The relationship of the prolonged PR interval with the long-term survival in patients with heart failure undergoing cardiac resynchronization therapy

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Aim. To assess the relationship between the prolonged PR interval (⩾200 ms) and the long-term survival of patients undergoing cardiac resynchronization therapy (CRT).

Material and methods. A total of 85 patients (mean age — 55,1±9,9 years; men — 81,2%) with NYHA class II-IV heart failure (HF) were examined. The mean follow-up was 34,0±21,2 months. Patients with PR<200 ms (n=52) made up group I, with PR⩾200 ms (n=33) — group II. Then the patients were divided into subgroups depending on the QRS duration: ⩾150 ms (n=33 in group I and n=14 in group II, respectively) <150 ms (n=19 in group I and n=19 in group II, respectively).

Results. In patients of group II, a history of myocardial infarction (MI) was more often registered (p=0,005), left ventricular ejection fraction (LVEF) was lower (p=0,032). In a multivariate analysis, MI (OR 3,217; CI 95% 1,188-8,712; p=0,022) and LVEF value (OR 0,869; CI 95% 0,780-0,968; p=0,011) had a significant relationship with the PR interval prolongation (⩾200 ms). The survival of patients of group I was 59,6%, group II — 18,2% (Log-rank test p<0,001). According to Cox regression model, the initial left ventricle end-systolic volume (OR 1,012; 95% CI 1,006-1,017; p<0,001), inferior wall MI (OR 1,690; 95% CI 1,131-2,527; p=0,011) and PR interval ⩾200 ms (OR 2,179; 95% CI 1,213–3,915; p=0,009) were associated with long-term mortality. In patients with PR⩾200 ms, survival rate was low, regardless of the QRS duration (21,4% in patients with QRS⩾150 ms, 15,8% in patients with QRS<150 ms; Log-rank test p=0,698) In patients with PR<200 ms, the survival rate of patients with QRS⩾150 ms was 72,7%, and for patients with QRS<150 ms — 36,8% (Log-rank test p=0,031).

Conclusion. In HF patients, PR interval prolongation (⩾200 ms) is associated with long-term mortality increase. The highest survival rates were observed in patients with PR<200 ms and QRS⩾150 ms. In patients with QRS⩾150 ms, the presence of PR⩾200 ms should be considered as an additional criterion for CRT.

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According to the current guidelines for the management of patients with heart failure with a reduced ejection fraction (HFrEF), the main criteria for patient selection in cardiac resynchronization therapy (CRT) are QRS ⩾150 ms and left bundle-branch block (LBBB) [1]. However, the use of these criteria in clinical practice has repeatedly raised doubts. The results of an individual meta-analysis with the studies, on the basis of which the guidelines for patient selection in CRT were changed, showed that the QRS duration, but not its morphology, was the only significant electrocardiographic (ECG) criterion affecting mortality in CRT patients [2]. It has been demonstrated that not all patients with wide QRS complex will have CRT equally effective [3], and therefore, the search for additional ECG selection criteria is a relevant objective.

Recent studies have shown the association of first-degree atrioventricular (AV) block, manifested by prolonging the PR interval >200 ms, with an unfavorable prognosis in patients with HF, coronary artery disease, as well as in the general population [4-6].

The relationship of first-degree AV block with the CRT effect on mortality reduction remains poorly understood.

The aim of the study was to evaluate the relationship between the prolonged PR interval (⩾200 ms) and the long-term survival of CRT patients, including in groups with different value of QRS duration.

Material and methods

Since 2003, a register of CRT operations has been kept at the Tyumen Cardiology Research Center. After a retrospective analysis of the ECG performed before implantation of CRT devices, 85 patients were selected from the register (81,2% of men, 18,8% of women; mean age 55,1±9,9 years). The study included patients with sinus rhythm (71,7%), paroxysmal atrial fibrillation (AF) (21,2%), as well as permanent AF after AV node ablation (7,1%). We excluded patients without ability to fully analyze the initial ECG data. The clinical characteristics of patients are presented in Table 1.

In all patients, implantation of CRT devices was performed with the following criteria: QRS ⩾120 ms, NYHA class II-IV HF, left ventricular ejection fraction (LVEF) ⩽35%. All patients received drug therapy in accordance with current guidelines [1]. The mean follow-up was 34,0±21,2 months.

CRT devices were implanted in all patients, in 64,7% — cardiac resynchronization therapy defibrillator (CRT-D). Examination of patients was carried out before device implantation and after 1, 3 months and every subsequent 6 months. Clinical examina-

tion, electrocardiography, echocardiography were performed. Echocardiography was performed on a Philips ultrasound machine (IE-33, USA). The measurement of cardiac chamber volumes and LVEF was carried out using a two-dimensional echocardiography by Simpson method. At each planned visit, atrioventricular and intraventricular delays were optimized in accordance with local clinical practice.

ECG was performed using a Poly-Spectrum 8/E system (Neurosoft, Russia) with a paper speed of 50 mm/s; the evaluation was carried out by two independent specialists. Depending on the initial PR interval value, patients were divided into two groups: group I — normal PR interval (<200 ms; n=52); group II — prolonged PR interval ⩾200 ms (n=33). Then, the patients were divided into subgroups depending on the QRS duration: ⩾150 ms (33 people in group I and 14 people in group II, respectively) and <150 ms (19 in group I and 19 in group II, respectively). Survival of CRT patients in groups was evaluated.

Statistical processing of the study results was carried out using the IBM SPSS Statistics 21 software package. The normality of the distribution of quantitative parameters was evaluated by the Kolmogorov-Smirnov test. All indicators had a normal distribution and were presented as M±SD (M — mean value, SD — standard deviation). When analyzing qualitative data, the Chi-squared test was used. When comparing quantitative data, the Student's t-test was used in the case of normal distribution, the Mann-Whitney test in the case of non-normal distribution. To identify correlations, the Pearson correlation coefficient was calculated. Multivariate analysis (binary logistic regression) was used to identify the independent relationship of the studied parameters with the prolongation of the PR interval. Survival was assessed by the Kaplan-Meier estimator. Cox regression model was used to assess the effect of clinical and functional parameters on patient survival. Differences were considered significant at $p<0,05$.

This study was performed in accordance with the Helsinki declaration. The study protocol was approved by the local ethics committees. All participants gave written informed consent.

Results

Patients of group II were more likely to have a history of myocardial infarction (MI), including inferior wall MI, and lower LVEF. According to binary logistic regression, the presence of MI (odds ratio (OR) 3,217; confidence interval (CI) 95% 1,188-8,712; p=0,022) and LVEF (OR 0,869; CI 95% 0,780-0,968; p=0,011) had a significant association with a prolongation of the PR interval ⩾200 ms.

Initial clinical and functional characteristics of patients (n=85)

Parameter	Group I (PR <200 ms) n=52	Group II (PR ≥200 ms) n=33	p
Age (years)	54,9±9,4	55,4±10,9	0,817
Gender (men, %)	75,0	90,9	0,067
ICM (%)	48,1	60,6	0,598
IM history (%)	21,2	42,4	0,023
IM localization: Anteroseptal Inferior wall	 7,7 13,5	 15,2 27,3	0,040
Rhytm: sinus paroxysmal AF permanent AF	 78,8 13,5 7,7	 60,6 33,3 6,1	0,055
AV node ablation	7,7	6,1	0,956
NYHA class of HF (%): II III IV	46,1 40,4 13,5	34,3 54,5 21,2	0,101
Left bundle branch block (%)	65,4	54,5	0,318
QRS (ms)	157,9±33,7	159,5±30,9	0,821
P (ms)	124,5±15,9	127,4±20,3	0,541
CRT-D (%)	65,4	63,6	0,869
6 minute walk test (m)	305,6±104,7	260,5±111,9	0,072
LVEF (%)	31,7±7,6	28,1±4,6	0,032
LVEDV (ml)	241,3±70,6	261,3±61,0	0,185
LVESV (ml)	167,6±59,3	189,6±52,0	0,084
Mitral regurgitation (%): normal mild moderate severe	 3,8 22,2 61,5 13,5	 - 15,2 78,8 6,0	0,738
PR interval, ms	168,3±19,5	222,3±21,2	<0,001
AV delay	121,6±16,8	123,2±12,9	0,706

Abbreviations: AV — atrioventricular, MI — myocardial infarction, ICM — ischemic cardiomyopathy, LVEDV — left ventricular end-diastolic volume, LVESV — left ventricular end-systolic volume, CRT-D — cardiac resynchronization therapy defibrillator, LVEF — left ventricular ejection fraction, AF — atrial fibrillation.

Correlation analysis did not reveal a significant association of first-degree AV block with gender (r=-0,094; p=0,392), body mass index (r=-0,0534; p=0,634) and left atrial volume (r=0,189; p=0,145), while there was a tendency towards correlation with the patients' age (r=0,614; p=0,055).

The survival of group I patients was 59,6%, of group II patients — 18,2% (Log-rank test p<0,001). Kaplan-Mayer curves characterizing the survival of patients in groups are presented in Figure 1.

In order to identify factors associated with the mortality of CRT patients, Cox regression analysis was performed. It included the following parameters: gender, age, primary diagnosis, MI history, MI localization, NYHA class of HF, PR ≥200 ms, QRS ≥150 ms, end-systolic and end-diastolic volumes of the left ventricle (LV), LVEF. As a result of direct step-by-step selection, three parameters were included in the model: initial LV end-systolic volume (OR 1,012; 95% CI 1,006-1,017; p<0,001), inferior wall MI (OR 1,690; 95% CI 1,131-2,527; p=0,011) and PR interval ≥200 ms (OR 2,179; 95% CI 1,213-3,915; p=0,009).

When dividing patients into subgroups depending on the QRS duration, it was found that patients with prolonged PR interval ≥200 ms had low survival rate, regardless of the QRS duration: 21,4% in patients with QRS ≥150 ms and 15,8% in patients with QRS <150 ms (Log-rank test p=0,698). In patients with PR interval <200 ms, the survival rate for patients with QRS ≥150 ms was 72,7% versus 36,8% for patients with QRS <150 ms (Log-rank test p=0,031) (Figure 2).

In order to compare the diagnostic significance of electrocardiographic parameters, Cox regression analysis was performed for two variables: QRS ≥150 ms (OR 0,603; 95% CI 0,333-1,091; p=0,095) and PR ≥200 ms (OR 2,487; 95% CI 1,571-5,160; p=0,001). This confirmed a more significant relationship between the PR interval value and mortality in comparison with the QRS duration.

Discussion

According to the current guidelines for the management of HF, the main method of selection of HFrEF patients for CRT is an ECG. It allows to assess the presence and severity of cardiac dyssinchrony by electrical markers — QRS duration and morphology [1].

The relationship between the wide QRS complex ≥150 ms and LBBB with the better effectiveness of CRT in mortality reduction was demonstrated in a number of large studies [1]. Based on the results of these studies, Russian and foreign guidelines for the management of HF were revised. Since 2012, the new selection criteria for CRT are the QRS duration >150 ms and LBBB. However, these changes did not improve the selection quality and did not increase the proportion of patients responding to CRT, and therefore, the search for an additional selection criterion seems relevant.

One of the potential additional factors associated with an unfavorable prognosis is first-degree AV block, manifested by prolonging the PR interval >200 ms. It was previously shown that first-degree AV block can lead to hemodynamic impairment, mitral regurgitation and AF in HF patients. It is also unfavorable prognostic factor for patients with coronary artery disease, as well as for general population [4, 5]. According to the results of the Framingham Heart Study, the presence of first-degree AV block in the general population was associated with an increased risk of mortality, AF, and pacemaker implantation during 20 years of follow-up [6].

The PR interval value may depend on a number of factors: genetic and anatomical characteristics, body weight, age, gender. The prevalence of first-degree AV block among young people in the general population (20-30 years of age) is 1-2%, among people over 60 years old — 3-4% [7]. In young patients, the development of AV block is most often caused by the increased activity of parasympathetic nervous system, and in patients older than 60 years of age — by heart diseases leading to fibrosis and sclerosis of the conduction system: for example, AV conduction slowing may occur with the left atrial dilatation and the development of fibrosis [4, 7].
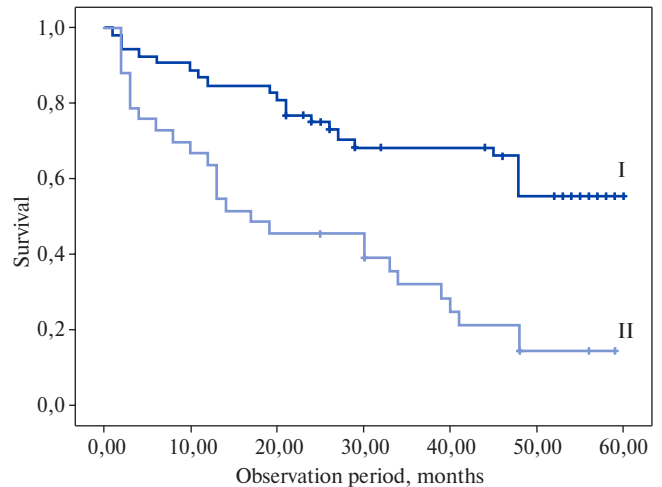

Figure 1. Survival of patients in groups depending on the PR interval.
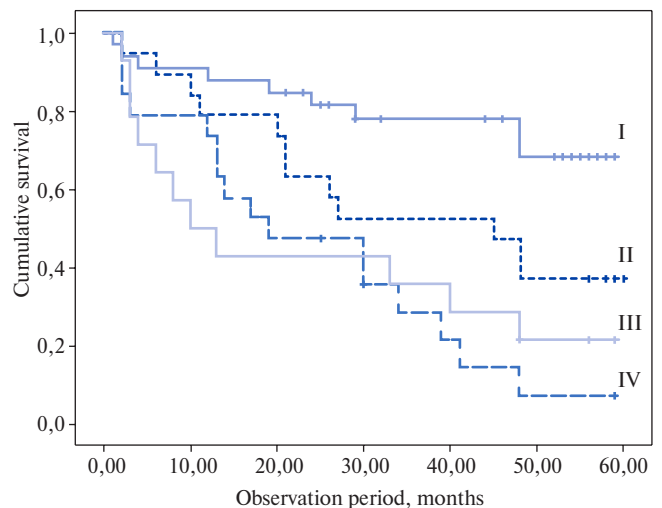**Note:** I — PR <200 ms (59,6%), II — PR ≥200 ms (18,2%), Log-rank test p<0,001.

Figure 2. Survival of patients in groups depending on the duration of QRS complex and the PR interval.
Note: I — QRS ≥150 ms, PR <200 ms (72,7%); II — QRS <150 ms, PR <200 ms (36,8%); III — QRS ≥150 ms, PR ≥200 ms (21,4%); IV — QRS <150 ms, PR ≥200 ms (15,8%). Log-rank test: I vs II p=0,031; III vs IV p=0,698; I vs III p=0,001; I vs IV p<0,001; II vs IV p=0,160.

Among HF patients with indications for CRT, the prevalence of first-degree AV block is significantly higher and can reach 50% [8].

In our study, first-degree AV block was detected in 38,8% of patients. Correlation analysis did not reveal any reliable relationships of PR interval value with gender, body mass index, left atrial dimension and volume, and LV dimension; there was only a tendency towards correlation with the patients' age at the time of implantation.

Previously, the association of first-degree AV block with the survival of CRT patients was evaluated, and the authors obtained contradicting results.

In an additional analysis of the ReTHinQ study, patients with prolonged PR interval >180 ms had a significantly more pronounced decrease in HF severity (NYHA functional classification) and LVEF increase; it should be noted that all patients included in the study had QRS ⩽130 ms [9]. According to the results of the COMPANION study, a favorable outcome in CRT patients was associated with a prolonged PR interval, without taking into account the QRS width and morphology [8]. When assessing the relationship between the PR interval and long-term survival in CRT patients without LBBB, it was shown that patients with prolonged PR interval ⩾230 ms had a significantly reduced mortality risk, while in patients with PR <230 ms, CRT did not reduce the mortality risk compared with implantation of a cardioverter defibrillator [10]. A number of studies have not demonstrated a relationship between the PR interval value and the survival of CRT patients [11]. Other studies have confirmed the association of adverse outcomes with prolonged PR interval. Thus, according to the results of an additional analysis of the CARE-HF study, first-degree AV block was a significant predictor of all-cause mortality and HF-related hospitalization [5]. When dividing patients into groups depending on the LBBB presence, prolonged PR interval was associated with an unfavorable outcome only in the group of patients without LBBB [12]. According to the results of the largest study (26451 patients), prolongation of PR interval >230 ms was an independent predictor of an adverse outcome in CRT patients; contrary to the results of other studies, this relationship was revealed only in patients with LBBB [13]. In study by Rickard J, et al. prolonged PR ⩾200 ms was associated with an unfavorable outcome in patients with LBBB and was a more significant mortality predictor than QRS widening [14]. In our study, in HF patients receiving CRT, prolongation of the PR interval ⩾200 ms was associated with a significantly higher long-term mortality. When dividing patients into groups depending on the QRS widening, it was found that patients with PR ⩾200 ms had a low survival rate, regardless of the QRS width. In patients with PR <200 ms, the QRS duration was of fundamental importance. The combination of PR <200 ms with widened QRS ⩾150 ms was associated with significantly improved long-term survival in CRT patients. Thus, prolongation of the PR interval ⩾200 ms was a more significant mortality predictor than the QRS width. These data confirmed the results of study by Rickard J, et al.

The increase in the frequency of adverse outcomes with prolonged PR interval can be explained by severe hemodynamic impairment caused by diastolic dysfunction, manifested by the fusion of the mitral E and A waves, shortening of left ventricular filling time, and the development of diastolic mitral regurgitation [15]. In addition, according to some researchers, prolongation of the PR interval is associated with more severe comorbidity and is a marker of the disease severity. So, in our study, a significant relationship of the prolonged PR interval with MI history and lower LVEF was found, and according to the results of Cox regression analysis, PR ⩾200 ms, history of inferior wall MI and the initial end LV-systolic volume had a significant relationship with long-term mortality in CRT patients. It is important to note that the asynergy of the basal and middle segments of the posterior septal, posterior and inferior LV walls is associated with injury to the atrioventricular node and/or the His bundle trunk. It can lead to the AV block, LBBB or its branches. Consequently, combination of QRS complex and PR interval prolongation was probably due to ischemic injury after MI.

When PR interval and QRS complex values were included in the Cox regression model, the latter did not show a significant relationship with long-term survival. It demonstrates a more significant role of diastolic disorders associated with AV conduction slowing before the CRT onset, compared with LV systolic dysfunction due to intraventricular and interventricular dyssynchrony.

Study limitations. This study was single-center, retrospective, and includes a small number of patients. We did not evaluate the CRT effect on clinical and functional parameters, and also did not assess the response to CRT in groups depending on the first-degree AV block presence. Also unclear is the possible effect of optimizing the operation parameters of CRT devices, in particular, the atrioventricular delay, on the survival of patients with different PR interval values.

Conclusion

1. In HF patients, PR interval prolongation (⩾200 ms) is associated with long-term mortality increase, regardless of the QRS duration.

2. The highest survival rates were observed in patients with normal PR (<200 ms) and QRS (⩾150 ms) values.

3. In patients with QRS ⩾150 ms, the presence of PR ⩾200 ms should be considered as an additional criterion for CRT.

Relationships and Activities: not.

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