

Review

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ARTERIAL HYPERTENSION AND MEDICAL SUPPORT OF PATIENTS WITH PERMANENT PACEMAKERS

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The review is devoted to clinical problems of arterial hypertension (AH) in patients with implanted pacemakers (EKS) and cardiac resynchronization therapy (CRT). Indications for pacemaker implantation and CRT are considered, especially the purpose and effectiveness of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARA, sartans), beta-blockers (BAB), diuretics, calcium channel blockers. We prove that the CRT and cardiac pacing do not cancel, but modify drug therapy of AH.

KEY WORDS: cardiac pacing, arterial hypertension, therapy of AH

АРТЕРІАЛЬНА ГІПЕРТЕНЗІЯ ТА МЕДИКАМЕНТОЗНА ПІДТРИМКА ПАЦІЄНТІВ З ІМПЛАНТОВАНИМИ ЕЛЕКТРОКАРДІОСТИМУЛЯТОРАМИ

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Огляд присвячений клінічним проблемам артеріальної гіпертензії (АГ) у пацієнтів з електрокардіостимуляторами (ЕКС) та кардіоресинхронізуючою терапією (КРТ). Розглянуто показання до імплантації ЕКС і КРТ, особливості призначення та ефективність діуретиків, бета-блокаторів, антагоністів кальцію, інгібіторів ангіотензіперетворюючого ферменту, антагоністів рецепторів ангіотензину II. Доведено, що ЕКС і КРТ не скасовують, а модифікують медикаментозну терапію АГ.

КЛЮЧОВІ СЛОВА: електрокардіостимулятори, артеріальна гіпертензія, терапія АГ

АРТЕРИАЛЬНАЯ ГИПЕРТЕНЗИЯ И МЕДИКАМЕНТОЗНОЕ СОПРОВОЖДЕНИЕ ПАЦИЕНТОВ С ИМПЛАНТИРУЕМЫМИ ЭЛЕКТРОКАРДИОСТИМУЛЯТОРАМИ

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Обзор посвящен клиническим проблемам артериальной гипертензии (АГ) у пациентов с имплантированными электрокардиостимуляторами (ЭКС) и кардиоресинхронизирующей терапией (КРТ). Рассмотрены показания к имплантации ЭКС и КРТ, особенности назначения и эффективность диуретиков, бета-блокаторов, антагонистов кальция, ингибиторов ангиотензипревращающего фермента, антагонистов рецепторов ангиотензина II. Доказывается, что ЭКС и КРТ не отменяют, а модифицируют медикаментозную терапию АГ.

КЛЮЧЕВЫЕ СЛОВА: артериальная гипертензия, электрокардиостимуляторы, терапия АГ

INTRODUCTION

Nowadays, permanent endocardial pacing (pacing) and cardiac resynchronization therapy is the most recognized and effective method of treatment for severe arrhythmias and conduction disorders, as well as for the resistant

chronic heart failure (CHF). Pacing significantly improves the quality of patient's life and reduces mortality.

The world's first pacemaker implantation was performed by A. Senning at the Karolinska Hospital in 1958, which was the impetus for the development and the elaboration of new highly

effective method of treatment for bradyarrhythmias [1–2].

In international practice, 5-letter code is used to describe the program of a pacemaker, which is a joint development of the working groups of the North American Society of Pacing and Electrophysiology (NASPE) and the British group of Pacing and Electrophysiology (BPEG), known as the common code NBG-NASPE/BPEG.

The first letter denotes a stimulated heart chamber (A-atrium-, V-ventricle, D-two chambers, O-absence of stimulation of the heart function).

The 2nd letter indicates detectable heart chamber (A-atrium, V-ventricle, D-two chambers, O-absence of stimulation of the heart function).

The 3rd letter indicates the method of response (I-inhibitory, T-trigger, D-double, O-absence).

The 4th letter indicates the device programmability features and the availability of frequency adaptation (R-simple, M-multiprogrammability, C two-way communication, R-frequency adaptation, O-absence).

The 5th letter defines antiarrhythmic function (P-antiarrhythmic stimulation, S-defibrillation, D-double, O-absence) [3–4].

The main indications for pacemaker implantation are atrioventricular (AV) block, sick sinus syndrome (SSS), bifascicular and three fascicular blocks, myocardial infarction (MI) and its associated arrhythmias, paroxysmal symptomatic ventricular and supraventricular tachycardia, and high functional classes (FC) of chronic heart failure (CHF) and hypertrophic cardio-myopathy (HCM) [5–6].

The main purpose of pacing is the simultaneous activation of both ventricles, in order to improve the mechanical efficiency of the ventricles [7–8]. Pacemaker implantation significantly increases the left ventricular ejection fraction and reduces the frequency of hospitalization [9–11].

Arterial hypertension (HT) is the leading problem of modern cardiology, due to its prevalence and adverse complications [12–13].

AH is the most common comorbidity in patients with a pacemaker, which has a significant impact on its current, and be for all on, the control of blood pressure (BP) [14].

AH is diagnosed at the level of systolic blood pressure (SBP) > 140 mm Hg = and / or diastolic blood pressure (DBP) \geq 90 mm Hg. If an increase is stable and confirmed by regular measurements of BP (not less than 2–3 times on different days for 4 weeks) [15], as evidenced by data from randomized controlled trials (RCTs) on the therapeutic benefits of lowering BP, since these indicators [16].

The prevalence of AH in the range 30–45 % of the general population, with a sharp increase in the aging, without any systemic trends to changes in BP in the last ten years [17–20]. According to the official statistics, more than 11 million people were registered in 2007 in Ukraine, which amounts for 29.9 % of the adult population [15].

According to the latest recommendations of the European Association of Hypertension and the European Cardiology Association (2013), they distinguish 3 grades of AH according to the level of blood pressure:

- Grade 1 (mild) – 140–159 mm Hg SBP, DBP 90–99 mm Hg.
- Grade 2 (moderate) – SBP 160–179 mm Hg, DBP 100–109 mm Hg.
- Grade 3 (severe) – SBP \geq 180 mm Hg, DBP $>=$ 110 mm Hg.
- Isolated AH – SBP \geq 140 mm Hg, DBP < 90 mm Hg.

The classification of organ damage is used to establish the stage of AH. This classification was developed by WHO experts (1963–1993) and adopted in Ukraine in 1992, according to the order of Ministry of Health of Ukraine № 206 from 30.12.1992. It is recommended for use according to the order № 247 from 1.08.1998 [15].

I stage – there is no objective evidence of target organ damage.

Stage II – there is objective evidence of target organ damage, with the absence of symptoms:

- Left ventricular hypertrophy (LVH)
- Generalized narrowing of the retinal arteries
- Microalbuminuria
- Atherosclerotic vascular disease

Stage III – there is objective evidence of target organ damage, the presence of symptoms on their part or dysfunction:

- Heart – heart attack (myocardial infarction), heart failure IIA-III st.
- Brain – a stroke, transient ischemic attack, vascular dementia, acute hypertensive encephalopathy.

- Fundus – hemorrhage and exudates in the retina and swelling of the optic nerve.
- Kidneys – proteinuria and/or the concentration of creatinine in the blood plasma > 133 mmol/L in males and > 124 mmol/l in women.
- Vessels – aortic dissection, occlusive peripheral arterial disease.

Stroke is the main cause of death in patients with AH [21]. Approximately two-thirds of strokes and half of all cases of IHD are due to AH, it becomes the cause of 7 million deaths and 64 million cases of disability per year [22–23].

In general the implantation of the pacemaker has a positive effect on patients' quality of life [24–27]. However, due to the improvement of the pumping function of the left ventricle, can cause instability of BP [28], as a result the progression of AH [29–31]. In this regard, drug therapy is not canceled, but should be modified. Drug therapy of AH in patients with implanted pacemaker and CRT is still poorly investigated.

ATRIOVENTRICULAR BLOCK

Atrioventricular block (AV block) is characterized by a delay or discontinuation of impulses through the AV node, as a result of the compensatory response in the form of the progression of AH, that was partially confirmed in studies [32–33]. According to [34], AH is the most common risk factor in patients with AV block.

There are three degrees of AV block. AV block of the 1st degree is abnormal prolongation of the interval P-R more than 0.2 sec., the second degree is divided into 2 types. The I type is characterized by progressive elongation of the P-R interval to the blocked contraction and is associated with a narrow QRS complex, II type – fixed Interval P-R before and after the blocked complexes and associated with a wide QRS complex. In a far-reaching AV block of the 2nd degree, two or more successive P waves are not conducted. In the 3rd degree AV conduction is absent [35–36].

In patients with hypertension occurs the development of CHF and increases the risk of sudden cardiac death due to prolonged asystole and bradycardia [37–38].

Cardiac pacing is the only accepted method of treatment of AV block high degrees [39]. The DDD mode is the choice of pacing mode for

patients with stored chronotropic sinus node function [40].

Cardiac pacing in patients with AV block, significantly improves the quality of their life and increases their physical performance [41], nevertheless, due to the normalization of the pump function, may cause progression of AH. These data partially was confirmed in the study [34], in which was found that 29.6 % of patients with normal BP before cardiac pacing had AH after the implantation, mostly first degree. In 48.1 % of patients with AV block with high BP before cardiac pacing, in the postoperative period occurred AH of the second degree.

SICK SINUS SYNDROME

Sick sinus syndrome (SSS), also called Sinus node dysfunction, is a group of abnormal heart rhythms (arrhythmias) presumably caused by a malfunction of the sinus node which is clinically manifested in the form of significant bradycardia inadequate growth of the heart rate, progression of AH, poor exercise tolerance, dizziness, fatigue [42]. In some cases, there is a tendency to supraventricular tachyar-rhythmia (brady-tachy – form of SSS) [43–45]. The incidence of SSS increases due to the aging of the population [46].

Cardiac pacing is the leading choice of treatment for the patients with SSS and it significantly reduces the symptoms, but without changes in survival [47].

In patients with SSS preferably one- or two-chamber atrial pacing, particularly in patients with atrial fibrillation (AF) and the influence on patients' quality of life [44, 48].

Stimulation in the AAIR mode is associated with a higher incidence of paroxysmal atrial fibrillation, so DDDR mode is more appropriate in such patients [49]. The Albertsen and Nielsen's resource [50] demonstrated that the AAIR mode exceeds DDDR and reduces episodes of AF. According to DANPACE resource, DDDR mode is more effective for treatment patients with SSS and comorbid disorders [51]. Dual-chamber pacing increases life expectancy and improves its quality [52–53].

Cardiac pacing in patients with AH and SSS leads to stabilization of heart rate and intracardiac hemodynamics [54], however there is destabilization of BP and progression of AH on this background. Only in the one study these data were confirmed [55], in which was found

out increase of SBP in patients with SSS after the cardiac pacing.

INTRAVENTRICULAR BLOCKS

Intraventricular blocks (IVB) occurred in the violation of intraventricular conduction, partly or complete block of one, two and three branches of the bundle of His. There are also various combinations of full and partial blocks of branches of the bundle of His.

IVB occur as a result of anatomic abnormalities (malformation, inflammation, sclerosis, degeneration) or the development of a functional block (for supraventricular tachyarrhythmia and others), always complicated by CHF and prone to progression [56]. A part of patients can have an increase of SBP and progression of hypertension [57–58]. Especially unfavorable prognosis has combination the block of the right and anterior branch of the left bundle of His.

Often is noted syncope in patients with block of two branches of the bundle of His. Despite the fact that syncope may be repeated, it is not associated with an increased risk of sudden death. Pacing in such patients exempt from transient neurological symptoms, but did not reduce the incidence of sudden death [59].

Biventricular stimulation in patients with IVB provides a coordinated contraction of ventricles, it reduces the width of the QRS complex, and reduces the intraventricular and interventricular asynchrony [60].

There is an increase of SBP in patients with the block of two branches of the bundle of His, which was demonstrated in the research [61], these data indirectly indicates the progression of AH.

PAROXYSMAL VENTRICULAR AND SUPRAVENTRICULAR TACHYCARDIAS

Paroxysmal ventricular and supraventricular tachycardia – type of arrhythmia are characterized by palpitations (paroxysms), with a heart rate from 140 to 220 or more per minute, arising under the influence of ectopic pulses, which leads to the replacement of normal sinus rhythm. As a rule, they are accompanied by increase of BP and progression of AH. Ectopic impulses can be generated in the atrium, AV node or ventricles [62–63].

Cardiac pacing may be useful for the treatment of patients with recurrent symptomatic ventricular and supraventricular

tachycardia [59, 64]. Antiarrhythmic device can detect tachycardia and automatically activate the stimulation, or respond to an external trigger. In some patients with long QT syndrome recurrent, brady-form of VT can be prevented by the overdrive stimulation. It is described that the combination of atrial pacing and beta-blockers shortens the QT-interval and helps to prevent sudden death [65].

Besides that ectopic ventricular activity may also be inhibited by such stimulation, severe and symptomatic arrhythmia is rarely preventable [66].

In a multicenter, randomized clinical trial SAFARI was demonstrated the safety and efficiency of preventive pacing algorithms that was designed for the prevention of AF in patients with bradycardia and paroxysmal AF. The biggest efficiency was achieved with initial frequent paroxysms of AF [67].

Bifocal stimulation of the right atrium or alternative monofocal stimulation of non-traditional outlets (eg. interatrial septum or the Bachman bundle), may provide additional advantages compared with a monofocal stimulation of the right atrial appendage in patients with symptomatic drug-refractory atrial fibrillation and concomitant bradyarrhythmia. In patients with SSS and intraatrial block (P is greater than 160 ms) biatrial stimulation can reduce the incidence of recurrent AF [68].

The research [69] described an increase of SBP and a slight increase of DBP in patients with AF after the cardiac pacing, which indirectly indicate the progression of AH.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is a genetic cardiovascular disease. It is defined by an increase in left ventricular wall thickness that is not solely explained by abnormal loading conditions. It is usually accompanied by AH high degrees. This is the most common of genetically caused cardiomyopathy (20 per 10 000) [70].

According to the results of the echocardiographic screening of the population in Ukraine (15 700 people), that was made by A.I. Minakov, occurrence of HCM was 0,47 %, that was much more than in other countries.

Invasive methods of treatment include implantation of a defibrillator for patients with a high risk of sudden death and two-chamber AV-stimulation.

In the early nonrandomized studies was demonstrated the reduction of the gradient between the left ventricle and outflow tract, in patients with dual-chamber pacing with a short AV delay, and a reduction of symptoms in some patients with hypertrophic obstructive cardiomyopathy [59, 71].

The research, including 8 people with dual-chamber pacing for a long period of time, found out the reduction of the gradient even after the cessation of the stimulation. That helped suggest that due to the stimulation happened ventricular remodeling. Two randomized studies have shown the improvement in subjective quality of life approximately in 50 % of the patients, which, however, was not associated with a decrease of the gradient and placebo effect. A third randomized study did not show any improvement in the quality of life in patients with a pacemaker, although it has been suggested that stimulation in elderly patients (over 65 years) was more effective [59, 71–72]. A small group of patients with obstructive HCM was held the VDD-stimulation with premature ventricular excitation, i. e. the short AV delay. In this group was observed an increase in exercise tolerance, cardiac reserve and improvement of clinical symptoms. In some patients was reduced efficacy of pacing at a high rate of atrial rhythm, fast AV-holding and congenital anomalies of the mitral valve.

Nowadays there is practically no evidence that pacing stops further progression of the disease and improves survival or quality of life [73]. The efficiency of pacing is determined mainly by the severity of the gradient (more than 30 mm Hg at rest and more than 50 mm Hg under a load). [59]

Cardiac pacing reduces the adverse hemodynamic disturbances, which are caused by obstruction the outflow tract of the left ventricular. In the research [74–75] was described the increase of the diameter and the volume of the outflow tract of the left ventricle, as a result of the generation of the excitation of the LV, in the course of this was observed the reduction of SBP and the increase of DBP, which indirectly indicates the progression of AH.

CHRONIC HEART FAILURE

Chronic heart failure (CHF) is one of the most severe and prognostically unfavorable complications of diseases of the cardiovascular

system. One of the main components of the formation of CHF is the remodeling of the heart, including the processes of hypertrophy and dilatation of the myocardium, leading to changes of systolic and diastolic function of the LV, as a result of the progression of AH. In most patients, medical therapy is ineffective [76].

The main causes of death in patients with CHF are the violation of the pumping function of the heart and SCD. According to the ATLAS data which was made in Great Britain, the cause of 33–50 % of all deaths is HF.

Modern devices of recent generations for treatment CHF include ACD with cardiac resynchronization therapy (CRT) which leads to protect the patient at high risk for life-threatening arrhythmias, improve the quality of life and clinical outcomes in HF. The common goal of such combined devices is to slow the progression of HF, reduce the time of treatment in hospital and the prevention of SCD [60].

Indications for cardiac pacing and CRT in patients with heart failure are patients with CHF III-IV functional class according to the NYHA classification, the ejection fraction of the left ventricular (LVEF) less than or equal to 35 %, despite the optimal medical therapy, in the presence of sinus rhythm and the duration of QRS more than 120 ms, [77] the duration of QRS more than 120 ms and of the left bundle branch block (LBBB), or the duration of QRS more than 150 ms, independently of the morphology of QRS [78–79].

Patients with less severe HF (ischemic cardiomyopathy FC I or II non-ischemic cardiomyopathy FC II), EF < or = 30 % and QRS > or = 130 ms have also benefit from pacing [80]. Reduced the systolic function of the right ventricular before implantation – one of the most important performance criteria of pacing [81].

Cardiac pacing, and to a much greater extent displacing its CPT, in patients with CHF and dyssynchrony improves such hemodynamic parameters as the left ventricular fraction (LVEF), the end-diastolic and the end-systolic volume and of left ventricular, the stroke volume of the left ventricle, pulmonary artery pressure and the 6-minute test walk away. [82–85].

In studies [86–87], the transition from the right ventricular pacing to biventricular significantly improved echocardiographic parameters such as the function of the left

ventricular [88–89], reduction of dyssynchrony and reduction of symptoms typical for CHF [90], regardless of ischemic or nonischemic etiology of CHF. Sideris S. et al. proved the effectiveness of CPT in the transition from right ventricular stimulation in the form of reduction of CHF FC, LVEF increased, reduction of the QRS complex, and improved the data of 6-minute walk test [91].

It should be noted that among the majority of patients suffering from CHF, only 1/3 of the patients received only slight improvement [92–93]. In the research [94] was noticed that 81 % of patients on the background of cardiac pacing had an increase of SBP, which indirectly indicates the progression of hypertension.

MEDICATION SUPPORT OF PATIENTS WITH CARDIAC PACING AND AH

The importance of a patient's management after the implantation of antiarrhythmic device cannot be overestimated. A modern pacemaker is a multiple programmable device with a large number of therapeutic and diagnostic functions, so it needs regular inspection and adjustment [95–96]. When it comes to the monitoring of patients with an implanted pacemaker, it should be an implied assessment of the entire pacing system, not just a single device. As the stimulation system consists of 3 main units: the pacemaker, the electrodes and the patient's heart, the assessment should be carried out of all of these units [97]. The main problems when checking the system of stimulation in general are analysis of the functioning of the pacemaker and the electrode(s) and timely detection and elimination of violations in the stimulation system; assessing the adequacy of installed programs of stimulation and the correction of parameters; the assessment of the state of the power supply; timely detection and elimination of complications; education [98]. The frequency and method of observation depends on many factors, including different cardiovascular diseases and medical problems, period of a pacemaker implantation. The first check is carried out in 1.5–3 months after surgery, in terms of formation of the chronic stimulation threshold, when it becomes possible to control the final energy stimulation parameters. It is generally accepted HCFA guidance (1984), according to which patients with a single-chamber pacemaker after implantation an appointment is recommended to be twice within six months, then annually, with two-chamber

pacemaker – twice for 6 months, then every six months. Regular dynamic monitoring of patients with a pacemaker and CRT is a mandatory procedure, which provides timely detection, diagnosis and correction of irregularities in their work with the optimization of pacing program, to achieve the best clinical effect and to prolong the lifetime of the device [98].

Cardiac pacing significantly extends the capabilities of drug therapy, but at the same time there are additional requirements for ambulatory monitoring of patients after implantation [99–100].

Drug support of patients with cardiac pacing, as a rule, generally meets with the standards [101]. However, we must consider the impact of drugs on the threshold of pacing, the result of which can become serious hemodynamic disturbances, pacing threshold increase of potassium, b-blockers, calcium channel blockers, quinidine, aymalin, izuprel, izadrin, and lower – prednisolone, norepinephrine, ephedrine [102].

It should be noted that the data on the effect of many drugs (calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists, and others.) used for the treatment of patients with cardiovascular disease and an implanted pacemaker, today is not enough. In the medical support of patients with hypertension and an implanted pacemaker is used angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARA, sartans), beta-blockers (BAB), diuretics, calcium channel blockers. For the treatment of comorbid cardiovascular diseases is used ivabradine, digoxin, statins, warfarin, dabigatran, rivaroxaban, apixaban, aspirin, amiodarone, which may influence the course of hypertension [103–104].

Systematic observation of patients with pacemaker and CRT, and the effectiveness of therapy depending on the QRS complexes and QTc were first described in the works [105–106]. According to the date [106] after the pacemaker implantation the QRS duration did not change – in 33 %, shortening – in 22 %, elongation – in 45 % of cases, at CRT extension occurred in 90 % of cases, while with the increase of the class of QRS duration increased the frequency of appointments of ACE inhibitors, BAB, diuretics. According to the date [105] after pacemaker implantation in 55 of cases occurred the elongation of the QTc

complex that was associated with higher degrees of hypertension. However, the therapeutic support of patients with AH and implanted pacemaker and CRT is still poorly investigated.

DIURETICS

Thiazide diuretics, appointed in small doses, not only as effective as the other groups of antihypertensive drugs, but also prevent the development of cardiovascular complications in patients with AH [66].

In the TOMHS and VACS researches was shown that hydrochlorothiazide, chlorthalidone, indapamide induced a good anti-hypertensive effect. In the long-term therapy drugs were effective in 50–70 % of patients with AH [108]. However, in the research [109] was shown that hydrochlorothiazide reduced SBP only at 7.5 mm Hg and DBP – 4.6 mm Hg.

In the LIVE study was shown, that therapy with indapamide resulted in a significant decrease in LVM, there was no similar results in the group of enalapril. Indapamide also largely reduced the severity of the left ventricular hypertrophy than enalapril [110].

The use of loop diuretics for AH is largely limited for the treatment of hypertensive crises, and concomitant severe cardiac and kidney failure. Potassium-sparing diuretics, in most cases do not have an independent value in the treatment of hypertension and is used in combination with thiazide or loop diuretics [15, 111].

Researches on the appointment of diuretics in patients with AH and a pacemaker were not carried out practically. According to researches [105, 107] the frequency of the use of diuretics increased in the acute postoperative period after cardiac pacing. The study, [112] showed that the use of furosemide in patients with pacemaker significantly reduced BP.

BETA-BLOCKERS (BAB)

Recently, BAB was the drugs of first-line treatment of AH [113]. However, in the studies [114, 115], was noted that the BAB conceded to calcium antagonists in terms of overall mortality and cardiovascular events. However, in a large meta-analysis made by Law et al, was shown, that the start of therapy with BAB as effective as the other major classes of antihypertensive agents, prevented coronary outcomes and highly effectively prevented cardiovascular events in patients with recent

myocardial infarction and in patients with HF [116]. The researches [117–119] showed that BAB effectively provided cardiovascular protection.

Less efficiency BAB provided in the case of prevention from stroke [120], due to their lesser ability to reduce SBP and pulse pressure [121]. Less preventive efficacy against stroke also has ACE inhibitors [120] although the latter, according to the date [121] lower central blood pressure better than the BAB.

Carvedilol has antioxidant and anti-proliferative properties [21–22, 122], that is important to consider in terms of effects to the risk factors for cardiovascular disease and protect the target organs in patients with AH.

The most promising in the treatment of patients with AH from all members of the class of BAB is carvedilol [122]. According to the date [123], BP decreased after a single dose of carvedilol, however, the maximum antihypertensive effect developed in 1–2 weeks.

Contraindications for the appointment of BAB are asthma, clinically symptomatic bronchial obstruction, heart rate < 55–60 beats / min, sick sinus syndrome, AV-block II and III (without pacemaker implantation), SBP < 90 mm Hg.

The treatment should be started with a minimum dose that in the future increase progressively, in the case of stable hemodynamic condition of the patient, every 2–4 weeks, to the target or the maximum tolerated dose, which should be considered as optimal [3].

Indications for the BAB in patients with coronary artery disease and pacemaker besides AH, chronic heart failure, permanent AF [124, 125], is the need to suppress the ECS-induced arrhythmias. Atrial pacing electrode passes to the ventricle stimulus from the atrium and if the pacemaker has the higher limit of rate, the re-entry wave through the AV node is capable to induct the following contraction [126]. BAB has a clear beneficial antiarrhythmic effect without increasing the pro-arrhythmogenic effect in these patients [127, 128]. In patients without induced ECG and CRT arrhythmia BAB are prescribed in small doses [129].

In the MADIT-CRT study carvedilol has shown a higher efficacy against metoprolol in reduction the frequency of hospitalizations from HF and mortality. Ventricular fibrillation occurred in 22 % of patients, taking carvedilol,

compared to 26 % treated with metoprolol [128].

The research [130] showed that BAB reduced the severity of cardiac dyssynchrony in patients with HF with a normal duration of the QRS complex, especially carvedilol.

In the research [131] were given the data on the effectiveness of different doses of BAB in patients with CRT. Patients were divided into 4 groups: without BAB, taking 50 % of the target dose, and target dose. Before CRT distribution of patients was as following: without BAB – 36 %, < 50 % of the target dose – 37 %, > 50 – 20% and with a target dose – only 7 % of patients. After 6 months of CRT the ratio were – 17 %, 22 %, 28 % and 33 %, respectively. It has shown that CRT has improved the dose of BAB to achieve the optimal pharmacological effect in patients with CHF [131].

According to the data [105,107], after cardiac pacing and CRT had increased the frequency and the dose of BAB. The proper selection of a dose of BAB is a leading factor in the favorable prognosis of patients with pacemaker and AH.

CALCIUM CHANNEL BLOCKERS

Among antihypertensive drugs for first-line treatment of AH calcium channel blockers occupy a special place due to their high clinical efficiency, low frequency of side effects and good tolerance [6, 15].

According to a meta-analysis of 9 randomized controlled trials, calcium channel blockers are not inferior to traditional classes of antihypertensive drugs (diuretics, blockers, ACE inhibitors) in reduction in overall mortality, the mortality from cardiovascular causes and frequency of MI [132–134].

According to [105, 107] cardiac pacing had no effect on the frequency and dosage of the prescription of calcium channel blockers. However, there are no data on the effect of calcium channel blockers in patients with AH and pacemaker.

DIHYDROPYRIDINE DERIVATIVES (AMLODIPINE)

Reliable prevention of hypertensive crises is one of the main advantages of amlodipine. The drug allows the daily monitoring of blood pressure with a single dose [135].

Comparing the effect of amlodipine with the influence of the other calcium antagonists it shows great efficiency in BP comparing with

verapamil and diltiazem. According to [136], receiving amlodipine (10.5 mg), and diltiazem (180–360 mg). The average daily BP decreased, using amlodipine to 137/84 mm Hg and diltiazem to 143/86 mm Hg.

According to the multinational study VALUE, in the group of amlodipine risk of MI was 19 % lower, also it was showed a significant reduction in the number of strokes, control of BP with monotherapy was achieved in 63 % of patients [137].

According to the date [138] amlodipine most effectively reduced the risk of total mortality, the incidence of ischemic heart disease and its complications, stroke, and it was comparable to the effectiveness with ACE inhibitors.

The research [139] showed after taking amlodipine there was an increase in heart rate in patients with cardiac pacing, for at least 15 minutes, with a decrease in systemic vascular resistance, and a statistically significant reduction in BP.

FENILALKILAMINA DERIVATIVES (VERAPAMIL)

According to the date [140], verapamil at a daily dose of 240–480 mg provided significant reduction of BP, at about 80–85 % of the patients suffering from mild (85–90 %) or moderate (75–80 %) AH. The main disadvantage of verapamil was the short duration of action. However, the introduction of a long-active form of the drug (verapamil SR) has become the solution of these problems. It also allowed taking it once a day without reducing the effectiveness of antihypertensive therapy [16].

In the research, [141] was shown that monotherapy with verapamil SR 240 mg allowed to normalize the level of diastolic BP (below 90 mm Hg) in 90 % of patients with mild AH, 77 % – with moderate hypertension and in 61 % of patients with severe AH.

Verapamil has antiarrhythmic properties and is widely used for the treatment of supraventricular arrhythmias [142]. The treatment of patients, based on the use of verapamil, also effectively reduces the mortality risk of developing cardiovascular disease and stroke, as well as in the treatment of BAB [141].

Verapamil should not be prescribed in SSS, AV block, sinus bradycardia (heart rate at rest in less than 55 minutes), it is undesirable to prescribe in severe heart failure [15].

There are few studies on the effect of verapamil in patients with cardiac pacing. According to the research [143], in patients receiving verapamil at a dose of 240 mg / day in patients with AF and cardiac pacing in the DDDR mode, there was a trend of increasing in percentage of stimulation and heart rate was not reduced. There are no data on the effect of verapamil in patients with AH and cardiac pacing.

BENZODIAZEPINES DERIVATIVES (DILTIAZEM)

Benzodiazepines derivatives are good in treatment of ischemic heart disease and AH. This was confirmed by the works [144–147], which proved the ability of the drug favorably influence on the prognosis of IHD by reducing the likelihood of re-infarction, as well as the results of studies of patients with AH, in which was proved the safety of prolonged use of diltiazem and reduction of cases of stroke [145–146].

It should be noted that in the European Guidelines for the treatment of AH (2013) it was pointed out, that in patients with AH in conjunction with angina, with carotid atherosclerosis or supraventricular tachyarrhythmia, diltiazem and verapamil – are the drugs of choice [16].

In the research [148] was noticed, that after a single dose of diltiazem there was a significant decrease in heart rate by 7.5 %, SBP and DBP by 9.2 % and 10.9 %, respectively. After 12 weeks of monotherapy with diltiazem SBP normalized during the waking period was achieved in 61 %, in the period of sleep – 50 %, per day – at 55.5 %. DBP normalization was achieved in 66 % of patients in all presented periods.

According to the NORDIL study a significant decrease in SBP and DBP was found in the appointment of diltiazem. It confirmed the efficacy of diltiazem in the prevention of stroke, myocardial infarction, death from cardiovascular causes, which is not inferior BAB [149].

There are no studies on the effect of diltiazem in patients with a pacemaker and AH. Diltiazem in patients with pacemaker is rarely used, limited to cases without concomitant heart failure. So in the study [150], was shown that the use of diltiazem did not cause T-wave inversion.

ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

ACE inhibitors are the most attractive for the treatment of AH, as they have not only the blood pressure-lowering effect, but also provide a protective effect on the target organs [151–152], which is especially important in patients with a pacemaker. This class of drugs combines the advantages of high antihypertensive efficacy and good tolerability, ensuring a high quality of life with a proven cardio, vascular- and renoprotective effect and the reduction in the incidence of cardiovascular complications and increases life expectancy of patients with their long-term use [151,153].

Several studies have demonstrated the ability of ACE inhibitors to reduce LVH [154]. G.Jennings and J.Wong also noted the greatest regression of LVH in patients treated with ACE inhibitors based on 32 studies. Numerous randomized studies CONSENSUS and SOLVD have shown, that treatment with ACE inhibitors led to reduction in mortality (relative risk reduction (RR) of 27 % in CONSENSUS and 16 % in SOLVD).

The results of the PRESERVE study showed that in patients with AH and LVH receiving enalapril 20 mg 1 time per day provided not only the control of blood pressure, but also was accompanied by a remodeling of the left ventricle. Using enalapril during 1 year in 56 % of cases resulted in a normalization of myocardial mass index (IMM) LV [155–156]. Enalapril prevented dilatation and dysfunction of LV [157–159], reduced the frequency of hospitalizations and deaths from cardiovascular causes [160].

In the studies [161–162] was demonstrated, that the use of captopril prevented the myocardial and vascular remodeling in patients with AH and myocardial infarction.

In the PROGRESS study involving 1923 patients was registered, that perindopril significantly (by 28 %) reduced the risk of a recurrent stroke in patients with cerebrovascular diseases on the background of AH, and without it. In this study, a therapy based on perindopril not only reduced the risk of recurrent stroke, but also significantly reduced the risk of cardiovascular disease (26 %) and the risk of myocardial infarction (38 %) [163].

It was noted that perindopril had a positive impact on hemodynamic parameters in a

reduction of pressure in the right atrium and increased cardiac output [164].

In the treatment with ramipril compared with placebo, in the HOPE study, was shown an increase in the frequency of regression of LV hypertrophy and reduction of frequency of its development or progression [165].

However, ACE inhibitors can cause renal failure, hyperkalemia, symptomatic hypertension, cough, and, rarely, angioedema. Also, ACE inhibitors should be used only in patients with normal renal function and with normal levels of potassium in the blood serum [166–167].

In individual cases, there are publications on the effect of ACE inhibitors in patients with pacemaker and CRT. According to the date [107], with the increase in frequency of using ACE inhibitors was observed the lengthening of the QTc interval by 31 % in patients with cardiac pacing. According to the date [106] has increased the frequency of using ACE inhibitors in patients with cardiac pacing. The use of ACE inhibitors in patients with a pacemaker and CRT has caused an increase of LVEF and the decrease of CSR LV [168]. However, there are no data on the effect of ACE inhibitors in patients with AH and pacemaker.

ANGIOTENSIN II RECEPTOR ANTAGONISTS (ARA)

The drug of choice for the treatment of hypertension are ACE inhibitors, but the presence of side effects like a cough and angioneurotic edema, ARA recommended as alternatives in such patients [169]. ARA reduces systolic and diastolic BP by 50–70 % within 24 hours (the next day after taking the drug, the level of BP is reduced on 60–75 % of the maximum effect) [170–172].

Along with the hypotensive effect, important is the ability ARA to effect on the risk of cardiovascular complications compared with other classes of antihypertensive agents. In the

LIFE study showed that in the group of losartan compared with atenolol observed 13 % reduction in major cardiovascular events. In the losartan group had greater regression of LVH according to the ECG [173–175].

ARA has a comparable antihypertensive effect to ACE inhibitors with a proved high organ protective function [176]. Yusuf S. et al. showed that comparing ARA and ACE telmisartan was equivalent to ramipril in reducing BP, syncope and frequency of side effects [177].

Contraindications to ARA are the same as to ACE inhibitors except angioedema and combinations with ACE inhibitors [166].

According to the date [107], with the increase of frequency using ARA observed lengthening of the QTc interval by 8–13 % in patients with pacemaker. There are no researches on the effect of ARA in patients with AH and a pacemaker. In Mantziari L. et al. research was demonstrated that the use of the optimal dosage of the ARA was a condition of a favorable prognosis in patients with an implanted pacemaker and CRT [178].

CONCLUSION

The analysis of the literature has shown that despite the fact that cardiac pacing and CRT in the presence of possible solutions to the problem of arrhythmias and HF it does not cancel, but modifies the medical support of patients, which has been little studied.

As for the features of the medical control of AH in patients with a pacemaker and CRT, this question has not been practically studied, and the existing proposals do not go beyond existing recommendations for treatment in the general population.

The foregoing determines the exceptional relevance of studying the problem of drug control of AH in these patients.

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