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**DIAGNOSTICS AND TREATMENT OF RESISTANT ARTERIAL HYPERTENSION**

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**Summary.** Resistant arterial hypertension is diagnosed when three antihypertensives assignment does not result in achieving target blood pressure, which for most patients is the level below 140/90 mm Hg, wherein one of the medicaments must be diuretic and all drugs must be assigned to optimal or maximum tolerated doses. Despite the high prevalence of resistant arterial hypertension, the lack of blood pressure control is often associated with an inadequate selection of antihypertensive therapy, blood pressure misjudgement or failure of patients to medical recommendations. Therefore, before carrying out diagnostic measures necessary to consistently assess the adequacy of patients receiving therapy that inherent in the definition of RAH and exclude pseudoresistance.

**Keywords:** resistant arterial hypertension, diagnostics, treatment.

**Резюме.** Резистентна артеріальна гіпертензія діагностується у випадках, коли призначення трьох антигіпертензивних препаратів не призводить до досягнення цільового артеріального тиску, яким для більшості пацієнтів є рівень нижче 140/90 мм рт.ст., при цьому одним з медикаментів повинен бути діуретик і всі препарати повинні бути призначені в оптимальних або максимально переносимих дозах. Незважаючи на високу поширеність резистентної гіпертензії, відсутність контролю артеріального тиску часто пов'язана з неадекватним підбором антигіпертензивної терапії, неправильною оцінкою рівня артеріального тиску або невиконанням пацієнтами лікарських рекомендацій. Тому перед початком проведення діагностичних заходів необхідно послідовно оцінити адекватність одержуваної пацієнтом терапії, що закладено в самому визначенні резистентної артеріальної гіпертензії, а також виключити псевдорезистентність.

**Ключові слова:** резистентна артеріальна гіпертензія, діагностика, лікування.

**Резюме.** Резистентная артериальная гипертензия диагностируется в случаях, когда назначение трёх антигипертензивных препаратов не приводит к достижению целевого АД, которым для большинства пациентов является уровень ниже 140/90 мм рт.ст., при этом одним из медикаментов должен быть диуретик и все препараты должны быть назначены в оптимальных или максимально переносимых дозах. Несмотря на высокую распространённость резистентной гипертензии, отсутствие контроля артериального давления часто связано с неадекватным подбором антигипертензивной терапии, неправильной оценкой уровня артериального давления или невыполнением пациентами врачебных рекомендаций. Поэтому перед началом проведения диагностических мероприятий необходимо последовательно оценить адекватность получаемой пациентом терапии, что заложено в самом определении резистентной артериальной гипертензии, а также исключить псевдорезистентность.

**Ключевые слова:** резистентная артериальная гипертензия, диагностика, лечение.

High blood pressure (BP) is the leading cardiovascular risk factors associated with an increase in total and cardiovascular mortality, sudden death, stroke, coronary heart disease, heart failure, atrial fibrillation, peripheral vascular disease and renal failure. Arterial hypertension (AH) occurs in almost 25% of the adult population and causes more than seven million deaths each year, ie about 13% of the total number of deaths worldwide [1, 2].

Despite recent advances in the study of hypertension and current treatment options, the problem of controlling high BP is still quite relevant. Particular attention is drawn to resistant hypertension (RAH), the prevalence of which is quite high and reaches 10-30% of patients with hypertension [3].

**Definition.** RAH is diagnosed when three antihypertensive assignments does not result in achieving target blood pressure, which for most patients is the level below 140/90 mm Hg, wherein one of the medicaments must be diuretic and all drugs must be assigned to optimal or maximum tolerated doses. In addition, resistant hypertension is defined as hypertension which requiring four or more medicines for treatment.

Although arbitrary number required to control blood pressure drugs, the determination is very useful from the point of view of both the clinician and researcher, since it helps to identify the phenotype of resistance to a wide antihypertensive treatment and diagnostic determining tactics, such as testing or causes of secondary hypertension selection treatment. Since patients with RAH

have a higher probability of detection of diseases, leading to the development of secondary hypertension. These include sleep apnoea, kidney disease, renal artery stenosis, primary aldosteronism. Much more rare causes include Cushing's syndrome, pheochromocytoma, hyperparathyroidism, coarctation of the aorta, intracranial tumours. Referral and specific treatment of these diseases can improve blood pressure control and long-term prognosis [2, 4].

Determination of heavy RAH (systolic and diastolic blood pressure >160/90 mm Hg) was applied for testing approaches to the suppression of sympathetic impulses, such as renal denervation of nerves and baroreflex activation. Moreover, the determination is of value in RAH establishing criteria by which clinicians can identify patients needing specialized care delivery [5, 6].

However, despite its usefulness in carrying out successful research and practical significance in the management of patients at high risk, has always been recognized that the definition of RAH is too broad and includes patients who were assigned to multiple antihypertensive drugs, but had uncontrolled blood pressure which is not due to the ineffectiveness of designated treatment, and for several other reasons. Hence the use of the terms "true RAH" and "pseudoresistance." The latter is used in cases when in RAH one cannot be excluded common causes of poor blood pressure control. These reasons include the white-coat effect, poor adherence to treatment and incorrectly picked up therapy. Until recently, the effect of these factors on the development pseudoresistance was largely unknown. However, in recent years has provided important information to quantify their assessment, allowing a better assessment of the true prevalence of RAH.

***Pseudoresistant arterial hypertension.*** The effect of "white coat" is to increase the blood pressure at the doctor office with lower blood pressure outside the clinic. When measuring the patient's blood pressure at home is very important the correct measurement techniques and the use of validated calibrated tonometer. It is considered that the magnitude of blood pressure equal to 140/90 mmHg measured at the doctor's, roughly equivalent levels of blood pressure 130-135 / 80-85 mm Hg when measuring home by a patient.

In the published study, the effect of white-coat hypertension, poor adherence to treatment and sub-optimal therapy in patients with pseudoresistance authors evaluated the patients who participated in a randomized, multicentre study conducted to study the clinical inertia and control of blood pressure [7]. Of 69 patients met the classical criteria of RAH were subjected to 24-hour ambulatory blood pressure monitoring and commitment prescribed antihypertensive treatment was monitored by an electronic system. Of these patients, 22% controlled by BP in an outpatient setting, indicating that the white-coat hypertension, and 29% did not adhere to the prescribed guidelines. The remaining 49% of patients had true RAH, based on elevated levels of ambulatory blood pressure and performance of all treatment recommendations.

Furthermore, most of the patients with true RAH didn't receive recommended antihypertensive treatment. Only 91% of patients receiving a diuretic (furosemide or hydrochlorothiazide, which due to its short half-life and destination only once per day, may not provide significant antihypertensive effect), while no received chlorthalidone [8]. None of the patients received spironolactone or eplerenone, showing it to be effective in the treatment of RAH. Moreover, the maximum dose of calcium antagonists and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor antagonists II, with a relatively small dosage range and tolerability were used only 15% and 40% patients, respectively [9, 10].

The role of white-coat hypertension, treatment adherence and optimal therapy were evaluated in other studies in patients with RAH, but usually these factors have been studied separately. For example, a number of studies in patients with pseudoresistance showed a high prevalence of white-coat hypertension. When cross-evaluation of Spanish and Brazilian cohort prevalence of hypertension white coat was 37% and 44%, respectively, of the number of subjects with uncontrolled hypertension [11, 12]. These observations emphasize the importance of changes in blood pressure is the doctor's office to confirm as true RAH, and to make changes in treatment. Excessive prescribing greater proportion of patients with pseudoresistance is a real risk if clinicians rely only on the level of clinical BP. However, it is also important to recognize that patients with white-coat hypertension are at high risk of developing true RAH within a short period of time.

Poor adherence to treatment is one of the most common causes of RAH. Among the subjects c pseudo-resistance about 30% did not follow the recommendations of doctors. Moreover, another study shows that of the 76 patients referred to a specialist clinic over the RAH 53% had poor adherence to antihypertensive therapy based on the toxicological testing of urine of patients for the presence of prescription medications or their metabolites. At the same time among the non-adherence of patients to 30% did not take any of the prescribed drugs. Given that the use of electronic monitoring systems and toxicological testing is not applicable to routine clinical practice, lack of adherence to treatment may be the most serious cause of poor control of blood pressure due to the difficulty of her identification. However, the increasing use of electronic medical records, including the determination of the frequency of purchase prescription medications may help clinicians and researchers to quantify the commitment to patients, both individually and in large populations of patients.

Demonstrated that in patients with RAH, with the exclusion of white-coat hypertension and patients with poor adherence, often noted the lack of optimal therapy is the lack of frequent diuretics and unassigned sufficient dose of hydrochlorothiazide dose - 25 mg, which should be the main, if not contraindicated diuretics in the treatment of RAH. Moreover, a significant number of patients do not receive an ACE, angiotensin II receptor antagonists and/or calcium antagonists. Therefore, to overcome clinical inertia is a fundamental factor in better controlling of RAH.

This view is also demonstrated in a retrospective analysis of 3350 patients with pseudo-resistance, where it was shown that the use of diuretics decreased in patients after the diagnosis of RAH [13]. These patients had an intensification of treatment was only 22% of clinic visits in which blood pressure was elevated. However, with the intensification of treatment likely to achieve control of blood pressure increased by 60%. While many patients may be guilty of lack of commitment to taking medication, many clinicians may also be guilty of an unassigned adequate antihypertensive treatment in patients with elevated blood pressure.

Distortion of the blood pressure in the direction of more high numbers can contribute to improper technique of blood pressure measurement is to measure blood pressure without rest, and the use of the standard cuff in patients with forearm circumference >35cm.

To prevent the error measurement techniques it is advisable to adhere to the following guidelines:

- Use calibrated instruments;

- The patient should sit in a comfortable position; the hand is on the table at the level of the heart;

- eliminates the use of coffee and strong tea for 1 h prior to the study;

- It is recommended not to smoke for 30 minutes before measuring blood pressure;

- Blood pressure was measured after 5 minutes of rest; if the blood pressure measurement procedure preceded significant physical or emotional stress, rest period should be extended to 15-30 minutes;

- cuff size should match the size of your hands: rubber inflated the cuff should cover at least 80% of the circumference of the shoulder; middle cuff is placed over the brachial artery, the lower edge of the cuff should be at 2.5 cm above the elbow; between the cuff and the shoulder must pass a finger;

- injecting air into the cuff to a pressure level at 20 mmHg over systolic blood pressure (by the disappearance of the pulse), should be fast, slow deflation (2 mmHg in 1 second);

- If the initial examination, measure blood pressure in both arms; further measurements are carried out on the arm where the blood pressure above;

- measurement of blood pressure on each hand should be performed at least 2 times at intervals of not less than a minute; when the difference >5 mmHg produce an extra measurement; assessing the average value of the two most recent measurements.

Thus, these data demonstrate that the true prevalence of RAH is only about 50% of all patients with RAH [14]. The reasons for this are the white-coat hypertension, errors in the technique of blood pressure measurement, poor adherence and non-optimal therapy. Studies confirm that

overcoming barriers to full control of blood pressure requires the use of ambulatory BP measurements accurate, reliable assessment of adherence to detect noncompliance of patients and clinicians use effective schemes of multicomponent antihypertensive treatment, including the maximum titration good tolerability and the preferred use of diuretics and antagonists mineralocorticoid receptors [15].

**True RAH.** The development of true RAH is promoted by specific, potentially reversible causes of secondary hypertension, such as renal artery stenosis and pheochromocytoma. It is shown that primary aldosteronism is much more common in hypertension than in the general population, reaching 20% at the RAH [1, 2, 4].

Sleep apnoea is closely linked to increases in blood pressure and is a predictor of hypertension in patients with normal tone. The men sleep apnoea is more common and is more severe. Transient hypoxemia and increase upper airway resistance leads to activation of the sympathetic-adrenal system, which causes an increase in cardiac output and peripheral vascular resistance, and fluid retention.

RAH also associated with excess body fluids that may be associated with renal failure, inadequate diuretic therapy and excessive intake of salt. Obesity and excessive alcohol consumption contributes to development of resistance [16].

Moreover, some medicines may contribute to resistance to treatment. The highest value in clinical practice has concomitant nonsteroidal anti-inflammatory drugs (NSAIDs) use. NSAIDs reduce the effectiveness of virtually all classes of antihypertensive drugs. Other drugs, such as sympathomimetic agents, steroids, cocaine, amphetamines as able to raise blood pressure and reduce the effects of antihypertensive therapy [17].

**Patient examination with RAH.** The first step in the assessment of patients with RAH is the need to confirm the true resistance to treatment by using the proper technique of measurement of blood pressure and exclusion of pseudoresistance.

After that you should identify the factors related to the patient's lifestyle, as well as to identify drugs that affect blood pressure. Should be documented target organ damage such as left ventricular hypertrophy, retinopathy, renal failure and cardiovascular complications. Patients must be screened to detect possible causes of secondary hypertension.

Biochemical study of patients with RAH should include an assessment of the metabolic profile with determination of sodium, potassium, glucose, and creatinine. It is advisable to examine the levels of plasma aldosterone and renin activity, an analysis of urine.

**Therapeutic recommendations.** Patients with RAH require an active therapeutic measures as are categorized as high risk of complications. Needs identification and correction of reversible risk factors such as overweight, eating high amounts of salt et al. Treatment of identified secondary forms of hypertension, use of effective combination therapy. Medications that worsen blood pressure control should be abolished, if possible, or used in minimally effective doses.

One of the key aspects of effective therapy is to improve adherence. Determined that the increase in the number of tablets taken compliance of patients is reduced. To simplify the regimen is expedient to use a long acting formulations providing single dose a day, as well as a fixed combination. Increases the commitment to the treatment and management of patients with home BP measurements diary. This information will allow the physician to analyse blood pressure outside the clinic and more objectively evaluate the effectiveness of treatment.

Should inform the patient for the treatment of hypertension; agree with him non-drug and medical methods. The ability to follow the doctor's recommendations for receiving medications and lifestyle modifications significantly increases when building a trusting relationship with the patient, the involvement of family members.

**Pharmacotherapy of RAH.** The leading role of increased intravascular volume in the development of resistance determines the efficacy of thiazide diuretics. In patients with chronic renal failure (CRF) (creatinine clearance <30 ml / min) should be preferred to loop diuretics [7, 8].

Numerous clinical studies have shown that the use of 2 different classes of drugs has been increasing antihypertensive effect. However, efficacy of combined treatment with 3 or more drugs

has been poorly studied.

The most reasonable are the following combination of three antihypertensive drugs:

ACE inhibitor (or angiotensin receptor blocker II) + calcium antagonist + diuretic;

ACE inhibitor (or angiotensin receptor blocker II) + dihydropyridine calcium antagonists + beta-blocker;

ACE inhibitor (or angiotensin receptor blocker II) + diuretic + beta-blocker;

dihydropyridine calcium antagonists + diuretics + beta-blocker.

**Endovascular treatment of RAH.** There are currently actively developing non-drug methods of influence on the pathogenic mechanisms of the RAH. A promising method is now considered sympathetic plexus catheter ablation of the renal artery, renal denervation or.

Hyperactivation of the sympathetic nervous system (SNS) and the progressive increase in blood pressure are mutually reinforcing and are involved in the formation of a vicious circle. In the kidney occurs vasoconstriction, reduced blood flow and filtration, increased renin secretion, increases the reabsorption of sodium and water. It has been shown that electrical stimulation of afferent nerve fibres increases blood pressure and renal causes vasospasm, while these fibres denervation, conversely, reduces blood pressure. The efficacy and safety of endovascular renal denervation actively studied worldwide [18, 19]. But US clinical study of renal denervation for the treatment of RAH SYMPPLICITY HTN-3 has not reached the key performance indicators.

The method of electrical stimulation of the carotid sinus baroreceptors is another method of influence on the activity of the SNS and is in electrical stimulation of the carotid sinus baroreceptors (BCS) to the reflex decrease in blood pressure. BCS, located at the bifurcation of the carotid arteries are involved in the regulation of blood pressure. When it comes increasing tension receptors, further impulses from them enters the vascular centre of the brain, which leads to lower blood pressure. In hypertension baroreceptor sensitivity decreases. When electrical stimulation electrodes are routed to the carotid sinus and carotid arteries are connected to a generator, which is sewn under the skin of the anterior chest wall [20, 21]. Stimulator implantation is performed vascular surgery, cardio or neurosurgeon. The results suggest promising method.

However, in addition to evaluating the effectiveness of these methods remain unclear various aspects of treatment: predictors of success and performance criteria of procedures, duration of response, the possibility of damage to the vascular endothelium, the risk of adverse effects.

Thus, despite the high prevalence of RAH, the lack of blood pressure control is often associated with an inadequate selection of antihypertensive therapy, blood pressure misjudgement or failure of patients to medical recommendations. Therefore, before carrying out diagnostic measures necessary to consistently assess the adequacy of patients receiving therapy that inherent in the definition of RAH and exclude pseudoresistance. Rational treatment should be adjusted individually according to concomitant diseases, evaluate the effectiveness of previous treatment and side effects.

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*Повний список літератури знаходиться в редакції.*