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Abstract: The article presents data from domestic and foreign literature on the evolution of ideas about hypertension and the evolution of manifestations of the disease or its clinic. The concept of the mechanisms of development of arterial hypertension is presented in detail.

Keywords: arterial hypertension, historical aspects.

MODERN PRINCIPLES OF TREATMENT OF ARTERIAL HYPERTENSION

Before starting treatment of a patient with hypertension, every physician should be aware of when to start pharmacotherapy, what target values of BP should be achieved with its help, taking into account the different severity of cardiovascular risk, what should be the treatment tactics and choice of drugs. The goal of treatment of any patient with arterial hypertension is to maximally reduce the risk of cardiovascular complications and death from them. This is the strategy that determines the choice of drugs.

In the 2013 recommendations, the target BP is considered to be less than 140 and 90 mmHg, and less than 140 and 85 mmHg for patients with diabetes mellitus. All

these indicators are justified by analysing the results of various clinical studies, both comparative and prospective, often involving meta-analyses [2, 3]. There are reliable data allowing to recommend to elderly and old age AH patients younger than 80 years old with CAD level of 160 mm Hg to reduce it to 140-150 mm Hg. It should be noted that in previous versions of the recommendations it was suggested to elderly people to reduce CAD to 130 mmHg and below, which caused protests from neurologists and geriatricians. At the same time, if an elderly patient well tolerates a decrease in BP below 140 mmHg, i.e. does not faint, does not experience dizziness, maintains good cognitive abilities, there is no need to artificially maintain BP at a higher level.

Treatment tactics for AH patients are determined individually and are aimed at improving the quality of life, elimination of symptoms of the disease. It should be noted that such therapeutic approach is currently used in the treatment of all cardiovascular diseases: strategy - improvement of survival and mortality, tactics - elimination of symptoms. An obligatory condition for management of a patient with any degree of risk is persistent and intensive non-medication correction of lifestyle and habits. If it is ineffective, it is necessary to eliminate risk factors with the help of drugs. Hypotensive therapy is prescribed taking into account risk assessment, target organ damage, comorbidities, and usually includes two or three drugs. Particularly

This situation is very relevant for Russia, where patients come to the doctor late, and already at the first visits they have high risk, comorbidities and high BP level.

The effectiveness of therapy is monitored by regular BP measurement, which is taught to the patient. Treatment of a patient with arterial hypertension is carried out in several stages:

1. cardiovascular disease risk assessment.

2. Treatment until the target BP is less than 140/90 mmHg.

or less than 140/85 mmHg:

- lifestyle changes;

- drug therapy.

3. ensuring that the doctor's recommendations are followed.

If this sequence is not followed, the effectiveness of the treatment is practically impossible to achieve

impossible.

Lifestyle changes

Lifestyle modification consists of dietary measures, exercise, smoking cessation, normalisation of body weight and reduction of alcohol consumption to a safe level. The effectiveness of lifestyle modification is equated to that of drug monotherapy. However, it should be emphasised that waiting for results from these interventions should not be a reason to postpone the initiation of pharmacotherapy in high-risk patients; these measures should be implemented in parallel.

The efficacy of lifestyle modification as an essential component of hypotensive therapy is no longer in doubt. Numerous publications have confirmed this position. Thus, in one of the meta-analyses [9] it was shown that limitation of sodium intake by 100 mmol per day leads to a decrease in the

on average by 5.8 mmHg of systolic and 2.5 mmHg of diastolic BP; decrease in

body weight by 4.5 kg - by 7.2 mmHg systolic and 5.9 mmHg diastolic; limiting alcohol intake to 2.7 servings per day - by 4.6 mmHg systolic and 2.3 mmHg

diastolic; increasing exercise to 3 workouts per week - by 7.3 mmHg systolic and 7.5 mmHg diastolic; and dietary adherence - by 10.3 mmHg systolic and 7.5 mmHg diastolic. diastolic; increasing exercise to 3 workouts per week - by 10.3 mm Hg systolic and 7.5 mm Hg diastolic, and dietary adherence - by 11.4 mm Hg systolic and 5.5 mm Hg diastolic. The Department of Family Medicine has similar experience. A series of measures (simple sessions of physical training, dietary correction) in patients with arterial hypertension carried out in 1998 in one of the districts of St. Petersburg made it possible to achieve an average decrease in BP by 11 and 7 mmHg, and the results were maintained for 2 years [6].

The diet and nutritional status of patients with AH should include two objectives: reduction of sodium intake and normalisation of body weight. The DASH study ("Dietary Approaches to the Treatment of AH") showed that a diet with reduced sodium intake, but rich in fruits and vegetables (sources of potassium), with a low fat content, but with a sufficient amount of lean dairy products (sources of calcium) led to a reduction in BP [10]. The patient should be advised to exclude canned food - pickles, pickles, canned meat, dry concentrates, including soups, bouillon cubes, factory-made seasonings, sausage products, even if they are of high quality, smoked meats, cheeses, and baked goods, as they contain soda (also sodium, only bicarbonate). To be well oriented in the quality of food, the patient should learn to read food labels, which indicate the composition of products, including the content of sodium. At the same time, it is necessary to increase the daily consumption of fresh fruits and vegetables, lean dairy products, cod, potatoes. Dietary measures to reduce body weight include limiting the total caloric content of food, as well as increasing the proportion of dietary fibre, grains, raw vegetables and fruits in the daily menu.

Smoking cessation has been shown to reduce fibrinogen levels

in blood, improves endothelial function, and prevents platelet aggregation. These effects

contribute to the prevention of strokes, so patients with AH should be advised to stop smoking. Smoking inhibits arterial relaxation, causes a powerful pressor effect and reduces the content of antioxidants in the blood [11]. Methods of smoking cessation have been described [6, 12]. It is important to provide the patient with support from family or health care providers, reassurance and prescription of nicotine replacement medication in accordance with current recommendations.

All patients, regardless of severity and risk level, are advised to reduce their body weight if they are overweight or obese and then maintain it at a normal level. It should be remembered that these measures should be followed for life, as obesity, like AH, is a chronic disease. Unfortunately, long-term weight loss programmes are not yet effective, and population-based programmes have failed in many countries. More effective approaches to this problem may be found in the future. In addition to the dietary measures already described, physical exercise can help to reduce body weight.

Prospective observational studies show that the risk of CVD and complications is 30% higher in those who were physically inactive in middle age. Even a single episode of exercise then leads to a reduction in BP over several hours [11]. The positive effect of exercise on the cardiovascular system is due to the peripheral vasodilating effect, the work of skeletal muscles, the production of active substances with protective properties for the cardiovascular system

system, improvement of lipid profile, reduction of insulin resistance. Absolutely,

The most important of the mechanisms is the cardiorespiratory training effect itself.

The antidepressant aspect of aerobic exercise also means a lot. Exercise should be constant, as the positive effects disappear when it stops. Aerobic exercise is used. It

is safe to start at an intensity level where the heart rate at the height of exertion reaches 50 per cent of the maximum age-related rate, and then increase the intensity until the heart rate reaches 70-80 per cent of the maximum age-related rate. Training frequency

Sessions are 3-5 per week, increasing to 5-6 per week. The duration of training is 30 to 45 minutes, with 5 minutes for warming up and 5 minutes for cooling down. Walking or running is best for patients with arterial hypertension. If it is possible to exercise on an exercise bike, cycling training is prescribed for 16-18 weeks [13]. Swimming, skiing, dancing, skating, tennis are also possible. However, the most important principle is to start gradually and slowly increase the load.

Alcohol consumption increases BP after a few hours. In addition, the hypertensive effect persists over the next 24 hours. The relationship between alcohol consumption and BP is believed to be linear. Given the negative effects of alcohol and on other systems and organs, it is best to stop its consumption, in extreme cases - to reduce the amount to a relatively safe. It is known that 14 servings per week for men and 9 for women are considered relatively safe. One serving of alcohol is about 12 grams of pure alcohol.

Drug therapy for AH

Management of patients with AH requires two questions: when to start drug therapy and which drug(s) to choose. If we follow both national and European recommendations, the main indications for starting drug therapy are: 1) the severity of the risk of cardiovascular complications and 2) the degree of blood pressure elevation. The algorithms of the National Recommendations can be used for risk stratification [3].

Patients with high-risk AH of II-III degree should start drug therapy immediately. In AH I degree, drug therapy is started just as quickly if there is diabetes mellitus,

target organ damage. The point of view has changed in relation to patients with high normal BP, AH I degree without risk of cardiovascular complications. According to the recommendations [2, 3], they do not need BP correction, but lifestyle changes should be carried out very persistently.

Currently, there are two approaches to initiating therapy: searching for the optimal drug for monotherapy and low-dose combination of two drugs. The advantage of monotherapy is minimisation of side effects, better adherence of the patient to treatment; however, this approach requires a very patient attitude on the part of both the physician and the patient. The long period of selection, change of medication, dose manipulation, careful BP monitoring all require understanding on the part of the patient, who must be an informed, trained ally, no less interested in the outcome than the physician. The combination of medications can help achieve target BP more quickly.

Modern medicine uses seven classes of hypotensive agents to treat patients with AH.

1. basic:

- diuretics;

- beta-adrenoblockers (BABs);

- slow calcium channel blockers (SCCBs);

- angiotensin-converting enzyme inhibitors (ACEIs);

- angiotensin II receptor blockers (ARBs).

2. Additional:

- imidazoline receptor agonists (IRA);

- central sympatholytic drugs.

There are several steps in choosing a drug: first, the class of drugs, then the drug within the class, then the choice of dosage form, and finally the specific drug given the manufacturer, i.e. generic or brand name.

First-line drugs are selected first. However, half of all patients with AH must take two drugs, and one third reach target BP with only three drugs [8, 14]. The following criteria can serve as a basis for decision making: what cardiovascular risk factors the patient has; what target organ lesions; clinical manifestations of CVD, kidney disease and diabetes; presence of comorbidities; interaction with other drugs; to what extent the risk of cardiovascular lesions will be reduced by using a drug of this class. When choosing a particular drug within the class of hypotensive drugs, it is necessary to take into account social and economic factors, variability of response to drugs in each patient, interaction with other drugs, the presence of comorbidities (contraindications).

The problem of choosing the dosage form (tablet, injection, prolonged or short-acting drug) is caused by the impact on the course of the disease and quality of life, and the manifestation of adverse effects. It is preferable to prescribe overnight agents, as they do not cause BP fluctuations associated with interval between doses.

The concentration of prolonged medication in the blood is kept stable. Patients also prefer to take the drug once, this preserves their quality of life, reduces the number of side effects, and therefore maintains their adherence to the doctor's recommendations.

If the course of the disease becomes threatening and emergency treatment is required, the medicine must work quickly. In this case, the short-acting dosage form is also suitable. Why do we have to take into account all these features? Because in practice the doctor is often confronted with

the patient is unable to buy a medicine that is recommended according to the evidence-based approach, or does not want to take the medicine because of side effects, or the target BP cannot be reached, the medicine is ineffective, or the side effects make it necessary to cancel the medicine. There is also the need to choose between the original drug and a generic. What is a generic? It is a drug with proven therapeutic interchangeability, produced after the patent for the original (brand name) drug has expired by other companies. The formula and structure of the generic should be the same as the original, but the technology, excipients, equipment, purification, etc. are different. Unfortunately, there is almost no testing of generics, the therapeutic effect is not proved in clinical trials, it is believed that the testing of brands is enough. But the frequency of side effects of generics may be higher, and the effectiveness may be lower, due to the peculiarities of production. However, the economic situation in the country may turn out in favour of generics, as is happening now in Russia.

Diuretics

Of the three groups of diuretics (loop diuretics, thiazide diuretics, potassium-saving diuretics), thiazide and thiazide-like diuretics are the most commonly used for the treatment of hypertension because of their moderate intensity but longer duration of action. The thiazide group includes hydrochlorthiazide, chlorthalidone, bendroflumethiazide, polythiazide, cyclothiazide; the thiazide-like group includes metolazone, quinetasone, indapamide, clopamide, xipamide, mefruzide.

Diuretics are known for their ability to positively influence prognosis in patients with AH, are cheap and are often recommended as monotherapy, especially in elderly patients.

On the other hand, metabolic effects of diuretics (retention of uric acid, calcium, dyslipidaemia, decreased tissue sensitivity to insulin) restrained their widespread use in AH. However, the emergence of new-generation thiazide diuretics, which have virtually no adverse effect on metabolism, allowed the use of this class of drugs without restrictions. Before starting therapy with diuretics, it is necessary to determine the content of potassium, uric acid and creatinine in the blood, lipidogram, parameters of carbohydrate metabolism. If you tell the patient about potassium-rich foods and convince him to follow the recommendations, it is unlikely that he will develop clinically significant hypokalaemia. Nevertheless, when collecting anamnesis and examining the patient, ask if he has cramps, weakness in the calf muscles, check the rhythm and signs of electrolyte abnormalities on ECG.

β-Arenoblockers

In the last few years, drugs of this class are no longer prescribed as widely as they used to be. Hypotensive effect of drugs of this class is due to several mechanisms. Firstly, it is a decrease in cardiac output due to a decrease in sympathetic tone, which means that the frequency and strength of heart contractions decreases. In general, the work of the heart becomes less intense. Secondly, the release of renin and the formation of angiotensin II are blocked. Finally, action in the synaptic space inhibits the release of norepinephrine. A number of other mechanisms also account for the antianginal action, the prevention of arrhythmic complications and finally, it improves cardiac health and inhibits neurohormonal activation. According to

According to the recommendations of the European Society of Cardiology [15], the prescription of β-adrenoblockers to a patient with AH is primarily indicated both

for BP control (class of recommendations I, level of evidence A) and especially after myocardial infarction, with concomitant CHD, tachyarrhythmia, and heart failure. At the same time, it is noticed that these drugs as monotherapy are not effective enough for elderly patients. When choosing a β-blocker, one should take into account the necessity of selective action on β 1 -adrenoreceptors, cardioprotective effect, which is more pronounced in lipo- and amphophilic drugs, and finally, retarded forms allowing to take the drug once. Today more than 40 molecules of β-blockers are known, but the most common are only about 10: selective - atenolol, betaxolol, bisoprolol, metoprolol, carvedilol, nebivolol, celiprolol; non-selective - propranolol, nadolol, oxprenolol, sotalol, timolol.

ACE inhibitors

These are the most common modern drugs, best suited for both mono- and combination therapy. The basis of their pharmacological mechanism is the blockade of the enzyme that promotes the conversion of the inactive form of angiotensin into the active form, angiotensin II. They attenuate the effects of activation of the renin-angiotensin system, including arterial vasoconstriction and aldosterone secretion, by reducing the formation of vasoconstrictors. Under the influence of long-term therapy with ACE inhibitors (iAPF) there is a reverse development of left ventricular and arterial wall hypertrophy. In addition, they have a number of properties that may be useful in patients with AH, in particular renoprotective, anti-ischaemic, anti-atherogenic.

The effect of ACE inhibitors for BP reduction and as the drug of choice in those cases where there is myocardial systolic dysfunction, myocardial infarction, congestive heart failure, diabetes mellitus, and, finally, for secondary prevention in patients at high risk of cardiovascular complications has been proven. Clinical trials

analysed by the European Society of Cardiology [16] did not show advantages of these drugs over other classes when administered as 1st line monotherapy in other conditions.

Use of angiotensin receptor blockers

The conversion of angiotensin I to angiotensin II occurs not only by the so-called chymase pathway but also by other means. Consequently, IAPPs are not able to completely suppress the hypertensive action of the renin-angiotensin system. Therefore, since the late 80's, the search for drugs that could affect not the formation of the active form of angiotensin, but to disrupt its interaction with target organs has been underway. The first drug of this class was losartan, synthesised in 1988. There are two main types of angiotensin (AT) receptors - type I and type II, AT1 and AT2 (not to be confused with angiotensin I and angiotensin II). Accordingly, a distinction is made between non-selective and selective AT receptor blockers. In clinical practice, only selective angiotensin receptor blockers of type 1 are used. Type 2 receptor blockers are used only in physiological studies. Several drugs of this class are known, tested in clinical trials and recommended for use. They are losartan, valsartan, irbesartan, candesartan, telmisartan and eprosartan.

In addition to excellent tolerability, sartans have high antihypertensive efficacy. In large studies as monotherapy, they caused sufficient antihypertensive effect (reduction of diastolic BP below 90 mmHg or at least by 10 mmHg) in 40-80% of patients with mild to moderate forms of essential hypertension. Thiazide diuretics and calcium antagonists not only enhance but also prolong the antihypertensive effect of these drugs. All known blockers of AT1-receptors at a single administration uniformly reduce BP during 24 h. Their maximum antihypertensive effect is achieved not earlier than 4-8 weeks after the start of therapy. Hypotension

after the first dose is uncharacteristic for these drugs. Sudden cancellation of AT1-receptor blockers is not accompanied by the development of rebound hypertension [17].

AT1-receptor blockers cause reverse development of left ventricular hypertrophy in patients with AH during long-term use. This is a very important effect, since it is now proven that left ventricular hypertrophy is an independent, independent risk factor for the development of complications of CVD. Thus, they have the ability to prevent complications and fatal outcomes due to their effect on LVH. This is also an indication for prescription to patients with diastolic myocardial dysfunction. Another important factor is the ability to reduce proteinuria, i.e. these drugs are indicated for patients with nephropathy, including diabetic nephropathy.

Calcium channel blockers

From the pharmacological point of view this is a very heterogeneous group of drugs. It is allowed to remind that in the organism calcium plays very many roles in various processes, in all systems and organs. Therefore, calcium channels, necessary for the passage of calcium ions into and out of the cell, are also present in all systems and organs. Calcium antagonists are usually divided into three main groups depending on their chemical structure:

1) phenylalkylamine derivatives (verapamil, gallopamil, etc.);

2) benzothiazepine derivatives (diltiazem, clentiazem, etc.);

3) dihydropyridine derivatives (nifedipine, amlodipine, nisoldipine, nitrendipine, felodipine, etc.).

Verapamil and diltiazem have negative ino-, chrono- and dromotropic effects, i.e. they can reduce myocardial contractility, decrease HR and slow down atrial-ventricular conduction. Nifedipine and other dihydropyridine derivatives have

more effect on blood vessels, practically not affecting the function of sinus node and atrial-ventricular conduction. The main mechanism of their action is the dilation of peripheral vessels. This reduces systemic resistance and decreases the volume of blood returning to the heart. That is why the reaction to the reception of dihydropyridine derivatives of calcium antagonists is tachycardia - it is a compensatory response of the heart to reduce blood volume. This group of calcium antagonists is mainly used for the treatment of arterial hypertension. Preference should be given to long-acting (slow-release) dosage forms. Reducing the incidence of stroke, calcium antagonists at the same time are inferior to diuretics and β-blockers in their effect on the development of heart attacks, i.e. heart attacks or acute coronary syndrome. It is also established that their use is accompanied by regression of left ventricular hypertrophy.

Other drugs for the treatment of AH

Not all drugs for the treatment of AH are used as 1st-line agents. This is due, firstly, to the insufficient number of randomised controlled trials to assess their efficacy and safety; the availability of more effective and safer drugs of the main classes. Nevertheless, in certain clinical situations there is a need to prescribe additional drugs. Imidazoline receptor agonists (IRA), α-adrenoblockers (AB) and direct renin inhibitors (DRIs) may be used as additional classes for combination therapy. No large RCTs have been conducted to assess the effect of these drug classes on hard endpoints. These classes have been studied in observational studies where indications for their preferred prescribing have been established.

Imidazoline receptors are located in the central nervous system and in the periphery (kidneys, pancreas). Activation of central I 1 -receptors leads to a decrease in BP and heart rate due to the central suppressive effect on the peripheral sympathetic nervous system. Both types of receptors are involved in the central

regulation of autonomic nervous system tone. Moxonidine improves parameters of carbohydrate metabolism, it can be especially recommended to patients with impaired glucose tolerance and diabetes mellitus. It is noted that moxonidine reduces the severity of proteinuria and slows down the rate of decline in the rate of glomerular filtration in diabetic nephropathy.

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