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# Resistant Hypertension

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Additional information is available at the end of the chapter

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## Abstract

The most common causes of therapeutic failure in hypertensive control are undiscovered secondary causes of hypertension and lack of patient/doctor compliance. In about 10% of cases, it can be attributed to resistant hypertension caused by a hyperactivity of the sympathetic nervous system, condition with a high cardiovascular risk to the patient. Resistant hypertension is failure to diminish blood pressure values to <140/90 mmHg (<140/85 mmHg for diabetic patients) with a lifestyle method and prescription of least three antihypertensive drugs in optimal doses, including a diuretic, or when patients use four or more antihypertensive drugs regardless of blood pressure control. Patients with resistant hypertension are typically presented with a long-standing history of poorly controlled hypertension. Early diagnosis and adequate treatment are needed to avoid end organ damage and to prevent cardiorenovascular remodeling. Cardiorenovascular morbidity and mortality are significantly higher in resistant hypertensive population. The need for the individualization of therapy and the use of the management strategies are also given weight in the treatment of resistant hypertension patients, including optional, innovative therapies, like a renal denervation or baroreflex activation. New innovative device therapies create an additional novel pathway of blood pressure-lowering procedures and should be prescribed by a specialist hypertension clinic.

**Keywords:** resistant hypertension, adherence, cardiorenovascular risk, sympathetic activation, innovative device therapies

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## 1. Introduction

Hypertension is chronic disease and is extremely complex. Hypertension has the largest prevalence of 30–45% of all cardiovascular risk factors. The achievement of blood pressure values below 140/90 mmHg is considered one of the main methods of achieving high long-term patient quality of life. Hypertension has an extreme phenotype, especially resistant

hypertension. Genetic factors may play a great role. Some genes have been associated with failure to antihypertensive medication treatment. Environmental factors contribute to the development of resistant hypertension—making importance of epigenetic. Resistant hypertension is a consequence of different pathophysiologic processes that are associated with high cardiovascular risk as consequences of increased stimulation of renin-angiotensin system and aldosterone production [1]. Arterial stiffness and atherosclerotic disease are also common in resistant hypertension patients. If pharmacological therapy with at least three antihypertensive drugs in optimal doses, including a diuretic, fails to reduce the office blood pressure to below 140/90 mmHg, patient suffer from drug-resistant hypertension [1, 2]. There are two types of drug-resistant hypertension: controlled and uncontrolled. Uncontrolled resistant hypertension patients cannot achieve blood pressure under 140/90 mmHg despite the use of three and more antihypertensive drugs (one of them being diuretic) and optimal lifestyle changes. The prevalence has been estimated between 8 and 13% of all antihypertensive drug-treated patients [2]. In last 50 years, the use of antihypertensive drugs has revolutionized the therapy of hypertension. Despite the available pharmacological inhibition of the sympathetic nervous system, about 50% of patients show suboptimal control, and pharmacotherapy does not provide adequate effects in everyday clinical practice [3–5]. The most common causes of therapeutic failure are undiscovered secondary causes of hypertension and lack of patient/doctor compliance. In about 10% of cases, it can be attributed to resistant hypertension caused by a hyperactivity of the sympathetic nervous system [6]. Overactivity of the sympathetic nervous system is a condition that confers a high cardio(reno)vascular risk to the patient [7, 8]. Renal sympathetic denervation produces multilevel inhibition of the sympathetic nervous system and triggers additional positive metabolic effects [9–11]. According to the results of different trials with renal sympathetic denervation for control of resistant hypertension, including Symplicity HTN-3, renal sympathetic denervation seems to be safe, and procedure-related complications of catheter-based renal sympathetic denervation were rare. Symplicity HTN-3 study did not show differences in systolic blood pressure reduction between treatment and control groups, but in the context of the study characteristics and the way it was conducted, there are several concerns about inexperienced doctors in the field of renal sympathetic denervation, the study population, and the medical treatment [11, 12]. Baroreceptor activation therapy or baropacing can be applied in patients with treatment-resistant hypertension too. When baroreceptors sense an increase in carotid transmural pressure, they respond by inhibiting sympathetic and stimulating parasympathetic centers in the brainstem [13]. Additional devices could be an option for patients with side effect of available antihypertension medications too control blood pressure.

## 2. Prevalence and etiology of resistant hypertension

The prevalence of resistant hypertension is unknown: epidemiological researches on resistant hypertension are missing. The data of frequency can be taken out from observational and big controlled clinical studies and is between 10 and 30% among patients with hypertension. Etiology of failure to diminish systolic and diastolic blood pressure with a therapeutic plan

that includes lifestyle modification and prescription of at least three different drugs in optimal doses is heterogeneous. First it is very important to understand the difference between uncontrolled (pseudoresistant or apparent) and real resistant hypertension. Potential very common reasons for uncontrolled but not resistant hypertension are weight gain (obesity, body mass index  $>30 \text{ kg/m}^2$ ), poor adherence, and the use of drugs such as nonnarcotic analgesics and nonsteroidal anti-inflammatory agents by mechanism of causing sodium retention. Other lifestyle factors that are associated with resistant hypertension are excessive dietary sodium intake and heavy alcohol intake. Secondary causes include unrecognized/untreated obstructive sleep apnea, primary aldosteronism, chronic parenchymal kidney disease, renal artery stenosis, and diabetes. Uncommon causes are pheochromocytoma, Cushing's disease, aortic coarctation, and intracranial tumors. The most common causes of pseudoresistance are poor adherence to antihypertensive therapy, white-coat effect, inaccurate measurement of blood pressure, pseudo-hypertension, and elderly patients [14, 15]. Other factors contributing to nonadherence with antihypertensive medication are African American race, gender (women tend to exhibit more nonadherence than men), higher adverse event incidence, polypharmacy, and higher drug costs. Poor adherence to antihypertensive therapy is the most important cause of unsuccessful blood pressure control. Analyses show that approximately 40% of patients will not continue their antihypertensive medications during the first year after diagnosing resistant hypertension. During 5–10 years of follow-up, those numbers reach 60% [16].

Inaccurate blood pressure measurement is not uncommon; it occurs when patients are not instructed to sit calmly and quietly and when the cuff is too small [17]. In diagnostic algorithm of resistant hypertension, stepwise approach is recommended. First is the optimization of control of blood pressure by excluding other causes of pseudoresistance. Very common cause of pseudoresistance is hypervolemia due to excessive sodium intake/retention, impaired kidney function, heart failure, and ineffective use of diuretics. Activity of neuronal sympathetic system which can be produced by chronic stress/pain, hypertension provoked by fear, hyperventilation, and vasoconstriction is an additional cause of pseudoresistance. The use of drugs like nonsteroidal anti-inflammatory agents, glucocorticosteroids, licorice, erythropoietin-stimulating agents, cyclosporine or tacrolimus, antidepressants, sympathicomimetics, oral contraceptives with estrogen, anti-VEGF, cocaine, and amphetamines are very often unrecognized cause of pseudoresistance. Undiagnosed secondary hypertension due to kidney diseases, renal artery stenosis, obstructive sleep apnea, or endocrinological disorders is the secondary common cause of pseudoresistant hypertension. Inappropriate blood pressure measurement and white-coat hypertension have to be excluded before diagnosis of true resistant hypertension. Suspicion of resistant hypertension requires an analysis of drugs which in the hypertensive patient is treated with.

### **3. Risk factors for resistant hypertension**

Hypertension is one of the leading modifiable factors in cardiovascular continuum. A hyperactivity of the sympathetic nervous system is a condition that confers a high cardiovascular risk to the patient. Resistant hypertensive patients often have comorbid cardiorenovascular

conditions, such as heart failure, atrial fibrillation, and chronic kidney disease. Studies have documented independent contribution of sympathetic activation to the cardiorenovascular disease [18, 19].

Cardiovascular risk doubles with increase of 20 mmHg systolic blood pressure and 10 mmHg diastolic blood pressure [20]. Particularly high cardiovascular risk is in patients with high systolic blood pressure and normal or low levels of diastolic blood pressure. Patients with chronic kidney disease and diabetic patients are special population with high cardiorenovascular risk. We do not know the real prevalence of chronic kidney disease in patients with resistant hypertension, and the prevalence of resistant hypertension in chronic kidney disease (I–IV stages) patients is also underestimated [6]. Obesity as well as chronic kidney disease could be the reason of resistance. Other risk factors that are usually related with resistant hypertension have a synergistic effect in development and worsening of resistant hypertension. Target-organ damage such as retinopathy, vascular dementia, chronic kidney disease, and left ventricle hypertrophy supports a diagnosis of poorly controlled resistant hypertension.

### **3.1. Cardiovascular risk in resistant hypertension**

Higher cardiovascular risk is noted in patients with resistant hypertension and diabetes or chronic kidney disease compared to general hypertensive population [19]. If we compared with the nonresistant hypertension patients, the resistant hypertension patients had a greater prevalence of comorbid conditions like diabetes mellitus (48% vs. 30%), chronic kidney disease (45% vs. 24%), ischemic heart disease (41% vs. 22%), and cerebrovascular disease (16% vs. 9%;  $P < 0.001$  for all) [19]. Sim and coauthors showed that patients with uncontrolled resistant hypertension (61.7%) are more frequent than controlled. When compared with controlled resistant hypertension patients, uncontrolled were at a greater risk for cerebrovascular and end-stage renal disease. The risk of end-stage renal disease and cerebrovascular disease was 25% and 23% greater, respectively, supporting the linkage between blood pressure and both outcomes [19].

## **4. Diagnostic workup of resistant hypertensive patients**

To determine true resistant hypertension, there is a need to exclude secondary causes of resistant hypertension like obstructive sleep apnea, atherosclerosis, and renal or hormonal disorders [2]. Diagnostic workup includes clinical examination, laboratory testing, and diagnostic methods to identify target organ damage as it is proposed by the European Society of Hypertension/European Society of Cardiology [8]. Pseudoresistant hypertension should not be confused for the real one in order to avoid unnecessary diagnostic procedures and treatments. Treatment of resistant hypertension involve the correct pharmacological approach, reduce therapeutic inertia (the physician), and involve taking medications regularly that have been proven to be effective and well tolerated (the patient). Patients have to be engaged in their management. There is the need for regular adherence with the prescribed regimen. We need diagnosis-based approach that takes into consideration not only a person's blood pressure but also the overall cardiovascular risk [19, 20].

#### **4.1. Medical history and clinical examination**

The medical history should document duration, severity, and progression of the hypertension, treatment adherence, and response to prior medications, including adverse events. Very important in medical history is current medication use, including herbal and over-the-counter medications. Loud snoring, daytime sleepiness, and witnessed apnea indicate obstructive sleep apnea. A history of peripheral or coronary atherosclerotic disease and worsening kidney function are suspicious for renal artery stenosis. Labile hypertension followed by palpitations and diaphoresis indicates the possibility of pheochromocytoma. In physical examination, carotid, abdominal, or femoral bruits indicate artery stenosis. Moon facies, abdominal striae, and central obesity suggest Cushing's disease. Diminished femoral pulses and difference between arm and thigh blood pressures are suspicious for aortic coarctation and/or aortoiliac disease.

#### **4.2. Biochemical evaluation**

Biochemical evaluation should include routine metabolic profile such as sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, albumin/creatinine ratio, and estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation and urate level. Reporting of estimated glomerular filtration (eGFR) rate is of most importance in recognition of early stages of chronic kidney disease characterized with slightly or moderately reduced eGFR and serum creatinine values usually within the population-based reference intervals [6]. Even in the setting of ongoing antihypertensive treatment, the ratio of aldosterone and renin is a useful diagnostic tool for primary aldosteronism, although such high ratio has low specificity and high negative predictive value. Additional analysis includes cortisol in 24-h urine and plasma cortisol. A 24-h urine collected during ingestion of the patient's normal diet can be helpful in estimating dietary sodium and potassium intake. Measurement of 24-h urinary metanephrines or plasma metanephrines is an effective screen for patients in whom pheochromocytoma is suspected.

#### **4.3. Diagnostic methods**

Numerous biological and lifestyle factors can contribute to the development of resistant hypertension. Some of them are the following: drugs, obesity or volume overload, diabetes, older age, renal diseases, aldosteronism, and obstructive sleep apnea. Less frequent are pheochromocytoma, Cushing's syndrome, thyroid diseases, and aortic coarctation. In diagnostic approach to resistant hypertension, history of a patient is very important, as well as his former adherence, adequate measurements of blood pressure, physical state, biochemical tests, and noninvasive imaging. It is of high importance that the evaluation of a patient includes 24-h ambulatory monitoring of blood pressure (AMBP). "Non-dipper" rhythm in AMBP can be often found in high-risk patients, such as chronic kidney patients and patients with obstructive sleep apnea.

The French Society of Hypertension gave the following recommendations for diagnostic approach to resistant hypertension: (A) standardized device and an appropriate cuff size should be used to avoid poor blood pressure measurement; (B) white-coat effect should be eliminated by ambulatory or home blood pressure measurement. Thresholds for uncontrolled

hypertension are home blood pressure measurement  $\geq 135/85$  mmHg, 24-h ambulatory blood pressure measurement  $\geq 130/80$  mmHg, daytime ambulatory blood pressure measurement  $\geq 135/85$  mmHg, and nighttime ambulatory blood pressure measurement  $\geq 120/70$  mmHg; (C) it is necessary to determine if the optimal triple-drug therapy is prescribed; (D) poor patient compliance should be assessed using a questionnaire, during drug analysis and pill count; and (E) it is suggested to search for factors that could influence treatment resistance (e.g., obesity, excessive dietary sodium intake, alcohol, drug interactions) [21]. If the diagnosis of resistant hypertension is confirmed, the patient should be referred to a hypertension specialist. After true resistant hypertension is confirmed, evaluation should include identification of the underlying cause and assessment of cardiovascular risk and end organ damage. Doppler of renal arteries, magnetic resonance angiography, or computed tomography angiography are highly recommended to assess the anatomy before renal sympatric denervation [21, 19].

## 5. Treatment strategy of resistant hypertension

Treatment strategy selects the best therapeutic options including lifestyle modifications and pharmacological and interventional treatment.

### 5.1. Lifestyle modifications

Definition of poor or unhealthy lifestyle is sedentary, overweight smoking, or drinking subjects with no exercise habits, on high-salt diet, with negative feelings about medicine [6]. More than 60% of patients with resistant hypertension are overweight and obese (12% BMI  $>40$  kg/m<sup>2</sup>) [6]. In both men and women, elevated blood glucose levels, hypertension, obesity, and hypercholesterolemia are among the leading risk factors contributing to death and illness. In an assessment of environmental, occupational, and metabolic risks contributing to death and disability, the study reports that tobacco was responsible for more than 7 million deaths and poor diet could be blamed for approximately one of five deaths. Appropriate lifestyle and dietary measures, smoking cessation, and weight reduction are highly recommended in patients with hypertension [22]. However, little is known about passive smoking and secondhand smoke and about the relationship between passive smoking and cardiovascular risk factors. Wu and authors found the positive association between passive smoking and blood pressure or hypertension [22]. Higher levels of physical activity have been linked to a lower risk of cardiovascular disease and diet. Authors from the Prospective Urban Rural Epidemiology (PURE) study, which is one of the world's largest epidemiological studies, find that the form of physical activity has no difference [23]. All of physical activity types are of benefit in reducing the risk of cardiovascular disease and premature death. The benefits of increased physical activity were seen regardless of whether that activity was recreational, occupational, or domestic [23].

### 5.2. Adherence

Adherence to antihypertensive medication is a key modifiable factor in the management strategy of hypertension. The nature of adherence is multidimensional. Blood pressure control has

to be multicomponent and patient-centered interventions to improve adherence. Strategies to improve antihypertensive medication adherence and blood pressure control include a multilevel approach that combines strategies at the level of the patient and healthcare provider, organization, and system. Very important are communication skills with hypertension patient, information exchange, and simplification of therapy. It is recommended to prefer antihypertensive agents with 24-h blood pressure control in once daily dose and fixed dose combination. Very important is low cost of antihypertensive agents, especially in low-income patients. Tele-health strategies; the use of experienced health professionals for intervention devices, especially in the field of renal sympathetic denervation; and self-monitoring of blood pressure at home are important too [14]. Treatment compliance must be closely monitored, but it is very difficult. The major problem is the lack of persistence of the prescribed regimens. Patients should be specifically asked how successful they are in taking all of their prescribed doses, including discussion of adverse effects and dosing inconvenience. Family members will often provide more objective assessments of a patient's adherence, but such input should generally be in the presence of the patient. Direct observation of therapy is the most accurate method but is impractical for chronic diseases. Methods such as self-reporting or pillbox counting are convenient; however, it is easy to manipulate them. The medication event monitoring system (MEMS) is a practical improvement, since it records the exact time and date of opening the pillbox and it electronically stores this information in the computer (later access and control is possible). Such devices seem to be the most reliable for monitoring patients to improve their adherence. Blood or urine measurements of drug levels or biologic markers are expensive and may falsely suggest adherence in patients who take their medications only around the time of their clinic visit or white-coat adherence. In routine clinical practice, it is too expensive and not available outside reference centers [14].

### 5.3. Multidrug therapy

Therapy is not easily applicable to daily clinical practice. Resistant hypertension is defined as uncontrolled blood pressure on office measurements, confirmed by out-of-office measurements and the concurrent use of three antihypertensive agents including a thiazide diuretic, a renin-angiotensin system blocker (converting enzyme inhibitors (ACE) or angiotensin II receptor blockers (ARB)), and long-acting calcium channel blocker, for at least 4 weeks, at optimal doses [21]. It is important to choose combination of antihypertensive medication in fixed doses to control blood pressure. Some antihypertensive medications have advantage to show improvement of arterial elasticity by measuring central blood pressure and pulse wave velocity, with alleviation of insulin resistance and inflammation. Multidrug therapy includes adding a mineralocorticoid receptor antagonist (aldosterone antagonists) such as spironolactone and eplerenone. Dosage of spironolactone or eplerenone is 12.5–25 mg/day. Both drugs are effective for resistant hypertension but have sexual side effects and can lead to hyperkalemia especially in patients with diabetes and chronic kidney disease [24]. If adverse effects occur, or in a case of a nonresponse, a  $\beta$ -blocker, an  $\alpha$ -blocker, or a centrally acting antihypertensive drug should be prescribed. General clinical examination and 24-h blood pressure monitoring have to be performed in all patients at baseline and after minimum 4 weeks of therapy to confirm resistant hypertension. In the case of failure to control blood pressure with antihypertensive multimodal regiment, with a nasal continuous positive airway pressure















