In the last decades, cardiovascular morbidity and mortality from diseases are on the leading positions in the Russian Federation. According to the World Health Organization, more than 16.5 million people a year die from cardiovascular diseases, including CHD ̶ more than 7 million, accounting for 29.3 and 12.6% of the total mortality accordingly. Mortality from myocardial infarction (MI) in the post-MI period remains also high so is the incidence of sudden cardiac death [1], which determines the need of diagnostic and preventive measures. New parameter "heart rate turbulence" (HRT) which reflects the short-term regression of the heart rhythm with subsequent acceleration after premature ventricular construction (PVCs)was scientifically proved in 1999 [2]. It was shown that in patients with postMI period the pathological is observed, which reflects high cardiovascular risk in the patients. [3,4]. However, it is still not clear whether the HRT reflects the high cardiovascular risk in patients without MI in the past.

The aim of the study was to improve the diagnostics of coronary heart disease in patients with HRT as a cardiovascular risk factor.

**Methods**

More than 3.000 24h electrocardiographic (ECG) record in patients with CHD were analyzed, that were treated in the department of cardiology in 2010-2011in clinical hospital №21 Ufa, and 205 patients meeting the criteria for inclusion were selected for the experimental group. Inclusion and exclusion criteria are presented in Table 1.

The primary endpoint in the study was overall mortality during the 4-5 year follow-up after the initial determination of HRT.

Heart rate turbulence can be determined by standard 24-hour ECG monitoring (**Fig. 1**) [3,6]. Two phases of HRT, the early sinus rate acceleration and late deceleration, are quantified by 2 parameters termed as turbulence onset (TO) and turbulence slope (TS). TO is calculated as: TO = (RR1+RR2) - (RR-2+ RR-1) (RR-2+RR-1)×100, where RR\_2 and RR\_1 are the 2 R-R intervals immediately preceding the PVCs coupling interval, and RR1 and RR2 are 2 R-R intervals immediately following the compensatory pause. TS is defined as the maximum positive regression slope assessed over any 5 consecutive sinus rhythm R-R intervals within the first 15 sinus rhythm R-R intervals after the PVCs. Normally, there is an acceleration of sinus rhythm after PVCs, which is reflected in the negative TO value with a subsequent slowdown with positive TS.

Patients with HRT are usually stratified into three categories: 1) HRT category 0 means TO *and* TS are normal (nTO and nTS accordingly); 2) HRT category 1 means 1 of TO *or* TS is abnormal (pTO and aTS accordingly); and 3) HRT category 2 means both TO *and* TS are abnormal.

24-hour ECG monitoring was performed by"Kardiotekhnika-04-8 (M)” ("INKART", St. Petersburg) 24h monitoring with hardware, allows to record and analyze forms of ventricular complexes in accordance with HRT analysis. HRT analysis was performed in 2010-2011 in time of patients` hospitalization, and later in 2011-2015 the follow up telephone contacts was performed annually to monitor the primary endpoint.

Group analysis is presented in mean values (M) and standard deviation (m). Statistical analysis was performed using survival tables and Kaplan-Meier survival regression models, particularly the proportional hazards model (Cox model). Model coefficients estimation was obtained by maximum likelihood. Statistical analysis was performed using “Statistica 10.0”program (module “Survival analysis”).

**Results**

The main part of patients with HRT was defined by ECG 24h records analysis in 2010-2011. The survival status was estimated by follow up telephone contact and by medical events registration in state medical statistical program "Promed" providing survival data during next 5 years.32 patients retired from the study because of contact lost and 173 patients remained available for analysis and long-term results. Table 2 shows the characteristics of patients in the study. The average age of the patients was 67.06±0.79 years, 67women,and 106 men. Patient’s height was 169.9±1.8 cm, weight - 84.6±3.0 kg, body mass index (BMI) - 29.4±0.89 kg/m2. The number of post-MI patients was 137, patients with coronary angiography / coronary stenting/or coronary artery bypass grafting – 23, after stroke– 10, with arterial hypertension – 130, diabetes mellitus – 21. Some other cardiovascular parameters: blood cholesterol - 4.78±0.08 mmol/l, and left ventricular ejection fraction - 54.0±1.06% were also identified.

InTable 3 the electrophysiological characteristics of VPC and HRT are presented.

The number of PVCs was 176.9±18.8/day, and average heart rate – 68.1±0.57 beats/min. HRT parameter TO was 0.96±0.25%, and TS – 6.14±0.38 ms/RR.

As described above, we investigated 2 HRT parameters, which have predictive power for patients prognosis: TS and TO [3,6]. TO was not significant for survival models, and we analyzed relationship of mortality and HRT in survival analysis with TS parameter only. Abnormal TS (aTS) is ≤ 2.5 ms/RR, and normal (nTS) ->2.5 [3,6]. Table 4 shows the mortality in the group based on TS.

**Survival in the 5-year interval depending on heart rate turbulence**

In first phase, the overall mortality over the 5-year period was evaluated. For calculation of mortality and survival graphs for the 5-year period the 2 groups of patients: with nTS and aTS were compared with each other.

*The mortality risk in patients with HRT*. Figure 2 presents mortality risk assessment within 5 years in patients with CHD and nTS. The graph was constructed by subtracting of given interval from the value of the survival function values of the next interval and then dividing by the "width" of the corresponding interval.

Mortality risk was minimal for the first 20 months after the initial HRT, it gradually increased later and the achieved the maximal probability in 30-45 months range.

*Mortality risk in patients with aTS.* In patients with CHD and aTS The following mathematical model of mortality during the observed period was used:

$λ\_{i}\left(x\_{i}\right)=λ\_{0}\left(t\right)\*e^{1.61\*TS\\_D\_{.}}$,

where$TS\\_D$ =$\left\{\begin{array}{c}1, if ts\leq 2.4\\0,if ts>2.4\end{array}\right.$

Testing of the model showed its significance: an estimated value of χ ^ 2- statistics 16.8, which exceeded the tabular value of 5.992, determined in 2 degrees of freedom and a significance level of p<0.05. Cox model parameters was statistically significant: presence of aTS influencedmortality risk over five year period - the presence of aTS in CHD patients compared to nTS enhanced mortality likelihood in 4.99 times. Considering the confidence level of 95% the mortality risk in the five-year period in compare with nTS increased into2.37-10.51 times.

Figure 3shows graph of mortality in 5-year time interval for patients with aTS. The function was constructed similarly as for patients with nTS(see above). In patients with aTS the mortality risk was minimal during the first 15 months after the start of monitoring, upraised from 20 to 30 months, and achieved maximum between 45 and 60 months.

Figure 4 shows both nTS and aTS mortality curves. The divergence of the curves starts from 24 months, and intensifies with years.

**Analysis of mortality depending on TS and myocardial infarction**

According to most of published data, pathological HRT has predictive power only in post-IM patients [7,8,9], so we compared Kaplan-Meier survival curves based on MI in the past and on nTS/aTS (Table 5).

While analyzing the data for five years 2 survival models depending on TS parameters and presence of MI in the past were created. In the first model, we compared survival curves in post-MI patients and nTS/aTS, and the second –in non-MI.

*Survival curves in post-MI patients and nTS/aTS.* For a more detailed analysis of difference in survival rates post-MI patients with nTS (n=106) and aTS(n=30) are investigated. Based on Kaplan-Meier survival graph (Fig. 5), according to Gehan's-Wilcoxon criteria, the survival rate in post-MI patients with nTS was considerably higher than with aTS (p=0.00026).

*The survival rate in non MI patients with nTS/aTS.* In this model, the compare of survival rates in non-MI patients with nTS (n = 30) and aTS (n=7) was performed. In Kaplan-Meier survival graphs (Fig. 6) the survival rate of patients without MI and with nTS were significantly higher than with aTS (p=0.00318).

**Discussion**

Populational cardiology based mostly on the success of evidence-based medicine. One of the modern achievements are cardiovascular risk scales, for example in patients with PVC in whom it is possible to estimate HRT [3]. We analyzed 173 patients with CHD, in whom was possible to estimate HRT. The 5-year observation was done to determine the primary end point – general mortality. Two HRT parameters were previously shown to have predictive power: TS and TO [3].In our study TO didn`t show impact on long-term survival of patients, only TS was analyzed. In the first step, we analyzed the 5-year survival rate depending on normal and abnormal TS (nTS/aTS). Presence of aTS in patients with CHD increased the death likelihood for 5.1 times in compare with nTS. The maximal mortality risk after HRT record was in 45-60 weeks range, and the divergence of survival curves started from the second year. On the second step, we compared the survival curves of patients with previous MI and with nTS and aTS. Existence of aTS significantly increased mortality in compare with nTS (p=0.00026). The role of HRT, a significant risk factor in patients with CHD with previous MI, has been proved in several large-scale retrospective and prospective studies [3,8,9].All HRT studies, except of CAST (Cardiac Arrhythmia Suppression Trial), used the same reference values of TO and TS parameters, that is, 0%, and 2.5 ms/RR intervals, accordingly. In patients with HRT category 2 (i.e. with aTO and aTS) mortality risk increased by 4,4-11,3 times within 2 years compared to patients with normal HRT (0 category).

Then, we compared survival curves with nTS and aTS in patients without MI. Parameter aTS also raised the mortality (p=0.00318) but surely less then in post-MI patients. Prognostic role of HRT in CHD patients without a history of MI was not properly studied [11, 12] and, based on presented data, aTS may predict mortality risk in patients without MI in the past [12,13].

**Conclusions.** It was proved that in patients with CHD and PVCs, abnormal TS parameter of HRT is highly predictive in determining the general mortality over a 5-year period, where the divergence of the survival curves starts from the second year of monitoring. Unlike other observations, the differences between survival graphs was shown not only for patients with previous MI but also without it.

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