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Chapter 7

Treatment-Resistant Hypertension: An Update in Device Therapy

Leandro Heleno Guimarães Lacerda, Ricardo Cambraia Parreira, Rebecca Vasconcellos, Swiany Silveira Lima, Anderson Kenedy Santos, Vanessa Fontana, Valéria Cristina Sandrim and Rodrigo Ribeiro Resende

Additional information is available at the end of the chapter

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Abstract

Resistant hypertension (RH) is a clinical condition in which the hypertensive patient has become resistant to drug therapy and is often associated with increased cardiovascular morbidity and mortality. Several signaling pathways have been studied and related to the development and progression of RH: modulation of sympathetic activity by leptin and aldosterone, primary aldosteronism, arterial stiffness, endothelial dysfunction, and variations in the renin-angiotensin-aldosterone system (RAAS).

Keywords: resistant hypertension, signaling pathways, blood pressure, drug resistance

1. Introduction

Systemic arterial hypertension (SAH) stands out as the major independent risk factor related to cardiovascular disease (CVD) and remains the greatest modifiable risk factor, despite the important advance in the knowledge of its pathophysiology and availability of effective methods for its treatment. There are approximately 13.3 billion people with SAH in the world, and in developed Western countries, better controls are obtained on blood pressure (BP) levels.
Resistant hypertension (HAR) affects on average 30% of the adult population, about 1.2 billion individuals worldwide. Although the exact prevalence of HAR is still not established, it is estimated that this condition reaches 12–15% of hypertensive individuals.

2. Resistant hypertension

Resistant hypertension (RH) is characterized by a condition in which the patient requires four or more antihypertensive medications, including a diuretic, regardless of blood pressure control. RH patients can be classified as controlled or uncontrolled according to the achievement of the blood pressure goals [1].

The RH affects approximately 13–25% of the hypertensive population [2–4] and represents a risk factor for cardiovascular events. Results from the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) showed increased hazard ratios for stroke (1.57), end-stage renal disease (1.95), heart failure (1.88), coronary heart disease (1.44), and all-cause mortality (1.30) in RH compared to nonresistant hypertensive subjects [5].

RH is a multifactorial condition, and several environmental and genetic factors contribute to the development and progression of the disease. Firstly, the identification of pseudoresistance must be performed to identify true resistant hypertensive patients, caused mainly due to poor BP measurements, lack of adherence, suboptimal therapy, and white coat hypertension. In addition, secondary causes of RH, such as primary aldosteronism, pheochromocytoma, renal artery stenosis, or Cushing’s syndrome should be identified since the pharmacological treatment will be specific for each condition. Among the factors associated with an increased risk for RH are: older age, African origin, female gender, overweight, and obesity [1, 6].

The RH presents three relevant characteristics: (1) high incidence of the following comorbidities: obstructive sleep apnea [7], thyroid disorders [7], primary aldosteronism [8, 9], reduced plasmatic renin activity, obesity [6], diabetes mellitus [1, 6]; (2) high prevalence of target organ damage; and (3) high blood pressure (BP) levels measured by ambulatory blood pressure monitoring (ABPM) [10–12].

The achievement of the BP goals relies on physician examination and on patient characteristics and compliance to pharmacological and nonpharmacological treatments. It is well know that obesity, excessive alcohol and/or salt intake, sedentary lifestyle, smoking, insulin resistance, difficulty in adopting dietary measures, and lack of adherence to therapeutic treatment affects BP control [12]. In addition, prescription of high-cost medicines by physicians, multiple administration regimens, suboptimal doses, and presence of adverse effects are associated with uncontrolled BP [13].

The factors associated with diagnostic and treatment of RH include lifestyle, detailed history of medication adherence, correct BP measurement, biochemical analysis for dosage of electrolytes, glucose, and creatinine, as well as determination of protein and sodium in the urine [12].

The exclusion of pseudohypertension is also necessary. For example, Mönckeberg’s sclerosis is a condition characterized by the loss of elasticity and thickening of the walls of the muscular
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**Table 1.** Forms of secondary hypertension associated with RH (modified from Vongpatanasin [14]).
arteries caused by a calcification of the tunica media constituted of smooth muscle. In the measurement of blood pressure by noninvasive methods, the patient presents high BP values, while in reality, the pressure is normal; therefore, it is necessary to use invasive measurement methods to correctly measure the BP [12]. In white coat hypertension, also a condition of pseudoresistance, the patient exhibits high values during the verification in the physician’s office. It can be excluded by 24-h ABPM. It is estimated that 30% of patients with elevated BP and with treatment of up to three drugs present this condition of white coat hypertension [12, 14].

In order to complete the diagnosis of RH, there are some clinical situations that are considered as secondary causes of this condition, such as: primary hyperaldosteronism, pheochromocytoma, fibromuscular dysplasia, patients with increased risk of atherogenesis [12], obstructive sleep apnea, renal artery stenosis, renal parenchymal disease, Cushing’s syndrome, and thyroid and parathyroid diseases [10]. These forms of secondary hypertension present high prevalence in association with RH, as can be verified in Table 1. Hyperaldosteronism results from the excessive production of aldosterone, a hormone that is produced in the adrenal glands and that decreases the excretion of sodium and increases the excretion of potassium by the kidneys, sweating, and saliva. The determination of the rate of aldosterone/renin ratio is used as screening tool for hyperaldosteronism diagnostic, and if any alteration is confirmed, diagnostic

![Figure 1. Recommendations for diagnosis of RH. Modified from Calhoun et al. [1] and Passarelli et al. [16]. Abbreviation: WCH, white coat hypertension.](image-url)
imaging and blood samples from each side of the adrenal glands are used to corroborate the diagnosis [12]. Obstructive sleep apnea consists of the collapsing of the pharynx walls hampering the adequate respiration of the individual. The patient is then submitted to a nocturnal polysomnography in order to monitor respiration and body functions during sleep for diagnosing the condition [15]. For more information on diagnostic and treatment methods, see Table 1 [14].

A flowchart (Figure 1) summarizes the steps involved in the diagnosis of RH according to the American Heart Association Statement [1, 16].

Although RH is a multifactorial condition, excess sodium, fluid retention, increased activation of the renin-angiotensin-aldosterone system, and higher sympathetic tone are among the most well-described mechanisms of BP elevation in RH. The complex pathophysiology of the development and progression of RH requires further investigation to identify molecular mechanisms that could be translated into diagnostic and more assertive therapeutic strategies. In the following sessions, the signaling pathways and the participation of miRNA in their regulation will be discussed.

3. Renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system (RAAS) is responsible for the hemodynamic equilibrium. This is possible due to the effects of this system on the kidneys, which act in the sodium water balance, and also due to the influence in the vascular resistance on the peripheral blood vessels, thus permitting the maintenance of the BP [17]. In order to the RAAS to produce a response, it is necessary for some type of alteration to occur in the circulating blood volume, such as blood loss, dehydration, or even pumping failure by the ventricles [18] (Figure 2).

Juxtaglomerular apparatus comprises afferent arterioles in the distal part of the ascending branch of the loop of Henle in the renal glomeruli. The cells that line these arterioles in the region of the apparatus are called juxtaglomerular cells and are able to recognize the BP inside these vessels [18]. Moreover, the cells that line the loop of Henle in the region of the juxtaglomerular

Figure 2. Hemodynamic control of RAAS. Modified from Maron and Leopold [18]. Abbreviation: ACE, angiotensin converting enzyme.
apparatus are called macula densa and respond to changes in the sodium concentration of the filtrate. By detecting these changes, the cells of the dense macula stimulate juxtaglomerular cells to produce an enzyme called renin that is released into the bloodstream. This enzyme is responsible for the production of angiotensin I (AngI) through the cleavage of angiotensinogen, which is synthesized and secreted by the liver. In the pulmonary and renal endothelium, an enzyme called angiotensin-converting enzyme (ACE), which hydrolyzes the circulating AngI in angiotensin II (AngII), is present. The angiotensin 1 receptor (AT1) is activated by AngII, thus promoting a vasoconstrictive response in the blood vessels, in addition to stimulating the adrenal gland to produce aldosterone. The renal tubules respond to the aldosterone by retention of sodium and water, which will promote increased blood volume and consequently, BP elevation [19, 20].

The RAAS constitutes the main signaling pathway involved in the long-term control of the BP. Innumerable regulators participate in this biochemical cascade of communication such as renin, angiotensinogen, AngI and II, ACE 1 and 2, and aldosterone and angiotensin-1-7 [Ang-(1-7)]. The deregulation of one or more effectors of this system contributes to failures in blood pressure control, usually leading to hypertension [21]. Resistant hypertension is accompanied by intravascular fluid retention that can be attributed, at least in part, to dysregulation in the renin-angiotensin-aldosterone system. Previous studies have found evidence of intravascular volume expansion (higher levels of brain-type natriuretic peptide—BNP and atrial natriuretic peptide—ANP) and aldosterone excess (higher levels of plasma and urinary aldosterone, aldosterone to renin ratio) in resistant hypertension compared to controls [22]. Similarly, another study reported higher volume of fluid by thoracic electrical bioimpedance, suggesting that the intensification of diuretic therapy in those patients could be beneficial [23]. ANP and BNP are hormones that regulate cardiovascular hemodynamics. They are secreted by cardiac atria and cardiac ventricles, respectively, in response to stretch or pressure. Natriuretic effects are mediated by subtype A-natriuretic peptide receptor, which is expressed in several tissues, including kidneys, blood vessels, adrenal glands, and adipose tissue. ANP produces its natriuretic actions by increasing glomerular filtration rate and inhibits sodium transport in proximal tubule and inhibition of aldosterone release in adrenal cells. The latter effect is also attributed to BNP [24]. Aldosterone is one of the most studied RAAS components in RH; several studies had shown that aldosterone excess is a common characteristic of RH. In addition, primary aldosteronism is the most common secondary cause in the patients with RH [8]. This condition is characterized by excessive autonomic secretion of aldosterone by the adrenal gland, being the production of adenomas and idiopathic hyperaldosteronism in the main forms [25, 26]. This secretion, stimulated by renin, promotes the retention of sodium and water, promoting the elevation of blood volume, and consequently the increase of BP. When it is released into the bloodstream, the aldosterone diffuses through the membrane into the cytosol of renal tubular epithelial cells, subsequently binding to a family of NRC2-type mineralocorticoid receptors. This aldosterone-receptor complex will be translocated to the nucleus, activating the synthesis of proteins related to sodium and potassium transport, such as Na+ K+ ATPase (Figure 3) [27].

An important signaling pathway in the primary aldosteronism is the phosphoinositide 3-kinase (PI3K) pathway with the activation of mammalian target of rapamycin (mTOR), when overactivation is involved in the tumorigenesis and metastasis in some types of human tumors such as renal cancer, adrenal carcinoma, and pheochromocytoma [28–30] (Figure 4) [29]. The PI3K/AKT/mTOR pathway is regulated in response to the signaling of growth factors such as the epidermal growth factor (EGF) through receptor tyrosine kinases (RTKs) [31].
Figure 3. Signaling pathway of Na+/K+-ATPase activity and aldosterone.

Figure 4. Signaling pathway involved in primary aldosteronism. Abbreviations: AKT, protein kinase B; EGFR, EGF receptor; ERK, extracellular regulated kinase; GPCR, G-protein coupled receptor; HB-EGF, heparin binding EGF; MAPK, mitogen-activated protein kinase; PIP2, phosphatidylinositol 4,5-biphosphate; PIP3, phosphatidylinositol (3,4,5)-triphosphate; PKC, protein kinase C; PLD, phospholipase; S1P, sphingosine-1-phosphate.
Another stimulus to the release of aldosterone is the action of sphingosine-1-phosphate (S1P) by means of the activation of the PI3K/AKT (protein kinase B) and mitogen-activated protein kinase (MEK)/extracellular regulated kinase (ERK) pathway in glomerular cells of the adrenal glands (Figure 4) [30]. S1P is a bioactive sphingolipid intracellularly formed that acts as a second messenger mediating regulatory processes such as cell differentiation, migration and contraction, modulation of immune response, and angiogenesis, and this molecule is considered to be the key hormone for hemodynamic stability in humans [32, 33]. Its action involves the activation of phospholipase D (PLD), calcium influx (Ca\(^{2+}\)) from the extracellular medium and phosphorylation of α and β isoforms of protein kinase C (PKC) [25, 26, 32].

Previous studies had shown excess of aldosterone in uncontrolled RH compared to controlled group. The same study demonstrated that aldosterone was correlated to arterial stiffness [34]. Furthermore, higher aldosterone levels were associated with the T allele for the polymorphism-344 C/T CYP11B2 (aldosterone synthase gene) in RH subjects, and this effect was shown to be more pronounced in patients under spironolactone treatment [35]. Studies have demonstrated significant reductions in blood pressure with addition of mineralocorticoid receptors antagonists, such as spironolactone, and that drug has been suggested as the optimal fourth-line drug for BP control in RH.

Angio-(1-7) is a heptapeptide that carries out an important function in the RAAS. This molecule is formed both by the action of ACE 1 (dependent pathway) and the hydrolysis of AngII by the ACE 2 (independent pathway) [36, 37], being the last one in the most important pathway in the formation of Ang-(1-7) [38]. This molecule produces its AngII endogenous counter-regulatory effects on RAAS (vasodilation, cardio protection, natriuresis, and diuresis, angiogenesis inhibition, and cellular growth) [39] through the binding to its specific receptor called Mas, a G protein-coupled receptor [25, 40, 41].

The ACE2/Ang-(1-7)/Mas signaling pathway consists in one of the RAAS axes that opposes, in terms of function, to another classical axis of this system, the ACE/AngII/AT\(_1\)R. The imbalance of these two opposing axes, mainly in the direction of the ACE/AngII/AT\(_1\)R axis, predisposes to cardiovascular diseases and other disorders [37, 41].

The Ang-(1-7)/Mas complex regulates different signaling pathways, such as PI3K/AKT and ERK signal, and involves the maintenance of some effectors like nitric oxide (NO) [25, 41], FOXO1 (forkhead box 1) [39] and cyclooxygenase-2 (COX-2) [40] (Figure 5). Studies report that due to the participation of the Ang-(1-7) in these mechanisms, this heptapeptide is related to pathological conditions such as fibrosis and inflammatory processes in some organs, like lungs, liver, and kidneys [42]. Other findings demonstrate that Ang-(1-7), through the interaction with its Mas receptor, stimulates the activation of the nitric oxide synthesis (eNOS) in endothelial cells, promoting vasodilation [25, 36, 41].

Another study demonstrates that Ang-(1-7), through the interaction with its specific Mas receptor, promotes the increase in nitric oxide (NO) and prostaglandins (PG) synthesis and release, leading to vasodilation and inhibition of cellular growth, opposing to the vasoconstrictor and proliferative effects mediated by the interaction of AngII with its AT\(_1\) receptors. The imbalance between these two axes of the RAAS, reflected by the imbalance between these peptides, which are observed in cardiovascular diseases, can lead to the decrease in NO and consequently to endothelial dysfunction (Figure 5) [43].
3.1. Sympathetic nervous system

Sympathetic nervous system regulates cardiac output and peripheral vascular resistance (vasoconstriction) through release of norepinephrine and epinephrine, resulting in increase in blood pressure. At the renal level, SNS activation increases renin release from juxtaglomerular cells and modulate tubular sodium reabsorption [44]. RH patients have reduced heart rate variability, which is a marker for SNS activity. It was shown that 63% of the patients present a non-dipping pattern (BP does not drop at night), which indicate sympathetic overflow. Moreover, sympathetic activation also increases sodium reabsorption and promotes renin secretion, and renal denervation has been investigated for the treatment of resistant hypertension. In spite first studies in humans had shown promising results, randomized and blinded clinical trials demonstrated no benefit on BP control compared to sham procedure [45]. Another intervention that has been tested is baroreflex activation therapy. Carotid sinus stimulation reduces BP in patients with uncontrolled RH, showing the import role of sympathetic activity in this condition [46–48].

3.2. Adipokines

Adiponectin and leptin are two of the adipokines produced in adipose tissue. Obesity is an important comorbidity in RH, and plasma levels of adiponectin and leptin were reported to be lower and higher, respectively, in RH [34, 49]. Leptin is a peptide hormone that is expressed

Figure 5. Signaling pathway of the SRAA axis. The figure shows the regulatory processes for the Ang-(1-7)/Mas in different signaling pathways, compared with the opposing RAAS classical axes of this system, the ACE/AngII/ATR. Abbreviations: AKT, protein kinase B; DAG, diacylglycerol; IP3, inositol triphosphate; PG, prostaglandin; PIP2, phosphatidylinositol 4,5-biphosphate; PIP3, phosphatidylinositol (3,4,5)-triphosphate; PLC, phospholipase C.
in a variety of tissues, such as lymphoid tissue, pituitary gland, skeletal muscle, placenta, and ovary [50]. However, white adipose tissue is the main responsible for the synthesis and secretion of this peptide, which has effects to act on the hypothalamus in order to decrease appetite and stimulate sympathetic activity of the nervous system (Figure 6) [51]. Elevated levels of leptin stimulate neurons in the hypothalamus to secrete a precursor protein that is cleaved in α-melanocyte stimulating hormone, which binds to melanocortin 3 and melanocortin 4 receptors. The binding of this peptide to the receptors stimulates the sympathetic nervous system, elevates the energy expenditure, decreases food intake, and activates the hypothalamic-pituitary-adrenal axis [52–54]. A mechanism that demonstrates which factors are involved in the generation of hypertension associated with obesity is represented below (Figure 6) [51].

3.3. Insulin resistance and hypertension: the role of the caveolin-1 (CAV1) gene

It was recently demonstrated that the gene caveolin-1 (CAV1), located in the chromosome 7q31.1 [55], constitutes a gene that is associated with metabolic dysfunction in animal and cellular models, especially in insulin resistance, proving to be a potential marker for this condition in human beings [56]. Genetic variations in CAV1 are involved in the mechanism of insulin signaling and vascular function (Figure 7), shown in studies with animal models and cell culture [57, 58].

Increase in homeostasis model assessment of insulin resistance (HOMA-IR) shows that CAV1 is not only a genetic marker for dysfunction but also provides information about a potential mechanism of development of insulin resistance and hypertension in humans [56].

CAV1 is a regulatory gene for insulin signaling and insulin receptor stability [56]. Specifically, CAV1 binds directly to the insulin receptor in the adipocytes and the disturbance of this complex by GM3 ganglioside causes alteration in insulin signaling [59] (Figure 7). In addition, the decrease in CAV1 activity results in a 90% reduction in insulin receptor levels in the adipocytes of knockout rats [60].
Although the role of CAV1 in insulin-mediated glucose uptake is not well elucidated [60], this gene demonstrated relevance in the translocation of glucose transporter 4 (GLUT4) to adipocyte [61] and muscle cells [62].

### 3.4. Vascular stiffness and endothelial dysfunction

Previous studies have showed the participation of vascular stiffness and endothelial dysfunction in the pathogenesis of resistant hypertension. An increased carotid-femoral pulse wave velocity was observed in RH patients compared to non-RH hypertension, demonstrating the impairment of elasticity in these vessels. In addition, flow-mediated dilation was found to be reduced in RH, reflecting an endothelial dysfunction [63].

#### 3.4.1. Epidermal growth factor receptor in the vascular smooth muscle

The activation of the signaling pathway of the epidermal growth factor receptor (EGFR) by matrix metalloproteinase (MMP), stimulated by G protein-coupled receptor (GPCR) agonists, such as catecholamines, endothelin-1 (ET-1) and AngII, leads to the increase of the oxidative stress, and promotes stimulation of the hypertrophic growth and consequently increase in the muscular tone in hypertension (Figure 8) [64]. Among these receptors, adrenoceptors and angiotensin receptors can be mentioned that contribute to the hypertension pathogenesis mainly through the vasoconstrictor effects produced after stimulation [65, 66].
The vasoconstrictor responses promoted by this pathway are mediated by phospholipase C (PLC), DAG, and Ca\(^{2+}\) besides the growth promotion pathway involving the tyrosine receptor and mitogen-activated protein kinases (MAPKs) (Figure 9) [67]. Studies have shown a connection between the GPCR stimulus with the MAPK signaling pathway (through the dependent activation of MPM) in the vascular smooth muscle cells [65, 68–70]. Associations

Figure 8. EGFR signaling pathway in vascular smooth muscle. The agonist action of the GPCRs stimulates NOX1 pathway and leads to the increase in the oxidative stress NOX1, which activates the signaling pathway of the EGFR. Abbreviations: AKT, protein kinase B; DAG, diacylglycerol; HB-EGF, heparin binding EGF; IP3, inositol triphosphate; NOX1, NADPH oxidase 1; PIP2, phosphatidylinositol 4,5-biphosphate; PIP3, phosphatidylinositol (3,4,5)-triphosphate; PLC, phospholipase C; ROS, reactive oxygen species.

Figure 9. Signaling pathways involved in the development and progression of RH. The vasoconstrictor responses promoted by this pathway are mediated by phospholipase C (PLC), DAG, and Ca\(^{2+}\) besides the growth promotion pathway involving the tyrosine receptor and mitogen-activated protein kinases (MAPKs).
have been made between GPCR stimulus by MPM’s such as MPM-2, MPM-3, and MPM-7 in cardiomyocytes, fibroblasts, and epithelial and endothelial cells [71] with consequent development of cardiovascular hypertrophy associated with hypertension [72–75] (Figure 9).

3.4.2. CYP4A (cytochrome P450-4A)/20-HETE (20-hydroxyeicosatetraenoic acid)

20-HETE is an arachidonic acid metabolite formed through reactions catalyzed by the cytochrome P450-4A enzymatic complex (CYP4A) in vascular smooth muscle cells and is related to vascular dysfunction and arterial hypertension (Figure 10) [76]. This molecule has vasoconstrictive action and exerts an important role in vascular function and in the development and progression of cardiovascular diseases [77]. Studies have demonstrated the relationship between genetic variations in precursors of 20-HETE formation and the elevation of this metabolite and the BP in humans [78, 79].

In Dahl SS (salt-sensitive) rats, a genetic model of salt-sensitive hypertension, 20-HETE has been shown to contribute to the increase in total peripheral resistance by reducing the ability of the vascular system to respond to direct vasodilation stimulation by reducing vascular function, thus contributing to an increase in BP [80, 81].

Some studies demonstrate that reactive oxygen species (ROS) are important molecules in the development of oxidative stress, playing an important role in vascular dysfunction in Dahl SS rats [82, 83]. The chronic exposure to low levels of AngII in these animals may lead to an increase in oxidative stress by elevating ROS cellular concentrations, thus contributing to the

Figure 10. AngII stimulates signaling pathway through 20-HETE. The stimulation of GPCR by AngII agonist activates PLA2, which shoots the signaling intracellular pathway leading to activation of PKC as release calcium influx. Abbreviations: LO, lipoxygenase; LT, leukotriene; PGE2, PG E2; PLA2, phospholipase A2; PGH2, PG H2; PGI2, prostacyclin; ROS, reactive oxygen species; TXA2, thromboxane A2.
reduction of vascular relaxation even when these animals are submitted to a sodium restriction diet or are normotensive [84].

4. Concluding remarks and future directions

Due to the difficulty of studying RH in animal and in vitro models, the studies are clinical and poorly understood in terms of mechanisms. Thus, we decided to describe the microRNAs that interact with the most relevant pathways in RH. To date, several miRNAs have been identified and are related to the complications of resistant hypertension.

Epigenetic as well as genetic factors are identified every day and they are associated with variation in blood pressure levels. As reviewed herein, mutation polymorphism in some signaling pathway gene may increase or decrease the expression of some microRNAs, which are involved both in RH development and therapy response as RH-associated complications such as renal failure, coronary artery disease, cardiac hypertrophy, stroke, and among others. Therefore, the use of microRNA as biomarkers in prevention, diagnosis, and therapy of this disease may help to understand the disease, improve pharmacology therapy as well as prevent complications.

Conflict of interest

The authors declare that they have no conflict of interests relating to this paper content.

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