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LEADING ARTICLE

Pathophysiological aspects and therapeutic effects of permanent cardiac pacing

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Abstract. This review article presents a critical analysis of recent clinical trials dedicated to the assessment of pathophysiological mechanisms of modern pacemakers (PM) cardiohemodynamic effects. It has been shown that even the use of "physiological" cardiac pacing modes does not always lead to adequate electromechanical conjugation and maximum restoration of the heart; therefore, not all successful heart rhythm and conduction disturbances corrections with PM implantation are associated with life quality and long-term prognosis improvement. The article highlights various therapeutic effects of cardiac pacing and its pathophysiological mechanisms in various groups of patients with implantable PM. The analysis will determine the course of future clinical studies in order to improve the effectiveness of this method.

Key words: pacemaker, cardiac pacing, cardiohemodynamics, cardiac resynchronization therapy.

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Introduction

Cardiac pacing was developed over half a century ago and introduced into practice as one of the most effective methods of arrhythmias and conduction impairments treatment that significantly changed the lives of the patients [1–3]. Abound 700.000 pacemakers (PM) per year are implanted worldwide [4]. The progress in PM development contributed to the expansion of its use not only in patients with classical electrocardiographic indications, but also due to its therapeutic effects of various pacing modes [5–8].

Large randomized clinical trials confirmed that optimizing of PM's cardiohemodynamic effects improved life quality and survival of the patients [9–12]. However, despite successful attempts to improve the quality of PMs, it has not been possible to compensate electrophysiological and mechanical functions of the heart yet [13, 14]. It should be noted that PMs and cardioverter defibrillators are implanted into the right ventricle in the majority of cases as well as biventricular pacing in patients with chronic heart failure (CHF) [15– 17]. Therefore, the study of cardiohemodynamic and therapeutic effects of permanent cardiac pacing and its effect on the long-term prognosis in patients with implantable antiarrhythmic devices remains important.

Pathophysiological mechanisms of cardiohemodynamic impairments during various cardiac pacing modes.

It should be noted that cardiohemodynamic effects and long-term prognosis of permanent ventricular pacing differ significantly in different categories of patients, that is associated not only with patient-dependent factors, but also with various pathophysiological effects of right ventricular pacing [13, 18–20]. This indicates that the choice of the PM type, the stimulated chamber of the heart and the PM mode should strictly correspond to heart rhythm disturbances and functional needs of the patient [5–7, 21]. The concept of the "physiological" cardiac pacing includes not only atrioventricular (AV) synchronization and adaptation of artificial rhythm frequency to functional status of the patient, but also optimizing ventricular systolic and diastolic electromechanical functions [1, 22, 23].

The role of chronotropic incompetence of implanted pacemaker and possibilities of hemodynamic effect optimization.

Frequency-adaptive pacemakers are the solution of this problem and are widely used in single and dual chamber pacing [3, 6]. It has been shown that patients with VVIR stimulation had 20-30% higher exercise tolerance compared with patients with VVI stimulation [2, 14]. Moreover, patients with VVIR and DDI stimulation after surgery due to AV blockade did not differ by the frequency of myocardial infarction, stroke, atrial fibrillation, and heart failure [12]. This means that frequency-adaptive pacemakers have more effective hemodynamic support of physical activity compared with a dual chamber atrioventricular fixed-rate pacing even with single-chamber ventricular pacing [1, 6, 7].

Moreover, hemodynamic effectiveness of various cardiac pacing modes depends on the severity of systolic and/or diastolic ventricular dysfunction. This is essential in patients with a fixed-rate cardiac pacing and left ventricular (LV) dysfunction [10, 20, 24]. The study of chronic inotropic regulation of the contractile function of the heart optimization in patients with AAI and VVI stimulation using the frequency of electric impulses ranged from 40 to 100 imp/min with a discrete value of 5 imp/min revealed 2 types of cardiohemodynamic parameters response [25]. Type I included significant increase in stroke and cardiac indices (SI, CI) as pacing frequency decreased from the baseline (60-65 imp / min) to 50 imp / min (average 56 ± 5 imp / min). On the contrary, type II included systolic indices improvement with increased pacing frequency above the baseline to 75-90 imp / min (78 ± 6 imp / min), mainly due to SI increase.

It is also remarkable that type I responce was observed mostly in patients with preserved systolic function and AAI stimulation, and type II was – in patients with more severe CHF and VVI stimulation. Thus, type I cardiohemodynamic response indicates an inadequately frequent cardiac pacing that leads to "pacemaker syndrome", and type II indicates not only the presence of myocardial insufficiency, but also "chronotropic incompetence" with a baseline pacing frequency — 60-65 imp/min.

Maintenance of sinus atrial rhythm and hemodynamic role of atrial systole in patients with ventricular pacing.

A comparative study of cardiohemodynamics in patients with VVI stimulation, especially with fixed-rate pacing, revealed significant differences depending on the spontaneous atrial rhythm [12]. Hemodynamic role of atrial rhythm was assessed in the following groups of patients with VVI stimulation: 1st group — spontaneous sinus atrial rhythm with sinus node

normal chronotropic function; 2nd group – sick sinus syndrome with severe bradycardia; 3rd group - persistent atrial fibrillation; 4th group - pacemaker retrograde atrial depolarization. It was revealed that patients from groups I and II had significantly higher ($p < 0.05$) ejection fraction (EF) of LV, stroke index (SI), CI and maximum anteroposterior myocardial fiber shortening compared with groups III and IV. Systolic blood pressure (BP) levels were significantly lower during pacemaker retrograde atrial depolarization compared with 1st and 2nd groups- 17.2 and 14.9%, respectively.

It has been shown that patients with atrial fibrillation and atrial sinus rhythm have LV systolic function deterioration during VVI stimulation because of ventricles diastolic filling dysfunction due to incomplete emptying of the atria and AV dissociation [1, 13, 15]. Pacemaker retrograde atrial depolarization causes pathological sequence of excitation and contraction of atria and ventricles that leads to AV valvular blood regurgitation, decreased cardiac output and systolic blood pressure [18, 26].

The role of pacemaker lead position on the parameters of cardiohemodynamics.

The results of clinical studies on the optimal stimulating electrode ventricle position in order to ensure the maximum hemodynamic effect differ significantly. Punjabi H.A. et al. (2014) study showed that the incidence of tricuspid regurgitation (TR) during two-year follow-up was 21% in patients with septal right ventricular position versus 68% apical right ventricular position ($p = 0.07$) [27]. In other study [26] the development of moderate and severe TR in patients with apical and septal electrode right ventricular positions was observed in 4.8% and 10.5% of cases, respectively, and in 8.3% of patients with left ventricular position. This means that implantation of the electrode in the LV does not decrease the frequency of TR compared to right ventricular implantation [24, 28].

It has been established that septal right ventricular electrode position causes narrow QRS complexes [16, 29]. This is associated with shorter period of ventricular activation due to better myocardial contractility and hemodynamic parameters. In addition, septal electrode position did not cause complications, such as electrode dislocation, pericardial perforation, pericarditis development and muscles contractions [19].

Important hemodynamic and prognostic value of pacemaker electrode position has been demonstrated in patients with cardiac resynchronization therapy (CRT). Dong Y. -X, et al. (2012) compared hemodynamic and clinical outcomes of CRT depending on left ventricular electrode position in patients with DDDR and DDD stimulation modes [28]. It has been shown that patients with anterior and posterolateral electrode positions had higher LV EF, and lower LV local contractility violation index and pulmonary artery systolic pressure compared with posterior and anterior electrode positions. During over 4 years of follow-up, functional class of CHF and mitral regurgitation decreased, and cumulative survival rate was 72% versus 48% ($p = 0.003$).

It is also remarkable that transvenous cardiac pacing made the apical position of the right ventricle more preferable due to easy electrode placement, contact stability, cardiac pacing reliability and electrode design [7, 14]. Guidelines on cardiac pacing and cardiac resynchronization therapy (2013) of the European Society of Cardiology and the European Heart Rhythm Association (ESC / EHRA) emphasize that implantation of the electrode in the right ventricular outflow tract and in the trunk of the His bundle is associated with high LV EF, especially in patients with baseline EF less than 45%, compared with apical position [6]. However, the results of the studies on exercise tolerance, the dynamics of heart failure functional class, quality of life and survival are still not conclusive.

The features of interventricular septum (IVS) movement in patients with ventricular pacing and its effect on cardiohemodynamics.

It has been shown that patients with apical right ventricular electrode position more frequently have pathological IVS movement compared with patients with septal electrode position [18, 20, 30]. This association is confirmed by abnormal IVS movement in patients with intermittent pacing and artificially stimulated ventricular complexes [18].

Sarvari S.I. et al. (2017) revealed abnormal movements ("flash") of IVS forward or backward from the ultrasonic probe in 77% of 74 patients with a fixed right ventricular pacing from the apical position [30]. At the same time, LVEF was lower and LV end systolic volume was higher compared with patients without abnormal LV movement. Moreover, patients with LV dysfunction had higher amplitude of abnormal IVS movement (5 ± 1 mm vs 2 ± 1 mm; $p < 0.001$) and lower amplitude of IVS systolic excursion (4 ± 1 mm vs 8 ± 2 mm; $p < 001$) compared with patients with normal LV function. It has been shown that the duration of ar-

tificial ventricular complex over 150 ms and the amplitude of septal "flush" over 3.5 mm with sensitivity and specificity predict the risk of LV dysfunction.

Patients with right ventricular pacing from the apical position had decreased IVS thickness during diastole after 12 and 24 months compared with preoperative values 15.3% (p=0.05) and 21.6% (p=0.008) on average, respectively [20]. Moreover, the IVS thickness to LV posterior wall thickness ratio during diastole also increased and was 12 months after — 1.22±0.03 (p<0.05), and 24 months after — 1.34±0.06. The frequency of detection and the severity of isolated IVS hypertrophy directly correlated with cumulative duration of right ventricular pacing.

The effect of the cumulative duration of ventricular pacing on cardiohemodynamics and prognosis

It has been established that the cumulative duration of the right ventricular pacing affects the long-term prognosis, primarily due to its negative cardiohemodynamic effects [13, 15, 20]. The duration of the right ventricular pacing depends on the ratio of the frequency of spontaneous and artificial heart rhythms and, therefore, the determination of the hemodynamically optimal low frequency of the artificial rhythm will contribute to the improvement of cardiovascular prognosis. It is also remarkable that the cumulative duration of ventricular pacing, that adversely affects cardiovascular prognosis, varies widely due to various cardiohemodynamic advantages and disadvantages of different pacing modes [18].

It has been shown that patients with VVIR stimulation with cumulative duration of right ventricular pacing over 40% of the time have significantly increased frequency of admissions due to heart failure decompensation compared with patients with cumulative duration less than 40% [11]. Moreover, the survival of patients with sick sinus syndrome and AAI and VVI stimulation did not differ significantly if the cumulative duration of isolated ventricular pacing was less than 40% of the time. Therefore, it is recommended to use DDDR stimulation especially in patients with permanent pacing.

The DAVID study (Dual Chamber and VVI Implantable Defibrillator) showed that patients with implanted cardioverter defibrillator due to LV systolic dysfunction with DDDR mode with base frequency of 70 impulses / min compared with VVI stimulation with frequency of 40 impulses / min had more frequent admissions and/or increased heart failure mortality [6]. Thus, despite AV synchronization maintenance during DDDR stimulation, the cumulative duration of ventricular pacing over 40% contributes to the deterioration of long-term prognosis.

However, Nielsen J.C. et al. (2011) study showed an upward trend in admission frequency due to heart failure decompensation during DDDR stimulation in patients with cumulative ventricular pacing over 80% of the time [31]. Thus, the cumulative duration of ventricular pacing is an independent predictor of adverse cardiovascular events.

Therapeutic effects of implantable pacemakers and its optimization by reprogramming pacing parameters

Controlled frequency-dependent hypotensive effect of cardiac pacing

Patients with implantable PMs usually refer to elderly population and often have arterial hypertension (AH) with very high cardiovascular risk, they require an adequate blood pressure correction [7]. It is also known that the development of complete AV blockade is often accompanied by isolated systolic hypertension, that significantly decreases after pacemaker implantation, sometimes up to "pacemaker syndrome" [13, 32, 33].

Mechanisms of cardiac pacing frequency-dependent hypotensive effect can include various physiological factors involved in the regulation of systemic blood pressure. They mainly include chrono-inotropic relations, for example, frequency-dependent changes of myocardial contractility (Frank-Starling law). In addition, there is a direct correlation between LV contractility and the level of aortic systolic blood pressure (Anrep effect). Baroreflex and humoral mechanisms for blood pressure lowering take place especially in patients with VVI-stimulation, that is associated with increased right atrium pressure and increased atrial natriuretic peptide secretion, that has vasoactive effect [34].

Over the last years, DDD type PMs with an algorithm providing hypertension control were widely used for the treatment of isolated systolic hypertension [9, 22]. The algorithm includes an alteration of 8-13 imposed QRS complexes series with shortened AV interval (20-80 ms) and 1-3 subsequent complexes with extended AV interval (100–180 ms). Neuzil P. et al. (2017) revealed systolic blood pressure decrease in patients with DDD stimulation with short AV interval, due to preload and SI decrease [33]. In this case,

systolic BP decreased from 165 ± 10 mmHg to 157 ± 14 mmHg 3 months after and to 142 ± 14 mmHg 6 months after PM implantation. As a result, the number of antihypertensive medications decreases. However, Do D.H. et al. (2017), noted that the use of short AV intervals during DDD stimulation can lead to the development of heart failure, "pacemaker syndrome" and atrial fibrillation, as well as sympathetic hyperactivity [9].

Manisty C.H. et al. (2012) studied the causes of hypotensive effect in patients with biventricular stimulation by programming AV interval in the range from 40 to 120 ms [20]. The SI was determined using doppler echocardiography and blood pressure — using digital photoplethysmography. They showed that the shortening of the AV interval causes immediate increase of blood pressure and SI, however, blood pressure, unlike SI, reduces after a few seconds. According to the authors, blood pressure decreases due to compensatory vasodilation, not due to SI decrease.

To evaluate the frequency-dependent hypotensive effect, we reprogrammed the pulse frequency from 50 to 90 impulses/min with a discrete value of 5 impulses/min in patients with isolated systolic hypertension [32]. The duration of cardiac pacing at each stage of the rhythm frequency was 2–3 days. As the frequency of artificial rhythm increased, systolic blood pressure decreased in patients with AAI and VVI stimulation. At a frequency of 80 impulses/ min, systolic blood pressure decreased from 13.1 to 21.5% and 17.6% ($p < 0.01$) on average, diastolic blood pressure did not change significantly. The results might indicate the chronotropic "incompetence" of the artificial heart rhythm at a base pulse frequency of 60 impulses / min. The antihypertensive effect can be explained by SI decrease that ranged from 11.8 to 18.3% and was 14.5% ($p < 0.05$) on average, and total peripheral vascular resistance had tendency to increase within normal limits.

Frequency-dependent antianginal effect of cardiac pacing

It is known, that the majority of patients with implantable pacemakers suffer from coronary artery disease and had myocardial infarction and/or coronary artery revascularization [35, 36]. Therefore, the optimization of coronary flow reserve by choosing the optimal pacing mode has great prognostic value. Stress echocardiography is often used in order to assess coronary flow reserve in patients with implantable PMs and consists of programmed increase of the artificial rhythm frequency and the study of local LV contractility impairment [37]. Plonska-Gosciniak E. et al. (2008) showed high sensitivity (91%) and specificity (75%), as well as positive and negative predictive value (81% and 88%, respectively) of stress echocardiography in the diagnosis of hemodynamically significant coronary stenosis (more than 50%) in patients with AAI / DDD and VVI stimulation including patients taking beta-blockers [38]. At the same time, positive stress test was observed in 60% of all cases. The local LV contractility impairment index with positive stress test in patients with AAI / DDD stimulation significantly increased from 1.32 to 1.49 and in patients with VVI stimulation from 1.36 to 1.65.

It is also remarkable that frequency-dependent pacing in patients with high coronary flow reserve and implantable PMs is justified on the one hand, and on the other hand, there is a possibility of sensor-controlled tachycardia development [39]. Therefore, modern PMs with DDDR mode have multisensor system that is used to avoid false pacing responses such as unmotivated frequent artificial rhythm [5, 6]. It is also recommended to switch from DDDR mode to VVI mode or to program lower and upper limits of pacing frequency to simulate effective beta-adrenoblockage (for example, 50 and 100 imp/min, respectively).

Moreover, technical AV delay in patients with DDD/ DDDR stimulation, should be selected in order not compromise the hemodynamic benefit of atrial systole by extended AV interval on one hand, and, on the other hand, AV delay should not be short making it difficult to relax and fill the LV, and aggravate coronary perfusion [23, 31]. In this case, PMs with an algorithm that provides frequency-controlled AV delay can be used.

Ibrahim M. et al. (2013) showed that the implantation of DDD PM in patients with complete AV block can cause destabilization of coronary heart disease, that manifests as increased number of angina attacks [40]. This can be explained by 2–3 times increase of the initial heart rate frequency as a result of P-managed ventricular pacing. Authors propose to limit the upper-frequency of DDD / DDDR pacing in patients with angina pectoris and myocardial infarction.

It is also remarkable that PM implantation not only affects the parameters of cardiohemodynamics, but also increases the activity of plasma and tissue coagulation factors and suppresses endothelium vasomotor function that can aggravate cardiovascular prognosis [34].

Bifocal atrial ventricular pacing for the treatment of patients with hypertrophic obstructive cardiomyopathy (HOCM)

Over the last years, sequential atrial ventricular pacing with shortened AV delay has been an alternative to surgical treatment in patients with HOCM [8]. The change in the sequence of excitation and ventricle contraction leads to subaortic gradient decrease (up to 25%) due to regional IVS contractility decrease and, as a result, the extension of LV outflow tract. The delay of the anterior cusp of the mitral valve systolic movement and its amplitude decrease also contributes to it. It is very important to select the shortest AV delay, that ensures premature depolarization of the heart apex, and does not lead to cardiohemodynamics impairment- cardiac output and blood pressure decrease.

Randomized placebo-controlled studies confirm the decrease of systolic pressure gradient in the LV outflow tract, and show an improvement of symptoms and life quality in patients with HOCM [41]. However, it was not possible to detect significant effect of DDD / DDDR stimulation on the course of the disease, the frequency of sudden cardiac death, and physical activity. They also noted diastolic dysfunction aggravation and end-diastolic pressure in the LV increase.

Therefore, the European Society of Cardiology guidelines for the diagnosis and treatment of HCM recommend to use DDD stimulation with shortened AV delay for the treatment of patients with systolic LV pressure gradient over 50 mmHg, refractory to drug therapy, who are not candidates for surgical correction and alcohol septal ablation.

Thus, the variety of cardiac pacing modes used in clinical practice, on the one hand, provide the need for technical and methodological electrocardiotherapy improvement and, on the other hand, stimulate further large and observational clinical studies in order to study the physiological interaction between heart and pacemaker and expand the spectrum of the use of this method.

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