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## **SIGNIFICANCE OF PULSE PRESSURE AND MANAGEMENT STRATEGY OF THE PATIENTS WITH PERMANENT CARDIAC PACING**

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Clinical importance of the pulse pressure (PP) in patients with permanent pacemaker (PM) is discussed in this review. Clinical characteristics, hemodynamic parameters, stimulation parameters, depending on the PP, and the ability to optimize medication with antihypertensive drugs are considered. Implanted pacemaker and CRT are changing the PP, which substantiates the need for additional medical supervision.

**KEY WORDS:** cardiac pacing, cardiac resynchronization therapy, pulse pressure, drug therapy

## **ЗНАЧИМІСТЬ ПУЛЬСОВОГО АРТЕРІАЛЬНОГО ТИСКУ ТА МЕДИКАМЕНТОЗНА ПІДТРИМКА ПАЦІЄНТІВ З ПОСТІЙНОЮ ЕЛЕКТРОКАРДІОСТИМУЛЯЦІЄЮ**

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В огляді обговорюється значення пульсового артеріального тиску (ПАД) у пацієнтів з імплантованим електрокардіостимулятором (ЕКС) і кардіоресинхронізуючою терапією (КРТ). Розглядаються клінічна характеристика, гемодинамічні показники, параметри стимуляції залежно від ПАД, а також можливість оптимізації медикаментозної терапії з використанням антигіпертензивних препаратів. ЕКС і КРТ змінює ПАД, що обґрунтовує необхідність додаткового медикаментозного контролю.

**КЛЮЧОВІ СЛОВА:** постійна електрокардіостимуляція, кардіоресинхронізуюча терапія, пульсовий артеріальний тиск

## **ЗНАЧИМОСТЬ ПУЛЬСОВОГО АРТЕРИАЛЬНОГО ДАВЛЕНИЯ И МЕДИКАМЕНТОЗНАЯ ПОДДЕРЖКА ПАЦИЕНТОВ С ПОСТОЯННОЙ ЭЛЕКТРОКАРДИОСТИМУЛЯЦИЕЙ**

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В обзоре обсуждается значение пульсового артериального давления (ПАД) у пациентов с имплантированным электрокардиостимулятором (ЭКС) и кардиоресинхронизирующей терапией (КРТ). Рассматриваются клиническая характеристика, гемодинамические показатели, параметры стимуляции в зависимости от ПАД, а также возможность оптимизации медикаментозной терапии с использованием антигипертензивных препаратов. ЭКС и КРТ изменяет ПАД, что обосновывает необходимость дополнительного медикаментозного контроля.

**КЛЮЧЕВЫЕ СЛОВА:** постоянная электрокардиостимуляция, кардиоресинхронизирующая терапия, пульсовое артериальное давление, медикаментозная терапия

## **INTRODUCTION**

Permanent cardiac pacing and cardiac resynchronization therapy (CRT) are the leading treatment methods of bradysystolic arrhythmias, as well as medical therapy resistant chronic heart failure (CHF) [1–2].

In 1985, the first pacemaker was implanted, and since then established as a highly effective method of bradyarrhythmias treatment. Permanent pacing reduces mortality, the number of admissions to hospitals, eliminates the symptoms of the disease and significantly improves the life quality (LQ), which is an additional goal of the treatment of patients with

bradyarrhythmias [1, 3]. The number of primary pacemaker implantations and replacements is increasing rapidly every year all over the world [4–5].

Both the first and the recent studies show that hemodynamics during pacing is associated not only with the general functions of the heart, but also with factors caused by the applied stimulation method [4].

5-letter code for a common nomenclature NBG-NASPE / BPEG stimulation that exists to describe the pacemaker programming since October 2001 was adopted. The first letter indicates the chamber paced (O – no, A – atria, the V – ventricle, D – dual chamber (A + V), S – single cardiac chamber (A or V)). The second letter indicates the chamber sensed (O – no, A – atria, V – ventricle, D – dual chambers, – single cardiac chamber). The third letter indicates how the pacemaker responds to a sensed event (O – no, T – trigger, I – suppression, D – indicates that there are dual modes of response (T + I)). The fourth letter indicates the possibility of programming (O – no, R – the pacemaker has rate modulation). The fifth letter specifies only the location or absence of multisite pacing, defined as stimulation sites in both atria, both ventricles, more than one stimulation site in any single chamber, or a combination of these (O – no, a – atria, V – ventricular, D – double function (A + V) [1].

The most common cause of pacemaker implantation is an AV block. The annual death rate from AV block before pacemakers' introduction into clinical practice reached more than 50 % [6]. Other indications for pacemaker implantation are sinus node dysfunction, chronic fascicular block, AV block associated with myocardial infarction (MI), hypersensitive carotid sinus syndrome [7], as well as for CRT in patients with CHF [1]. However, the indications for CRT are under discussion and development [8–10].

The important factor in the assessment of the clinical status of patients is the pulse pressure (PP) [11–14], which characterizes the work of the cardiovascular system, the degree of arteries walls tone and pumping function of the left ventricle (LV) [15–16]. Normal PP is considered to be 40–60 mm Hg, but not more than 60 % of the systolic blood pressure (SBP). Its value depends on the volume of blood that had accumulated during diastole and was ejected by the ventricle into the aorta in systole phase [17–18]. Another factor influencing the

PP is the resistance encountered by the blood mass in the aorta during systole. PP has an important role in the regulation, because it reflects the blood volume pulse, while SBP and diastolic blood pressure (DBP) are its derivatives [19–21].

Changing of PP disrupts the normal blood supply to organs and tissues, increases the load on the heart and blood vessels, what is associated with decreasing of patients LQ, the progression of heart failure, the advent of life-threatening arrhythmias, increased complications of cardiovascular diseases (CVD) and sudden death in the world [22–27]. 54 % of adult deaths happen due to a stroke, and 47 % are associated with coronary heart disease (CHD) [28–31].

Low PP is associated with increased heart rate (HR) and is accompanied by rapid fatigue, weakness, dizziness and disorientation. Factors leading to such changes are: HF, aortic stenosis, hypovolemia, renal failure, pathology of adrenal and thyroid gland, trauma, accompanied by heavy bleeding, hypothermia, physical exertion [22, 32].

High PP is associated with a decreased HR and is accompanied by restlessness, agitation, anxiety, fear. Such conditions can be caused by stenosis or insufficiency of the aortic valve, atherosclerosis, increased intracranial pressure, endocarditis, anemia, hyperthyroidism [23–27, 33]. Increased PP with reduced DBP and insufficient blood filling of the coronary arteries are the cause of pain in the heart.

There are evidence of both the positive DDD and VVI [34], and the negative impact of AAI and DDD pacing modes on PP [35].

Multicenter studies indicate reduced risk of future development of HF and death, as well as the improvement of the clinical picture mostly in patients with PP > 40 mm Hg in one year after implantation of CRT-D [36]. However, high PP is associated with the development of CVD and death. It is necessary to pay attention to the impact of permanent pacemaker implantation and CRT on the various degrees of PP.

PP as a response function of neurohumoral control defines a new perspective for the analysis of the processes occurring in hemodynamics. In patients with implanted pacemaker and CRT heterogeneity PP requires careful selection of drug therapy and monitoring of its effectiveness.

## **1. CONDITIONS REQUIRING PACEMAKER IMPLANTATION AND PP**

### **1.1. Acquired av block in patients with implanted pacemaker and pp**

The frequency of the occurrence of AV blocks increases with age. The prevalence of I degree AV block is 0.45–5 % [37], in patients older than 60 years it is registered in 4,5–14,4 % of all cases; over 70 years – 40 %; after MI – in 8–13 %. The incidence of II degree AV block is – 9 %, III degree AV block reaches the maximum value in people older than 70 years [38] – in 2.5–8 % of patients with MI. The incidence of iatrogenic AV block is 0.5–3 % of all cases. According to WHO statistics, 17 % of sudden deaths due to acute HF occur due to the AV block. Most often, this pathology is diagnosed during a routine inspection by a physician or cardiologist. There are number of causes of AV block: diseases of ischemic, inflammatory, neoplastic and autoimmune nature. Heart defects, radiofrequency ablation, valve replacement, as well as drug intoxication can lead to rhythm disturbances [1].

AV block is anatomically divided into supra, intra- and infra-Hisian. I degree AV block is characterized by an abnormal PR-interval lengthening of more than 0.2 seconds and is usually asymptomatic. When PR interval is more than 0.3 sec (significant I degree AV block), it can cause symptoms due to catheter ablation of the fast path of AV connection with the continued conduction on a slow track. With such a blockade due to inadequate atrium contraction in the immediate vicinity of the ventricular systole, the hemodynamic consequences and symptoms similar to retrograde (ventricle-atrium) holding (pacemaker syndrome) may appear. Clinically manifested by shortness of breath, dizziness, palpitation, pulsation, and chest pain [6, 39–41]. When significant I degree AV block occurs, the atrium contraction comes prior to them complete filling, ventricular filling is impairing, pulmonary capillary pressure is increasing, stroke volume and end-diastolic pressure are increasing, that leads to increasing of PP. However, in the work of Alonso A., et al. PP associated with height of P wave, rather than with PR interval [42]. The reduction of symptoms and improvement in cardiac function is observed on the background of pacemaker implantation patients with PR interval > 0,3 sec by reducing of AV conducting time [39, 41].

Dual-chamber pacing with a shortened AV delay improves the condition of patients with long PR interval with LV dysfunction [43], and in some cases effect on the disappearance of orthostatic hypotension and indirectly normalizes PP [44].

II degree AV block Mobitz I is characterized by a progressive lengthening of the PR interval to the blocked contraction with a narrow QRS complex [45]. II degree AV block Mobitz II is characterized by a fixed PR-interval before and after the blocked complexes, usually associated with a wide QRS complex, and the damage of conducting occurs below the branch block trunk (on the background of the anterior-wall MI). In patients with II degree AV block of the first type hemodynamics worsens due to a loss of AV synchronization even without bradycardia. As the transition to an advanced AV block in this situation is not common, the stimulation is usually not indicated. An exception is the presence of severe symptoms – dizziness or syncope, chest pain if the block is associated with myocarditis or MI accompanied by SBP increasing, which indirectly indicates an increase in PP [6]. The second type of II degree AV block patients are often symptomatic, have a worse prognosis, often the progression to AV block of III degree is observed. Thus, the second type of II degree AV block and wide QRS complex shows diffuse lesion of the conduction system, and it is an indication for pacemaker implantation irrespective by symptoms.

In case of III degree AV block (complete blockage) AV dissociation occurs (no AV-conducting), and it is a sign of a serious organic lesion. An advanced II degree and complete AV blocks causes Morgagni-Adams-Stokes attacks, which are accompanied by HR slowing to 40 or less beats per minute (bpm), increasing PP, dizziness, weakness, darkening in eyes, loss of consciousness, pain in the heart. III degree AV block is the indication for pacemaker implantation. There are studies about the positive impact of DDD and VVI pacing modes in elderly patients with complete AV block, but with a single-chamber pacing a significant dilatation in the left atrium and decreased LV diastolic function is observed, which is an indirect effect on the reduction of PP [46–47].

In patients with AV block the reduction in frequency of symptoms of arterial hypertension (AH) is explained by the BP lowering during the 1 year observation period after pacemaker

implantation in the DDD/DDDR modes [48]. A slower decline in blood pressure (BP) in severe AH stage and grade is revealed. These indirectly show the PP decrease in patients with AV block and with DDD/DDDR pacing modes.

The survey [49] studied the influence of percent stimulation (< 10 % – group A, > 40 % – group B) on the structure and function of the heart in patients with AV block with a dual-chamber pacemaker. There are enlargements of atrium and LV and decreased ejection fraction (EF) in group B in comparison with the group A. There is indirect evidence of the growth of PP in patients with rhythm disturbances with increasing percentage of stimulation, which adversely affects the outcome of CVD.

In the study [50] in patients with AV block with VVI pacing mode during daily monitoring of BP an increase in PP by reducing ventricular pacing rate during the night is observed. The average level of PP is fixed at a constant frequency of ventricular stimulation during the day, but it is not a physiological decrease in BP during sleep, it is associated with an increased rate of target organ damage.

Presented publication of the PP changes after pacemaker implantation in patients with AV block are singular, and do not completely reflect the problem.

### **1.2. Bifascicular and trifascicular block in patients with implanted pacemaker and pp**

The right bundle branch block (RBBB) can occur in healthy people, in anterior-wall MI and pulmonary embolism. The left leg bundle branch block (LBBB) is usually associated with the structural heart disease (CHD, CHF). The RBBB and LBBB predisposing factors include: atria septal defect, stenosis of the pulmonary artery, chronic obstructive pulmonary disease, aortic stenosis with calcification, cardiomyopathy, myocarditis, hyperkalemia, progressive muscular dystrophy, an overdose of drugs (quinidine, procainamide, strofantin), surgery and tumors of the heart, Lenegre Lev disease [51–52].

Bifascicular block is determined in electrocardiogram (ECG) as conduction disturbances below the AV node in two branches of RBBB or LBBB is determined. Trifascicular and alternating block are defined as a block of all three branches, either consecutively or at different times. Patients with such ECG changes and symptomatic advanced AV block have a high mortality rate

and a significant incidence of sudden death [53–58].

Bundle branch blocks are usually asymptomatic because they do not cause changes in the HR, however patients with bifascicular block can have syncope [51, 59], due to decreased LVEF and increased end-diastolic pressure [60–61]. Increased SBP in patients with bifascicular and trifascicular block is observed [35]. These data indirectly indicates an increase of PP among patients in this group.

Electrophysiology study (EPS) can be useful in therapy assessment and selection for induced ventricular arrhythmias, which are often present in patients with bifascicular and trifascicular blocks, [1]. Meanwhile an increased risk of sudden death irrespective of the results of EPS is associated with syncope in patients with permanent or transient III degree AV block. Permanent pacing is indicated at bifascicular or trifascicular blocks if syncope of unclear genesis is present or used therapy may cause AV block, especially if the loss of consciousness are caused by transient III degree AV block [34]. Selecting of the pacing mode is performed the same way as in the AV block. Accordingly, the change of PP and its therapy at the given group are similar to the parameters in patients with an implanted pacemaker due to AV block.

Reduced SBP < 110 mm Hg correlates with a high risk of death and worsening HF in patients with an implanted pacemaker during the LBBB and moderate HF. Indirectly, the data indicate a decrease of PP in patients with LBBB and moderate HF. CRT reduces the risk of complications and increases the PP [62].

In the study [35] the daily monitoring of BP evaluated a decrease of PP in patients with bifascicular or trifascicular blocks, that is most by pronounced in the DDDR mode in late period after pacemaker implantation. However, there is an increasing of the PP at dual chamber pacing in DDD mode, in comparison with a single-chamber [34], which adversely influences the cardiovascular system function and an additional drug support is requires.

### **1.3. Sick sinus syndrome (sss) in patients with implanted pacemaker and pp**

The dysfunction of sinoatrial (SA) node disturbs the frequency of atria contractions, what causes pathological bradycardia, asystolic pause and increases PP [63]. The incidence of the SSS is less than 0.2 % [64]. There are

internal and external factors that can cause SA node dysfunction: CHD or MI, AH, systemic diseases of connective tissue, endocrine disorders, neuromuscular disease, surgical injuries [64–65].

Paroxysmal tachycardia on the background of SSS can occur in some patients [66]. Therefore, patients experience a permanent emotional stress in addition to disturbances of hemodynamics during the paroxysms. This leads to the decreasing of LQ and manifests by disability, faintness, fatigue, circulation insufficiency events, memory impairment [67]. 17-year study [68] that involved 213 patients with SSS, shows a high risk of sudden death, HF, stroke, atrial fibrillation (AF) and requires a permanent pacemaker implantation. Increasing of the BP is also associated with the SSS, which indirectly influences on increase of the PP in the current pathology.

There are indications for the pacemaker implantation: SSS with documented symptomatic bradycardia or pauses, clinically manifested by chronotropic incompetence; symptomatic sinus bradycardia as a result of long-term drug therapy, which cannot be discontinued or replaced with another treatment; syncope of the unknown origin, when major deviations from the normal function of the SN identified or provoked by the EPS [1]. AV stimulation, combined with pacemaker settings that minimize ventricular pacing is the optimal strategy for the treatment of SSS [1, 69]. It improves LQ, reduces cardiovascular and total mortality and incidence of AF [70], reduces thromboembolic complications and pacemaker syndrome events which associated with loss of AV synchrony and manifests by weakness, dizziness, syncope, followed by decreasing of the myocardium contractile function [71].

We found only one study [72], where in patients with SSS the increase of cardiac productivity is observed on a background of atrium pacing, which leads to increase of cardiac index up 30%, stroke volume by 15% and decrease of preload. However, there is an increase of PP ( $59,2 \pm 2,3$  mm Hg) Despite the improvement in hemodynamics. There is a decrease of cardiac productivity on the background of ventricular pacing, thereby there is a decrease of cardiac index and stroke volume by 15–20 %, increase of preload and decrease of PP ( $54,3 \pm 2,2$  mm Hg).

#### **1.4. Carotid sinus syndrome (css) and neurocardiogenic syncope in patients with implanted pacemaker and pp**

CSS is manifested by syncope or presyncope as a response to carotid sinus stimulation due to its high sensitivity [73]. The data [74] indicate that the syncope is common in all age groups with the peaks in adolescence and elderly. The recurrence rate of syncope increases linearly from 0.3 % during 30 days to 22 % within two years of observation. The mortality rate for one year varies between 5.7 and 15.5 %. Most of syncopes of unclear genesis are caused by a CSS in elderly patients. Passive orthostatic test (head-up tilt-table testing) is used for the diagnostics of neurocardiogenic syncope [75–76]. Before the test all cardio- and vasoactive drugs should be canceled. Duration of the test is 45 minutes or until syncope develops. Neurocardiogenic syncope is classified by ECG data in the three leads and by BP data [77–78]:

- mixed type: duration  $\leq 10$  seconds, HR  $\leq 40$  bpm, the absence of asystole  $> 3$  sec, lowering of BP precedes the HR reduction;
- cardioinhibitory type: duration  $> 10$  seconds, HR  $> 40$  bpm, the absence of asystole  $> 3$  sec, lowering of BP precedes the HR reduction;
- cardioinhibitory type with asystole: the lack of asystole  $> 3$  seconds, hypotension (decreasing of SBP to 80 mm Hg) with decreasing in HR at the same time;
- vasodepressor type: HR  $\geq 10$  % from baseline when syncope is present, a significant decrease of the SBP.

The significant decrease of SBP and slight decrease of DBP are indirectly associated with reduction of the PP in patients with CSS [75, 79].

The indications for pacemaker implantation are recurrent syncope caused by carotid sinus stimulation in patients who needs a minimal pressure on the area of the carotid sinus to cause episodes of ventricular asystole  $> 6$  sec duration in the absence of drugs depressing SN function or slowing AV conduct.

The study [80], which includes 138 elderly patients with the CSS, history of syncope and positive tilt-table testing in 67.4 % of cases showed that pacemaker implantation completely suppresses the symptoms in 83.3 % of cases. However symptoms remain unchanged in 10.9 % of the mixed CSS that is associated with preservation of vasodepressor

component. There is indirect evidence that the pacemaker implantation did not normalize PP in patients with vasodepressor type of CSS in comparison with cardioinhibitory type.

### **1.5. Hypertrophic cardiomyopathy (hcm) and neurocardiogenic syncope in patients with implanted pacemaker and pp**

HCM is a genetic CVD of the myocardium, characterized by local ventricular hypertrophy, diastolic dysfunction and the development of arrhythmias [81]. The incidence of HCM is 1 in 500 people worldwide [82–84]. Factors that increase the sudden death in these patients, include: heredity, the presence of syncope, severe LV hypertrophy or obstruction of the LV outflow tract on echocardiography, abnormal BP response to exercise [81].

The study [85] presents a clinical case of a patient with apical HCM, CAD and AH. His PP is 56 mm Hg and HR is 50 bpm during the rest. During the exercise test PP decreases to 32 mm Hg and HR increases to 162 bpm. Multicenter study [86] indicates that the decreasing of the SBP up to 10 mm Hg and indirect decreasing of the PP during physical exertion is an independent factor for the development of CVD and increased mortality.

Clinically HCM is manifested by shortness of breath, weakness, chest pain, syncope, arrhythmias (tachycardia, bradyarrhythmia, AF, front and LBBB).

Implantation of the defibrillator and dual chambers synchronized AV-stimulation are invasive methods of HCM treatment in patients with high risk of sudden death [1]. Pacemaker reduces the frequency of myectomy application, alcohol ablation, and reduces the risk of sudden death [87–89]. Dual-chamber pacing mode with a short AV delay improves hemodynamics when outflow tract obstruction is present by restoring the sequence of LV excitation, which provides an increase in the diameter and volume of outflow tract and reduction of LV obstruction, increase of SAP and indirectly increases PP.

In end-stage HCM for relieving HF symptoms CRT is recommended [1]. LV and left atria reverse remodeling are present in this group of patients [90] that improves hemodynamic and indirectly increases the PP.

Schinkel A.F. et al. [91] studied 2190 patients with HCM, syncope (41 %), reduced PP during exercise (25%), LV hypertrophy (20 %) and unstable ventricular tachycardia (46 %).

One year after the implantation of CRT the cardiac mortality is reduced to 0.6 % in this group of patients.

### **1.6. Chf in patients with implanted pacemaker and pp**

The prevalence of CHF is 1–2 % in the population and it increases to 10 % in elderly patients [92]. Mortality is 20 % among those who is under 75 years old and 40 % – over 75 years [1]. Currently, HF is classified according to the LVEF: systolic HF with reduced EF (< 45–50 %) and diastolic HF with preserved EF. CAD and MI are associated with systolic HF, and AH and diabetes – with diastolic HF [93–95]. CHF characterized by a decrease in LQ, social and psychological consequences. Clinically it is characterized by shortness of breath, fatigue and reduced physical activity. Tachycardia, tachypnea, decrease of the EF, low SBP and PP indicates a poor prognosis and advanced stage of the CHF [94, 96]. Biton Y. et al. show that the increase of the PP  $\geq$  75 mm Hg in response to exercise has a more favorable outcomes for systolic HF and the PP < 75 mm Hg increases the risk of death in this case [62].

There are evidence of low PP association with high risk of cardiovascular complications and increased mortality in patients with II-IV functional classes of HF, after myocardial MI [62, 97].

In a study [36] it is demonstrated that low PP is associated with a worse outcome in hospitalized patients with systolic HF, however when PP > 40 mm Hg the opposite LV remodeling occurs by reducing of LV end-systolic volume.

There are indications for CRT: III-IV functional class (FC) of HF in patients with sinus rhythm, the QRS duration  $\geq$  120 ms and EF  $\leq$  35 %; III-IV FC of HF with the duration of the QRS  $\geq$  150 ms and EF  $\leq$  35 %; II FC of HF in sinus rhythm, the QRS duration  $\geq$  120–130 ms and EF  $\leq$  30–40 %; with QRS complex duration  $\geq$  150 ms, EF  $\leq$  30 % [1]. There are indications for CRT in patients with a permanent or long-term persistent AF: III-IV FC of CHF with QRS complex duration  $\geq$  120 ms EF  $\leq$  35 %, with the holding AV ablation in patients with a rare ventricular rate (lesser than 60 per minute at rest and lesser than 90 per min under a load).

In the study [98] in 1177 patients with systolic HF the effect of CRT-D and pacemaker

is compared. It is noted that the CRT-D implantation, EF < 35 % and the QRS complex duration  $\leq 130$  ms are associated with a high mortality, as compared to the pacemaker.

CRT increases exercise tolerance, blood oxygen saturation, and improves LQ, reduces re-hospitalization and mortality due to HF [72, 77], helps to restore the myocardial contraction synchrony, improves the contractility of the LV and leads to the LV reverse remodeling, what increasing LVEF. It is accompanied by PP normalization [36, 62].

The study [36] observes that the positive echocardiographic response occurs when PP > 40 mm Hg for one year after implantation of CRT-D in patients with systolic HF. Also in this group, the risk of HF development and death reduces on 50 % in comparison with a low-PP group (<40 mm Hg).

There is an increase of SBP on 8.5 mm Hg in 15 patients with III-IV FC CHF with EF < 40 %, QRS complex duration  $\geq 125$  ms after using biventricular CRT in combination with right ventricular stimulation [99]. It indirectly indicates an increase of the PP in this type of stimulation.

## **2. MEDICAMENT SUPPLEMENT OF PATIENTS WITH IMPLANTED ECS AND PP**

The contemporary implantable ECS as well as CRT are high technological complex and programmed devices for arrhythmias prevention and execution of algorithms for reduction of right ventricular stimulation and ultimately, for elevation of LQ and mortality reduction in cardiovascular pathology [1].

A constant control of ECS work and of the state of CRT is required and aimed to reveal some diagnostic and corrective mistakes in their work with the following optimization of the program for achievement of the best clinical effect and prolongation of devices' service terms as well as for resolution of the problem of management [2, 100]. The first programming of the device is carried out directly during the operation and then on the following 3<sup>rd</sup> and 7<sup>th</sup> days. In 6–12 weeks after implantation a chronic threshold of stimulation is formed. The thresholds of stimulation should be checked in this period and if it is necessary. To be regulated. On the 6<sup>th</sup> and 12<sup>th</sup> months after operation the correction of ECS work is controlled. Again and in the future if there are no complaints of the patient the latter is

observed once a year. An important task is also an evaluation of the battery work and when its exhaustion is revealed the battery should be replaced [101].

ECS and CRT don't always decrease a frequency of recurrent hospitalizations and fatal outcomes [102]. In this case an additional medicament supplement is not abolished. A usage of some groups of medications and decrease of PP in a different degree influence on the reduction of the risk of cardiovascular complications [103]. Some of the drugs, such as beta-adrenoblockers (BAB), calcium channel blockers (CCB), chinidine, aimaline, isuprel, isadrine are capable to increase of ECS threshold and on the contrary, such agents as prednisolone, norepinephrine, and ephedrine are able to decrease of ECS threshold [104–106].

It should be noted that the action of the drugs influenced on the variability of PP in patients with implanted ECS or performed CRT is not enough elucidated in the contemporary literature.

### **2.1. Diuretics in patients with implanted ecs and pp**

Although in patients with implanted ECS diuretics don't change PP, but some agents of this group of drugs prescribed to hypertensive patients can decrease it. So, in patients with isolated systolic AH indapamide decreases risk of cardiovascular complications due to reduction of PP < 60 mm Hg [107].

The ASPIRANT study [108] demonstrated that spironolactone was less effective in reduction of PP in patients with AH and initial DBP over 97 mm Hg. In patients with resistant AH the contribution of spironolactone (25–50 mg daily) to reduction of PP realizes in 12 weeks of therapy due to decrease in SBP be 8.7 mm Hg (the PATHWAY-2 study) [109].

By analogy, a loop diuretic furosemide (40–60 mg daily) in persons with AH compared to placebo in 8.8 weeks of treatment can decrease PP due to more marked reduction of SBP (by 8 mm Hg) then of DBP (by 4 mm Hg) [110].

High doses of furosemide (over 80 mg daily) in patients aged older 60 years with CHF of III-IV FC, LVEF  $\leq 35$  %, QRS duration  $\geq 120$  ms and LBBB or RBBB are shown to increase a risk of cardiovascular mortality probably due to PP growth. So, before CRT and high daily doses of furosemide an average PP was 45 mm Hg and then in a year after CRT and furosemide therapy there was a decrease in PP

to 39.6 mm Hg but two years later the further more marked growth of PP to 51.8 mm Hg was observed [111].

The MADIT-CRT study has shown a negative effect of diuretics on the course of CHF in patients with CRT developed in an increase of frequency of hospitalization and complications. However torasemide administration could improve a clinical picture in such patients [112].

## **2.2. Bab in patients with implanted ecs and pp**

The influence of nebivolol in patients aged older 70 years with CHF was studied depending on initial BP after CRT. Prescription of nebivolol 2.5–5–10 mg daily compared with placebo was discovered to decrease PP by 1.5 mm Hg (PP was 56.4 mm Hg in the group of treatment vs 57.9 mm Hg in placebo group). However even such insignificant PP reduction in patients with CHF after CRT diminishes development of cardiovascular complications and mortality [113].

Combination of BAB with angiotensin converting enzyme (ACE) inhibitors in patients with CHF and hypertensive CSS positively influenced on the further clinical outcome [114–115], the best outcome after CRT is observed at high doses of antihypertensive agents [116]. In patients with dual chambered ECS carvedilol 6.25 mg daily promotes a reduction of PP be 10 mm Hg due to positive influence on SBP [105].

In 18 % of patients with SSS a usage of BAB after implantation of dual chambered ECS is associated with development of the 2<sup>nd</sup> and 3<sup>rd</sup> degree AV block [117].

BAB is used in the treatment of ECS and CRT-induced arrhythmias of supraventricular and ventricular origin. Prescription of BAB to the patients with CHF after implantation of ECS or executed CRT in decreased a risk of ECS' complications [112, 118–119]. Alongside with a prolongation of QRS complex' duration a frequency of BAB prescription was found out to be grown [120].

In patients without arrhythmias induced by ECS and CRT, BAB is used in small daily doses due to a growth of frequency of unfavorable outcomes and hospitalizations [121].

## **2.3. Ccb in patients with implanted ecs and pp**

Amlodipine as one of the hypotensive agents can be used for reduction of PP in patients with

implanted ECS. It has been noted a reliable decrease in PP by 5.1 mm Hg without change of HR in such patients already in 8 weeks of treatment with amlodipine 10 mg daily [122].

A tendency to elevation of the threshold of ECS without an influence on with verapamil 240 mg daily in 2 months of treatment in patients with supraventricular tachyarrhythmia or AF and implanted DDDR ECS HR is discovered [123].

Higher velocity of coronary flow was revealed in treatment with verapamil compared with its withdrawal in patients with HCM. The endothelium depended vasodilatation is known to be impaired in such patients and therapy with verapamil promotes a restoration of vasodilatation response in the conditions of stress associated with ECS [124].

## **2.4. The inhibitors of ace, antagonists of angiotensine ii receptors (aar ii) in patients with implanted ecs and pp**

Administration of ACE inhibitors or AAR II in patients with CHF in CRT leads to long term favorable outcomes. These groups of agents improve prognosis in CRT in cases of their usage in optimal daily doses [125].

Lisinopril 2.5 mg daily combined with BAB, diuretic, acetylsalicylic acid and digoxin is reported to improve a total state of patients with performed CRT due to CHF and constant form of AF [105]. Therapy with lisinopril is occurred to reduce PP resulted in SBP decrease by 10 mm Hg after 14 months of treatment.

Right ventricular ECS can evoke a ventricular dyssynchrony, aggravate cardiac output and increase a PP [49]. In patients with full AV block and dual chambered ECS a usage of ACE inhibitors decrease a frequency of hospitalizations and cardiovascular complications.

## **CONCLUSION**

PP is an independent predisposing and prognostic factor for cardiovascular complications and mortality, and therefore is being intensively studied.

The implantation of pacemaker and CRT, solves the problem of bradysystolic arrhythmias and HF, and leads to regular changes in PP among the other hemodynamic parameters. The PP role and abilities of its optimization, including due to medical management of patients, is still not studied appropriately.

## REFERENCES

1. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association / [M. Brignole, A. Auricchio, G. Baron-Esquivias et al.]. // *Eur Heart J.* – 2013. – № 34. – p. 2281–329.
2. Rapsang A. Pacemakers and implantable cardioverter defibrillators--general and anesthetic considerations / A. Rapsang, P. Bhattacharyya. // *Braz J Anesthesiol.* – 2014. – № 64. – p. 205–14.
3. TUGENDHAT: a pilot randomized study on effects of biventricular pacing in patients with bradycardia pacing indication and normal systolic function on heart failure, atrial fibrillation and quality of life (results of 12 month follow-up) / [M. Taborsky, D. Rihova, T. Mraz et al.]. // *Bratisl Lek Listy.* – 2013. – № 114. – p. 323–9.
4. Reverse ventricular remodeling and long-term survival in patients undergoing cardiac resynchronization with surgically versus percutaneously placed left ventricular pacing leads / [J. Rickard, D.R. Johnston, J. Price et al.]. // *Heart Rhythm.* – 2015. – № 12. – p. 517–23.
5. Trends in permanent pacemaker implantation in the United States from 1993 to 2009: increasing complexity of patients and procedures / [A. Greenspon, J. Patel, E. Lau et al.]. // *J Am Coll Cardiol.* – 2012. – № 60. – p. 1540–5.
6. 2015 HRS/EHRA/APHS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing / [B. F. Wilkoff, L. Fauchier, M. K. Stiles et al.]. // *Arrhythmia.* – 2016. – № 32. – p. 1–28.
7. Kumar P. Device Therapies: New Indications and Future Directions / P. Kumar, J. D. Schwartz. // *Current Cardiology Reviews.* – 2015. – № 11. – p. 33–41.
8. Yu C. M. Cardiac resynchronization therapy: state of the art 2013 / C. M. Yu, D. L. Hayes. // *European Heart Journal.* – 2013. – № 34. – p. 1396–403.
9. Brabham W.W. The role of AV and VV optimization for CRT / W. W. Brabham, M. R. Gold // *Journal of Arrhythmia.* – 2013. – № 29. – p. 153–161.
10. Lewis G. F. Developments in Cardiac Resynchronisation Therapy / G. F. Lewis, M. R. Gold // *Arrhythmia & Electrophysiology Review.* - 2015. - № 4. – p. 122-28.
11. Central pulse pressure but not brachial blood pressure is the predominant factor affecting aortic arterial stiffness / [W. K. Xiao, P. Ye, Y. Y. BaiY et al.]. // *Nan Fang Yi Ke Da Xue Xue Bao.* – 2015. – № 35. – p. 34–9.
12. Pulse pressure amplification in relation to body fatness / [A. Wykretowicz, A. Rutkowska, T. Krauze et al.]. // *British Journal of Clinical Pharmacology.* – 2012. – № 73. – p. 546–552.
13. Beat-to-beat, ambulatory hour-to-hour, and home day-to-day variabilities in blood pressure, pulse pressure, and heart rate in comparison with each other and with target-organ damage / J. K. Johansson, P. J. Puukka, R. Virtanen, A. M. Jula. // *Blood Press Monit.* – 2015. – №20. – p. 113–20.
14. Outcome-driven thresholds for ambulatory pulse pressure in 9938 participants recruited from 11 populations / [Y. M. Gu, L. Thijs, Y. Li et al.]. // *Hypertension.* – 2014. – № 63. – p. 229–37.
15. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension / [G. Mancia, R. Fagard, K. Narkiewicz et al.]. // *Journal of Hypertension.* – 2013. – № 31. – p. 1925–38.
16. Clinical Practice Guidelines for the Management of Hypertension in the Community A Statement by the American Society of Hypertension and the International Society of Hypertension / [M. A. Weber, E. L. Schiffrin, W. B. White et al.]. // *J Clin Hypertens (Greenwich).* – 2014. – № 16. – p. 14–26.
17. Zhestkost' sosudistoy stenki u patsiyentov s arterial'noy gipertoniyei / [O. D. Ostroumova, A. I. Kochetkov, I. I. Kopchenov et al.]. // *Sistemnyye gipertenzii.* – 2015. – № 2. – s. 43–48.
18. Drapkina O. M. Zhestkost' sosudistoy stenki u patsiyentov s arterial'noy gipertoniyei / O. M. Drapkina, R. N. Shepel', V. T. Ivashkin. // *Klinicheskaya meditsina Kazakhstana.* – 2015. – № 2. – s. 6–10.
19. Visit-to-visit variability in systolic blood pressure: correlated with the changes of arterial stiffness and myocardial perfusion in on-treated hypertensive patients / [H. Song, F. Wei, Z. Liu et al.]. // *Clin Exp Hypertens.* – 2015. – № 37. – p. 63–69.
20. Doppler indexes of left ventricular systolic and diastolic flow and central pulse pressure in relation to renal resistive index / [T. Kuznetsova, N. Cauwenberghs, J. Knez et al.]. // *Am J Hypertens.* – 2015. – № 28. – p. 535–45.

21. Lyzohub V. H. Age-related features of neurohumoral effects of dopamine activity on the cardiovascular system in elderly people / V. H. Lyzohub, O. V. Dolynna, T. V. Zaval's'ka. // *Lik Sprava*. – 2012. – № 8. – p. 13–21.
22. International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators. Significance of white-coat hypertension in older persons with isolated systolic hypertension: a meta-analysis using the International Database on Amb / [S. S. Franklin, L. Thijs, T. W. Hansen et al.]. // *Hypertension*. – 2012. – № 59. – p. 564–71.
23. Relative effectiveness of clinic and home blood pressure monitoring compared with ambulatory blood pressure monitoring in diagnosis of hypertension: systematic review [Electronic resource] / [J. Hodgkinson, J. Mant, U. Martin et al.] // *BMJ*. – 2011. – Access to resource: <http://dx.doi.org/10.1136/bmj.d3621>.
24. Effects of olmesartan on arterial stiffness in rats with chronic renal failure / Y. C. Chuang, M. S. Wu, Y. K. Su, K. M. Fang. // *Cardiovasc. Diabetol.* – 2012. – № 13. – p. 11–66.
25. A reverse dipping pattern predicts cardiovascular mortality in a clinical cohort / [B. K. Kim, Y. M. Kim, Y. Lee et al.]. // *J Korean Med Sci*. – 2013. – № 28. – p. 1468–73.
26. Elevated Pulse Pressure is Associated with Hemolysis, Proteinuria and Chronic Kidney Disease in Sickle Cell Disease [Electronic resource] / [E. M. Novelli, M. Hildesheim, C. Rosano et al.] // *PLoS ONE*. – 2014. – Access to resource: <http://doi.org/10.1371/journal.pone.0114309>.
27. Bidani A. K. Hypertension and Chronic Kidney Disease Progression: Why the Suboptimal Outcomes? / A. K. Bidani, K. A. Griffin, M. Epstein. // *American journal of medicine*. – 2012. – № 125. – p. 1057–62.
28. Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011–2012 / T. Nwankwo, S. S. Yoon, V. Burt, Q. Gu. // *NCHS Data Brief*. – 2013. – № 133. – p. 1–8.
29. Association between Usual Sodium and Potassium Intake and Blood Pressure and Hypertension among U.S. Adults: NHANES 2005–2010 [Electronic resource] / [Z. Zhang, M. E. Cogswell, C. Gillespie et al.] // *PLoS ONE*. – 2013. – Access to resource: <http://doi.org/10.1371/journal.pone.0075289>.
30. Heart Disease and Stroke Statistics—2012 Update: A Report From the American Heart Association [Electronic resource] / [V. L. Roger, A. S. Go, D. M. Lloyd-Jones et al.] // *Circulation*. – 2012. – Access to resource: <http://doi.org/10.1161/CIR.0b013e31823ac046>.
31. Usual blood pressure, peripheral arterial disease, and vascular risk: cohort study of 4.2 million adults [Electronic resource] / [C. A. Emdin, S. G. Anderson, T. Callender et al.] // *BMJ*. – 2015. – Access to resource: <http://doi.org/10.1136/bmj.h4865>.
32. Arterial stiffness and pulse-pressure amplification in overweight/obese African-American adolescents: relation with higher systolic and pulse pressure [Electronic resource] / [G. L. Pierce, H. Zhu, K. Darracott et al.] // *Am J Hypertens*. – 2013. – Access to resource: <http://doi.org/10.1093/ajh/hps014>.
33. Aortic and Carotid Arterial Stiffness and Epigenetic Regulator Gene Expression Changes Precede Blood Pressure Rise in Stroke-Prone Dahl Salt-Sensitive Hypertensive Rats [Electronic resource] / [V. L. Herrera, J. L. Decano, N. Giordano et al.] // *PLoS ONE*. – 2014. – Access to resource: <http://doi.org/10.1371/journal.pone.0107888>.
34. Hemodynamic effect of atrioventricular and interventricular dyssynchrony in patients with biventricular pacing: Implications for the pacemaker syndrome / [R. Mollazadeh, L. Mohimi, M. Zeighami et al.]. // *J Cardiovasc Dis Res*. – 2012. – № 3. – p. 200–203.
35. Davidovich I. M. Vliyaniye razlichnykh rezhimov postoyannoy elektrokardiostimulyatsii na sutochnyy profil' arterial'nogo davleniya u lits s ishemicheskoy bolezn'yu serdtsa v sochetanii s gipertonicheskoy bolezn'yu / I. M. Davidovich, T. E. Neapolitanskaya. // *Dal'nevostochnyy meditsinskiy zhurnal*. – 2012. – № 2. – s. 14–18.
36. Comparison of low versus high (>40 mm Hg) pulse pressure to predict the benefit of cardiac resynchronization therapy for heart failure (from the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy Trial) / [S. Sherazi, I. Goldenberg, A. J. Moss et al.]. // *Am J Cardiol*. – 2014. – № 114. – p. 1053–8.
37. First-degree atrioventricular block is associated with heart failure and death in persons with stable coronary artery disease: data from the Heart and Soul Study / [R. K. Crisel, R. Farzaneh-Far, B. Na et al.]. // *European Heart Journal*. – 2011. – № 32. – p. 1875–78.
38. Heidenreich P. A. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association / P. A. Heidenreich, J. G. Trogon, O. A. Khavjou. // *Circulation*. – 2011. – № 123. – p. 933–44.
39. Laurent G. First-degree atrioventricular block and pseudopacemaker syndrome / G. Laurent, J. C. Eicher, J. E. Wolf. // *Arch Cardiovasc Dis*. – 2013. – № 106. – p. 690–3.
40. Holmqvist F. First-degree AV block—an entirely benign finding or a potentially curable cause of cardiac disease? / F. Holmqvist, J. P. Daubert. // *Ann Noninvasive Electrocardiol*. – 2013. – № 18. – p. 215–24.

41. Marked First Degree Atrioventricular Block: an extremely prolonged PR interval associated with Atrioventricular Dissociation in a young Nigerian man with Pseudo-Pacemaker Syndrome: a case report / O. Ogunlade, A. O. Akintomide, O. E. Ajayi, O. A. Eluwole. // *BMC Res Notes*. – 2014. – № 7. – p. 781.
42. Association of blood pressure and aortic distensibility with P wave indices and PR interval: the Multi-Ethnic Study of Atherosclerosis (MESA) [Electronic resource] / [A. Alonso, E. Z. Soliman, L. Y. Chen et al.] // *J Electrocardiol*. – 2013. – Access to resource: <http://doi.org/10.1016/j.jelectrocard.2013.01.009>.
43. Holmqvist F. Adverse effects of first-degree AV-block in patients with sinus node dysfunction: data from the mode selection trial / F. Holmqvist, A. S. Hellkamp, K. L. Lee. // *Pacing Clin Electrophysiol*. – 2014. – № 37. – p. 1111–9.
44. De Maria E. Disappearance of orthostatic hypotension after pacemaker implantation in a patient with a long PR interval / E. De Maria, P. L. Fontana, S. Cappelli. // *Indian Heart Journal*. – 2013. – № 65. – p. 95–99.
45. Association of longer QT interval with arterial waveform and lower pulse pressure amplification: the Nagahama Study / [Y. Tabara, Y. Takahashi, K. Kohara et al.]. // *Am J Hypertens*. – 2013. – № 26. – p. 973–80.
46. Comparison of DDD versus VVIR pacing modes in elderly patients with atrioventricular block / [B. Kılıçaslan, A. F. Vatansver, E. E. Kılıçaslan et al.]. // *Turk Kardiyol Dern Ars*. – 2012. – № 40. – p. 331–6.
47. Biventricular pacing for atrioventricular block and systolic dysfunction / [A. B. Curtis, S. J. Worley, P. B. Adamson et al.]. // *N Engl J Med*. – 2013. – № 368. – p. 1585–93.
48. Funktsional'nyy klas sertsevoyi nedostatnosti ta osnovni sertsevo-sudynni stany u patsiyentiv iz implantovanykh elektrokardiostymulyatoramy na richnomu etapi aparatnoyi i medykamentoznoyi / I. M. Kolomytseva, D. YE. Volkov, D. A. Lopyn, M. I. Yabluchans'ky. // *Aktual'ni problemy suchasnoyi medytsyny: visnyk Ukrayins'koyi medychnoyi stomatolohichnoyi akademiyi*. – 2015. – № 3. – s. 136–40.
49. Feng J. L. Long-term effect of different right ventricular apex pacing ratio on heart structure and function of patients with dual chamber pacemaker / J. L. Feng, Y. Zhang, Z. P. Li. // *Beijing Da Xue Xue Bao*. – 2014. – № 46. – p. 879–82.
50. Manhyleva T. A. Osobennosti sutochnoy dynamyky arterial'noho davlenyya u bol'nykh s arterial'noy hipertenziyey pry postoyannoy y peremennoy chastote sokrashchenyy zheludochkov serdtsa / T. A. Manhyleva. // *Sertse i sudyny*. – 2011. – № 2. – s. 76–82.
51. Prevention of syncope through permanent cardiac pacing in patients with bifascicular block and syncope of unexplained origin: the PRESS study / [M. Santini, A. Castro, F. Giada et al.]. // *Circ Arrhythm Electrophysiol*. – 2013. – № 6. – p. 101–7.
52. Hurtado-Hernández Z. Acute neurological deficit, pleural chest pain and trifascicular block: presentation of a case of atypical infectious endocarditis / Z. Hurtado-Hernández, A. Segura-Domínguez. // *Semergen*. – 2014. – № 40. – p. 47–9.
53. Bussink B. E. Right bundle branch block: prevalence, risk factors, and outcome in the general population: results from the Copenhagen City Heart Study / B. E. Bussink, A. G. Holst, L. Jespersen. // *European Heart Journal*. – 2013. – № 34. – p. 138–46.
54. Lotina A. S. Prognostic value of left bundle brunch block in patients with acute coronary syndrome / A. S. Lotina, D. V. Dupliakov, A. D. Érlikh. // *Kardiologija*. – 2013. – № 53. – p. 35–9.
55. Prevalence and long-term prognosis of patients with complete bundle branch block (right or left bundle branch) with normal left ventricular ejection fraction referred for stress echocardiography / [A. A. Supariwala, J. R. Po, S. Mohareb et al.]. // *Echocardiography*. – 2015. – № 32. – p. 483–9.
56. Relation of New Permanent Right or Left Bundle Branch Block on Short- and Long-Term Mortality in Acute Myocardial Infarction Bundle Branch Block and Myocardial Infarction / [A. Melgarejo-Moreno, J. Galcerá-Tomás, L. Consuegra-Sánchez et al.]. // *Am J Cardiol*. – 2015. – № 116. – p. 1003–9.
57. Prognostic values of bundle branch blocks for cardiovascular mortality in Japanese (24-year follow-up of NIPPON DATA80) / [Y. Nakamura, T. Okamura, T. Inohara et al.]. // *J Electrocardiol*. – 2013. – № 46. – p. 360–5.
58. Impact of left bundle branch block on heart rate and its relationship to treatment with ivabradine in chronic heart failure / [J. C. Reil, M. Robertson, I. Ford et al.]. // *Eur J Heart Fail*. – 2013. – № 15. – p. 1044–52.
59. Empiric pacemaker compared with a monitoring strategy in patients with syncope and bifascicular conduction block--rationale and design of the Syncope: Pacing or Recording in The Later Years (SPRITELY) study / [A. D. Krahn, C. A. Morillo, T. Kus et al.]. // *Europace*. – 2012. – № 14. – p. 1044–8.
60. Vyskubova Ye. V. Kompensatornyye mekhanizmy podderzhaniya kontraktil'noy funktsii levogo zheludochka u bol'nykh s polnoy blokadoy levoy nozhki puchka Gisa / Ye. V. Vyskubova, V. M. Pokrovskiy. // *Kubanskiy nauchnyy meditsinskiy vestnik*. – 2012. – № 2. – s. 44–6.

61. Low diastolic blood pressure was one of the independent predictors of ischemia-like findings of electrocardiogram in patients who underwent coronary angiography / [S. Fujishima, N. Murakami, J. Haga et al.]. // *J. Cardiol.* – 2012. – № 62. – p. 230–5.
62. Inverse Relationship of Blood Pressure to Long-Term Outcomes and Benefit of Cardiac Resynchronization Therapy in Patients With Mild Heart Failure: A Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy Long-Term Follow-up / [Y. Biton, A. J. Moss, V. Kutiyafa et al.]. // *Circ Heart Fail.* – 2015. – № 8. – p. 921–6.
63. Choudhury M. Choudhury M. Biology of the Sinus Node and its Disease / M. Choudhury, M. R. Boyett, G. M. Morris. // *Arrhythmia & Electrophysiology Review.* – 2015. – № 4. – p. 28–34.
64. Incidence of and risk factors for sick sinus syndrome in the general population / [P. N. Jensen, N. N. Gronroos, L. Y. Chen et al.]. // *J Am Coll Cardiol.* – 2014. – № 64. – p. 531–8.
65. Ewy G. A. Sick sinus syndrome: synopsis / G. A. Ewy. // *J Am Coll Cardiol.* – 2014. – № 64. – p. 539–40.
66. Right versus left atrial pacing in patients with sick sinus syndrome and paroxysmal atrial fibrillation (Riverleft study): study protocol for randomized controlled trial [Electronic resource] / [T. T. Ramdjan, L. J. van der Does, P. Knops et al.] // *Trials.* – 2014. – Access to resource: <http://doi.org/10.1186/1745-6215-15-445>.
67. A comparison of single-lead atrial pacing with dual-chamber pacing in sick sinus syndrome / [J. C. Nielsen, P. E. Thomsen, S. Hojberg et al.]. // *European Heart Journal.* – 2011. – № 32. – p. 686–96.
68. Association of sick sinus syndrome with incident cardiovascular disease and mortality: the Atherosclerosis Risk in Communities study and Cardiovascular Health Study [Electronic resource] / [A. Alonso, P. N. Jensen, F. L. Lopez et al.] // *PLoS One.* – 2014. – Access to resource: <http://doi.org/10.1371/journal.pone.0109662>.
69. Health economic evaluation of single-lead atrial pacing vs. dual-chamber pacing in sick sinus syndrome / [L. Oddershede, S. Riahi, J. C. Nielsen et al.]. // *Europace.* – 2014. – № 16. – p. 866–72.
70. AAIR or DDDR pacing for sick sinus syndrome: the physiologic conundrum / L. Padeletti, G. Pontecorvoli, A. Michelucci, H. G. Mond. // *Europace.* – 2012. – № 14. – p. 781–2.
71. HRS/ACCF expert consensus statement on pacemaker device and mode selection. Developed in partnership between the Heart Rhythm Society (HRS) and the American College of Cardiology Foundation (ACCF) and in collaboration with the Society of Thoracic Surgeons / [A. M. Gillis, A. M. Russo, K. A. Ellenbogen et al.]. // *Heart Rhythm.* – 2012. – № 9. – p. 1344–65.
72. Kolpakov P. Ye. Uchashchayushchaya elektrokardiostimulyatsiya serdtsa u kardiokhirurgicheskikh bol'nykh / P. Ye. Kolpakov, A. A. Yeremenko. // *Vestnik aritmologii.* – 2003. – № 31. – s. 5–9.
73. Gauer R. L. Evaluation of syncope / R. L. Gauer. // *Am Fam Physician.* – 2011. – № 84. – p. 640–50.
74. Syncope recurrence and mortality: a systematic review / [M. Solbiati, G. Casazza, F. Dipaola et al.]. // *Europace.* – 2015. – № 17. – p. 300–8.
75. At the heart of the arterial baroreflex: a physiological basis for a new classification of carotid sinus hypersensitivity / [W. Wieling, C. T. Krediet, D. Solari et al.]. // *J Intern Med.* – 2013. – № 273. – p. 345–58.
76. Head turning-induced hypotension in elderly people [Electronic resource] / [Y. Schoon, M. G. Olde Rikkert, S. Rongen et al.] // *PLoS One.* – 2013. – Access to resource: <http://doi.org/10.1371/journal.pone.0072837>.
77. Seifer C. Carotid sinus syndrome / C. Seifer. // *Cardiol Clin.* – 2013. – № 31. – p. 111–21.
78. Syncope : epidemiology, definition, classification, pathophysiology and prognosis / [C. H. Heeger, A. Rillig, F. Ouyang et al.]. // *Herz.* – 2014. – № 39. – p. 423–8.
79. Krediet C. T. Dissection of carotid sinus hypersensitivity: the timing of vagal and vasodepressor effects and the effect of body position / C. T. Krediet, D. L. Jardine, W. Wieling. // *Clin Sci (Lond).* – 2011. – № 121. – p. 389–96.
80. The role of pacemaker in hypersensitive carotid sinus syndrome / [R. Lopes, A. Gonçalves, J. Campos et al.]. // *Europace.* – 2011. – № 13. – p. 572–5.
81. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC) / [P. M. Elliott, A. Anastakis, M. A. Borger et al.]. // *Eur Heart J.* – 2014. – № 35. – p. 2733–79.
82. Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 3: Hypertrophic Cardiomyopathy, Arrhythmogenic Right Ventricular Cardiomyopathy and Other Cardiomyopathies, and Myocarditis: A Scientific Statement of the American Heart Association / [B. J. Maron, J. E. Udelson, R. O. Bonow et al.]. // *J Am Coll Cardiol.* – 2015. – № 66. – p. 2362–71.
83. New perspectives on the prevalence of hypertrophic cardiomyopathy / C. Semsarian, J. Ingles, M. S. Maron, B. J. Maron. // *J Am Coll Cardiol.* – 2015. – № 65. – p. 1249–54.

84. A validation study of the 2003 American College of Cardiology/European Society of Cardiology and 2011 American College of Cardiology Foundation/American Heart Association risk stratification and treatment algorithms for sudden cardiac death in patients with [Electronic resource] / [C. O'Mahony, M. Tome-Esteban, P. D. Lambiase et al.] // Heart. – 2013. – Access to resource: <http://doi.org/10.1136/heartjnl-2012-303271>.
85. Apical hypertrophic cardiomyopathy associated with chronic hypertension: diagnostic and management implications / C. Macatangay, R. Marfatia, E. Kaloudis, E. Avelar. // Conn Med. – 2012. – № 76. – p. 147–50.
86. Low exercise blood pressure and risk of cardiovascular events and all-cause mortality: systematic review and meta-analysis / P. A. Barlow, M. G. Schultz, C. M. Shing, J. E. Sharman. // Atherosclerosis. – 2014. – № 237. – p. 13–22.
87. Initial experience of a cohort of patients with hypertrophic cardiomyopathy undergoing biventricular pacing / [C. A. Rinaldi, S. Kirubakaran, C. A. Bucknall et al.]. // Indian Pacing Electrophysiol J. – 2011. – № 11. – p. 5–14.
88. Maron B. J. Historical perspectives on the implantable cardioverter-defibrillator and prevention of sudden death in hypertrophic cardiomyopathy / B. J. Maron. // Card Electrophysiol Clin. – 2015. – № 7. – p. 165–71.
89. Very late effects of dual chamber pacing therapy for obstructive hypertrophic cardiomyopathy / [A. Lucon, L. Palud, D. Pavin et al.]. // Arch Cardiovasc Dis. – 2013. – № 106. – p. 373–81.
90. Effect of cardiac resynchronization on gradient reduction in patients with obstructive hypertrophic cardiomyopathy: preliminary study / [R. Lenarczyk, A. Woźniak, O. Kowalski et al.]. // Pacing Clin Electrophysiol. – 2011. – № 34. – p. 1544–52.
91. Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis / [A. F. Schinkel, P. A. Vriesendorp, E. J. Sijbrands et al.]. // Circ Heart Fail. – 2012. – № 5. – p. 552–9.
92. Hradec J. Chronic heart failure / J. Hradec. // Cas Lek Cesk. – 2015. – № 154. – p. 260–8.
93. Berezin A. Ye. Sistolicheskaya i diastolicheskaya serdechnaya nedostatochnost': dve storony odnogo protsessu? Obzor literatury / A. Ye. Berezin. // Ukraïn's'kiy mediclniy chasopis. – 2014. – № 3. – s. 91–96.
94. Gupta A. Guidelines in review: 2013 ACCF/AHA Guideline for the Management of Heart Failure [Electronic resource] / A. Gupta, G. Ghimire, F. G. Hage // J Nucl Cardiol. – 2014. – Access to resource: <http://doi.org/10.1007/s12350-013-9832-x>.
95. Alsamara M. Heart failure with preserved ejection fraction. Expert Rev / M. Alsamara, R. Alharethi. // Cardiovasc. Ther. – 2014. – № 12. – p. 743–50.
96. Differing prognostic value of pulse pressure in patients with heart failure with reduced or preserved ejection fraction: results from the MAGGIC individual patient meta-analysis / [C. E. Jackson, D. Castagno, A. P. Maggioni et al.]. // Eur Heart J. – 2015. – № 36. – p. 1106–14.
97. A low pulse pressure predicts mortality in subjects with heart failure after an acute myocardial infarction: a post-hoc analysis of the CAPRICORN study / [C. J. Petrie, A. A. Voors, M. Robertson et al.]. // Clin Res Cardiol. – 2012. – № 101. – p. 29–35.
98. Cardiac-resynchronization therapy in patients with systolic heart failure and QRS interval  $\leq 130$  ms: insights from a meta-analysis / [R. M. Shah, D. Patel, J. Molnar et al.]. // Europace. – 2015. – № 17. – p. 267–73.
99. Extrasystolic stimulation with bi-ventricular pacing: an acute haemodynamic evaluation / [B. Stegemann, A. Mihalcz, C. Földesi et al.]. // Europace. – 2011. – № 13. – p. 1591–6.
100. Zhang Q. Incidence, definition, diagnosis, and management of the cardiac resynchronization therapy nonresponder / Q. Zhang, Y. Zhou, C. M. Yu. // Curr Opin Cardiol. – 2015. – № 30. – p. 40–9.
101. Practical questions around individual with a pacemaker or an implantable cardioverter defibrillator / [C. Manaouil, S. Fantoni, D. Montpellier et al.]. // Presse Med. – 2012. – № 41. – p. 736–44.
102. Patients with pacemaker or implantable cardioverter-defibrillator / P. M. Schulman, M. A. Rozner, V. Sera, E. C. Stecker. // Med Clin North Am. – 2013. – № 97. – p. 1051–75.
103. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis / [D. Etehad, C. A. Emdin, A. Kiran et al.]. // Lancet. – 2016. – № 387. – p. 957–67.
104. Antiplatelet agents increase hemorrhagic risk in patients undergoing a cardiac pacemaker or ICD implantation / W. Amara, I. Ben Youssef, F. Monsel, J. Sergent. // Ann Cardiol Angeiol (Paris). – 2011. – № 60. – p. 267–71.
105. Shanina I. V. Experience of management of the patient with the resynchronization biventricular pacing without destruction of atrio-ventricular node suffering from chronic heart failure and permanent atrial fibrillation / I. V. Shanina, D. E. Volkov, D. A. Lopin. // Journal of V. N. Karazin` KhNU. – 2013. – № 25. – p. 72–76.

106. Diagnosis and choice of the management strategy in patients with cardiac resynchronization therapy in case of chronic heart failure with multimorbidity / [D. G. Drokin, I. V. Shanina, D. E. Volkov et al.]. // *Journal of V. N. Karazin` KhNU.* – 2013. – № 26. – p. 61–65.
107. Kisliak O. A. Pulse wave velocity and pulse pressure in patients with arterial hypertension / O. A. Kisliak, A. V. Starodubova. // *Kardiologiya.* – 2014. – № 54. – p. 34–8.
108. The effect of spironolactone in patients with resistant arterial hypertension in relation to baseline blood pressure and secondary causes of hypertension / [J. Vaclavik, R. Sedlak, J. Jarkovsky et al.]. // *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* – 2013. – № 157. – p. 50–5.
109. Widimský J. PATHWAY-2 Study: spironolactone vs placebo, bisoprolol and doxazosin to determine optimal treatment of resistant hypertension. Spironolactone high effective in lowering blood pressure in drug resistant hypertension / J. Widimský. // *Vnitr Lek.* – 2015. – № 61. – p. 1067–71.
110. Blood pressure-lowering efficacy of loop diuretics for primary hypertension [Electronic resource] / [V. M. Musini, P. Rezapour, J. M. Wright et al.] // *Cochrane Database Syst Rev.* – 2015. – Access to resource: <http://doi.org/10.1002/14651858.CD003825.pub4>.
111. Development and Validation of Predictive Models of Cardiac Mortality and Transplantation in Resynchronization Therapy / [E. A. Rocha, F. T. Pereira, J. S. Abreu et al.]. // *Arq Bras Cardiol.* – 2015. – № 105. – p. 399–409.
112. Techeniye khronicheskoy serdechnoy nedostatochnosti i medikamentoznaya terapiya patsiyentov s implantiruyemyimi elektrokardiostimulyatorami / I. N. Kolomytseva, D. Ye. Volkov, D. A. Lopin, N. I. Yabluchanskiy. // *Ukrain'skiy terapevtichnyy zhurnal.* – 2015. – № 4. – s. 101–106.
113. Influence of systolic blood pressure on clinical outcomes in elderly heart failure patients treated with nebivolol: data from the SENIORS trial / [M. / Montero-Perez-Barquero, M. Flather, M. Roughton et al.]. // *Eur J Heart Fail.* – 2014. – № 16. – p. 1009–15.
114. Högye M. Chronic heart failure with impaired left ventricular function (systolic heart failure) / M. Högye, T. Forster. // *Orv Hetil.* – 2012. – № 153. – p. 2021–9.
115. Drugs and pacemakers for vasovagal, carotid sinus and situational syncope [Electronic resource] / [J. J. Romme, J. B. Reitsma, C. N. Black et al.] // *Cochrane Database Syst Rev.* – 2011. – Access to resource: <http://doi.org/10.1002/14651858.CD004194.pub3>.
116. Treatment with higher dosages of heart failure medication is associated with improved outcome following cardiac resynchronization therapy [Electronic resource] / [S. Schmidt, D. Hürlimann, C. T. Starck et al.] // *Eur Heart J.* – 2014. – Access to resource: <http://doi.org/10.1093/eurheartj/eh514>.
117. Development of Atrioventricular Block and Diagnostic Value of Stored Electrograms in Patients With Sick Sinus Syndrome and Implanted Pacemaker / [J. Hosoda, T. Ishikawa, S. Sumita et al.]. // *Circ J.* – 2015. – № 79. – p. 1263–8.
118. Hoppe U. C. Heart rate reduction as a therapeutic strategy: novel options / U. C. Hoppe. // *Internist (Berl).* – 2006. – № 47. – p. 1289–93.
119. Maltseva M. S. Importance of QTc interval duration in pacing parameters optimization and therapeutic management of the patients with permanent cardiac pacing / M. S. Maltseva, D. E. Volkov. // *Journal of V. N. Karazin` KhNU.* – 2014. – № 27. – p. 50–73.
120. Shanina I. V. Frequency of detached cardiac drugs prescribing in patients of different classes QRS complex duration on the permanent pacing background / I. V. Shanina, D. E. Volkov. // *Journal of V. N. Karazin` KhNU.* – 2014. – № 27. – p. 33–7.
121. Beta-blocker utilization and outcomes in patients receiving cardiac resynchronization therapy / A. Voigt, A. Shalaby, E. Adelstein, S. Saba. // *Clin Cardiol.* – 2010. – № 33. – p. 1–5.
122. Dzizinskiy A. A. Dinamika pul'sovogo davleniya na fone lecheniya amlodipinom i karvedilolom u bol'nykh arterial'noy gipertoniyei / A. A. Dzizinskiy, K. V. Protasov, O. V. Fedorishina. // *Lechashchiy vrach.* – 2008. – № 6. – s. 108–10.
123. A controlled study on the effect of verapamil on atrial tachycarrhythmias in patients with brady-tachy syndrome implanted with a DDDR pacemaker / [G. Boriani, E. Bertaglia, A. Carboni et al.]. // *Int J Cardiol.* – 2005. – № 104. – p. 73–6.
124. Verapamil improves the pacing-induced vasodilatation in symptomatic patients with hypertrophic cardiomyopathy / [P. P. Dimitrow, M. Krzanowski, J. Grodecki et al.]. // *Int J Cardiol.* – 2002. – № 83. – p. 239–47.
125. Relation of dosing of the renin-angiotensin system inhibitors after cardiac resynchronization therapy to long-term prognosis / [L. Mantziari, K. Guha, Z. Khalique et al.]. // *Am J Cardiol.* – 2012. – № 109. – p. 1619–25.