articles and identified reviews were inspected to identify pertinent articles that could have been missed in the initial search.

Diagnosis

Clinical history and physical examination: Clinical history and physical examination should be performed in order to confirm the diagnosis of RH and to evaluate the best therapeutic scheme available, considering the adequate choice of the available medications and the blood pressure goals to be achieved. The existence of clinical entities that also contribute to the poorly controlled hypertension should be investigated, such as pseudo-resistance (non-adherence, non-optimized therapeutic schemes, inadequate life habits, white coat hypertension and inaccurate blood pressure measurement). We also have to evaluate if there is already established target organ damage. It is also important to identify the medications in use by the patient, some of them which may cause blood pressure elevations. In many clinical scenarios, the resistance to the established treatment is due to multiple etiologies, which must be properly identified and managed.^{3,10} Table 1 shows several medications that can interfere with blood pressure control.

Table 1 Medications that can interfere with blood pressure control

Nonnarcotic analgesics
Nonsteroidal anti-inflammatory agents, including aspirin
Selective COX-2 inhibitors
Sympathomimetic agents (decongestants, diet pills, cocaine)
Stimulants (methylphenidate, dexamethylphenidate, dextroamphetamine, amphetamine, methamphetamine, modafinil)
Alcohol
Oral contraceptives
Cyclosporine
Erythropoietin
Natural licorice
Herbal compounds (ephedra or ma huang)

Data form¹⁰

Measurement of blood pressure

In the office: Applying the adequate technique to measure blood pressure is indispensable in RH investigation, considering it is one of the requirements to rule-out pseudo-resistance. Among the requirements recommended to the accurate blood pressure measurement, it is mostly important that: the patient stays at least 5 minutes sitting on a chair, in a calm environment; the cuff used has an adequate size; the patient's arm is positioned at the level of the heart; and that at least two readings are obtained within a one-minute interval, from which an average is obtained.^{10,11} The blood pressure

should be measured in both arms, and the higher reading should be used as reference¹⁰. In relation to the patient positioning, it should ideally be seated, with the legs uncrossed, the feet on the floor, and the back supported in the chair³. However, during treatment, the patients should also be evaluated while lying in bed and in orthostatic position, so that orthostatic complications related to treatment can be identified.¹⁰

Ambulatory blood pressure monitoring and home blood pressure monitoring: Although the suspicion of RH can be made in the office evaluation through the finding of high blood pressure despite the use of, at least, three antihypertensive agents, one of them being a diuretic (if tolerated), in optimal dosage; the use of out-of-office monitoring is mandatory for diagnosis confirmation as well to establish management.^{10,12,14}

The ambulatory blood pressure monitoring (ABPM) is considered the gold-standard for the determination of blood pressure values.^{15–18} This method allows a considerable amount of readings, which includes measurements performed during night-time; also, it ensures the absence of observer bias and helps diagnosing white coat hypertension.^{19,20} ABPM is considered the best predictor of cardiovascular morbimortality for high blood pressure patients.²¹ However, the efficacy of this technique can be limited by some factors, such as the cuff size, patient movement and corporal position, short term blood pressure variation, and sleep interference.²²

In situations of low tolerance to ABPM (sleep and labor interference), home blood pressure monitoring (HBPM) can be used, however it is important to emphasize that this technique has some limitations when compared to ABPM,²³ being characterized with high specificity and low sensibility¹³. HBPM does not ensure effective night-time evaluation—the period in which the blood pressure is more predictive of cardiovascular events,²⁴ which also means the inability of this method to diagnose isolated nocturnal hypertension (which has the same cardiovascular risk as an altered ABPM).²⁵ HBPM is also not able to detect masked and sustained hypertension (high cardiovascular risk diseases) in more than 25% of patients.¹² Table 2 describes the blood pressure limits for the diagnosis of arterial hypertension, based on different International Cardiology Societies Guidelines for the management of arterial hypertension (Tables 3–5).

Table 2 Definitions of hypertension according to office, ambulatory, and home blood pressure levels according to the ESC/ESH Guidelines

Category	SBP (mmHg)	DBP (mmHg)
Office BP ¹	≥140 and/or	≥90
Ambulatory BP		
Daytime (or awake) mean	≥135 and/or	≥85
Night-time (or asleep) mean	≥120 and/or	≥70
24 h mean	≥130 and/or	≥80
Home BP mean	≥135 and/or	≥85

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure

Refers to conventional office BP rather than unattended office BP

Data form³⁰

Table 3 Definitions of hypertension according to office, ambulatory, and home blood pressure levels according to the Brazilian guidelines

Category	SBP (mmHg)		DBP (mmHg)
Office BP	≥140	and/or	≥90
AMBP			
Awake	≥135	and/or	≥85
Asleep	≥120	and/or	≥70
24 h mean	≥130	and/or	≥80
HMBP	≥135	and/or	≥85

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure

Data form³⁹**Table 4** Definitions of hypertension according to office blood pressure levels according to the American Guidelines

BP Category	SBP		DBP
Normal	<120 mmHg	and	<80 mmHg
Elevated	120-129 mmHg	and	<80 mmHg
Hypertension			
Stage 1	130-139 mmHg	or	80-89 mmHg
Stage 2	≥140 mmHg	or	≥90 mmHg

Dataform⁵**Table 5** Corresponding values of SBP/DBP for clinic, HBPM, daytime, nighttime, and 24-hour ABPM measurements

Clinic	HBPM	Daytime ABPM	Nighttime ABPM	24-Hour ABPM
120/80 mmHg	120/80 mmHg	120/80 mmHg	100/65 mmHg	115/75 mmHg
130/80 mmHg	130/80 mmHg	130/80 mmHg	110/65 mmHg	126/75 mmHg
140/90 mmHg	135/85 mmHg	135/85 mmHg	120/70 mmHg	130/80 mmHg

ABPM, indicates ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; HBPM, home blood pressure monitoring; SBP, systolic blood pressure

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Adherence to pharmacological treatment

Therapeutic nonadherence is an important factor to be evaluated when facing RH suspicion, since the drugs used to treat hypertension cannot be effective if not taken in the correct posology.^{26,27}

The indirect strategies to verify patient adherence to treatment, such as counting the number of pills used and asking patients about difficulties with the prescription (collateral effects and costs) are useful, but are prone to misconception and can result in diagnostic error.²³

The gold-standard methods for the evaluation of therapeutic adherence are: the witnessed use of the medication²⁸ and the direct or indirect measurement of drug concentrations in corporal fluids (blood and urine).²⁹ However, even though the dosing of drug metabolites can establish if the medication is present or not in the patient's body, it cannot determine if the medication regimen was properly followed.³

Thus, it is noted that both the indirect methods as well as the

direct methods have limitations and can result in diagnostic error. Therefore, it is important that a combination of these methods is used the medical approach, so that higher sensitivity and specificity are obtained. Besides that, it is also necessary that this analysis is carried out on all medical consultations. For being a process related to the interference of multiple psycho-social agents, the therapeutic adherence is a dynamic event and, thus, cannot be investigated in a single encounter.²³

Exclusion of secondary causes

Secondary hypertension can be identified in about 10% of the patients with high blood pressure, and is defined by the presence of identifiable causes of blood pressure elevation, that can be diagnosed and treated. The specific approach to these alterations can result in a marked improvement in blood pressure control and in some cases, it is also possible to achieve cure of the underlying condition, provided that the intervention was made early in the diagnosis.^{4,5}

Obstructive sleep apnea (OSA)

Obstructive Sleep Apnea has a prevalence of about 25-50% in patients with hypertension³⁰ and is a common sleep disorder defined by the chronic collapse of upper airways during sleep, with resulting episodes of apnea or hypopnea.³¹ The hypoxemia caused by the respiratory dysfunction results in systemic endothelial dysfunction as well as intensification of the activity of the sympathetic nervous system and the renin-angiotensin system (RAS), which together cause vasoconstriction in several body regions. The activation of RAS is also related with sodium and water retention, which results in intravascular volume expansion and, as consequence, elevation of blood pressure levels.³²⁻³⁴

The patients with this condition have a phenotype characterized by obesity, large neck and macroglossia. The presence of symptoms is frequent, such as daytime sleepiness, irritability, difficulty to concentrate and snoring.^{4,30,35} Thus, when the presence of OSA is suspected, screening tests such as the Epworth Sleepiness Score and the Berlin Questionnaire should be performed. If necessary, the diagnosis of this clinical situation can also be confirmed by polysomnography.^{4,30,36,37}

Renovascular disease

Renovascular Disease (RD), with a prevalence of 5-34%³⁰ is a result of renal artery stenosis (uni or bilateral). The main etiologies of renal artery stenosis are atherosclerotic disease (more common in adult patients), fibromuscular dysplasia (more common in children and young adults), and less frequently Takayasu's arteritis. About 90% of the cases of renal artery stenosis are caused by atherosclerotic disease.³⁸⁻⁴⁰ The narrowing of the renal artery results in decreased renal blood flow and by consequence, pathologic activation of the RAS, causing abnormal blood pressure elevation.³⁸

The RD of atherosclerotic origin represents about 90% of the diagnosed cases, being the most common cause. Advanced age, diabetes, smoking, diffuse atherosclerosis, recurrent pulmonary edema, worsening of the renal function when starting ACE inhibitors or ARBs, and abdominal bruising are among the main features that suggest this condition. The occurrence of fibromuscular dysplasia is more common in women and abdominal bruises are also common in this clinical setting.^{4,5,30,41}

After clinical suspicion, the renal arteries evaluation can be done by renal duplex Doppler ultrasound, abdominal computed tomography or

by magnetic resonance. In cases which there is evidence of narrowing or in uncertain cases, it is recommended to perform a renal artery angiography, considered the gold-standard for the diagnosis.^{4,30}

Primary aldosteronism

Primary Aldosteronism (PA), with a prevalence of 8-20%³⁰ is a disorder characterized by high production of aldosterone, occurring in an inappropriate manner and relatively autonomous of the regulatory mechanisms, such as the RAS. The excessive production of aldosterone increases sodium and water reabsorption in the kidneys, and also creates an electric gradient that favors potassium secretion into the luminal space. There is also inhibition of the plasmatic renin activity. As a result, there is an intravascular volume expansion, with promotes elevations in blood pressure. Among the main causes of this disorder, are the aldosterone-producing adenoma and the adrenal hyperplasia.⁴²

In most of the cases patients present asymptomatic and, when present, symptoms are non-specific. The main clinical features include fatigue, asthenia, polyuria, polydipsia, intestinal constipation, headaches and palpitations. Hypokalemia can be present in less than half of the cases.^{4,43}

The screening for this condition is done by plasmatic aldosterone dosing, plasmatic renin activity and primarily by the ration between these two parameters.⁴⁴ To perform the dosing of these markers, the serum levels of potassium should be normal and the use of mineralocorticoid receptor antagonists should be suspended for at least four weeks. When the diagnosis is probable, in most of the cases it is necessary to perform confirmatory tests, and the most commonly used are the oral sodium loading test and the intravenous saline infusion test. The computed tomography of the adrenal glands is the test of choice for the identification of the disease subtype and to guide management.^{41,42,45}

Renal parenchymal disease

Renal Parenchymal Disease, with a prevalence of 1-2%³⁰ is a significant cause of secondary hypertension in children.⁴⁶ Alterations in the renal parenchyma promote a renal function unbalance, resulting in intravascular volume expansion and in an exacerbation of vasoconstriction, which are responsible for elevations in blood pressure.^{47,48}

In several cases, patients are asymptomatic. However, the presence of diabetes, urinary changes, anemia, and urinary tract changes can suggest the existence of disease of the renal parenchyma. If there is clinical suspicion, the urinary analysis and the albumin/creatinin ration are the main methods of screening for this condition. Renal ultrasonography can also be used in this investigation.^{4,30} Finally, there are several other less common causes of secondary hypertension (Table 6).

Although it is apparently easy to recognize RH, its prevalence is still not well determined, in part due to the difficulty in making a reliable diagnosis, mainly when it is necessary to exclude pseudo-resistance (nonadherence and suboptimal therapy).⁶ However, it is necessary to emphasize the importance of the medical ability in recognizing true RH, since the patients considered resistant to the antihypertensive therapy have higher risks for the development of end organ damage and adverse outcomes (such as myocardial infarction, stroke, heart failure and chronic kidney disease).⁴⁹⁻⁵²

In conclusion, early identification of these patients allows medical professionals to establish more directed and aggressive therapeutics, when compared to the strategies aimed to patients classified as “good responders”. With the better understanding of all the above aspects involved with RH, unfavorable outcomes could be avoided and a better life quality could be ensured for patients suffering from this dangerous clinical setting.

Table 6 Other causes of secondary hypertension

Cause	Prevalence	History and clinical findings	Screening investigations
Phaeochromocytoma	0,1-0,6%	Episodic symptoms (the 5 “P’s”): paroxysmal hypertension, pounding headache, perspiration, palpitations, and pallor; Also common: anxiety, orthostatic hypotension, labile BP, BP surges precipitated by drugs (e.g. beta-blockers, sympathomimetics, opioids and tricyclic antidepressants), positive family history of pheochromocytoma.	24-h urinary fractionated metanephrines or plasma metanephrines.
Cushing’s syndrome	<0,1%	Moon face, central obesity, skin atrophy, hirsutism, impotence, fatigue, psychological changes, polydipsia, polyuria and chronic steroid use.	24 h urinary cortisol, dexamethasone testing.
Thyroid disease (hyper – or hypothyroidism)	<1%	Hyperthyroidism: palpitations, accentuated heart sounds, exophthalmia, weight loss, anxiety, heat intolerance; Hypothyroidism: weight gain, fatigue, obstipation, cold intolerance, hoarseness, bradycardia, myxedema,	Thyroid-stimulating Hormone, Free Thyroxine.
Hyperparathyroidism	Rare	Hypercalcemia, hypophosphatemia.	Parathyroid hormone, Ca ²⁺ .

Dataform^{4,5,35}

Compliance with ethics guidelines

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the author’s.

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Conflicts of interest

All authors declare that they have no conflicts of interest.

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