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# RESISTANT ARTERIAL HYPERTENSION

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**SUMMARY**

Resistant hypertension is defined as a lack to lower 140 mmHg (systolic blood pressure) and 90 mmHg (diastolic blood pressure) values of ambulatory blood pressure (BP) response using 3 antihypertensive agents of different classes, one of which should be a diuretic in patients fully adherent to antihypertensive therapy. Prevalence of resistant hypertension is ranging from about 5 to 50 % in various cohorts. Initial management requires identification of true treatment resistance by out-of-office BP measurements, assessment of adherence and screening for treatable causes of uncontrolled BP. Recent studies try to indicate possible biomarkers of resistance hypertension. Treatment include lifestyle changes, enhancing treatment adherence and optimization of the doses. An invasive approach to resistant hypertension should be kept for persistently severe cases managed in a specialized hypertension center. This article aims to familiarize readers with the evaluation and management of resistant hypertension by outlining the most recent evidence-based treatment options.

**Key words:** *blood pressure, arterial hypertension, resistant hypertension, treatment of resistant hypertension, biomarkers of resistance hypertension, invasive approach.*

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Arterial hypertension is one of the main risk factors for the development of fatal cardiovascular complications. According to the ESSE-RF study conducted in 2012-2013 in Russian Federation, the prevalence of hypertension among adult population was 43.5% [1], which indicates its high prevalence. Among patients with arterial hypertension, a group of patients with resistant to AH therapy is distinguished. Resistance arterial hypertension is associated with a two-fold to six-fold increase in the risk of cardiovascular complications [2, 3], and therefore the problem of its diagnosis and treatment is extremely urgent.

According to the recommendations of the Russian Medical Society for Arterial Hypertension 2013, AH is considered resistant to therapy, when applied treatment, such as lifestyle changes and rational combined antihypertensive therapy consisting of three drugs, including a diuretic, in maximally tolerated doses does not lead to achievement of target level of blood pressure [4]. If the target level of blood pressure is achieved by using 4 or more antihypertensive drugs, then such AH is called controlled arterial hypertension. In Russia, the terms “resistant” and “refractory” arterial hypertension are equivalent, whereas in the Recommendations of the American College of Cardiology / American Heart Association for Arterial Hypertension in adults in 2017, a separation of these terms is proposed. Refractory hypertension is understood as a more severe phenotype of hypertension, in which the target level of arterial blood pressure remains unreachable with the intake of at least 5 antihypertensive drugs of various classes, including a long-acting thiazide diuretic and an antagonist of mineralocorticoid receptors.

The true prevalence of resistant hypertension is unknown. According to various studies, the proportion of patients with resistant to therapy arterial hypertension can reach up to 5-50% in different cohorts of patients [5]. According to the National Health and Nutrition Examination Survey (NHANES), conducted in the United States in 2003-2008 and involving more than 15,000 adults with arterial hypertension, the proportion of people with resistant hypertension was 8.9±0.6% [6]. In the European study

"de la Sierra et al." in which a database of patients with arterial hypertension of the Spanish Registry of outpatient blood pressure monitoring was studied, of more than 60,000 patients, 14.8% had resistant hypertension. At the same time, the majority of patients with resistant hypertension (12.2%) had uncontrolled resistant hypertension, and only 2.6% reached the target level of blood pressure when taking 4 or more antihypertensive drugs [7].

In a recent cross-sectional study CRIC (Chronic Renal Insufficiency Cohort), in which 3367 patients with chronic kidney disease were included, 40.4% of participants had resistant arterial hypertension [8].

Over time, there has been a trend towards an increase in the number of patients with resistant hypertension, which is associated both with an increase in life expectancy and with an increase in the proportion of the population suffering from obesity and type 2 diabetes mellitus [9].

It is necessary to distinguish true resistant hypertension and pseudo-resistant arterial hypertension. To the mistaken diagnosis of resistant hypertension (pseudo-resistant AH) lead such conditions as: "white coat" hypertension, intake of exogenous agents that increase blood pressure, poor adherence to treatment, inadequately antihypertensive therapy, as well as incorrect technique of blood pressure measurement.

According to the definition, the "white coat" hypertension is the form of hypertension, in which the increase in blood pressure is observed only in a clinical setting, while during the ambulatory blood pressure monitoring (ABPM) and patient self-measurement using a home blood pressure monitoring device, the blood pressure is within normal values. White-coat hypertension is common among patients with hypertension and can be between 2 and 23% according to different authors [10]. White coat hypertension is more common among the elderly with isolated systolic hypertension [11].

The incorrect technique of blood pressure measuring is a common cause of overdiagnosis of arterial hypertension and wrong determination of resistant hypertension. Recently conducted retrospective analysis “Bhatt et al” involved 130 patients observed in a specialized clinic, and it was found that 33% of patients were incorrectly diagnosed with uncontrolled resistant AH due to the incorrect technique of blood pressure measuring [12]. These are the most common errors in blood pressure measuring: a single measurement of blood pressure, using a cuff of a smaller size, conversation during blood pressure measurement, measurement of blood pressure immediately after exercise or smoking, drinking coffee and strong tea 1 hour before the study, arm position below heart level.

Another reason for the incorrect diagnosis of resistant hypertension is a low adherence to treatment. About 40% of patients with recently diagnosed arterial hypertension stop taking antihypertensive therapy during the first year of treatment [13, 14]. According to Jung et al., 76 patients with refractory hypertension went to the clinic for renal artery sympathetic nerve radiofrequency denervation and 53% from them show poor medication compliance. Among this group of patients, 30% did not take any antihypertensive drug, 70% of people took the drug only partially, 85% of which took less than half of the prescribed drugs. The study controlled the levels of antihypertensive drugs or their metabolites in urine [15].

An actual problem in the diagnosis of true resistant hypertension remains inappropriately selected drug therapy. According to Weitzman et al, among the 172432 patients with essential hypertension, 35.9% of patients were diagnosed with uncontrolled resistant hypertension., about 21% of these received smaller doses of drugs than was prescribed, 9% did not receive a diuretic, 48% took less than 3 antihypertensive drugs, and 20% did not take any of the prescribed drugs. After the exclusion of these patients, only 2.2% of all patients were eligible for uncontrolled resistant arterial hypertensions diagnose [16].

According to some reports, nearly half of all diagnoses of resistant hypertension are most likely different forms of pseudo-resistant hypertension [17]. Therefore, before diagnosis resistant hypertension, it is necessary to exclude all the above-mentioned reasons for possible pseudo-resistance.

According to the recommendations for the diagnosis and treatment of hypertension of the European society of cardiology and the European society of hypertension 2013, true resistant hypertension may occur with obesity, alcohol abuse, excessive consumption of sodium, long-term consumption of drugs that have a vasopressor mechanism and cause sodium retention in the body (non-steroidal anti-inflammatory drugs, corticosteroids, cyclosporine, erythropoietin preparations, oral contraceptives, sympathomimetics, antidepressants, etc.); obstructive sleep apnea syndrome [18]; undiagnosed irreversible damage to target organs; undiagnosed secondary forms of hypertension, which include primary hyperaldosteronism, stenosis of renal arteries [19].

Except currently known predictors of the development of resistant arterial hypertension, such as obesity, old age, diabetes mellitus, chronic kidney disease, there are no laboratory markers of resistant hypertension. In connection with this, studies the role of the matrix metalloproteinase (MMP) system and the tissue inhibitor of metalloproteinase (TIMP), in particular MMP-2 and TIMP-2, in the pathogenesis of resistant arterial hypertension have great interest. Matrix metalloproteinases belong to extracellular zinc-dependent endopeptidases family, capable to destroy all types of extracellular matrix proteins. Matrix metalloproteinases (MMPs) are involved in tissue remodeling, angiogenesis, and apoptosis.

According to the research, MMP and TIMP are associated with arterial hypertension and target organ damage [20, 21]. In a study by Andrea R. Sabbatini et al. the levels of MMP-2 and TIMP-2 in the refractory course of arterial hypertension and the association of these metalloproteinases with target organ damage, including vessel stiffness and myocardial hypertrophy, were studied [22]. In a study of 116 patients with controlled hypertension, 116 patients with resistant hypertension and a control group of 19 patients with normal BP, an increased level of TIMP-2 and a decreased ratio of MMP-2 / TIMP-2 in patients with resistant hypertension was found in comparison with other groups. The level of MMP-2 was the same among groups with elevated blood pressure. In addition, an independent high-level association of TIMP-2 and a low ratio of MMP-2 / TIMP-2 to the level of arterial pressure in the resistant AH group was revealed. Also, the level of TIMP-2 directly correlated with the severity of left ventricular hypertrophy in the general group with elevated blood pressure, but not separately in the group of resistant hypertension. Logistic regression analysis revealed that only the level of TIMP-2, but not MMP-2, was significantly and independently associated with the resistant course of hypertension after taking into account the risk factors for resistant hypertension (age, sex, race, type 2 diabetes, BMI, aldosterone level ). Thus, the authors of this study suggest that TIMP-2 is a significant predictor of resistant arterial hypertension and can be used as a potential biomarker of this phenotype of hypertension in further studies.

However, in the study of Leonardo Lacerda et.al, there was no correlation between the level of MMP-2, MMP-9, TIMP-1, TIMP-2 and insufficient control of blood pressure level [23]. This study, conducted in 2015, is the first of its kind to study the association of matrix metalloproteinases and their tissue inhibitors with a resistant course of arterial hypertension. 76 patients with resistant hypertension were included in the study, of which 2 subgroups were formed: patients with controlled resistant hypertension (n = 41) and uncontrolled resistant hypertension (n = 35). As a result of the study, similar levels of MMP-9, TIMP-1, MMP-2, TIMP-2, MMP-9 / TIMP-1 and MMP-2 / TIMP-2 were obtained in both groups. And, despite the fact that the level of MMP-2 and the ratio of MMP-9 / TIMP-1 correlated with the level of DBP, aldosterone and age in the group of uncontrolled resistant hypertension, according to the authors, this has no connection with the formation of resistance to antihypertensive therapy and these biomarkers do not predict insufficient control of blood pressure in the group of resistant hypertension. It should be noted that this study has a restriction in the form of a small sample of patients, and an insufficient degree of correlation in the revealed indicators may be a consequence of insufficient statistical strength or a second-order error.

Also, a possible index of resistant hypertension may be an increased resistance index. The resistance index is the ratio of the difference between the maximum systolic and final diastolic velocities to the mean blood flow velocity. This index reflects the state of the microcirculatory bed (tonus, the condition of the wall of arterioles and capillaries). The normative value is 0.6-0.7. It is known that elevated resistance index, measured with Doppler ultrasonography, correlates with the degree of renal dysfunction in patients with arterial hypertension. In a study by Yohei Dol et al, it was shown that a high resistance index is independently associated with cardiovascular and renal adverse outcomes. The resistance index can be used to assess the risk of adverse cardiovascular and renal outcomes in patients with essential hypertension [24]. In a recently published study Kintis K et al in J. Hypertension, differences in hemodynamic parameters were studied in patients with controlled hypertension and resistant hypertension, including resistance index measurement. In logistic regression analysis, it was shown that resistant hypertension was the strongest predictor of the resistance index over 0.7. The value of the resistance index of 0.648 had a sensitivity of 78% and a specificity of 72% as a predictor of resistant hypertension. Thus, the authors conclude that an increased resistance index may be associated with a resistant course of hypertension and may help to detect such group of patients [25].

In the recommendations for diagnosis and treatment of the AH of the European Society of Cardiology and the European Society for Hypertension, 2013, the main therapeutic approaches to the treatment patients with resistant hypertension were formulated. First of all, the doctor needs to make sure that the drugs in the multi component therapy really have an antihypertensive effect. Otherwise, they must be excluded from therapy (I C). Mineralcorticoid receptor antagonists, amiloride, and alpha-adrenoblocker doxazosin can be used if there is no contraindication to their use (IIa B). In case of ineffective drug therapy, it is possible to consider the use of invasive methods, such as radiofrequency denervation of the renal arteries and baroreflex-activating therapy (IIb C). Until more data will be available on the long-term efficacy and safety of renal artery sympathetic nerve radiofrequency denervation and baroreflex-activating therapy, it is recommended to perfume these invasive procedures only by an experienced surgeon, as well as further diagnostics and dynamic observation should be performed only in specialized centers for AH (I C). Invasive methods are recommended only for patients with true resistant hypertension with an SBP ≥160 mmHg. or DBP≥110 mmHg. and confirmed by the BP increase by the method of ambulatory blood pressure monitoring (I C).

For better understanding of the basic approaches to the treatment of resistant hypertension, it is necessary to refer to the existing data on the pathogenesis of the development of resistance to treatment. An important role is played by volume overload, often hidden, in patients with resistant hypertension. Thus, intensification of diuretic therapy under the control of impedance cardiography that helps to assess the amount of fluid in the chest or indirect biochemical markers of the intravascular volume, for example, the level of natriuretic peptide, significantly improved the blood pressure control [26]. The reason for volume overload is multifactorial and includes such conditions as elderly age, obesity (BMI >30 kg / $m^2$), chronic kidney disease, belonging to the Negroid race, hyperaldehistonism, excessive intake of salt [27].

In the pathogenesis of the development of resistant hypertension, the activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system (RAAS), and the inadequate production of nitric oxide (NO), leading to endothelial dysfunction, oxidative stress also participate.

Activation of the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), and insufficient production of nitric oxide (NO), leading to endothelial dysfunction, oxidative stress, also participate in the pathogenesis of the development of resistant hypertension. At present time, great importance in the formation of resistance to treatment is given to secondary hyperaldosteronism. According to the researches, elevated blood plasma aldosterone levels were determined in patients with resistant hypertension, in which primary hyperaldosteronism was excluded. [28]. Aldosterone is a steroid hormone produced by the adrenal cortex in response of the stimulating effect of angiotensin II. Aldosterone binds to the mineralocorticoid receptors of the renal tubules and thereby activates the reabsorption of sodium and the secretion of potassium in the collective tubules of the kidneys, which leads to sodium retention in the body and an increase in intravascular volume of blood and hypokalemia. In addition, aldosterone activates the sympathetic nervous system and promotes the development of fibrosis, inflammation and remodeling, including the cardiovascular system. In observational studies, a direct correlation was found between elevated plasma level of aldosterone and blood pressure in both hypertensive patients and normotensive patients [29]. One of the possible mechanisms for the formation of resistant hypertension is the phenomenon of "escaping" aldosterone, when aldosterone level rises to normal values despite treatment with angiotensin converting enzyme or angiotensin II receptor blockers. This phenomenon occurs in 10% of patients taking angiotensin converting enzyme or angiotensin II receptor blockers for more than 6 months, and more than 50% of patients with treatment for more than 1 year, which leads to increased sodium retention, increased blood pressure and other undesirable consequences. This hypothesis contributed to the increased interest in drugs that block the negative effect of aldosterone, such as antagonists of mineralcorticoid receptors [30].

Thus, secondary hyperaldosteronism and increased intravascular volume are the links of the pathogenesis of the formation the resistant hypertension and determine the importance of using adequate doses of diuretic drugs, including antagonists of

mineralcorticoid receptors as first-line drugs. Recent studies have demonstrated the effectiveness of antagonists of mineral corticoid receptors in reducing blood pressure in resistant hypertension. For example, in a double-blind, placebo-controlled study, ASPIRANT-EXT compared the addition to therapy of 25 mg of spironolactone and placebo in 150 patients with resistant hypertension. After 8 weeks, there was a significant decrease in SBP and DBP in the spironolactone group. In a well-known study PATHWAY-2, which studied the effectiveness of spironolactone in the group of resistant AH, antagonists of mineral corticoid receptors (AMCR) showed its greater effectiveness in reducing blood pressure compared to alpha1-blocker doxazosin, beta-blocker bisoprolol and placebo. Also, an inverse relationship was found between the degree of blood pressure reduction and the plasma renin level in response only in the spironolactone treatment group, in contrast to the bisoprolol, doxazosin and placebo groups, which confirms the role of sodium retention and increased intravascular volume in the formation of resistant hypertension [31].

Taking into account that nowadays there are no innovative approaches of drug therapy for resistant hypertension, it is especially interesting to investigate new combinations of existing antihypertensive agents. Taking into account that hypervolemia is one of the pathogenetic links in the development of resistant hypertension, it seems rational to use a combination of different mechanisms of action of diuretic drugs. The effectiveness of dual diuretic therapy (antagonists of mineral corticoid receptors and thiazide / thiazide-like drugs or loop diuretic) has been proven in many studies [32]. However, not always the prescription of two-component diuretic therapy in combination with other major classes of antihypertensive drugs not always helps to normalize blood pressure. Data on the possibilities of using triple diuretic therapy began to accumulate over the past few years, but the number of such studies is still extremely small. In the Beaussier H. study 164 patients were included, two treatment approaches were compared in patients with resistant hypertension: sequential nephron blockade (use of triple diuretic therapy) and blockade of the renin-angiotensin-aldosterone system (the use of an angiotensin-converting enzyme inhibitor and a renin-angiotensin receptor antagonist, which is now considered to be an irrational combination). As a result, the use of triple-diuretic therapy proved to be a more effective method than the sequential blockade of RAAS: about 58% of patients from the first group achieved target BP levels, compared with 20% of patients in the second group [33,34]. This approach in the triple-diuretic therapy use seems promising; however, further research is needed to introduce it into broad practice.

In addition to the drug therapy methods of treatment, recently there is non-drug treatment methods: renal artery sympathetic nerve radiofrequency denervation (RDN), baroreflex-activating therapy (BAT), creation of arteriovenous fistula, surgical neurovascular decompression. There are a number of large studies in which the effectiveness RDN has been studied, but their results are contradictory. In the studies Simplicity HTN-1 and Simplicity HTN-2, which included patients with resistant hypertension, a persistent decrease in office BP after RDN application was shown [35]. In the Simplicity HTN-3 study, the renal artery denervation technique showed no benefit in reducing blood pressure in comparison with the control group [36]. Such results may be due to design research deficiencies and the lack of standardization of drug therapy. Since 2012 a large register study Global Sypmlicity Registry aimed to determine the long-term effectiveness of RDN was conducted and according to preliminary data, a significant decrease in blood pressure was noted during the 6-month follow-up period [37]. In the Russian Federation (RF), this method of treating patients with resistant AH is used in large cardiological centers and leads to a pronounced hypotensive effect [38]. Baroreflex-activating therapy was studied in the framework of PIVOTAL and DEBuT-HT studies. In a study Rheos Pivotal, which included 256 patients with resistant AH, it was shown that in 12 months after implantation of the device 63% of patients reached the target level of systolic blood pressure (<140 mm Hg. art.), and in 81% of patients blood pressure decreased by at least 10% of the baseline [39]. It was also observed that over time the therapeutic effectiveness of this method increased. However, devices for performing baroreflex-activating therapy are not currently registered in the Russian Federation, which is why there is no Russian experience in using this technique.

The feasibility of creating arteriovenous fistulas in the group of patients with resistant hypertension was studied in the framework of a multicenter open-label randomized controlled ROX CONTROL HTN trial. In 6 months after randomization in the group of active treatment (application of the device for arterivenous fistula creation) in comparison with the group of drug therapy there was a significant decrease in office (by 27/10 mm Hg) and outpatient blood pressure (14/14 mmHg) [40].

In experimental studies it was shown that the microvascular decompression of the rostral ventrolateral sections of the medulla oblongata in zone IX and X pairs of cranial nerves during surgical interventions for various pathologies of the nervous system led to a decrease in blood pressure. Information on the effectiveness of this technique is limited to a few clinical cases and requires further randomized trials.

Currently, despite the existing effective antihypertensive drugs, as well as non-pharmacological methods, it was not possible to achieve complete control of blood pressure in patients with resistant hypertension, which causes further search for possible methods for resistance overcoming.

Researches of resistant hypertension is being conducted in the world and focuses on the new antihypertensive drugs, the use of non-drug treatment, the intensification of diuretic therapy and lifestyle modification, which includes dieting, weight loss, regular physical activity.

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