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# The risk of venous thromboembolism in patients with heart failure

Vereina N. K., Agasyan D. G., Chulkov V. S.

**Aim.** To quantify the risk of venous thromboembolism (VTE) in hospitalized patients, depending on the severity of heart failure (HF).

**Material and methods.** Current cross-sectional study included 132 patients hospitalized in the cardiology department in 2019. All participants were divided into 2 groups: group 1 (n=48) — patients with class I-II HF; group 2 (n=84) — patients with class III-IV HF. A total quantitative assessment of the VTE risk was carried out according to the Caprini risk scoring method.

**Results.** All patients hospitalized in the cardiology department, regardless of HF class, had a higher and highest risk of VTE and required prophylactic anticoagulation. Highest VTE risk had 85% of patients with class I-II HF; 97,6% — patients with a class III-IV HF. Mean score of ⩾10 was observed in every fifth patient. Atrial fibrillation requiring long-term anticoagulant therapy was observed in 51,5% of patients. There were no absolute contraindications for parenteral prophylactic anticoagulation at the time of hospitalization in the study population.

**Conclusion.** All patients admitted to the cardiology department had a higher and highest risk according to the Caprini risk score, regardless of HF class. More than half of the patients had indications for long-term anticoagulant therapy. The remaining patients required the parenteral prophylactic anticoagulation.

**Key words**: heart failure, venous thromboembolism, prevention.

**Relationships and Activities:** not.

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Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, according to epidemiological studies, annually cause about 10 million deaths worldwide and take third place after myocardial infarction and stroke [1]. Heart failure (HF) is one of the most common risk factors for VTE, especially in hospitalized patients [2]. Meta-analysis by Tang L, et al., which included 46 studies, showed that the overall incidence of VTE in this population was 2,48% (95% confidence interval (CI) 0,84-5,61); without thromboprophylaxis — 3,73% (95% CI 1,05-7,31) and with thromboprophylaxis — 1,47% (95% CI 0,64-3,54). In general, the relative risk of VTE for hospitalized patients with HF was 1,51 (95% CI 1,36-1,68) [3]. An assessment of VTE risk in all hospitalized patients older than 40 years in Russia is recommended to be carried out in accordance with the Russian clinical guidelines for the diagnosis, treatment and prevention of venous thromboembolism (2015) [4]. This document includes the Caprini risk score (2005) for the most important VTE risk factors [5]. The individual score allows assigning patient to a certain category: low risk (0-1 points), moderate risk (2 points), higher (3-4 points) and highest risk (⩾5 points). With higher and highest VTE risk and without high bleeding risk, the patient should receive prophylaxis with unfractionated heparin, low-molecular-weight heparins or fondaparinux sodium, if the patient does not receive long-term anticoagulation therapy for other indications. At moderate risk, non-pharmacological interventions are recommended. According to this score, congestive HF for at least 1 month is estimated at 1 point. However, the combination of HF and other independent characteristics (age ⩾60 years, body mass index >25 kg/m$^2$, limited excursion, varicose veins and others) resulting in categorizing a patient with class I-II HF as the higher and highest risk of VTE.

On the other hand, factors such as concomitant liver and kidney failure, single and dual antiplatelet therapy use, and gastrointestinal pathology increase the risk of bleeding in this population. In this regard, the adequate determination of indications for primary prevention remains relevant issue.

The aim of the study was to quantify the VTE risk in hospitalized patients, depending on the severity of HF.

## Material and methods

Type: cross-sectional study with an assessment of VTE risk at the time of hospital admission. Study population was patients hospitalized in the cardiology department of Chelyabinsk City Clinical Hospital № 1 from September 1 to November 1, 2019. Inclusion criteria were HF and presence of echocardiography data records for the last year. Exclusion criteria were acute coronary syndrome, active bleeding, as well as cancer, including its history in the last 5 years. We used continuous sampling method involving 132 patients. In addition to the factors related to Caprini risk score, the following were taken into account: nosological structure and characteristics of HF (stage, class) according to Russian clinical guidelines (2018) [6]; indications for the long-term anticoagulation therapy (atrial fibrillation, thrombosis history), comorbidity, stage of chronic kidney disease, and current therapy, including antiplatelet agent use.

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The medical ethics committee of South Ural State Medical University (Russia) approved this study (protocol № 12, 29.08.2019). All participants gave written informed consent.

Statistical processing was carried out using MedCalc statistical software (version 19.1.3, Belgium). Quantitative parameters data are presented as a median and an interquartile range (Me; Q25-Q75). To assess the differences of quantitative parameters between two groups, Mann-Whitney U-test was used. Qualitative parameters are described by absolute and relative frequencies with assessment of intergroup differences using the Pearson's chi-squared test, and at expected frequencies <5 — using two-tailed exact Fisher's test. Differences were considered significant at $p<0,05$.

## Results

The study included 132 patients, which were divided into 2 groups: group 1 (n=48) — patients with class I-II HF; group 2 (n=84) — patients with class III-IV HF. Group 1 was dominated by patients with preserved and mid-range ejection fraction (85,4% vs 48,8%, $p_{1-2}<0,001$). At the same time, every second patient in group 2 had HF with reduced (<40%) ejection fraction (51,2% vs 14,6%, $p_{1-2}<0,001$). The distribution depending on HF stages was as follows: group 1 — 3 patients with stage I ($p_{1-2}=0,046$), 45 patients with stage IIa ($p_{1-2}<0,001$); group 2 — 36 patients with stage IIa, 45 patients with stage IIb ($p_{1-2}<0,001$), 3 patients with stage III ($p_{1-2}>0,05$).

Clinical characteristics of patients are presented in Table 1.

Indications for hospitalization in both groups were hypertensive crisis, atrial fibrillation and other cardiac rhythm disturbances. The mean age of patients in both groups was >70 years, which already made it possible to assess the VTE risk at 2 points. Patients in group 2 had higher mean age, smoking prevalence, as well as significantly higher incidence

**Table 1**

**Clinical characteristics of patients with class I-II and III-IV HF**

| Parameter | Group 1 (n=48) | Group 2 (n=84) | P |
|---|---|---|---|
| Age, years (Me; Q25-Q75) | 70,5 (56,5-80,5) | 74,5 (64,0-82,5) | <0,001 |
| Gender, men, n (%) | 13 (27) | 32 (38) | 0,20 |
| Smoking, n (%) | 9 (18,8) | 29 (34,5) | 0,055 |
| Body mass index >25 kg/m$^2$ | 41 (85,4%) | 79 (94%) | 0,098 |
| Hypertension, n (%) | 46 (95,8) | 72 (85,7) | 0,07 |
| Coronary artery disease. Angina pectoris, n (%) | 17 (35,4) | 75 (89,3) | <0,001 |
| History of myocardial infarction, n (%) | 13 (27,1) | 48 (57,1) | <0,001 |
| Heart defects, n (%) | 10 (20,8) | 33 (39,3) | 0,03 |
| Atrial fibrillation, n (%) | 20 (41,7) | 48 (57,1) | 0,088 |
| Diabetes, n (%) | 10 (20,8) | 22 (26,2) | 0,491 |
| Chronic obstructive pulmonary disease, n (%) | 3 (6,3) | 4 (4,8) | 0,715 |
| Chronic kidney disease with glomerular filtration rate <60 ml/min/m$^2$, n (%) | 5 (10,4) | 13 (15,5) | 0,599 |
| Anemia, n (%) | 18 (37,5) | 65 (77,4) | <0,001 |
| Ischemic stroke (up to 1 month old) | 1 (2,1%) | 2 (2,4%) | 0,612 |
| Varicose veins | 30 (62,5%) | 69 (82,1%) | 0,098 |
| Bed rest | 4 (8,3%) | 39 (46,4%) | <0,001 |

of coronary artery disease, acquired heart diseases, and limited excursion ⩾3 days. In total, 68 people (51,5%) had atrial fibrillation without statistical differences between the groups. Chronic venous disorders ⩾C2 (CEAP classification) were observed in 62% of patients in group 1 and 82% in group 2, which made it difficult to diagnose HF-related congestion. Anemia, mainly mild hypochromic, was 2 times more common in group 2. No differences were found in the incidence of inflammatory respiratory and gastrointestinal diseases.

The total quantitative risk assessment of VTE by Caprini score is presented in Table 2.

**Table 2**

**Caprini risk score categories in hospitalized patients with HF**

| Parameter | Group 1 (n=48) | Group 2 (n=84) | P |
|---|---|---|---|
| Low, n (%) | 0 | 0 | >0,05 |
| Moderate, n (%) | 0 | 0 | >0,05 |
| Higher, n (%) | 7 (14,6) | 2 (2,4) | 0,077 |
| Higher, n (%) | 41 (85,4) | 82 (97,6) | 0,077 |
| Mean score ⩾10 | 4 (8,3) | 22 (26,2) | 0,013 |

All patients hospitalized in the cardiology department, regardless of HF, belonged to the higher and highest risk categories of VTE and required prophylactic anticoagulation. In the group of patients with class III-IV HF, more than 97% of patients were at high risk; every fifth patient had an average score of ⩾10. However, only 1 patient had a history of VTE (deep vein thrombosis) in group 2 and none in group 1. A total of 51,5% of patients had atrial fibrillation and the average $CHA_2DS_2$-VASc score was 4,5; all these patients had indications for long-term anticoagulant therapy. In group 1 of the remaining 28 patients with sinus rhythm, 12 people had indications for antiplatelet therapy due to coronary artery disease; in group 2, of 36 people with a sinus rhythm, 30 patients had indications for single antiplatelet therapy and 3 people — for dual antiplatelet therapy due to a history of percutaneous coronary intervention. It should be noted that there are currently no evidence-based studies on the adequacy of antiplatelet therapy for the VTE prevention in hospitalized patients, including those with HF. There were no any absolute contraindications for the administration of prophylactic anticoagulation at the time of hospitalization in both groups.

## Discussion

Epidemiological studies in various populations showed a high variability in the prevalence of VTE in HF patients, which is often due to asymptomatic cases of thrombosis, difficulties in timely diagnosis, and the similarity of symptoms of VTE and HF [3, 7]. The contribution of VTE to the all-cause mortality in HF patients is also not fully determined. In a pro-

spective study by Bounameaux H, et al. it was shown that pulmonary embolism may be a primary cause of death in 3-10% of HF patients [8]. When analyzing the national database in the USA for the 2000-2013, the authors noted an increase of VTE prevalence from 0,76% in 2000 to 1,46% in 2013 and decrease in VTE mortality during hospitalizations with HF from 10,8% in 2000 to 7,2% in 2013 [9]. The main pathogenetic mechanisms for increasing the VTE risk in hospitalized cardiovascular patients can be endothelial injury and endothelial dysfunction, dysfunction of anticoagulant protein C system with increased plasma concentrations of pro-inflammatory cytokines (interleukin-6, tumor necrosis factor, etc.), PAR activation, blood stasis with reduced cardiac output, tissue injury with expression of tissue factor activating coagulation cascade, fibrinolysis slowing [10]. Additional risk factors for VTE in HF patients can be: old age, immobilization, infections, frequent central venous catheter use, implantation of pacemakers and defibrillators, which increase the risk of infectious complications and, in general, hypercoagulability. It should be noted that identification of some factors by Caprini score (for example, thrombophilia) is difficult and inappropriate in the general population, and was not performed in our study. However, it must be remembered that underestimation of genetic factors in some cases can lead to an undercount of VTE risk.

The results obtained in our study in patients with class III-IV congestive HF is confirmed in several other studies. So, in the MEDENOX study (Prophylaxis in Medical Patients with Enoxaparin), an almost 2-fold increase in the VTE incidence in patients with class IV compared with class III HF was detected (21,7% vs 12,3%) [11]. This was one of the first evidence-based studies on the efficacy and safety of low-molecular-weight heparins (enoxaparin at a dose of 40 mg) in the primary prevention of VTE. Direct oral anticoagulants (DOACs) for the primary prevention of VTE in hospitalized non-surgical patients were studied in randomized, double-blind, placebo-controlled studies: ADOPT (Apixaban Dosing to Optimize Protection From Thrombosis) — apixaban at a dose of 2,5 mg twice daily up to 30 days [12]; MAGELLAN (Multicenter, Randomized, Parallel Group Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Acutely Ill Medical Patients Comparing Rivaroxaban with Enoxaparin) - rivaroxaban at a dose of 10 mg for 35±4 days [13] and APEX (Acute Medically Ill VTE) Prevention With Extended Duration Betrixaban Study) — betrixaban at a loading dose of 160 mg and then 80 mg for 35-42 days [14]. All drugs were compared with enoxaparin at a dose of 40 mg for 6-14 days. Longer-term use of DOACs was due to high incidence of VTE in the first month after hospital discharge. The proportion of HF patients in this study was 38-44%. Analysis of these three studies by Yami M, et al. demonstrated greater efficacy of longer-term use of DOACs compared with the standard course of enoxaparin for symptomatic VTE (relative risk — RR 0,63; 95% CI 0,46-0,88 ) and all VTEs in general (RR 0,78; 95% CI 0,68-0,90), but without significant differences in asymptomatic VTE (RR 0.84, 95% CI 0,70-1,01) and VTE-related mortality (RR 0,70, 95% CI 0,45-1,08). However, the use of DOACs was accompanied by a higher bleeding risk. So, the RR of major bleeding for the three drugs was 1,99 (95% CI 1,08-3,65); RR of clinically relevant non-major bleeding — 1,86 (95% CI 1,16-2,97) [15]. Betrixaban had the highest safety. In the Russian Federation, an indication for the DOACs use for the primary VTE prevention in hospitalized non-orthopedic patients has not been recorded.

We have not revealed absolute contraindications for the prophylactic anticoagulation at the time of hospital admission. At the same time, it is necessary to take into account the high incidence of anemia in the studied population, which required a further differential diagnosis between anemia of chronic disease and iron deficiency anemia and finding the source of bleeding.

**Study limitations.** The limitations of our study may be due to with a small sample size that does not allow us to estimate the absolute and relative risks of VTE in patients with HF. Cross-sectional study design does not allow dynamically monitoring and evaluating various interventions for the VTE in HF patients. Another limitation may be the features of diagnostics in all patients with HF, which did not allow assessing high-risk thrombophilia, as well as the inability to perform venous ultrasound, which could help identify patients with asymptomatic lower extremity venous thrombosis.

## Conclusion

Thus, all patients hospitalized in the cardiology department had a higher and highest risk of VTE by Caprini score. In the group of patients with class I-II HF, 85% of patients had a highest risk, and with class III-IV HF — 97,6% of patients; mean score of ⩾10 was observed in every fifth patient. Indications for long-term anticoagulant therapy, mainly for atrial fibrillation, were in 51,5% of patients. The remaining patients, with the exclusion of a high bleeding risk, required parenteral prophylactic anticoagulation.

**Relationships and Activities:** not.

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# Long-term mortality risk in hospitalized patients with heart failure after myocardial infarction

Galyavich A. S.[1], Mingalimova I. M.[2], Galeeva Z. M.[1], Baleeva L. V.[1]

**Aim.** Comparative assessment of laboratory and instrumental parameters of patients with heart failure (HF) after myocardial infarction at admission and discharge from the hospital to determine the long-term mortality risk.

**Material and methods.** The clinical outcomes of 117 patients with stage II-III (Strazhesko-Vasilenko Classification) heart failure (64 men and 53 women) were studied. All patients admitted to the hospital underwent laboratory and instrumental examination. The average follow-up for patients after discharge from the hospital was 3 years (12 to 44 months). The long-term mortality risks of HF patients were compared according to the examination data upon admission and discharge from the hospital.

**Results.** The long-term mortality risk factors of HF patients at admission are the levels of pro-brain natriuretic peptide (proBNP) (risk 1,08, p=0,001), D-dimer (risk 1,062, p=0,018), urea (risk 1,048, p=0,016), creatinine (risk 1,006, p=0,016), alanine transaminase (risk 1,002, p=0,009). The long-term mortality risk factors of HF patients at discharge are urea (risk 1,141, p=0,001), N-terminal proBNP (risk 1,101, p=0,002), and the number of neutrophils (risk 1,064, p=0,002).

**Conclusion.** There is a difference in risk factors for long-term mortality risk of HF patients at admission and discharge from the hospital.

**Key words:** heart failure, long-term risk.

**Relationships and Activities:** not.

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Over the previous three decades, significant progress has been achieved in the treatment of heart failure (HF) using angiotensin-converting enzyme inhibitors, beta-blockers, mineralocorticoid receptor antagonists. Nevertheless, patients with HF usually have an unfavorable prognosis [1]. There are numerous studies to assess the risk of adverse events in HF patients; a number of prognostic scales have been proposed [2-4]. However, these scales are not always convenient in clinical practice.

The aim of our study was a comparative assessment of laboratory and instrumental parameters of patients with decompensated HF at admission and discharge from the hospital to determine the long-term mortality risk.

## Material and methods

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The local medical ethics committee approved this study. All participants gave written informed consent. The inclusion criterion was HF confirmed by clinical and laboratory tests in patients 1 year or more after myocardial infarction. There were following exclusion criteria: cancer, blood disorders, obstructive pulmonary diseases, patient unwillingness to participate in the study.

The clinical outcomes of 117 patients (64 men and 53 women) with stage II-III HF (Strazhesko-Vasilenko Classification) were studied. The average follow-up after discharge from the hospital was 3 years (12 to 44 months). The inclusion criterion was HF in patients with a myocardial infarction history. There were following exclusion criteria: atrial fibrillation, severe liver disease, blood disorders, cancer, patient unwillingness to participate in the study.

All patients received medications in accordance with the Russian Heart Failure Society guidelines [5].

All patients admitted to the hospital underwent following examinations: complete blood count, determination of N-terminal pro-brain natriuretic peptide (N-proBNP) level, liver tests (aspartate transaminase (AST), alanine transaminase (ALT), bilirubin, alkaline phosphatase), total protein, albumin, renal function (blood urea and creatinine concentrations, glomerular filtration rate estimation using MDRD equation), carbohydrate metabolism (blood glucose, glycated hemoglobin), coagulation (prothrombin time, fibrinogen and D-dimer tests), highly sensitive C-reactive protein, parameters of myocardial injury (myoglobin, troponin I), serum electrolytes (potassium, sodium, calcium, magnesium), electrocardiography, the Simpson's method of echocardiography with determination of cavity dimensions and left ventricle ejection fraction (LVEF). For each patient, 71 parameters were analyzed during their hospital stay.

Statistical processing was carried out using the parametric and non-parametric methods for data analysis. The accumulation, adjustment, systematization of the baseline data and visualization of the results were conducted using Microsoft Office Excel 2016. Statistical analysis was performed using the IBM SPSS Statistics v.23 software package. The dependence of patient survival on the studied factors was analyzed using the Cox regression model. The data obtained at hospital admission, after discharge and survival on outpatient stage after 44 months of the mean follow-up were assessed and compared.

**Table 1**

**Comparison of significant risk factors for long-term mortality with baseline hazard in HF patients at admission to hospital**

| Risk factor | Hazard changes in the presence of a factor | | p |
|---|---|---|---|
| | $h_i(t)/h_0(t)$ | 95% CI | |
| Alanine transaminase, ME/L | 1,002 | 1,001-1,004 | 0,009 |
| Urea, mmol/L | 1,048 | 1,009-1,088 | 0,016 |
| Creatinine, μmol/L | 1,006 | 1,001-1,011 | 0,016 |
| Hematocrit, % | 0,928 | 0,866-0,994 | 0,034 |
| Hemoglobin | 0,98 | 0,961-0,999 | 0,044 |
| Color index | 0,011 | 0,0-0,971 | 0,049 |
| D-dimer, ng/ml | 1,062 | 1,01-1,117 | 0,018 |
| NT-proBNP, ng/ml | 1,08 | 1,039-1,123 | <0,001 |
| Left ventricular ejection fraction by Simpson's method, % | 0,965 | 0,936-0,995 | 0,022 |

**Abbreviations:** $h_i(t)$ — predicted hazard for long-term mortality in patient i at time t (%), $h_0(t)$ — shared baseline hazard for long-term mortality at time t (%), CI — confidence interval, BNP — brain natriuretic peptide.

**Table 2**

**Comparison of significant risk factors for long-term mortality with baseline hazard in HF patients at discharge from the hospital**

| Risk factor | Hazard changes in the presence of a factor | | p |
|---|---|---|---|
| | $h_i(t)/h_0(t)$ | 95% CI | |
| Duration of treatment, days | 1,086 | 1,002-1,177 | 0,048 |
| Urea, mmol/L | 1,141 | 1,08-1,206 | <0,001 |
| Glomerular filtration rate, ml/min | 0,968 | 0,943-0,994 | 0,015 |
| Hemoglobin | 0,975 | 0,961-0,99 | 0,001 |
| Color index | 0,007 | 0,0-0,542 | 0,025 |
| Neutrophils, % | 1,064 | 1,024-1,105 | 0,002 |
| Lymphocytes, $ng^{-1}$ | 0,427 | 0,221-0,826 | 0,012 |
| Lymphocytes, % | 0,93 | 0,89-0,971 | 0,001 |
| Prothrombin time | 1,056 | 1,001-1,113 | 0,045 |
| Quick's prothrombin time | 0,981 | 0,963-0,999 | 0,038 |
| NT-proBNP, ng/ml | 1,101 | 1,036-1,171 | 0,002 |
| Serum sodium | 0,913 | 0,847-0,985 | 0,019 |
| Left ventricular ejection fraction by Simpson's method, % | 0,965 | 0,936-0,995 | 0,022 |

**Abbreviations:** $h_i(t)$ — predicted hazard for long-term mortality in patient i at time t (%), $h_0(t)$ — shared baseline hazard for long-term mortality at time t (%), CI — confidence interval, BNP — brain natriuretic peptide.

## Results

The all-cause out-hospital mortality of patients with HF after myocardial infarction during the follow-up period was 22,2% (26/117).

Among the analyzed laboratory and echocardiographic parameters upon hospital admission of patients with HF, the following factors were significant: values of ALT, urea, creatinine, hematocrit, hemoglobin, color index, D-dimer, NT-proBNP and LVEF by Simpson's method. These parameters in HF patients observed at admission to the hospital are presented in Table 1.

Among the analyzed laboratory and echocardiographic parameters during discharge from the hospital, the following factors were significant: duration of treatment, values of urea, glomerular filtration rate, hemoglobin, color index, neutrophil count, lymphocyte count, prothrombin time, Quick's prothrombin time test, NT-proBNP, serum sodium and LVEF by Simpson's method. These parameters in HF patients observed at discharge from the hospital are presented in Table 2.

## Discussion

At least 50 biomarkers for assessment of HF severity were studied in clinical trials [6]. There is an opinion of authors [7] that the routine clinical data obtained upon admission of HF patients do not sufficiently predict repeated hospitalizations, but they are more useful as predictors of mortality. At the same time, the authors emphasize that neither the determination of NT-proBNP, nor cardiac troponin levels upon admission improve prediction.

Over the years, researchers have developed various scales for assessing the risk of adverse outcome for HF patients. A meta-analysis of 64 predictive models [8] and a meta-regression of 117 predictive models [9] showed only moderate accuracy in mortality prediction. One of the prognostic scales [2] is devoted to assessing simple parameters of congestive HF (dyspnea, edema, jugular vein distention). The study included 2061 patients with decompensated HF with LVEF <40% and two or more signs of fluid retention. The follow-up period lasted 9 months. Daily, shortness of breath, orthopnea, lower limb swelling, the degree of jugular vein distention, and lung wheezing were evaluated using a 4-point score (0-3). Based on the sum of the scores of three parameters (orthopnea, jugular vein distention and lower limb swelling), a combined congestion scale was developed. The composite endpoints were hospitalizations for HF, all-cause mortality, and their sum. Using the multivariate Cox regression model, the outcomes were estimated at the hospital discharge. Comparisons of the parameters at hospital admission and discharge showed its decrease from 4,07±1,84 to 1,11±1,42. The levels of BNP and NT-proBNP decreased from 734 pg/ml and 4857 pg/ml at admission to 477 pg/ml and 2834 pg/ml at discharge, respectively. The number of points at hospital discharge was associated with an increased risk of end-

points by the 30th day of follow-up and at the end of the study.

In one relatively new analysis, several prognostic risk scores were compared: CHARM, GISSI-HF, MAGGIC, and SHFM [3]. The MAGGIC showed the best overall accuracy, similar to the GISSI-HF but better than the CHARM and particularly better than the SHFM. Researchers have come to the conclusion that performance of prognostic risk scores is still limited and physicians are reluctant to use them in daily practice.

In the previous decade, researchers have developed various prognostic risk scores for mortality and/or hospitalization for HF progression [10] but they have not received wide clinical application. A multiparametric prognostic score has been proposed for patients with reduced LVEF [11], which, from the authors' point of view, is more informative than the SHFM.

In addition, researchers [12] propose using the five strongest predictors of mortality in HF patients: old age, high blood urea nitrogen and NT-proBNP, low hemoglobin levels and non-use of beta-blockers.

The analysis of the initial clinical, laboratory, biochemical, and echocardiography data allowed us to answer very important clinical question — what factors can affect the prognosis of outpatients with HF. To this end, we analyzed the clinical, laboratory, biochemical and instrumental parameters of HF patients at admission to the hospital.

The highest long-term mortality risk upon admission to the hospital for HF patients was due to the levels of the NT-proBNP (risk 1,08, p=0,001), D-dimer (risk 1,062, p=0,018), urea (risk 1,048, p=0,016), creatinine (risk 1,006, p=0,016), ALT (risk 1,002, p=0,009).

The highest long-term mortality risk upon discharge from the hospital for HF patients was due to urea (risk 1,141, p=0,001), NT-proBNP (risk 1,101, p=0,002), neutrophil count (risk 1,064, p=0,002).

The findings may indicate several important management features for HF patients.

According to our data, the prognosis of outpatients with HF depends on the following parameters: HF severity confirmed by the NT-proBNP values; coagulation status (D-dimer); functional state of the kidneys (serum urea and creatinine); functional state of the liver (ALT).

The last two factors may reflect the congested liver and kidneys.

This should lead the doctor to the idea that a patient with HF should take drugs to reduce the severity of HF and diuretics, taking into account the increased risk of thrombosis in this category of patients.

According to our data, the prognosis of HF patients at the hospital stage with adequate therapy is corrected, mainly due to the reduction of kidneys and liver congestion. This is due to the fact that when a patient is discharged from the hospital, the long-term significance of factors such as creatinine and ALT decrease, and the role of D-dimer disappears (possibly due to anticoagulant therapy). However, there remains a risk factor such as serum NT-proBNP, indicating that patients should continue conventional therapy (angiotensin-converting enzyme inhibitors, beta-blockers, mineralocorticoid receptor antagonists).

The contribution of neutrophil count to long-term unfavorable prognosis was unexpected for us. It is known that neutrophils are key mediators in cardiac remodeling, causing an inflammatory response to remove necrotic tissue [13]. The experiment demonstrated the involvement of neutrophils in the mechanisms of cardiac dysfunction, expressed in an increase in type I collagen, which contributed to the remodeling progression and the formation of HF [14]. Our data suggest that peripheral blood neutrophils to some extent contribute to the prognosis of HF patients. This fact must be taken into account when evaluating patients upon discharge from the hospital and upon further outpatient observation.

A comparison of the factors involved in the long-term unfavorable prognosis of HF patients upon hospital admission and discharge leads us to another important conclusion — with an adequate therapy, the long-term prognosis of patients can be significantly changed by reducing both the number of factors and their role.

**Study limitations:** small sample size.

## Conclusion

The long-term mortality risk factors of HF patients at admission are the levels of proBNP (risk 1,08, p=0,001), D-dimer (risk 1,062, p=0,018), urea (risk 1,048, p=0,016), creatinine (risk 1,006, p=0,016), ALT (risk 1,002, p=0,009). The long-term mortality risk factors of HF patients at discharge are urea (risk 1,141, p=0,001NT-proBNP (risk 1,101, p=0,002), and the neutrophil count (risk 1,064, p=0,002).

**Relationships and activities:** not.

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# Beta-adrenergic reactivity of erythrocytes and the progression of heart failure in patients after myocardial infarction

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**Aim.** To identify the associations between beta-adrenergic reactivity of erythrocytes and the progression of heart failure (HF) in patients after myocardial infarction (MI).

**Material and methods.** The study included 50 patients with HF and history of MI 6 months ago. To determine the level of sympathoadrenal system activity, we analyzed beta-adrenergic reactivity by changing the osmotic resistance of erythrocytes by use of adrenoceptor blocking agent.

**Results.** The frequency of HF progression after index MI was 26% (n=13). All patients were divided into 2 groups depending on the presence/absence of HF progression in the postinfarction period.

When determining beta-adrenergic reactivity, it was found that patients with HF progression compared with patients without it had the higher level of beta-adrenergic reactivity of membrane (β-ARM) of erythrocytes: 58,8 (50,9; 78,0) CU and 46,8 (38,0; 66,3) CU, p=0,025). A ROC analysis made it possible to establish the β-ARM level ⩾49,53 CU a cut-off point, which can be considered as a marker of HF progression in patients after MI (sensitivity 92,3%, specificity 62,2%). This level of β-ARM is associated with a more than five-fold increase of HF progression risk in patients after MI (OR 5,48; 95% CI 1,28-23,37; p=0,024).

**Conclusion.** In patients with HF and MI history, there is a decrease in the adrenergic reactivity of erythrocyte cell membrane, which is reflected by an increase of β-ARM above normal range of 20 CU. At the same time, β-ARM in patients with HF progression compared with patients without it is significantly increased. Established cut-off point of β-ARM (⩾49,53 CU) allows predicting the HF progression with high sensitivity and specificity.

**Key words:** adrenergic reactivity, heart failure, myocardial infarction, sympathoadrenal system.

Relationships and Activities: not.

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Heart failure (HF) is a prime medical and socio-economic problem, the relevance of which increases with age [1, 2]. Follow-up of a representative sample of the European part of the Russian Federation (according to the EPOCHA-CHF study) revealed a significant increase in the number of patients with HF over the past 16 years from 4,9 to 8,5%, and the number of patients with severe class III-IV HF increased from 1,8 to 3,1% [1]. According to foreign studies, HF incidence in the population is 2-3%, increasing with age to 7% [3].

One of the main causes of HF is coronary artery disease (CAD). CAD, including myocardial infarction (MI), is identified in 60-70% of patients with HF [1, 4]. An important aspect is the study of the long-term prognosis of patients after MI. This is especially urgent due to big number of available diagnostic and therapeutic approaches to the management of patients with acute coronary pathology [5].

Activation of the sympathoadrenal system (SAS) plays an important role in the pathogenesis of HF and MI [6-8]. Increased sympathetic tone makes a significant contribution to the pathogenesis of HF and affects the course and prognosis of the disease [6, 9, 10]. According to published data, high norepinephrine levels are observed in patients with HF, especially in the advanced stages [9].

At the beginning of this century, R. I. Struk and I. G. Dlusskaya developed an original method for studying the functional state of SAS, based on assessing the degree of adrenergic receptor desensitization to the long-term or regularly occurring effects of high catecholamine levels [11]. So, this is an express method for determining adrenergic reactivity for assessing the destructive effect of catecholamines on membrane cell structures. Inhibition of erythrocyte osmolysis depends on the number of functionally active β-adrenergic receptors on the cell surface and indicates their adrenergic reactivity [11]. In recent decades, experimental studies have established that erythrocytes demonstrates the general patterns of changes in membrane and cell structures under the action of catecholamines and can reflect systemic manifestations of SAS activity [12].

With long-term pronounced catecholamine stimulation, the number of adrenergic receptors on the erythrocyte membrane decreases and their functional state changes as a manifestation of the desensitization of the cell membrane [13]. This fact is a reflection of the single feedback principle of the neuroendocrine system, which demonstrates the inverse relationship between the blood catecholamine levels and the number of cell membrane receptors for them. Accordingly, with an increase of SAS mediators in the blood, the adrenergic receptors of erythrocyte cell membranes desensitize, and beta-adrenergic reactivity of membrane (β-ARM) of erythrocytes increases, while the actual adrenergic reactivity decreases. Conversely, with a decrease in the mediator concentration, β-ARM values decrease, and adrenergic reactivity increases [11]. Thus, the study of the functional state of β-adrenergic receptors to determine the β-AWP value in cardiovascular diseases is an urgent direction aimed at early diagnosis and prognostication. This is also can be used in actual clinical practice due to the high method availability.

Currently, there are few publications in Russia devoted to the problem of studying the functional state of SAS using the presented method in HF, and there are practically no studies evaluating adrenergic reactivity in HF after MI. In this regard, the aim of this study was to identify the association of erythrocyte beta-adrenergic reactivity with progression of HF in patients after MI.

## Material and methods

The study included 50 patients (80% men) 6 months after MI with NYHA class I-III HF. There were following exclusion criteria: thyrotoxicosis; cancer; mental disorder; autoimmune disease; end-stage liver and kidney disease; acute or exacerbation of chronic infectious diseases; decompensated diabetes; valvular heart disease; NYHA class IV HF.

The data collection on the features of acute MI was carried out based on research and information database "Acute myocardial infarction register" of the Tomsk National Research Medical Center (Cardiology Research Institute). We also analyzed outpatient medical records, case histories, and discharge from them.

The mean age of patients at the inclusion time was 57,0±11,5 years in the male cohort (n=40) and 72,1±10,2 years in the female (n=10). Therefore, men were significantly younger than women ($p<0,001$, $t=-3,79$). The diagnosis of HF was established in accordance with Russian and European guidelines for the management of heart failure [1, 2]. The clinical condition of patients, in addition to determining the class of HF, was assessed using the clinical state scale (CSS) in V. Yu. Mareev's modification. We also analyzed the quality of life of patients by the EQ-5D-3L questionnaire, as well as the therapy taken by patients at the inclusion time.

At the time of inclusion in the study, all patients underwent beta-adrenergic reactivity analysis to determine the change in erythrocyte osmotic resistance by use of adrenoceptor blocking agent with the BETA-ARM AGAT reagent kit. This method is based on the inhibition of erythrocyte hemolysis with beta-blocker use. Human erythrocytes undergo hemolysis, the degree of which is determined by the

**Table 1**

**Clinical and anamnestic characteristics of patients after MI, depending on clinical course of heart failure**

| Parameter | Group 1 (progressive heart failure) n=37 | Group 2 (progressive heart failure) n=13 | p |
|---|---|---|---|
| Age, Me (Q25;Q75), years | 59,0 (48,5;63,5) | 70,0 (49,0;78,0) | 0,093 |
| Male/Female, n (%) | 29 (78,4)/8 (21,6) | 11 (84,6)/2 (15,4) | 0,99 |
| CSS score, Me (Q25;Q75), points | 2,0 (2,0;4,0) | 5,0 (3,0;7,0) | 0,006 |
| EQ-5D-3L, Me (Q25;Q75) score, points | 3,0 (2,0;4,0) | 4,0 (3,0;5,0) | 0,134 |
| History of smoking, n (%) | 9 (24,3) | 3 (23,1) | 0,99 |
| Characteristics of MI: | | | |
| Q-wave MI, n (%) | 28 (75,6) | 8 (61,5) | 0,462 |
| STEMI, n (%) | 34 (91,9) | 10 (76,9) | 0,257 |
| Complications, n (%) | 25 (67,6) | 6 (46,2) | 0,171 |
| Coronary angiography data at the time of MI: | | | |
| Single-vessel stenosis ⩾ 50%, n (%) | 3 (8,1) | 4 (30,8) | 0,065 |
| Multi-vessel stenosis ⩾ 50% (two or more CA), n (%) | 29 (78,4) | 7 (53,8) | 0,149 |
| Echocardiographic data at the time MI: | | | |
| LVEF, Me (Q25; Q75), % | 58,0 (51,3;63,0) | 56,0 (44,5;61,5) | 0,256 |
| LVMI, Me (Q25; Q75), mm | 98,0 (89,8;115,0) | 112,5 (99,8;119,5) | 0,043 |
| End-systolic volume, Me (Q25; Q75), ml | 45,0 (35,0;60,8) | 53,0 (43,5;81,0) | 0,123 |
| End-diastolic volume, Me (Q25; Q75), ml | 110,5 (87,5;125,0) | 110,0 (105,0;161,5) | 0,230 |
| E/A, Me (Q25; Q75), CU | 0,84 (0,74;1,19) | 0,81 (0,71;1,26) | 0,658 |
| Background disease: | | | |
| Hypertension, n (%) | 31 (83,8) | 11 (84,6) | 0,99 |
| Obesity, n (%) | 9 (24,3) | 6 (46,2) | 0,140 |
| Type 2 diabetes, n (%) | 5 (13,5) | 1 (7,7) | 0,99 |

**Abbreviations:** CA — coronary artery, CSS — clinical state scale, LVEF — left ventricular ejection fraction, LVMI — left ventricular mass index, Me (Q25; Q75) — median and interquartile range, MI — myocardial infarction.

optical density of the supernatant. The beta-blocker solution is added to the experimental sample, where it binds to the beta-receptors of the cell membrane and inhibits hemolysis. The optical density of the supernatant in the experimental sample is expressed as a percentage of the optical density in the control sample. Percent units are taken as conventional units (CU) of β-AWP. Normal ranges of β-AWP were considered from 2 to 20, which were proposed by the authors of this method (R.I. Stryuk and I.G. Dlusskaya (2003)). β-AWP >20 CU indicated reduced adrenergic reactivity, reflecting a decrease in the number of adrenergic receptors on the erythrocyte membrane.

Endpoint analysis (progression of HF) was performed after follow-up of 6 months. HF progression was recorded in cases of an increase in HF functional class.

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The medical ethics committee of Tomsk National Research Medical Center (Cardiology Research Institute) approved this study. All participants gave written informed consent.

Statistical processing was carried out using Statistica 10 and SPSS 20.0 (demo version) software. Qualitative characters are presented as absolute and relative values of n (%). Nominal data analysis was performed using the Pearson's chi-squared test and the two-sided Fisher's exact test if the expected character value in at least one cell of the contingency table was <5. Analysis of quantitative data for distribution normality was carried out using the Shapiro-Wilk test. Quantitative characters corresponding to the normal distribution are presented as mean value and standard deviation (M±SD). Student's t-test was used in the case of a normal distribution and the equality of variances. Quantitative data that do not correspond to the normal distribution are presented

**Table 2**

**Analysis of therapy in groups at the time of inclusion in the study**

| Parameter | Group 1 (stable heart failure) n=37 | Group 2 (progressive heart failure) n=13 | p |
|---|---|---|---|
| β-blockers, n (%) | 32 (86,5) | 11 (84,6) | 0,99 |
| ACE inhibitors, n (%) | 20 (54,1) | 11 (84,6) | 0,095 |
| ARB, n (%) | 5 (13,5) | 1 (7,7) | 0,99 |
| Diuretics, n (%) | 6 (16,2) | 5 (38,5) | 0,09 |
| MRA, n (%) | 3 (8,1) | 2 (15,4) | 0,595 |

**Abbreviations:** ACE inhibitors — angiotensin-converting enzyme inhibitors, ARB — angiotensin II receptor blockers, MRA — mineralocorticoid receptor antagonists.

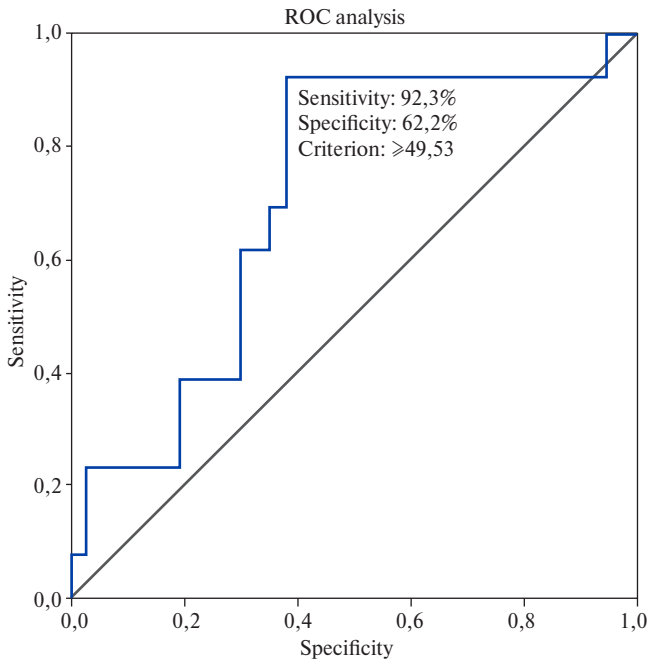


**Figure 1.** Sensitivity and specificity of β-AWP levels in stratification of the progression risk for heart failure in patients after MI (ROC analysis).

as the median and interquartile range (Me (Q25;75)). To compare the quantitative characters in two independent samples with non-normal distribution, the Mann-Whitney U-test was used. ROC analysis with the construction of a characteristic curve and the estimation of area under the curve (AUC) and odds ratio (OR) were performed to determine and characterize the associations between the studied factors. Differences were considered significant at $p<0,05$.

## Results

According to inclusion criteria, all patients after MI who were included in the study had HF. Distribution of patients depending on class was as follows: class I — 23 patients (46%), class II — 19 patients (38%), class III — 8 patients (16%).

Analysis of MI revealed that the vast majority of patients were diagnosed with Q-wave MI (72%, n=36) and ST-segment elevation MI (88%, n=44). In general, index MI was characterized by a typical clinical picture (94%, n=47). Complications occurred in 62% of cases (n=31). Moreover, almost every second patient (42%, n=21) at the time of MI had a history of CAD, the duration of which in 24% of cases (n=12) was >5 years.

During the 6-month follow-up, HF progression was diagnosed in 26% of patients (n=13). All patients were divided into 2 groups, depending on the presence/absence of HF progression after MI. Group 1 included 37 patients with stable HF; group 2 — 13 patients with HF progression after MI (Table 1).

According to the CSS, the clinical status of group 2 patients was more severe: the score was 5 (3,0;7,0), which was 2,5 times higher than in group 1 (2 (2,0; 4,0); p=0,006). However, the level of quality of life did not significantly differ in the studied groups (p=0,1). The clinical picture of MI, complications of acute MI, severity of coronary atherosclerosis, and the background diseases did not significantly differ between groups with stable and progressive HF (p>0,05). Parameters of left ventricle (LV) structural and functional state also did not differ significantly between groups. However, according to echocardiography, LV mass index was slightly higher in group 2 patients (p=0,043), while LV hypertrophy was comparable.

At the time of inclusion in the study, there were no significant differences in taking certain groups of drugs in the studied groups. So, the main classes of drugs recommended for the HF treatment, such as β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists were prescribed equally often in both groups. The need for diuretic therapy was slightly higher in the group of patients with pro-

gressive HF (16,2% vs 38,5%). However, due to the small number of patients, these differences were not significant (p=0,09) (Table 2).

Analysis of beta-adrenergic reactivity at the inclusion time showed that patients of group 2 had higher β-AWP compared with group 1 (58,8 (50,9;78,0) CU vs 46,8 (38,0; 66,3) CU, respectively; p=0,025). At the same time, in both studied groups, the β-AWP values significantly exceeded standard rate of 20 CU.

To identify relationships between the beta-adrenergic reactivity levels and the probability of HF progression after MI, and to assess the possibility of using the β-AWP for stratifying the risk of HF progression in patients after MI, an ROC analysis was performed with AUC, which was 0,71 at p=0,025 (95% confidence interval (CI) 0,55-0,87). When analyzing the ROC curve, it was found that β-AWP ⩾49,53 CU can be considered as a marker of HF progression in patients after MI (sensitivity 92,3%, specificity 62,2%) (Figure 1).

We also found that β-AWP ⩾49,53 CU were observed in 37,8% of patients (n=14) in the group with a stable HF, while similar values of β-AWP in patients with progressive HF were diagnosed much more often — in 76,9% of patients (n=10) Odds ratio calculation showed that the level of β-AWP ⩾49,53 CU associated with a more than five-fold increase of HF progression risk in patients after MI (OR 5,48; 95% CI 1,28-23,37; p=0,024).

## Conclusion

The general position that catecholamine increase is accompanied by desensitization of membrane adrenergic receptors is confirmed by the numerous clinical and experimental studies. There is little number of studies on the functional state of SAS in HF patients, but the results of these studies reflect a significant excess of the average beta-adrenergic reactivity in HF patients compared with patients without HF, as well as an increase in patients with more severe HF [4, 12, 14]. In earlier studies, the authors conclude that beta-adrenergic reactivity of cell membranes may be diagnostically valuable in assessing HF severity and, together with other clinical data, be a criterion for an individual reaction of organism in adaptation process during SAS activation [15]. All this indirectly confirm the theory that the adrenergic reactivity of erythrocytes to a certain extent reflects the general adrenergic reactivity of the organism and can be extrapolated to it [11].

Our study also confirms the hypothesis that the β-AWP value is significantly associated with the clinical course of HF in patients after MI. We showed that in patients with progressive HF after MI, a decrease in adrenergic reactivity (β-AWP increase) is characteristic, which is consistent with the results of previous studies in patients without a history of MI [14, 15]. In this study, β-AWP ⩾49,53 CU was first established as a marker of HF progression in patients after MI.

## Conclusion

In patients with HF and MI history, there is a decrease in the adrenergic reactivity of erythrocyte cell membrane, which is reflected by an increase of β-ARM above normal range of 20 CU. At the same time, β-ARM in patients with HF progression compared with patients without it is significantly increased.

Established cut-off point of β-ARM (⩾49,53 CU) allows predicting the HF progression with high sensitivity and specificity (92,3 and 62,2, respectively). β-AWP ⩾49,53 CU associated with a more than five-fold increase of HF progression risk in patients after MI (OR 5,48; 95% CI 1,28-23,37; p=0,024).

**Relationships and Activities:** not.

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# Heart failure in human immunodeficiency virus-infected patients

Goryacheva O. G., Koziolova N. A.

**Aim.** To determine the features of heart failure (HF) development in patients with human immunodeficiency virus (HIV) infection.

**Material and methods**. In a general hospital, 160 patients were examined during the year. All of them were divided into 2 groups: group 1 (n=100) — HIV-infected patients with specific clinical picture of HF; group 2 (n=60) — patients without HIV infection and with HF verified by echocardiography and concentration of N-terminal prohormone of brain natriuretic peptide (NT-proBNP).

**Results.** In comparison with group 2, HIV-infected patients had the following statistically significant differences: lower left ventricular ejection fraction (LVEF), lower prevalence and severity of left ventricle diastolic dysfunction, higher LV mass index (LVMI), and lower NT-proBNP. HIV-infected patients had statistically significant moderate inverse relationship of LVEF (r=-0,43; p=0,015), E/e' (r=-0,32; p=0,045), LVMI (r=-0,46; p=0,002) and strong relationship of NT-proBNP (r=-0,54; p<0,001) with CD4 T-lymphocyte count in 1 $mm^3$ in the presence of HF symptoms and signs and an increase in NT-proBNP over 125 pg/ml. In group 1, there was a significantly higher prevalence of smoking, chronic alcoholism, drug use, chronic hepatitis C and cirrhosis (especially manifested by hepatomegaly and splenomegaly in combination with ascites and hepatic cytolysis), chronic pancreatitis, pneumonia and inflammatory diseases accompanied by higher erythrocyte sedimentation rate and C-reactive protein concentration, and lower hemoglobin level. HIV-infected patients were statistically less likely to use all groups of drugs for HF treatment, with the exception of spironolactone, and more likely to use drugs for multimorbidity treatment.

**Conclusion.** The HF prevalence in hospitalized HIV-infected patients, estimated on the basis of symptoms and NT-proBNP increase >125 pg/ml, was 54%; on the basis of LVEF decrease <50% — 32%. The clinical picture of HIV-infected patients is characterized by various symptoms, including those typical for HF with normal NT-proBNP level, due to the high prevalence of comorbidities and concurrent medication.

**Key words**: heart failure, human immunodeficiency virus.

**Relationships and Activities:** not.

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Cardiac injury in HIV-infected patients is a common pathology in clinical practice. A number of researchers have identified a certain form of cardiac pathology in HIV-infected patients — HIV-associated cardiomyopathy. It is associated with the direct damaging effect of HIV infection on the myocardium, accompanied by apoptosis of cardiomyocytes and fibroblasts [1]. Cardiac injury in HIV infection has a multifactorial pathogenesis, characterized not only by a direct damaging effect, but also by the influence of a secondary infection, leading to the development of myo-, peri- and endocarditis, and by the use of antiretroviral therapy with cardiotoxicity [2, 3].

The patterns of the heart failure (HF) formation, its phenotypes, such as cardiac dysfunction in HIV-infected patients have been little studied and the effectiveness of conventional HF therapy has not been investigated. The choice of certain type of antiretroviral treatment in this category of patients has also not been determined. So, according to some reports, in 8% of HIV-infected people there is myocardial injury with severe dilatation of the cavities and a significant contractility decrease [2]. HF with systolic dysfunction of the left ventricle (LV) in HIV-infected patients occurs 10 years earlier than in patients without HIV infection [4]. With antiretroviral therapy, early diastolic dysfunction (DD) is formed due to the stimulation of myocardial fibrosis [3].

Thus, the presented study attempted to identify the features of HF formation in HIV-infected patients in order to further study the problem and select HF and antiretroviral therapy.

The aim of this study was to determine the features of HF formation in HIV-infected patients.

## Material and methods

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The local medical ethics committee approved this study. All participants gave written informed consent.

**Table 1**

**Comparison of parameters reflecting the clinical course and severity of heart failure between groups (n=160)**

| Parameter | Group 1 (HF and HIV infection, n=100) | Group 2 (HF, n=60) | p |
|---|---|---|---|
| CSS, points | 5,89 [3,22; 5,12] | 6,33 [3,98; 6,38] | 0,128 |
| 6MWT, m | 437,2±126,9 | 372,4±41,2 | <0,001 |
| Mean HF FC | 2,3 [1,4; 3,2] | 2,5 [1,8; 3,5] | 0,128 |
| RHR, bpm | 86,76±16,27 | 78,75±11,53 | 0,001 |
| RHR >70 bpm, abs./% | 76/76,0 | 36/0,60 | 0,050 |
| LVEF, % | 56,0±11,1 | 65,3±15,7 | <0,001 |
| LVEF >50%, abs./% | 68/68,0 | 45/75,0 | 0,447 |
| LVEF 40-49%, abs./% | 26/26,0 | 10/16,7 | 0,242 |
| LVEF <40%, abs./% | 6/6,0 | 5/8,3 | 0,809 |
| E/A | 1,26 [1,0; 1,62] | 1,11 [0,86; 1,68] | 0,089 |
| E/e´ mean | 11,8 [4,5; 17,3] | 15,0 [10,5; 19,3] | <0,001 |
| E/e´ mean >14, abs./% | 24/24,0 | 41/68,3 | <0,001 |
| LV IVRT, ms | 94,0±35,7 | 92,7±18,9 | 0,682 |
| LVDD, abs./% | 40/40,0 | 41/68,3 | 0,002 |
| Left atrial volume/BSA, ml/m$^2$ | 29,21 [24,11; 38,06] | 25,12 [15,41; 34,03] | 0,106 |
| Left atrial volume/BSA >34 ml/m$^2$ | 36/36,0 | 11/20,0 | 0,051 |
| LVMI, g/m$^2$ | 132,2 [96,5; 151,0] | 109,2 [78,6; 118,5] | <0,001 |
| LVMI >110 g/m$^2$ for men, >95 g/m$^2$ for women | 88/88,0 | 28/46,7 | <0,001 |
| NT-proBNP, pg/ml | 159,1 [49,9; 539,7] | 234,6 [187,1; 558,6] | <0,001 |
| NT-proBNP >125 pg/ml, abs./% | 54/54,0 | 60/100,0 | <0,001 |

**Abbreviations**: A — peak late filling velocity, BSA — body surface area, CSS — clinical state scale, E — peak early filling velocity, e' — velocity of early diastolic mitral annulus motion, FC — functional class, HIV — human immunodeficiency virus, HF — heart failure, IVRT — isovolumic relaxation time, LVEF — left ventricular ejection fraction, LVDD — left ventricular diastolic dysfunction, LVMI — left ventricular mass index, NT-proBNP — N-terminal pro-brain natriuretic peptide, RHR — resting heart rate, 6MWT — six-minute walk test.

**Table 2**

**Anamnestic characteristics of groups (n=160)**

| Parameter | Group 1 (HF and HIV infection, n=100) | Group 2 (HF, n=60) | p |
|---|---|---|---|
| Age, years | 36,0±6,3 | 54,0±8,6 | <0,001 |
| Gender, M/F, abs./% | 63/37 (63/37) | 16/44 (27/73) | <0,001/<0,001 |
| Smoking, abs./% | 67 /67,0 | 16/26,7 | <0,001 |
| Chronic alcoholism, abs./% | 46/46,0 | 0/0 | <0,001 |
| History of narcotic use, abs./% | 87/87,0 | 0/0 | <0,001 |
| HTN, abs./% | 28/28,0 | 52/86,7 | <0,001 |
| CAD, abs. | 2/2,0 | 21/35,0 | <0,001 |
| IM history, abs./% | 1/1,0 | 9/15,0 | <0,001 |
| Type 2 diabetes, abs./% | 8/8,0 | 10/16,7 | 0,156 |
| AF, abs./% | 2/2,0 | 7/11,7 | 0,027 |
| Ventricular rhythm disturbances, abs./% | 30/30,0 | 15/25,0 | 0,618 |
| History of TIA, stroke, abs./% | 4/4,0 | 5/8,3 | 0,426 |
| History of CABG, PCI, abs./% | 0/0 | 5/8,3 | 0,014 |
| Chronic hepatitis C, abs./% | 83/83,0 | 1/1,7 | <0,001 |
| Cirrhosis, abs./% | 46/46,0 | 1/1,7 | <0,001 |
| Chronic pancreatitis, abs./% | 31/31,0 | 4/6,7 | 0,001 |
| History of infectious endocarditis, abs./% | 4/4,0 | 0/0 | 0,297 |
| Pneumonia, abs./% | 18/18,0 | 3/5,0 | 0,035 |
| Inflammatory diseases, abs./% | 11/11,0 | 0/0 | 0,020 |
| Thromboembolism (history, acute phase), abs./% | 8/8,0 | 2/3,3 | 0,400 |
| Osteoarthritis, abs./% | 0/0 | 10/16,7 | <0,001 |

**Abbreviations:** AF — atrial fibrillation, CABG — coronary artery bypass grafting, CAD — coronary artery disease, HIV — human immunodeficiency virus, HTN — hypertension, MI — myocardial infarction, PCI — percutaneous coronary intervention, TIA — transient ischemic attack.

In a general hospital, 160 patients were examined during the year. All of them were divided into 2 groups: group 1 (n=100) — HIV-infected patients with specific clinical picture of HF; group 2 (n=60) — patients without HIV infection and with HF verified by echocardiography and concentration of N-terminal prohormone of brain natriuretic peptide (NT-proBNP). There were following inclusion criteria: typical symptoms and specific signs of stable HF; verified HIV infection (group 1); typical symptoms and specific signs of stable heart failure, confirmed by echocardiography and NT-proBNP increase >125 pg/ml (group 2). There were following exclusion criteria: acute coronary syndrome <3 months ago; acute or decompensated HF; history of stroke or transient ischemic attack <3 months old; active cancer; dementia and mental illness preventing the patient from signing informed consent.

The assessment of the HF functional class (FC) was carried out using the clinical state scale (CSS) in V. Yu. Mareev's modification and the six-minute walk test (6 MWT).

Echocardiography was performed using VIVID T8 system (GE Healthcare, USA) according to the standard methodology recommended by the American Society of Echocardiography and European Association of Echocardiography. The LV ejection fraction (LVEF) was determined by the Simpson's method. Preserved LVEF was considered 50% or more, mid-range — 40-49%, reduced — <40%. Assessment of LV diastolic function was carried out with determination of transmitral flow velocity characteristics and visualization of mitral annulus motion.

The serum NT-proBNP levels were determined using the Vector Best reagent kit (Russia) by enzyme-linked immunosorbent assay on an Immulite 1000 analyzer (DPC, USA).

Statistical processing was performed using the Statistica 13.0. An analysis of the distribution type was carried out using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Quantitative characters are presented as follows: mean values and standard deviations with normal distribution (M±SD); median, lower and upper quartiles with non-normal distribution (Me [LQ; UQ]). For qualitative characters, the absolute frequency of character manifestation and detection percentage (%) were estimated. For a statistical analysis of the normally distributed

**Table 3**

**Clinical and laboratory characteristics of groups (n=160)**

| Parameter | Group 1 (HF and HIV infection, n=100) | Group 2 (HF, n=60) | p |
|---|---|---|---|
| BMI, kg/m$^2$ | 20,8±4,0 | 28,1±6,3 | <0,001 |
| BMI >30 kg/m$^2$, abs./% | 10/10,0 | 21/33,3 | <0,001 |
| SBP, mmHg | 128,4±19,5 | 124,9±14,5 | 0,159 |
| DBP, mmHg | 79,1±15,0 | 85,2±7,4 | 0,004 |
| Ascites, abs./% | 12/12,0 | 1/1,7 | 0,044 |
| Hepatomegaly, abs./% | 66/66,0 | 19/31,7 | <0,001 |
| Splenomegaly, abs./% | 32/32,0 | 1/1,7 | <0,001 |
| Hemoglobin, g/L | 118,4 [101,7; 138,4] | 129 8 [113,9; 149,0] | 0,005 |
| Fasting plasma glucose, mmol/L | 5,1 [4,3; 6,8] | 5,4 [4,8; 8,3] | 0,128 |
| Total cholesterol, mmol/L | 5,1 [3,6; 6,5] | 5,7 [2,8; 7,1] | 0,098 |
| CD4-T lymphocyte count, cells/mm$^3$ | 150 [43; 300] | - | - |
| Serum sodium, mmol/L | 141,8±6,5 | 139,4±8,4 | 0,074 |
| Serum potassium, mmol/L | 4,0 [3,6; 4,5] | 4,2 [3,8; 4,6] | 0,541 |
| Total bilirubin, μmol/L | 11,0 [10,0; 16,0] | 14,5 [9,6; 18;1] | 0,726 |
| ALT, ME/L | 31,0 [20,1; 60,4] | 22,4 [18,5; 24,3] | 0,018 |
| AST, ME/L | 44,5 [30,3; 75,0] | 25,8 [19,6; 31,9] | 0,008 |
| Serum creatinine, μmol/L | 86,4 [66,2; 107,1] | 79,1 [55,4; 101,3] | 0,084 |
| GFR (CKD-EPI), ml/min/1,73 m$^2$ | 84,3±32,0 | 77,6±18,1 | 0,028 |
| GFR (CKD-EPI) <60 ml/min/1,73 m$^2$, abs./% | 18/18,0 | 8/13,3 | 0,580 |
| ESR, mm/h | 32,2 [25,3; 59,0] | 18,6 [15,3; 34,8] | <0,001 |
| C-reactive protein, mg/l | 34,0 [12,1; 96,2] | 4,8 [3,7; 9,8] | <0,001 |

**Abbreviations:** ALT — alanine aminotransferase, AST — aspartate aminotransferase, BMI — body mass index, DBP — diastolic blood pressure, ESR — erythrocyte sedimentation rate, GFR — glomerular filtration rate, HIV — human immunodeficiency virus, HF — heart failure, SBP — systolic blood pressure.

data obtained, the parametric methods were used — Student's t-test, for qualitative characters — chi-squared test. With non-normally distributed data, nonparametric statistics were used to compare quantitative and qualitative characters: the Wilcoxon T test and the Chi-squared test with Yates's correction, respectively. Differences were considered significant at p<0,05. A correlation analysis was carried out using Spearman's rank correlation coefficients.

## Results

Table 1 presents the diagnostic criteria and characteristics of HF development in groups of subjects.

Given the comparability of the groups by severity of clinical manifestations, an objective assessment of the presence and incidence of HF in HIV-infected patients was performed based on NT-proBNP increase >125 pg/ml and amounted to 54%; on echocardiography LVEF decrease <50% — 32%; on LVDD — 40%; on combination of LVDD with an increase in the left atrial volume index >34 ml/m$^2$ and LV mass index (LVMI) >110 g/m$^2$ in men and >95 g/m$^2$ in women — 87%; on NT-proBNP increase >125 pg/ml and/or LVEF <50% and/or LVDD and changes in the cardiac structure — 98%.

HIV-infected patients had significantly lower LVEF, less severe LVDD, higher LVMI, and lower NT-proBNP levels. HIV-infected patients had significant moderate inverse relationship of LVEF (r=-0,43; p=0,015), E/e' (r=-0,32; p=0,045), LVMI (r=-0,46; p=0,002) and strong relationship of NT-proBNP (r=-0,54; p<0,001) with CD4 T-lymphocyte count in 1 mm$^3$ with HF symptoms and signs and an increase in NT-proBNP over 125 pg/ml..

Anamnestic characteristics of groups are presented in Table 2.

Clinical and laboratory characteristics of groups are presented in Table 3.

In group 1, there was a significantly higher prevalence of smoking, chronic alcoholism, drug use, chronic hepatitis C and cirrhosis (especially manifested by hepatomegaly and splenomegaly in combination with ascites and hepatic cytolysis), chronic pancreatitis, pneumonia and inflammatory diseases accompanied by higher erythrocyte sedimentation

**Table 4**

**Structure of treatment of heart failure and comorbidities in groups (n=160)**

| Group of drugs (abs./%) | Group 1 (HF and HIV infection, n=100) | Group 2 (HF, n=60) | p |
|---|---|---|---|
| ACE inhibitors | 25/25,0 | 36/60,0 | <0,001 |
| ARA | 5/5,0 | 21/35,0 | <0,001 |
| Diuretics (loop and/or thiazide) | 14/14,0 | 17/28,3 | 0,044 |
| Beta blockers | 10/10,0 | 44/73,3 | <0,001 |
| Spironolactone | 25/25,0 | 6/10,0 | 0,025 |
| Digoxin | 0/ 0 | 3/5,0 | 0,014 |
| Anticoagulants | 2/2,0 | 3/5,0 | 0,558 |
| Antiplatelet agents | 0/0 | 36/60,0 | <0,001 |
| Statins | 1/1,0 | 12/20,0 | <0,001 |
| Antianginal agents (calcium antagonists, nitrates, trimetazidine, ivabradine) | 2/2,0 | 21/35,0 | <0,001 |
| Blood glucose-lowering drugs | 2/2,0 | 3/5,0 | 0,558 |
| Antibiotics | 73/73,0 | 6/10,0 | <0,001 |
| NSAIDs | 48/48,0 | 12/20,0 | 0,002 |
| Fluconazole | 11/11,0 | 0/0 | 0,020 |
| Iron supplements | 11/11,0 | 0/0 | 0,020 |
| Proton pump inhibitors | 23/23,0 | 5/8,3 | 0,032 |

**Abbreviations:** ACE inhibitors — angiotensin-converting enzyme inhibitors, ARA — angiotensin receptor antagonists, HIV — human immunodeficiency virus, HF — heart failure, NSAIDs — non-steroidal anti-inflammatory drugs.

rate and C-reactive protein concentration, and lower hemoglobin level. It was associated with symptom variety, including typical for HF, such as dyspnea, palpitation, weakness, fatigue, fluid retention, liver enlargement. HF patients without HIV infection were older, mostly women, more often had a history of hypertension, coronary artery disease, myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention, atrial fibrillation, and were more likely to use drugs for HF treatment. HIV-infected patients had a lower body mass index.

Table 4 presents the structure of treatment of HF and comorbidities in groups.

HIV-infected patients were significantly less likely to use all groups of drugs for HF treatment, with the exception of spironolactone, which is used for treatment of ascites in HIV-infected patients.

Patients with HIV infection significantly more often used drugs for multimorbidity treatment, such as antibiotics, non-steroidal anti-inflammatory drugs, fluconazole, iron supplements, proton-pump inhibitors.

Only 19% of HIV-infected patients received antiretroviral therapy.

The studies presented reflect problems associated with NT-proBNP levels. This study did not reveal As a result of the study, no early markers of myocardial damage were detected (galectin-3, sST2, micro-ribonucleic acid-27), which could confirm the presence of heart failure in patients with normal levels of NT-proBNP. The study included patients with acute inflammatory pathology (pneumonia, acute inflammatory diseases), which can be caused by unconfident accompanied myocarditis.

The limitations of the study are a small sample size of patients with HIV infection and significant heterogeneity of this group by NT-proBNP levels. The study did not assess early markers of myocardial injury (galectin-3, sST2, micro-ribonucleic acid-27), which could confirm the HF in patients with normal NT-proBNP levels. The study included patients with acute inflammatory pathology (pneumonia, acute inflammatory diseases), which could be the cause of unverified myocarditis, accompanied by transient HF.

## Conclusion

The prevalence of HF in HIV-infected patients is unknown. In our study, the incidence of HF in HIV-infected patients, estimated based on the clinical symptoms and NT-proBNP increase >125 pg/ml, was 54%. In study by Alvi RM, et al., the HF incidence in HIV-infected patients was 16,8% [5]. A lower incidence rate of HF was probably due to the fact that 90% of the patients received antiretroviral therapy, 62% of them with a health-promoting effect. Therefore, this therapy suppressed immuno-medi-

ated damage to cardiomyocytes and fibroblasts. The authors found that an NT-proBNP increase in HIV-infected patients is associated with cocaine use, LVEF decrease, progression of HF and significant CD4 T-lymphocyte count decrease in 1 $mm^3$. We also obtained significant relationships between LVEF and NT-proBNP with the CD4 T-lymphocyte count in 1 $mm^3$.

The prevalence of LVEF changes in HIV-infected patients is debatable. In our study, only 6% of HIV-infected patients with HF had LVEF <40%, 26% — from 40 to 49%, 68% — >50% According to European data, HIV-infected people are more likely to have HF with reduced EF (40%), in 30% — HF with preserved EF, in 15% — HF with mid-range EF; in 15% the diagnosis of HF is uncertain [6]. The difference of above-mentioned data with our study can be explained by the overdiagnosing of HF in patients with normal NT-proBNP levels. Using earlier and more accurate biomarkers of myocardial injury, such as galectin-3 or sST2, the diagnosis of HF would be confirmed in every third patient with a normal level of myocardial stress [7]. There are studies that are consistent with our findings on LVEF in HIV-infected patients. Thus, in study by Chaudhary S, et al., cardiomegaly with LV contractile function reduction was recorded only in 8 of 73 HIV-infected patients; left heart structural changes were detected in 52,1%, while NT-proBNP increase was found only in 26,7% [8].

An analysis of the results of our study showed that there are certain difficulties in the diagnosis of HF in HIV-infected patients, which are associated with a high incidence of comorbidities and multimorbidities. This, on the one hand, leads to the symptoms and signs typical for HF that are not related to it, and on the other hand, affecting the clinical course of HF with both increasing and decreasing the concentration of natriuretic peptides [9]. According to study by Wagnew F, et al., anemia observed in 22,3% (95% CI 18,5-26,0%) of HIV-infected patients, clinically manifested by the dyspnea and tachycardia without established HF [10]. In study by Christensen S, et al., the incidence of hepatitis B (5,9% vs 03,%, p<0,001) and hepatitis C (8,8% vs 0,3%, p<0,001) in HIV-infected patients with hepatomegaly, and in case of cirrhosis, with ascites and splenomegaly, was significantly higher in comparison with patients without HIV infection [11].

Visceral adiposity, autoimmune hypothyroidism, a high frequency of taking mineralocorticoid receptor antagonists to suppress congestion in cirrhosis in HIV-infected patients can lead to a decrease in the natriuretic peptides levels, even with HF [12]. Taking certain antiviral drugs, such as synthetic low-molecular weight interferon inducer tilorone, which induces the formation of interferons (alpha, beta, gamma, lambda), suppress myocardial stress estimated by the NT-proBNP concentration [13].

The use of antiretroviral therapy in HIV-infected patients, especially in the high-dose regimen at the beginning of treatment, exacerbates myocardial dysfunction and, with prolonged use, leads to myocardial fibrosis and severe HF with high NT-proBNP levels with prolonged use [14].

Given the variety of clinical symptoms and high prevalence of multimorbidities in HIV-infected patients, Scherzer R, et al. divided patients depending on the level of biomarker increase into 3 clusters with a certain phenotype of myocardial injury [15]. Cluster 1 (n=143) was characterized by the lowest level of markers such as NT-proBNP, C-reactive protein, sST2 and others. In cluster 2, a predominant increase in sST2, NT-proBNP, and growth differentiation factor 15 (cardiac phenotype) was found. Cluster 3 (n=103) had higher levels of C-reactive protein, IL-6, and D-dimer (inflammatory phenotype). This approach of dividing HIV patients into clusters allowed the authors to show the versatility of pathogenetic mechanisms and forms of HF. Inflammatory phenotype was associated with increased risk of LVDD by 51% and a 3,3-fold higher 7-year mortality risk; cardiac phenotype was associated with increased risk of pulmonary hypertension by 67% and a 3,1-fold higher risk of all-cause mortality.

Thus, the study of HF development in HIV-infected people has demonstrated that many aspects of the prevalence, diagnosis, and therapy selection have not been investigated; current data are contradictory. Therefore, further research is necessary in order to improve the quality of life and prognosis of patients with HIV infection.

## Conclusion

The HF prevalence in hospitalized HIV-infected patients, estimated on the basis of symptoms and NT-proBNP increase >125 pg/ml, was 54%; on the basis of LVEF decrease <50% — 32%. The clinical picture of HIV-infected patients is characterized by various symptoms, including those typical for HF with normal NT-proBNP level, due to the high prevalence of comorbidities, multimorbidities and concurrent medication. HIV-infected patients were significantly less likely to use all groups of drugs for HF treatment, with the exception of spironolactone, compared with subjects without HIV infection. Only 19% of HIV-infected patients received antiretroviral therapy.

**Relationships and activities:** not.

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

Soldatova A. M., Kuznetsov V. A., Gizatulina T. P., Malishevsky L. M., Dyachkov S. M.

**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.

**Key words:** cardiac resynchronization therapy, heart failure, first-degree AV block.

**Relationships and Activities:** not.

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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 examination, 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.

**Table 1**

**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:<br>Anteroseptal<br>Inferior wall | <br>7,7<br>13,5 | <br>15,2<br>27,3 | 0,040 |
| Rhytm:<br>sinus<br>paroxysmal AF<br>permanent AF | <br>78,8<br>13,5<br>7,7 | <br>60,6<br>33,3<br>6,1 | 0,055 |
| AV node ablation | 7,7 | 6,1 | 0,956 |
| NYHA class of HF (%): II<br>III<br>IV | 46,1<br>40,4<br>13,5 | 34,3<br>54,5<br>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 (%):<br>normal<br>mild<br>moderate<br>severe | <br>3,8<br>22,2<br>61,5<br>13,5 | <br>-<br>15,2<br>78,8<br>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].

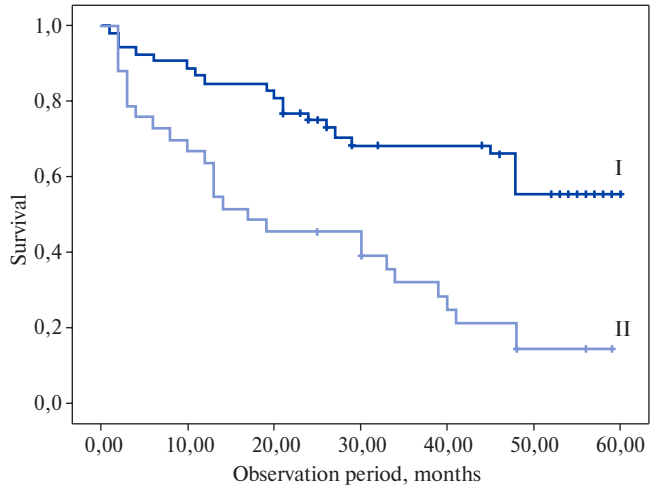


**Figure 1.** Survival of patients in groups depending on the PR interval.
**Note:** I — PR <200 ms (59,6%), II — PR ⩾200 ms (18,2%), Log-rank test p<0,001.

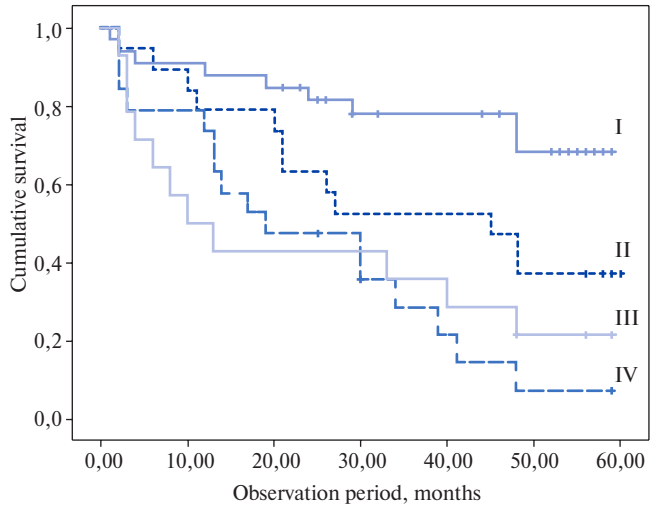


**Figure 2.** Survival of patients in groups depending on the duration of QRS complex and the PR interval.
**Note:** I — QRS ⩾150 ms, PR <200 ms (72,7%); II — QRS <150 ms, PR <200 ms (36,8%); III — QRS ⩾150 ms, PR ⩾200 ms (21,4%); IV — QRS <150 ms, PR ⩾200 ms (15,8%). Log-rank test: I vs II p=0,031; 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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# Ventricular-arterial coupling parameters and its prognostic value in patients with decompensated heart failure

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**Aim.** To assess ventricular-arterial coupling (VAC) parameters and their prognostic value in patients with decompensated heart failure (HF).

**Material and methods**. VAC parameters were evaluated upon admission using two-dimensional echocardiography in 355 patients hospitalized with decompensated HF. VAC was expressed as the ratio between arterial elastance (Ea) and end-systolic LV elastance (Ees). The optimal VAC range was considered 0,6-1,2. Parameters of left ventricular (LV) efficacy were calculated using the appropriate formulas. Differences were considered significant at p<0,05.

**Results.** The median values of Ea, Ees and VAC were 2,2 (1,7;2,9) mmHg/ml, 1,8 (1,0;3,0) mmHg/ml and 1,32 (0,75;2,21) respectively. In 63% of patients, VAC disorders were detected: 55% of patients had VAC >1,2 (predominantly patients with HF with reduced ejection fraction (HFrEF)-79%), 8% of patients had VAC <0,6 (all patients with HF with preserved ejection fraction (HFpEF)). Normal VAC was observed in 78%, 42%, and 1% of patients with HFpEF, HF with mid-range EF and HFrEF, respectively. There was significant correlation between Ea/Ees ratio and levels of NTproBNP (R=0,35), hematocrit (R=-0,29), hemoglobin (R=-0,26), pulmonary artery systolic pressure (PAPs) (R=0,18), dimensions of left atrium (R=0,32) and right ventricle (RV) (R=0,32).

After 6 months, rehospitalization with decompensated HF was recorded in 72 (20,3%) patients, 42 (11,8%) patients died. Ea decrease <2,2 mmHg/ml and PAPs increase >45 mmHg increased the risk of rehospitalization with decompensated HF and all-cause mortality 2,5 and 3,7 times, respectively.

**Conclusion.** Impaired VAC was diagnosed in 63% of patients with decompensated HF. However, the increased risk of all-cause mortality and rehospitalization with decompensated HF over the 6 months was associated with Ea decrease <2,2 mmHg/ml and PAPs increase >45 mmHg.

**Key words**: ventricular-arterial coupling, arterial elastance, ventricular elastance, heart failure.

**Relationships and Activities.** The study was supported by PFUR Program "5-100".

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Ventricular-arterial coupling (VAC) is one of the main parameters of cardiac and aortic performance, and also plays an important role in representing the pathophysiology of cardiovascular diseases. VAC reflects how optimal is the transfer of stroke volume from the left ventricle (LV) to systemic arterial circulation [1]. Noninvasively, it is evaluated by the ratio of arterial elastance (Ea) to LV end-systolic elastance (Ees) [2]. Normal ranges of VAC varies from 0,6 to 1,2.

Elastance shows how much pressure will change when its volume changes. Ees reflects myocardial contractility and stiffness of LV [3]. Ea reflects a certain parameters characterizing arterial load: peripheral resistance, impedance, and systemic arterial compliance. As the disease progresses, both Ea and Ees can become abnormal, but the Ea/Ees ratio may remain within normal ranges.

The following parameters are used to describe LV energy: pressure-volume area (PVA), LV stroke work (SW), potential energy (PE), LV transfer efficiency (SW/PVA) (Figure 1).

PVA is circumscribed by three sides (the end-diastolic pressure–volume relation curve, the end-systolic PV relation (ESPVR) line and the systolic segment of the PV trajectory). PVA consists of two parts: the external mechanical work (the area within the PV trajectory) and the potential mechanical work (area underneath the ESPVR), which represents the PE that accumulates in the LV wall during systole [4].

Only exact concordance of Ees and Eas can lead to the most effective LV work to transfer the necessary blood volume against a certain pressure.

In patients with heart failure (HF) with reduced ejection fraction (HFrEF), an Ees decrease is observed due to a LV contractility reduction [5]. Decrease in cardiac output and increase in heart rate (HR) and peripheral resistance leads to an Ea increase. As a result, in this category of patients, the VAC increases by three to four times, the energy and mechanical work of the LV decreases, and the PE increases.

Patients with HF with preserved ejection fraction (HFpEF) have a lower VAC values compared with a healthy population due to an increase in Ea and Ees by about 40% and 50%, respectively. At the same time, adaptation reserves of external work increasing are reduced with an increase in load [6].

It has been shown that an assessment of VAC has independent diagnostic and prognostic value and can be used to clarify risk and monitor therapeutic interventions. Thus, study of 41 patients with myocardial infarction showed an association between VAC and 5-year cardiovascular mortality (p=0,019) [7].

Thus, treatment aimed at improving the interaction between myocardial performance and vascular function can affect the progression of cardiovascular diseases [8, 9]. So, significant improvement in VAC and LV work during therapy in 42 patients with decompensate HF was noted [10].

The aim was to study the parameters of VAC and their effect on the prognosis in patients with decompensated HF (DHF).

## Material and methods

The study included 355 patients hospitalized with DHF (median age 75 years; mainly men). Most subjects had a history of hypertension; half had a history of myocardial infarction; one in four had a history of chronic kidney disease and rehospitalizations for 12 months; the median of N-terminal pro-brain natriuretic peptide (NTproBNP) was 3763 pg/ml. There were following exclusion criteria: acute coronary syndrome; end-stage kidney and liver disease; cancer and autoimmune disease; edema of another nature. Classification of HF phenotypes was carried out depending on the LV ejection fraction (LVEF): <40% — HFrEF, 40-49% — HF with mid-range EF (HFmrEF), ⩾50% — HFpEF. Among patients with DHF, 44% had HFrEF, 20% — HFmrEF, and 36% — HFpEF. The median length of hospital stay was 9 (interquartile interval 7;10) days.

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The local medical ethics committee approved this study. All participants gave written informed consent.

Echocardiographic parameters were evaluated for all patients using the Vivid 7 Ultrasound System (General Electric, USA).

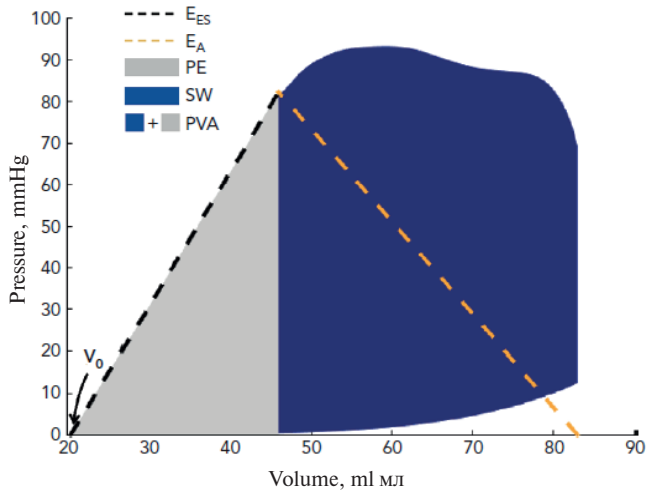


**Figure 1.** Pressure–volume loop analysis.
**Abbreviations:** Ea — arterial elastance, Ees — ventricular elastance, PE — potential energy, PVA — pressure-volume area, SW — stroke work [4].

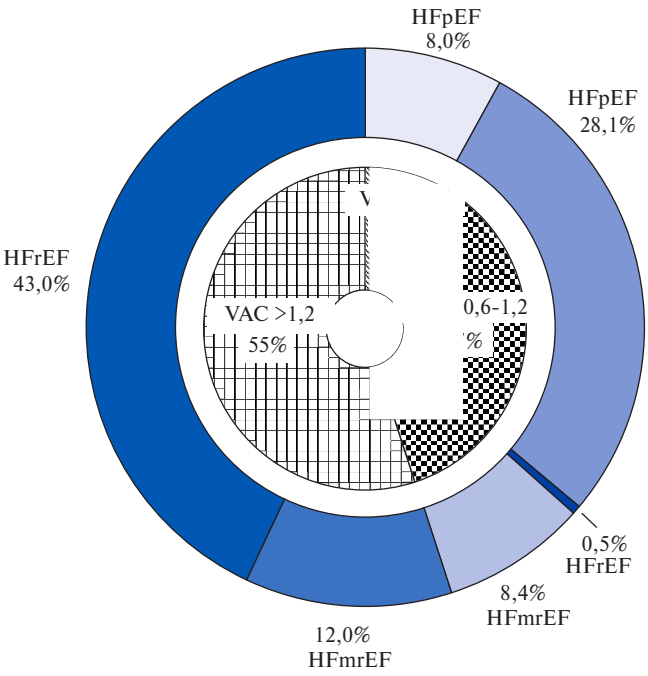


**Figure 2.** Distribution of HF phenotypes depending on the VAC.
**Abbreviations:** HFmrEF — heart failure with mid-range ejection fraction, HFpEF — heart failure with preserved ejection fraction, HFrEF — heart failure with reduced ejection fraction, VAC — ventricular-arterial coupling.

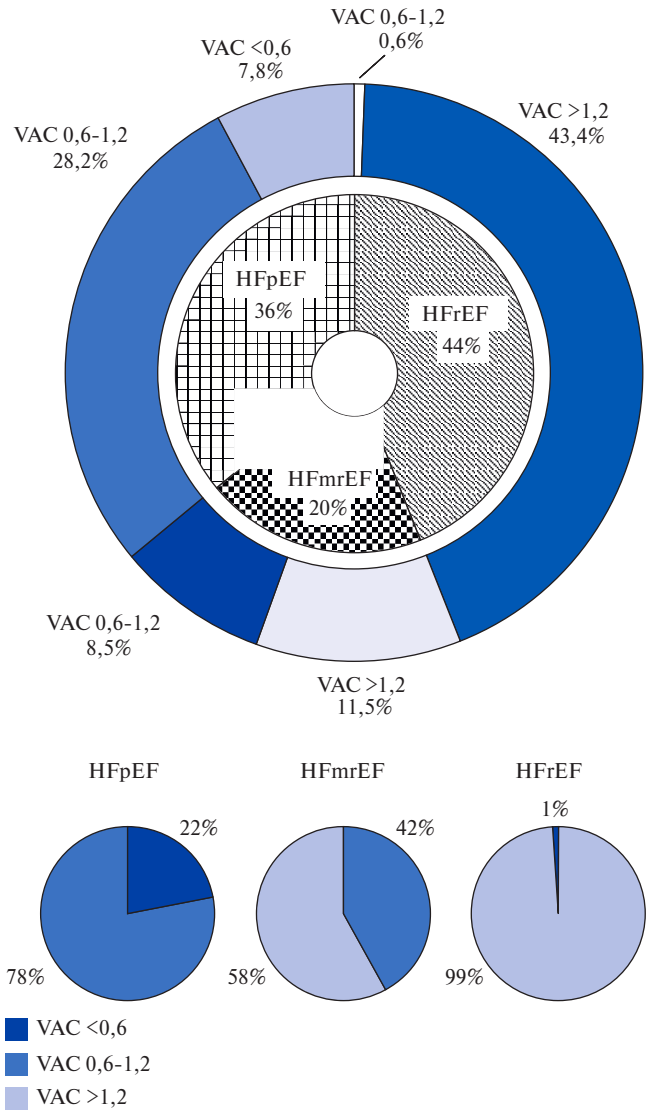


**Figure 3.** Distribution of VAC depending on the HF phenotypes.
**Abbreviations:** HFmrEF — heart failure with mid-range ejection fraction, HFpEF — heart failure with preserved ejection fraction, HFrEF — heart failure with reduced ejection fraction, VAC — ventricular-arterial coupling.

VAC was expressed as the ratio between Ea and Ees. Ees was obtained as the ratio of end systolic pressure (ESP) to end systolic volume (ESV); Ea was obtained as the ratio of ESP to stroke volume (SV). ESP was calculated as ESP=0,9 x systolic blood pressure (SBP).

The parameters characterizing LV energy were calculated:

Potential energy (PE): ESPxESV/2-EDPxESV/4, where EDP-end diastolic pressure;

External mechanical work, or stroke work (SW): SW=ESPxSV;

Pressure-volume area (PVA): PVA=SW+PE;

LV mechanical efficiency: SW/PVA.

After 6 months, adverse outcomes (rehospitalizations with DHF and all-cause mortality) were recorded by a structured telephone survey

Statistical processing was performed using the Statistica software for Windows (version 8.0). The type of distribution was determined by the Kolmogorov-Smirnov test and the Shapiro-Wilk test. To compare the quantitative characters in two different groups, the Mann-Whitney U test was used. For qualitative characters in two and three groups, the significance of differences was evaluated using the Pearson's chi-squared test. To assess the diagnostic effectiveness, ROC analysis with area under the curve (AUC) was used. The significance of differences in one group at different points was evaluated using the Wilcoxon test. Differences were considered significant at $p<0,05$. Kruskal-Wallis test was used for comparing the quantitative parameters in the three groups (lower significance level $p<0,017$).

## Results

Patients hospitalized with DHF had the following medians of Ea, Ees and VAC: 2,2 (1,7; 2,9) mm Hg/ml, 1,8 (1,0; 3,0) mm Hg/ml and 1,32 (0,75; 2,21), respectively.

In 223 (63%) patients, there were VAC abnormalities (values outside the range of 0,6-1,2): VAC decrease (<0,6) was observed in 28 (8%) patients (all

**Table 1**

**Differences between groups depending on the VAC**

| Parameter | VAC 0,6-1,2 (N=132) | VAC <0,6 (N=28) | VAC >1,2 (N=195) | p | r |
|---|---|---|---|---|---|
| SBP, mm Hg, (Me (IQR)) | 140 (130;160) | 145 (130;170)$^{§§}$ | 130 (114;150)** | <0,001 | -0,24 |
| SBP <110 mm Hg, n (%) | 11 (8,3) | 1 (3,6) | 35 (17,9) | 0,01 | |
| Heart rate, bpm, (Me (IQR)) | 86 (74;100) | 80 (70;90)$^{§}$ | 94 (76;115)* | 0,0007 | 0,20 |
| NT-proBNP, pg/ml, (Me (IQR)) | 2884 (1489;4718) | 2801 (929;4458)$^{§}$ | 4458 (2855;5926)* | 0,004 | 0,35 |
| Hematocrit, (M±SD) | 0,38±0,07 | 0,35±0,09$^{§}$ | 0,41±0,07* | 0,009 | -0,29 |
| LVEF, %, (Me (IQR)) | 55 (50;60)$^{††}$ | 69 (68;72)$^{§§§}$ | 33 (25;38)** | <0,001 | -0,88 |
| RV, cm, (Me (IQR)) | 3,0 (2,7;3,5) | 3,0 (2,7;3,5)$^{§}$ | 3,3 (3,0;3,7)** | <0,001 | 0,32 |
| LA, cm, (Me (IQR)) | 4,5 (4,2;4,9)$^{†}$ | 4,2 (4,0;4,7)$^{§§§}$ | 4,8 (4,5;5,2)** | <0,001 | 0,32 |

**Note:** * — p<0,01, ** — p<0,001 — significance of differences compared with the group with normal (0,6-1,2) VAC, † — p<0,05, †† — p<0,001 — significance of differences compared with the group with reduced (<0,6) VAC, § — p<0,05, §§ — p<0,01, §§§ — p<0,001 — significance of differences compared with the group with increased (<1,2) VAC.

**Abbreviations:** LA — left atrium, LVEF — left ventricular ejection fraction, NT-proBNP — N-terminal pro-brain natriuretic peptide, RV — right ventricle, SBP — systolic blood pressure, VAC — ventricular-arterial coupling.

patients with HFpEF); VAC increase (>1,2) — in 195 (55%) patients (79% of patients with HFrEF) (Figure 2).

Only 2 (1%) patients with HFrEF, 30 (22%) patients with HFmrEF and 100 patients with HFpEF had normal VAC values (Figure 3).

Analysis of hemodynamic, laboratory, and echocardiographic data (Table 1) depending on the VAC showed that patients with VAC >1,2 compared with patients of the other two groups were characterized by higher values of NT-proBNP, hematocrit, heart rate, diameters of right ventricle (RV) and left atrium (LA), lower values of SBP and LVEF.

Comparison of VAC parameters depending on LVEF demonstrated that patients with HFrEF compared with patients with other HF phenotypes were characterized by the lowest Ees and highest VAC values. Patients with HFmrEF compared with HFpEF had lower Ees and higher VAC values (Figure 4). Patients with different phenotypes of HF (depending on LVEF) did not differ in Ea.

When studying the parameters of LV energy (Figure 5), it was found that as the LVEF decreased, an increase in potential energy was observed, as well as a decrease in the external work and mechanical efficiency of the LV.

In patients with VAC >1,2, the median length of hospital stay was 10 (8;12) days, in patients with VAC 0,6-1,2 — 9 (8;12) days, in patients with VAC <0,6 — 11 (8;14) days. No significant differences were found in the hospitalization length in patients with different VAC. During hospitalization, 1,5% of patients died.

After 6 months, 42 (11,8%) patients died. Rehospitalizations with DHF was recorded in 72 (20,3%) patients. No significant differences were found in the VAC and LV energy between patients with/without adverse outcomes. Patients with adverse events had significantly lower Ea (2,1 (1,7; 2,8; 2,8) vs 2,3 (1,9; 3,0) mm Hg/ml, p=0,048) and Ees levels (1,5 (0,7; 2,5) vs 1,9 (1,0; 3,1) mm Hg/ml, p=0,03). Patients with adverse outcomes compared with patients without adverse outcomes were characterized by lower values of SBP (130 (115;150) vs 140 (130;160) mmHg), higher values of NT-proBNP (4687 (3277;6220) vs 3396 (1555;5052) pg/ml) and pulmonary artery systolic pressure (PASP) (53 (46;66) vs 45 (34;64) mmHg), larger RV dimensions (3,3 (3,0;3,7) vs 3,0 (2,8;3,5 ) cm).

In multivariate analysis, independent predictors of adverse outcomes were Ea (β=-0,63), PASP (β=1,02). Using ROC analysis, the following threshold values for Ea and PASP were obtained, indicating an unfavorable prognosis: decrease in Ea <2,2 mm Hg/ml and increase in PASP >45 mm Hg raised the risk of rehospitalizations with DHF and all-cause mortality by 2,5 and 3,7 times, respectively (Table 2).

## Discussion

The results of our study showed that more than half of patients hospitalized with DHF have a VAC abnormalities: 55% — increased, 8% — reduced.

According to a study of 72 patients with stable HF and LVEF >45% (all had a history of hypertension, more than half (62%) were women, mean age 71 years), a decrease in VAC was observed in 52% of patients [11]. In our study, patients with HFpEF were characterized by a normal and reduced VAC (78 and 22%, respectively). An increase in the proportion of patients with normal VAC and DHF may be associ-

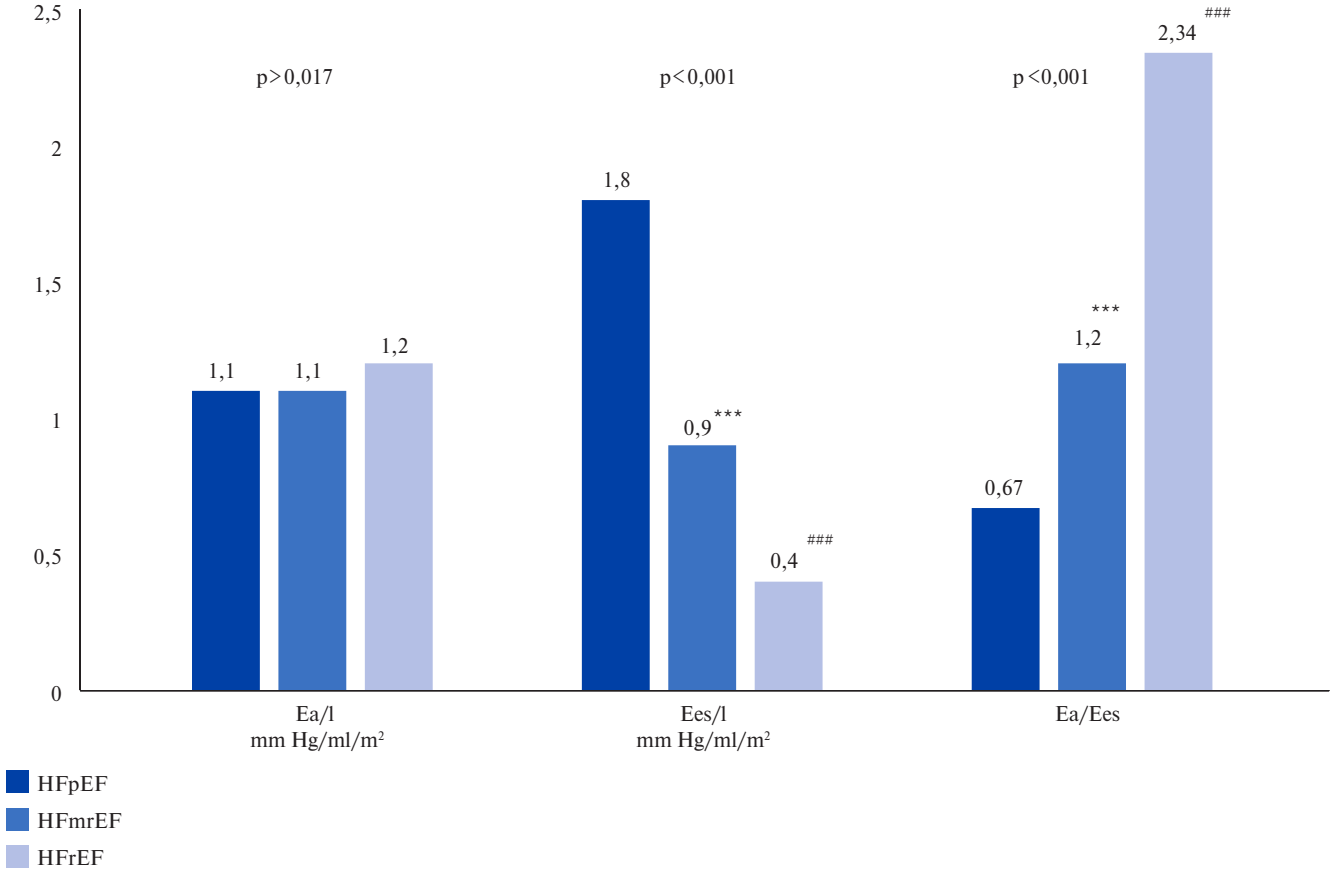


**Figure 4.** Characteristics of VAC parameters depending on LVEF.
**Note:** *** — p<0,001 - significance of differences compared with the HFpEF group, ### — p<0,001 — significance of differences compared with the HFmrEF and HFpEF groups.
**Abbreviations:** Ea — arterial elastance, Ees — ventricular elastance, HFmrEF — heart failure with mid-range ejection fraction, HFpEF — heart failure with preserved ejection fraction, HFrEF — heart failure with reduced ejection fraction, VAC — ventricular-arterial coupling.

ated with the "pseudonormalization" of the VAC. This phenomenon is characterized by normal VAC for LVEF of 45-54% in combination with more severe clinical HF manifestations (increased NT-proBNP levels and 6-minute walk distance).

In a study of 96 patients with stable HFrEF <40% (all patients with hypertension, mean age 63 years, 56% men), 87% of patients had a VAC >1,2 [11]. In our study, 99% of patients with decompensated HFrEF had a VAC increase. It is likely that the increase in the proportion of patients with an elevated VAC is associated with more severe structural and functional changes in the myocardium with DHF.

In a study of 466 patients with HFrEF (median follow-up 3,4 years), an association of VAC with the functional class of HF, NT-proBNP increase, and adverse outcomes (death, heart transplantation, LV assist device implantation, cardiovascular hospitalization) was revealed [12].

In a study of 891 patients with a previously diagnosed or suspected coronary artery disease who have negative stress echocardiography, VAC was measured at peak stress and at rest. It was found that all-cause mortality was higher in patients with impaired VAC reserve [13].

In our study, there were no significant differences in the VAC values in groups with/without rehospitalizations with DHF or all-cause death after follow-up of 6 months. In multivariate analysis, independent predictors of unfavorable prognosis were Ea (β=-0,63) and PASP (β=1,02).

According to published data, a decrease in arterial elasticity in HF is associated with several mechanisms, such as abnormal smooth muscle tone, a decrease in elastin/collagen of arterial wall, and a change in vessel geometry [1]. Since the LV and arterial work are interconnected, a decrease in afterload and cardiac output in severe HFrEF leads to mean BP reduction, resulting in a decrease in arterial elastance [14]. The afterload reduction may be partially caused by vasodilators.

In our study, it was found that in patients with DHF, the arterial elastance has a greater effect on the

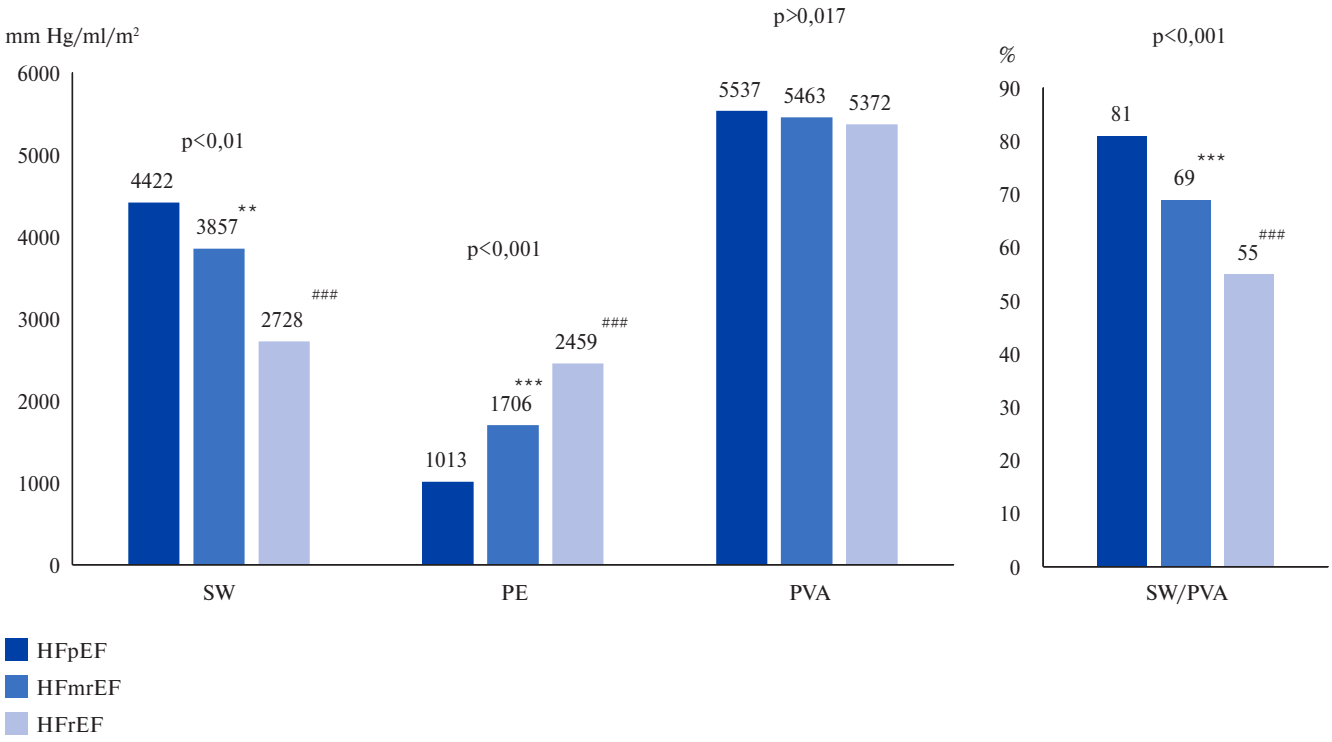


**Figure 5.** Characteristics of LV energy depending on LVEF.
**Note:** ** — p<0,01, *** — p<0,001 — significance of differences compared with the HFpEF group, ### — p<0,001 — significance of differences compared with the HFmrEF and HFpEF groups.
**Abbreviations:** HFmrEF — heart failure with mid-range ejection fraction, HFpEF — heart failure with preserved ejection fraction, HFrEF — heart failure with reduced ejection fraction, PE — potential energy, PVA — pressure-volume area, SW — stroke work, VAC — ventricular-arterial coupling.

**Table 2**

**Predictors of unfavorable prognosis based on ROC analysis**

| Parameter | Threshold value | AUC | 95% CI | Sensitivity, % | Specificity, % | OR |
|---|---|---|---|---|---|---|
| Ea | <2,2 | 0,593 | 1,39-4,34 | 63,6 | 57,6 | 2,5 |
| PASP | >45 | 0,634 | 1,74-7,45 | 75,9 | 51,3 | 3,7 |

**Abbreviations:** AUC — area under the curve, CI — confidence interval, Ea — arterial elastance, OR — odds ratio, PASP — pulmonary artery systolic pressure.

unfavorable prognosis than the LV end-systolic elastance. These data also confirm an aggressive load reduction in acute HF and show that LV resistance has less pathophysiological significance than arterial elasticity.

**Study limitations.** One of the limitations is that at the hospitalization, there may have been some delays in performing examinations related to the severity of the patient's condition. Also, given the large number of patients with atrial fibrillation, the assessment of central BP was carried out using an equation, and not using applanation tonometry. In addition, we evaluated the outcomes after 6 months. Probably, longer follow-up in this category of patients is necessary in order to fully assess the VAC effect on the prognosis.

## Conclusion

The results of our study confirm the impaired cardiovascular function in patients with DHF. With disease progression, Ea and Ees may deviate from normal values, and the ratio of Ea/Ees may be close to normal values. Therefore, the measurement of each component of this ratio can describe and quantify the interaction of the heart and blood vessels. In our study, the VAC parameters are associated with a risk of adverse outcomes in the studied population. Thus, treatment aimed at improving VAC by enhancement of both or each of its components can delay the progression of HF and possibly improve prognosis.

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# Diagnostic value of N-terminal pro-B-type natriuretic peptide in hemodialysis patients

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**Aim.** To assess the diagnostic value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in hemodialysis (HD) patients.

**Material and methods.** A total of 80 patients over the age of 18 with an end-stage renal disease (ESRD) on HD were included in this study. NT-proBNP serum levels were measured for all patients in addition to traditional clinical and biochemical studies. Transthoracic echocardiography and bioimpedance spectroscopy using the Body Composition Monitor (BCM) device (Fresenius, Germany) were performed for all patients on HD. Patients were divided into two groups depending on the hydration status determined by BCM. Patients were also divided into three groups depending on the ejection fraction (EF) of the left ventricle: HF with reduced EF (less than 40%) (HFrEF), mid-range EF (from 40% to 49%) (HFmrEF), and HF with preserved EF (50% or more) (HFpEF). Three groups of patients were identified according to quartile level of NT-proBNP (<1095 pg/ml (n=20); 1095-4016 pg/ml (n=40); >4016 pg/ml (n=20).

**Results.** The median of the NT-proBNP serum level was 2114,6 [1095; 4016] pg/ml. A significant increase in the NT-proBNP levels was found in HD patients with hyperhydration ($p<0,05$). Statistically significant differences were generally found between the concentration of NT-proBNP depending on the LVEF (n=80). However, in pairwise comparisons, significant differences were found only between the groups of patients with HFpEF and HFmrEF ($p=0,02$); a tendency to differences was revealed when comparing the groups of HFpEF and HFrEF ($p=0,07$). A proportional increase in the concentration of prohormone to the increase in systolic dysfunction was found while analyzing the median NT-proBNP, both among all patients and after separation into groups depending on the hydration status. A tendency to increase the frequency of new cardiovascular events, systolic and diastolic myocardial dysfunction in group of patients with prohormone increase was revealed.

**Conclusion.** NT-proBNP serum levels in HD patients are significantly higher than the average population levels. A significant increase in the NT-proBNP levels was found in hemodialysis patients with hyperhydration. NT-proBNP should be used as an additional method for the diagnosis of heart failure on HD, including clarifying of the phenotype of heart failure depending on left ventricle EF. NT-proBNP high levels in patients on HD may be associated with a risk of developing cardiovascular events, systolic and diastolic myocardial dysfunction. It is necessary to use an examination algorithm for the differential diagnosis of heart failure and hyperhydration syndrome during dialysis: clinical examination, bioimpedansometry, transthoracic echocardiography, determination of serum NT-proBNP level.

**Key words:** chronic kidney disease, hemodialysis, NT-proBNP, heart failure, cardiovascular diseases.

**Relationships and Activities:** not.

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Despite advances in dialysis technology, cardiovascular mortality in the population of patients receiving extracorporeal therapy remains high [1-4]. Hemodialysis (HD) patients have both structural and functional cardiovascular changes. Factors such as volume (fluid) overload, hypertension [5], vascular access features [6, 7], anemia, hypoalbuminemia, neurohumoral disorders, the effects of systemic inflammation and drugs [1, 8], and cardiovascular calcification [9] increase the risk of left ventricular (LV) dysfunction. These factors can lead to the development and/or progression of irreversible cardiac dysfunction and severe heart failure (HF), increasing the probability of adverse outcomes in HD patients [10, 11]. The prevalence of HF in HD patients is still the matter of debate [10, 12]. The difference in data on the true HF prevalence in patients on HD is due to many factors and depends on the characteristics of the studied patient population and the difficulties of its diagnosis.

In the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, HF is defined as a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress [13]. However, these "typical" symptoms in HD lose their value, because they can be observed even in patients without HF. The similarity of the clinical symptoms of HF and hyperhydration in the HD patients demonstrates the need for additional diagnostic methods to differentiate these conditions. Such methods, in addition to traditional clinical assessment, include transthoracic echocardiography (TTE), hydration status evaluation by bioelectrical impedance analysis (BIA). It is relevant to use for HF diagnosis and monitoring the N-terminal pro-B-type natriuretic peptide (NT-proBNP) released from ventricular myocytes in response to excessive stretching associated with elevated filling pressure [14, 15].

## Material and methods

The study included 80 patients (52 men — 65%) with end-stage renal disease (ESRD) who received HD during hospitalization at the Saratov Regional Clinical Hospital and have been under observation since the start of extracorporeal therapy. The follow-up period ranged from 1 to 135 months. Patients received hemodiafiltration 3 days a week for at least 4 hours of session time on Fresenius 5008 machine (Germany) using a bicarbonate dialysis solution and high-flux dialyzers. All patients received adequate dialysis (actual dialysis dose per hemodiafiltration session (spKt/V) >1,4; substitution solution volume >63 L/weak).

There were following inclusion criteria: age 18 years or more; signed informed consent. The exclusion criteria were: poor heart visualization by TTE; valvular heart disease (congenital and/or acquired before starting renal replacement therapy); acute infectious diseases (HIV, hepatitis B, C, sepsis, infective endocarditis, tuberculosis, etc.) or chronic disease exacerbations (peptic ulcer, cholecystitis, etc.); cancers and lymphoproliferative disorders, including their history.

Two groups of patients were divided depending on the hydration status. Depending on left ventricular ejection fraction (LVEF), three groups of patients were distinguished: patients with reduced EF (<40%) (HFrEF), with mid-range EF (40% to 49%) (HFmrEF), and with preserved EF (50% or more) (HFpEF).

According to the NT-proBNP level, 3 groups of patients were distinguished based on quartiles to assess the clinical characteristics of each group as the quartile level of prohormone increased: <1095 pg/ml (n=20); 1095-4016 pg/ml (n=40); >4016 pg/ml (n=20).

All 80 patients underwent conventional clinical examination and biochemical tests. We determined the serum level of NT-proBNP by enzyme-linked immunosorbent assay (ELISA) using the NTproBNP-IFA-BEST reagent kit manufactured by AO Vector-Best, Novosibirsk. The reaction results were recorded using the iMark photometer (BioRad, USA). The NTproBNP concentration in the analyzed serum and control samples was determined according to the calibration curves using the Zemfira photometer control program and stated in pg/ml. The reference value is the concentration of NT-proBNP <200 pg/ml, determined in the blood serum of 165 healthy individuals aged 20-50 years. In the inter-dialytic period, all patients underwent TTE on the Acuson 128 XP/10 ultrasound system and BIA on the BCM machine.

The statistical processing was carried out using the IBM SPSS Statistics 23 software package. For the description of quantitative parameters with normal distribution, mean value and standard deviation (M±SD) were used; to describe the parameters with non-normal distribution the median, lower and upper quartiles were used (Med; 25-75%). To assess the differences in quantitative parameters in two independent groups, the Mann-Whitney test was used. When comparing variables in more than two independent groups, Kruskal-Wallis test was used. To assess the differences in the frequency of occurrence

**Table 1**

**Initial clinical and laboratory characteristics of the studied patients receiving hemodialysis**

| Parameter | All patients(n=80); M±SD; Med;25-75% | Patients without hyperhydration (n=62); M±SD; Med;25-75% | Patients with hyperhydration (n=18); M±SD; Med;25-75% | Comparison of groups of patients with normal hydration status and hyperhydration; p value |
|---|---|---|---|---|
| Gender (men/women) | 52/28 | 41/21 | 11/7 | |
| Age, years | 58 [42,5;64,5]<br>53,9±13,8 | 58 [46;66]<br>55±13,3 | 58 [37;62]<br>50,3±15,2 | 0,29 |
| Total time of dialysis, months | 44 [16;94] | 42 [18;86] | 47,5 [9;117] | 0,87 |
| BMI, kg/m$^2$ | 25,6 [22;29,6] | 28,4 [24,5;31,2] | 21,6 [21;22] | 0,002* |
| Ultrafiltration rate, ml/kg/h | 8,2 [6,5;10,1] | 8,1 [6,5;9,9] | 9,6 [6,8;13,2] | 0,13 |
| Effective dialysis time, min/week. | 732 [728;739] | 732 [728;739] | 734 [728;740,5] | 0,91 |
| spKt/V | 1,6 [1,49;1,74] | 1,6 [1,49;1,71] | 1,6 [1,5;1,9] | 0,46 |
| Substitution solution volume, l/weak. | 73 [68,6;78,3] | 72,9 [69,4;78,1] | 75,9 [68,1;78,5] | 0,9 |
| Albumin, g/L | 40 [39;43] | 41 [39;43] | 39,5 [37;42] | 0,27 |
| Bicarbonate, mmol/L | 20 [18,2;21,4] | 20,1 [18,6;21,7] | 19,6 [17,3;20,8] | 0,2 |
| Hemoglobin, g/L | 112 [102;127] | 116 [103;127] | 109 [98;119] | 0,24 |
| CRP, mg/L | 4,5 [1,9;10,7] | 4,2 [1,4;7,35] | 7,2 [3;13,6] | 0,06 |
| PTH, ng/L | 388,5 [277;610] | 379 [276;592] | 480 [300;721] | 0,4 |
| Ca, mmol/L | 2,1 [2;2,3] | 2,1 [2;2,3] | 2,1 [2;2,3] | 0,97 |
| P, mmol/L | 1,6 [1,3;1,8] | 1,6 [1,3;1,8] | 1,7 [1,4;1,8] | 0,8 |
| NT-proBNP, pg/ml | 2114,6 [1095;4016] | 1856 [986;2721] | 2379 [2040;26865] | 0,042* |

**Note:** * — p<0,05.

**Abbreviations:** BMI — body mass index, spKt/V — dialysis dose per hemodiafiltration session, CRP — C-reactive protein, PTH — parathyroid hormone.

of the observed parameters in three independent groups, the Pearson's chi-squared test was used. Differences were considered significant at p<0,05.; p<0,1 was considered as a tendency towards difference.

The study was approved by the ethics committee of the V. I. Razumovsky Saratov State Medical University (Russia). All participants gave written informed consent.

## Results

The age of men was 57,5 [41,5; 63,5] years; total dialysis time — 44 [15; 113] months; the median age of women — 59,5 [49; 66] years, the median total dialysis time — 44,5 [18; 79,5] months. The median serum NT-proBNP level was 2114,6 [1095; 4016] pg/ml, in men — 2143,5 [1087,6; 13750,7] pg/ml, in women — 2044,3 [1095; 2572] pg/ml

The clinical and laboratory characteristics of the studied population and the results of comparing the groups of patients with normal level of hydration and hyperhydration are presented in Table 1. When comparing the NT-proBNP level in patients depending on their hydration status, a statistically significant increase of the prohormone level in hyperhydration patients was revealed.

The concentrations of NT-proBNP in patients (n=80) were compared depending on LVEF (Figure 1) and statistically significant differences were found in patients of three groups. Pairwise comparison revealed the statistically significant differences of NT-proBNP levels between HFpEF and HFmrEF (p=0,02) groups and tendency to differences in HFpEF and HFrEF groups (p=0,07).

NT-proBNP levels were different in patients with normal hydration status and hyperhydration depending on LVEF (Figures 2 and 3). However, the differences identified were not statistically significant, probably due to insufficient sample size.

When analyzing the median NT-proBNP level in all patients as a whole and depending on the hydration status, we observed that the prohormone gradually increased with a decrease in EF.

Significant differences in the age of patients in groups depending on the prohormone quartile were

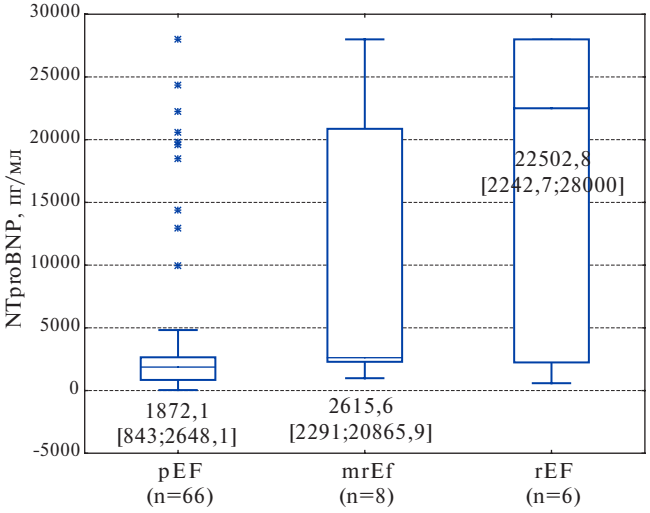


**Figure 1.** NT-proBNP level depending on LVEF (n=80, H=6,07, df=2, p=0,048).
**Abbreviations:** pEF — preserved ejection fraction, mrEF — mid-range ejection fraction, rEF — reduced ejection fraction.

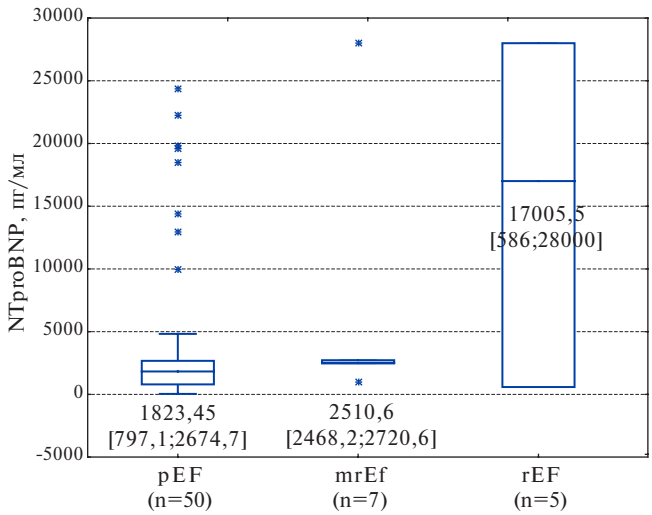


**Figure 2.** NT-proBNP level depending on LVEF in normal hydration patients (n=62, H=2,466, df=2, p=0,29).
**Abbreviations:** pEF — preserved ejection fraction, mrEF — mid-range ejection fraction, rEF — reduced ejection fraction.

established. Pairwise comparisons demonstrated statistically significant differences in age between groups with levels of NT-proBNP <1095 pg/ml and 1095-4016 pg/ml (p=0,01); a tendency to difference was detected in groups with NT-proBNP <1095 pg/ml and >4016 pg/ml (p=0,057). Thus, patients with a higher NT-proBNP quartile were older (Table 2).

Significant differences in the incidence of new cardiovascular events (CVE) were detected in patients of all three groups. Pairwise comparisons revealed differences between groups with NT-proBNP levels <1095 pg/ml and 1095-4016 pg/ml (p=0,01), and between groups with NT-proBNP levels <1095 pg/ml and >4016 pg/ml (p=0,0024) (Table 2).

The incidence of atrial fibrillation also differs in all three groups. In a pairwise comparison, significant differences were found between groups of patients with NT-proBNP 1095-4016 pg/ml and >4016 pg/ml (p=0,013); a tendency to difference was detected in patients with NT-proBNP <1095 pg/ml and >4016 pg/ml (p=0,051).

A tendency to increase the incidence of new cardiovascular events, systolic and diastolic dysfunction in patients with a prohormone increase was established (Table 2).

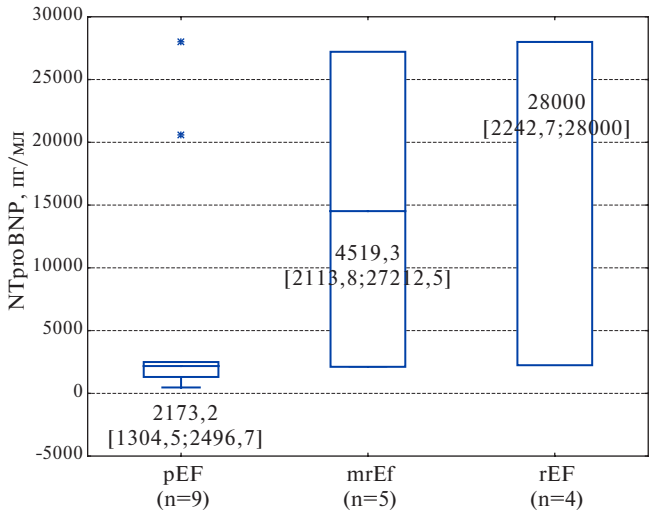


**Figure 3.** NT-proBNP level depending on LVEF in hyperhydration patients (n=18, H=1,6, df=2, p=0,44).
**Abbreviations:** pEF — preserved ejection fraction, mrEF — mid-range ejection fraction, rEF — reduced ejection fraction.

## Discussion

The significant value of NT-proBNP for HF diagnosis is >125 pg/ml [13]. Serum levels of NT-proBNP in HD patients significantly exceeded the average population values. It is noteworthy that the scatter in the prohormone concentration was significant: from values several times larger than normal ones to extreme concentrations that are many times higher than the upper boundary of the reference interval. Such an increase in the NT-proBNP level is probably due to the severity of structural and functional cardiac changes in patients undergoing extracorporeal therapy. A significant NT-proBNP increase was noted in patients with hyperhydration, which, most likely, is a reaction of excessive prohormone production in response to an increase in filling pressure with volume overload. All this complicates the interpretation of the NT-proBNP level and use of prohormone

**Table 2**

**Clinical characteristics of patients in groups depending on serum NT-proBNP level**

| Parameter | NT-proBNP <1095 пг/мл (n=20); M±SD; Med;25-75% | NT-proBNP [1095-4016] пг/мл (n=40); M±SD; Med;25-75% | NT-proBNP >4016 пг/мл (n=20); M±SD; Med;25-75% | p value |
|---|---|---|---|---|
| Gender (men/women) | 13/7 | 23/17 | 16/4 | |
| Age, years | 48,5 [39,5;57,5]<br>48±12,7 | 59,5 [48;66]<br>56±13 | 59,5 [42,3;66,8]<br>55,5±15,4 | 0,043* |
| New cardiovascular events on HD | 2 (10%) | 17 (42,5%) | 11 (55%) | 0,008* |
| Fatal cardiovascular events on HD | - | 5 (12,5%) | 3 (15%) | 0,21 |
| Number of patients with hyperhydration | 2 (10%) | 9 (22,5%) | 7 (35%) | 0,16 |
| Systolic dysfunction | 2 (10%) | 8 (20%) | 7 (35%) | 0,14 |
| Diastolic dysfunction | 17 (85%) | 37 (92,5%) | 20 (100%) | 0,18 |
| HFpEF | 16 (80%) | 30 (75%) | 11 (55%) | 0,058 |
| HFmrEF | 1 (5%) | 4 (10%) | 3 (15%) | 0,65 |
| HFrEF | 1 (5%) | 1 (2,5%) | 4 (20%) | 0,23 |
| AF | 2 (10%) | 5 (12,5%) | 8 (40%) | 0,026* |
| Obesity (BMI >30 kg/m$^2$) | 6 (30%) | 7 (17,5%) | 2 (10%) | 0,25 |
| ACE/ARB therapy | 1 (5%) | 8 (20%) | 4 (20%) | 0,38 |

**Note:** * — p<0,05.

**Abbreviations**: HD — hemodialysis, HFpEF — heart failure with preserved ejection fraction, HFmrEF — heart failure with mid-range ejection fraction, HFrEF — heart failure with reduced ejection fraction, AF — atrial fibrillation, BMI — body mass index, ACE inhibitors — angiotensin-converting-enzyme inhibitors, ARB — angiotensin II receptor blockers.

for the diagnosis and monitoring of HF in HD patients [10].

It is important to determine the NT-proBNP level in patients with different phenotypes of HF depending on LVEF. Of particular interest is the study of the NT-proBNP role in the diagnosis of HFpEF. Despite the relevance, in recent years there have been only few studies devoted to this issue.

In the study by Antlanger M, et al. (2017), patients were divided into three groups: without HF, with HFpEF, and with HFrEF. In these groups, there was a significant increase in prohormone levels above reference values, which is consistent with our data. The level of NT-proBNP was significantly higher in HFrEF patients than in patients without HF, while there were no significant differences between patients with HFpEF and without HF. From the study it follows that determination of NT-proBNP levels can be used only to exclude HFrEF, but not to differentiate patients with HFpEF and without HF [10].

In our study, when assessing the NT-proBNP level both in all patients as a whole and depending on the hydration status, the prohormone concentration was higher than the normal level, not allowing to exclude the HF, and increased with EF decreasing. The revealed significant differences between the NT-proBNP levels in patients with HFpEF and HFmrEF and a tendency to differences in patients with HFpED and HFrEF demonstrate the potential of NT-proBNP use in the differential diagnosis of HF phenotypes depending on LVEF.

NT-proBNP is considered as a CVE risk factor and unfavorable prognosis both in the general population and in patients with cardiovascular disease and chronic kidney disease [14]. According to our results, NT-proBNP increase in HD patients can also be associated with a risk of CVE, systolic and diastolic dysfunction. The preliminary data obtained indicate the need for further research of this marker as a predictor of CVE and an adverse outcome in patients on HD.

**Study limitations.** The obtained results are preliminary due to small sample size. The research of revealed tendencies in a larger patient population, prospective observation, and further study of NT-proBNP as a CVE predictor in patients receiving extracorporeal therapy are required.

## Conclusion

The serum NT-proBNP level in HD patients is significantly higher than the average population val-

ues. A significant NT-proBNP increase in hyperhydration patients was found. Determination of NT-proBNP should be used as an additional method for the HF diagnosis in HD patients, including for clarifying its phenotype depending on LVEF. An increase of NT-proBNP concentration in HD patients is associated with a risk of CVE, systolic and diastolic dysfunction. The similarity of HF and hyperhydration manifestations during dialysis requires the use of additional differential diagnosis methods using a sequential algorithm: clinical assessment, BIA, TTE, and NT-proBNP determination.

**Relationships and Activities**: not.

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