Karanadze N.A.[1, 2], Begrambekova Yu.L.[1, 2], Borisov E.N.[1, 2], Orlova Ya.A.[1, 2]
[1] Medical Research and Educational Center, Lomonosov Moscow State University, Moscow, Russia
[2] Faculty of Fundamental Medicine, Lomonosov Moscow State University, Moscow, Russia

Red cell distribution width as a predictor of impaired exercise capacity in patients with heart failure

Aim	To test a hypothesis that increased values of red cell distribution width (RDW) in patients with chronic heart failure (CHF) can be related with low exercise tolerance.
Material and methods	102 patients were evaluated who had CHF with mid-range and reduced left ventricular ejection fraction (LV EF) without anemia (72% men, mean age 66±10.2 years). Cardiopulmonary stress test (CPST), echocardiography, 6-min walk test (6MWT), blood count, and measurements of N-terminal pro-brain natriuretic peptide (NT-pro-BNP) and serum iron were performed.
Results	The average LV EF was 39±8.7%; the peak oxygen consumption (VO_{2peak}) was 13.7±4.8 ml/kg/min; and the median NT-pro-BNP was 595.3 pg/ml (Q_{1-3}1443–2401). RDW variables, including the RDW coefficient of variation (RDW-CV) and RDW standard deviation (RDW-SD), were not significantly related with serum iron or hemoglobin concentrations. A one-factor linear regression analysis showed a significant correlation of VO_{2peak} with RDW-SD (p=0.039). A multivariate linear regression analysis with adjustments for LV EF, hemoglobin concentration, and age did not reveal any significant correlation of VO_{2peak} with RDW variables. The distance covered in the 6MWT was significantly associated with RDW-CV both in the one-factor analysis and with adjustments for LV EF, hemoglobin and serum iron concentrations, and age.
Conclusion	This study showed that high RDW values in CHF patients without anemia predicted low exercise tolerance regardless of the age, LV systolic function, and hemoglobin and serum iron concentrations. A 16% increase in RDW-CV significantly decreased the likelihood of covering a distance longer than 360 m during 6 min.

Keywords	RDW; RDW-CV; RDW-SD; red cell distribution width; exercise tolerance; peak oxygen consumption (VO_{2peak}); 6MWT; CHF; cardiopulmonary stress test (CPST); heart failure
For citations	Karanadze N.A., Begrambekova Yu.L., Borisov E.N., Orlova Ya.A. Red cell distribution width as a predictor of impaired exercise capacity in patients with heart failure. Kardiologiia. 2022;62(4):30–35. [Russian: Каранадзе Н.А., Беграмбекова Ю.Л., Борисов Е.Н., Орлова Я.А. Ширина распределения эритроцитов как предиктор низкой толерантности к физической нагрузке у пациентов с хронической сердечной недостаточностью. Кардиология. 2022;62(4):30–35]

Corresponding author Begrambekova Yu. L. E-mail: julia.begrambekova@ossn.ru

Reduced exercise tolerance is one of the earliest and the most specific symptoms of chronic heart failure (CHF) [1]. It may be caused by several causes, including decreased cardiac output, pathological remodeling of the respiratory system, and skeletal muscle dysfunction. Gradually decreasing exercise tolerance and concomitant reduced physical activity form a vicious circle. While aggravated peripheral circulation disorders and skeletal muscle dysfunction are described in hypodynamic terms, abnormalities in skeletal muscles play a leading role in limiting the functional performance of patients, exacerbating the hyperactivation of the renin-angiotensin-aldosterone and sympatho-adrenal systems [2–5]. A number of studies have shown that reduced exercise tolerance and functional performance assessed by cardiopulmonary stress testing (CPLT), peak oxygen consumption (VO_{2peak}) and respiratory efficiency (VE/VCO_2) demonstrate higher or comparable value in assessing the prognosis for patients with heart failure than cardiac output [6, 7]. Non-cardiac mechanisms of exercise tolerance reduction have lately attracted the attention of researchers. In particular, inadequate ability of the blood to effectively bind and deliver oxygen becomes an important factor in decreased exercise tolerance. Even when not related to anemia, iron deficiency is associated with reduced functional performance of patients with CHF [8, 9]. Recent evidence has shown that red blood cells (RBCs) can form a kind of sensor for general and cardiovascular health [10–12]. Routinely automatically measured components of complete blood count include red cell distribution width (RDW) expressed in terms coefficient of variation (RDW-CV) and standard deviation (RDW-SD) comprising quantitative measures of anisocytosis, i.e., variation in circulating RBC size. Although these indicators have long been considered as markers of iron, vitamin B12, or folic acid deficiency, as well as increased RBC destruction due

ISSN 0022-9040. Kardiologiia. 2022;62(4). DOI: 10.18087/cardio.2022.4.n1813

to hemolysis or after blood transfusion, a growing body of evidence supports the view that RDW represents a complex indicator reflecting several interrelated pathological processes occurring in severe and long-term chronic diseases, such as coronary artery disease [13], chronic renal failure [14], and CHF [10]. A significant role in these pathological processes is played by impaired renal function, erythropoietin deficiency, portal vein stasis, and systemic inflammation, as well as micronutrient deficiency due to malabsorption [15]. Elevated RDW is suspected to be an integrative measure of several potentially important pathophysiological processes in HF. As well as transporting oxygen and carbon dioxide, RBCs are scavengers of reactive oxygen and nitrogen species, whose levels increase in chronic inflammation. Adequate RBC deformability is needed to perform these critical functions [16].

Objective

To examine the hypothesis that elevated RDW may be associated with low cardiorespiratory endurance and poor exercise tolerance in CHF patients.

Material and methods

The single-center, cross-sectional study included 102 patients with CHF with mid-range and reduced left ventricular ejection fraction (LVEF) without anemia. The study was approved by the ethics committee of the Medical Scientific and Educational Center of the Lomonosov Moscow State University (Minutes No. 4/17 dated November 27, 2017). All patients signed informed consent to be included in the study. Exclusion criteria were: acute and chronic inflammatory diseases; altered hematopoiesis and anemia; heart attack or stroke within less than 3 months before the inclusion; orthopedic disorders preventing from performing the 6-minute walk test (6MWT); inability to understand the study and thus sign informed consent.

All patients were being treated for CHF according to the clinical guidelines [1]. All patients took angiotensin-converting enzyme (ACE) inhibitors (n=94) or angiotensin receptor-neprilysin inhibitors (ARNIs) (n=8), all patients received diuretics, while 90.2% of patients received beta-blockers.

Laboratory tests included complete blood count, N-terminal pro-brain natriuretic peptide (NT-proBNP), and serum iron. Blood chemistry tests were performed on a Beckman Coulter AU480 biochemistry analyzer (Germany); complete blood count (5 diff) was conducted in a Sysmex XN 2000 hematology analyzer (Japan). RDW-CV was determined automatically by the hematology analyzer according to a special formula, which takes into account mean corpuscular volume (MCV) and standard deviation from MCV (%). RDW-SD measured in femtoliters (fL) is a direct measurement of the width of the RBC histogram at the 20% of the curve height; the histogram height is taken as 100%. Reference values: RDW-CV 11.5–14.5%; RDW-SD 37.0–47.0 fL. All laboratory tests were performed on an empty stomach.

All patients underwent echocardiography with the determination of LVEF. 6MWT was used to assess exercise tolerance.

All patients underwent cardiopulmonary stress testing. The examination was conducted on a SCHILLER CARDIOVIT AT 104 PC Ergo-Spiro treadmill using a modified Bruce protocol. This comprises is a step-by-step protocol with continuously increasing workload, with the load being increased every 3 minutes due to a 5-degree increase in the inclination angle of the platform at the first three steps and the speed of the walking belt at subsequent steps. A twelve-lead electrocardiogram was recorded throughout the exercise, with the following parameters evaluated breath-by-breath every 30 seconds: oxygen consumption in liters per body weight; carbon dioxide (VCO_2); minute ventilation (VE); ventilatory equivalents for carbon dioxide (VE/VCO_2).

Statistical analysis

Depending on the type of distribution, all continuous values are expressed either as the mean (M) and standard deviation (SD) or the median (Me), lower (Q1) and upper (Q4) quartiles. The hypothesis of normal distribution of an indicator was verified using the Shapiro–Wilk test. Spearman's rank correlation coefficient was calculated to describe the correlations between the various parameters. Multiple linear and logistic regression models were used to evaluate the effects of the indicator taking the contribution of other influencing variables into account. The statistical significance of the model was estimated by maximum likelihood. Wald statistics and the corresponding significance level are provided for these models. The p value<0.05 was used as the level of statistical significance.

Results

The study included 102 patients, 72% of whom were male, while the median age was 71.3 [62.6; 76.4] years.

Mean LVEF was 39 ± 8.7%; VO_2 peak was 13.2 ± 4.8 mL/kg/min; median NT-pro-BNP was 595.3 [1443–2401] pg/mL. The patient characteristics are given in Table 1.

The width of RBC distribution was significantly correlated in patients with CHF with several clinical and functional state indicators (Table 2).

RDW-CV and RDW-SD were not significantly correlated with serum iron levels (r=0.165 and r=0.176, respectively) and hemoglobin (r=–0.224, p=0.096 and r=0.016, respectively) in our sample of CHF patients without signs of anemia. Univariate linear regression analysis showed a significant correlation between VO_{2peak} and RDW-SD (p=0.039) and a trend to correlate with RDW-CV (p=0.068). In multivariate linear regression

analysis adjusted for LVEF, hemoglobin levels, or age, there was no significant correlation between VO_{2peak} and RDW. The 6MWT distance was significantly correlated RDW-SD and RDW-CV in the univariate regression analysis. The correlation was confirmed when LVEF, hemoglobin levels, and patient age were introduced in the model for RDW-CV (0.043) (Table 3). It is notable that the factors included in the model determined the walking distance by more than 50% (determination coefficient R2=0.517, p<0.0001).

Further evaluation of the RDW effect on exercise tolerance assessed by 6MWT was carried out using multivariate logistic analysis. The walking distance was divided by the median (more or less than 369 m) and taken as a binary dependent variable. Continuous values were used for the influencing variables RDW-CV, LVEF, hemoglobin, serum iron, and patient age. The model presented in Table 4 shows that, irrespective of the patient's age, LVEF, and hemoglobin levels, elevated RDW-CV reduced the likelihood of walking 360 m or more. Similar data were obtained when serum iron was introduced into the model instead of hemoglobin. Both indicators could not be used in one model due to their high correlation (r=0.68, p<0.01).

RDW-CV and age were the main factors determining walking distance in this model. These parameters were included in the following model (Table 5).

The curve expressing the dependence of the 6MWT distance on age and RDW-CV is provided in Figure 1. The curve presented in Figure 1 shows the determining influence of RDW-CV on the walking distance. When RDW-CV exceeds 16%, walking distance has no significant correlation with age. Based on these data, we constructed a binary logistic regression model, where walking distance (≥360 m/<360 m) was used as the dependent variable, while age (continuous values) and RDW-CV (binary – ≥16%/<16%) were used as the influencing variables (Table 6).

RDW-CV >16% decreases the likelihood to walk 360 m or more by almost 46.4% (Table 6). Thus, regardless of age, increased RDW-CV >16% is statistically significantly correlated with poor exercise tolerance in patients with CHF. The area under the ROC-curve was 0.84 (Figure 2).

A similar analysis was performed for RDW-SD. While it remained significantly correlated with walking distance when adjusted for age (p=0.014), when LVEF and hemoglobin were introduced in the model, the correlation between these parameters was not statistically significant.

Table 1. Patient characteristics (n=102)

Parameters	Value
BMI, kg/m2	28.9 [24.8; 32.9]
SBP, mm Hg	115.0 [105.0; 130.0]
DBP, mm Hg	80.0 [70.0; 85.0]
HR, bpm/min	70.0 [64.0; 77.0]
SHOCS, score	6.0 [5.0; 8.0]
6MWT distance, m	360.0 [280.0; 430.0]
Hemoglobin, g/L	143.0 [127.0; 152.0]
RDW-CV, %	14.1 ± 1.8
RDW-SD, fL	47.7 [45.0; 51.8]
Serum iron, μmol/L	20.4 [15.9; 25.1]
NYHA FC	2.6 ± 0.5
LVEF, %	39.9 ± 8.7
VO_{2peak}, mL/kg/min	13.2 ± 4.8
VE/VCO_2	29.40 [25.12; 36.39]
NT-proBNP, pg/mL	595.3 [213.5; 1443]

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; LVEF – left ventricular ejection fraction; SHOCS – Symptomatic Hospital and Outpatient Clinical Score; VO_{2peak} – peak oxygen consumption; VE/VCO_2 – respiratory efficiency; 6MWT – 6-minute walk test; RDW-CV – red cell distribution width – coefficient of variation; RDW-SD – red cell distribution width – standard deviation – difference between the maximum and minimum red cell volume in the test sample; FC – functional class of heart failure; NT-proBNP – N-terminal pro-brain natriuretic peptide.

Table 2. Correlation of RBC distribution width with functional status and other parameters (Spearman's rank correlation coefficients and statistical significance)

Parameter	Age	NT-proBNP	LVEF	$VO_{2пик}$	VO_2 AT	VE/VCO_2	6MWT
RDW-CV	–0,02, p>0,05	0,480, p<0,05	–0,374, p<0,05	–0,482, p<0,05	–0,382, p<0,05	–0,395, p<0,001	–0,455, p<0,05
RDW-SD	–0,08, p>0,05	0,597, p<0,01	–0,346, p=0,07	–0,178, p>0,05	–0,210, p>0,05	–0,234, p>0,05	–0,373, p<0,05

RDW-CV – red cell distribution width – coefficient of variation; RDW-SD – red cell distribution width – standard deviation – difference between the maximum and minimum red cell volume in the test sample; LVEF – left ventricular ejection fraction; VO_{2peak} – peak oxygen consumption; VE/VCO_2 – respiratory efficiency; VO_2 AT – aerobic threshold; 6MWT – 6-minute walk test; NT-proBNP – N-terminal pro-brain natriuretic peptide.

Table 3. Effect of RDW-CV on walking distance considering other factors (R2 = 0.517, p<0.0001 for the model)

Parameters	BETA	BETA std.err	p
RDW-CV	–0,233	0,112	0,043
Hemoglobin	0,070	0,122	0,568
LVEF	0,249	0,104	0,021
Age	–0,623	0,113	<0,001

RDW-CV – red cell distribution width – coefficient of variation; LVEF – left ventricular ejection fraction.

Discussion

ISSN 0022-9040. Kardiologiia. 2022;62(4). DOI: 10.18087/cardio.2022.4.n1813

Table 4. Contribution of RDW-CV and other factors in exercise tolerance (6MWT distance (≥360 m/<360 m) taking into consideration other factors (p = 0.00015 for the model)

Parameters	RDW-CV	Age	LVEF	Hemoglobin
Wald's Chi-square	7.123	7.751	1.822	0.095
OR	0.433	0.888	1.062	0.979
95% CI	0.230–0.815	0.815–0.968	0.971–1.162	0.849–1.128
p	0.010	0.008	0.184	0.759

RDW-CV – red cell distribution width (coefficient of variation);
LVEF – left ventricular ejection fraction; OR – odds ratio; CI – confidence interval

Figures 1. Dependence of 6MWT distance on age and RDW-CV

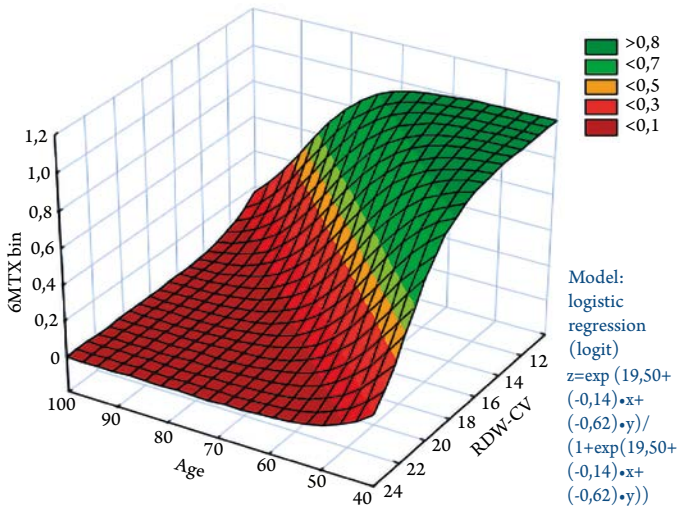


Table 5. Contribution of RDW-CV in exercise tolerance (6MWT distance (≥360 m/<360 m) taking into consideration age (p = 0.00003 for the model)

Parameters	Age	RDW-CV
Wald's Chi-square	7.828	8.821
OR	0.896	0.484
95% CI	0.828–0.970	0.296–0.791
p	0.005	0.003

RDW-CV – red cell distribution width (coefficient of variation);
OR – odds ratio; CI – confidence interval

Table 6. Effect of RDW-CV (≥ 16/<16) on 6MWT distance (≥ 360 m/< 360 m) taking into consideration patient's age (p <0.0001 for the model)

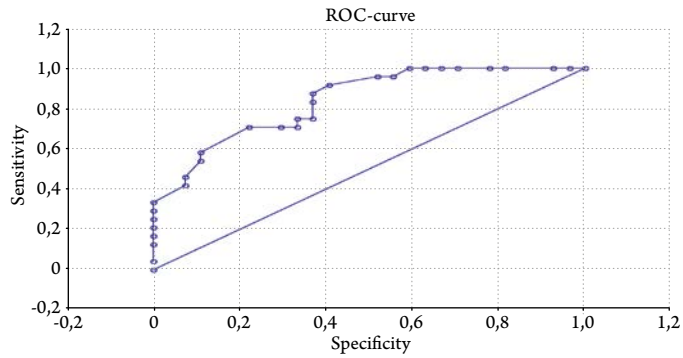
Parameters	OR	95% CI	p
Age, years	0.862	0.786–0.944	0.001
RDW-CV (≥ 16%/< 16%)	0.536	0.556–0.855	0.007

OR, odds ratio; CI, confidence interval.

In this study, increased RDW in CHF patients without anemia was associated with low exercise tolerance irrespective of age, LV systolic function, hemoglobin, and serum iron levels. In our work, consistent with other researches, changes in RDW were not clearly correlated with hemoglobin levels and remained independently related with exercise tolerance irrespective of the hemoglobin levels. Thus, RDW remained an independent predictor of the result following adjustment for hemoglobin, remaining a more powerful predictor of endpoints than hemoglobin in the CHARM subanalysis, as well as a predictor of death in the Duke Databank [7]. In both databases, RDW had only an insignificant moderate negative correlation with hemoglobin (with a correlation coefficient –0.27 in the CHARM program and –0.40 in the Duke Databank). In our sample, correlation coefficients between hemoglobin and RDW were close, but insignificant.

This was likely to be due to the small size of the sample and non-inclusion of patients with anemia. These and other papers suggest that increased RDW in patients with HF, even in the absence of anemia and iron deficiency, reflects the progression of ineffective erythropoiesis, inability to use available iron, decreased hemoglobin performance and, thus, hypoxia [6].

Figures 2. Способность модели прогнозировать дистанцию 6MTX ((≥360 м / <360 м) по RDW- CV (16% и более /менее 16%) с учетом возраста пациентов. Площадь под кривой – 0,84, p<0,001



This complex of pathological changes naturally influences exercise tolerance.

There is new evidence that RDW is a highly sensitive and early integral indicator reflecting ineffective erythropoiesis due to the spectrum of abnormalities associated with chronic inflammation. Förhécz et al. [10] showed that markers of inflammation, erythropoietin levels, and reduced functional availability of iron correlate with RDW. In the study by Emans et al. [17], functional iron availability, activity of

erythropoiesis and interleukin-6 were independent predictors of RDW, while erythropoietin resistance, also suggested by many researchers, was not correlated. There are several studies investigating the effects of different treatment tactics on the RDW indicators. Yasuhiro Nishiyama et al. [18] obtained interesting data on the influence on this exercise tolerance indicator. They studied the effect of workout on RDW and correlated indicators of hematopoiesis in patients with coronary artery disease for 3 weeks. Although RDW and serum erythropoietin levels remained unchanged in the control group, they decreased in the workout group (from 44.4 ± 4.7 μL to 43.4 ± 3.8 μL, p<0.01, and from 27.9 ± 15.8 mIU/mL to 22.9 ± 8.2 mIU/mL, p<0.005, respectively). In the workout group, RDW was negatively correlated with VO_{2peak} (r= –0.55, p<0.01); however, there was no significant correlation between changes of these indicators. In other papers, RDW was a marker of low exercise tolerance; here, a weak but statistically significant correlation between the VO_{2peak} and RDW in patients with CHF was observed [19, 20]. Reduced RDW due to workouts a compared to the control group (p<0.0001) irrespective of the baseline levels of VO_{2peak}, hemoglobin, and NT-proBNP [20] confirms the positive effect of exercises on the effectiveness of erythropoiesis. In our study, RDW-SD lost significant correlation with VO_{2peak} when LVEF, hemoglobin, and patient age were introduced in the model. This may be due to the VO_{2peak} reflecting functional capacity of the lungs, heart, and blood to deliver oxygen on the one hand and the ability of the peripheral muscles to extract blood-borne oxygen during exercise on the other. The integral nature of this indicator makes it the gold standard for determining cardiopulmonary endurance, helping to explain the absence of the independent correlation between VO_{2peak} and RDW in the study by Yasuhiro Nishiyama and in our study, as well as the weak correlation (r= – 0.248, p=0.009) in the study by Van Craenenbroeck et al. [20].

The correlation of RDW with exercise tolerance – and, more importantly, with a patient's prognosis – requires a more in-depth study of this aspect of CHF pathogenesis. RDW can potentially be considered both as a marker of ineffective erythropoiesis and as an integral marker of chronic systemic inflammation. Among the advantages of RDW in research and clinical practice is its wide availability due to its forming part of routine complete blood count analysis.

Conclusion

In our study, increased RDW-CV was independently associated with low exercise tolerance irrespective of age, LV systolic function, hemoglobin and serum iron levels. RDW- CV above of 16% significantly reduced the likelihood of walking 360 meters or more in 6 minutes. Our findings form a basis for future research aimed at identifying new targets for interventions that increase exercise tolerance in patients with CHF.

Limitations

Small sample size (n=102) and the inability to arrange prospective follow-up due to the epidemiological situation.

Funding

The study was a part of the State Assignment of the Lomonosov Moscow State University Medical Research and Educational Center.

No conflict of interest is reported.

The article was received on 02/09/2021

REFERENCES

1. Tereshchenko S.N., Galyavich A.S., Uskach T.M., Ageev F.T., Arutyunov G.P., Begrambekova Yu.L. et al. 2020 Clinical practice guidelines for Chronic heart failure. Russian Journal of Cardiology. 2020;25(11):311–74. [Russian: Терещенко С.Н. Галявич А.С., Ускач Т.М., Агеев Ф.Т., Арутюнов Г.П., Беграмбекова Ю.Л. и др. Хроническая сердечная недостаточность. Клинические рекомендации 2020. Российский кардиологический журнал. 2020;25(11):311-74]. DOI: 10.15829/1560-4071-2020-4083
2. Nolan J, Flapan AD, Capewell S, MacDonald TM, Neilson JM, Ewing DJ. Decreased cardiac parasympathetic activity in chronic heart failure and its relation to left ventricular function. British Heart Journal. 1992;67(6):482–5. DOI: 10.1136/hrt.67.6.482
3. Florea VG, Mareyev VY, Achilov AA, Popovici MI, Coats AJ, Belenkov YN. Central and peripheral components of chronic heart failure: determinants of exercise tolerance. International Journal of Cardiology. 1999;70(1):51–6. DOI: 10.1016/s0167-5273(99)00047-9
4. Ferguson DW, Berg WJ, Roach PJ, Oren RM, Mark AL. Effects of heart failure on baroreflex control of sympathetic neural activity. The American Journal of Cardiology. 1992;69(5):523–31. DOI: 10.1016/0002-9149(92)90998-e
5. Anker SD, Chua TP, Ponikowski P, Harrington D, Swan JW, Kox WJ et al. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. Circulation. 1997;96(2):526–34. DOI: 10.1161/01.cir.96.2.526
6. Allen LA, Felker GM, Mehra MR, Chiong JR, Dunlap SH, Ghali JK et al. Validation and Potential Mechanisms of Red Cell Distribution Width as a Prognostic Marker in Heart Failure. Journal of Cardiac Failure. 2010;16(3):230–8. DOI: 10.1016/j.cardfail.2009.11.003
7. Felker GM, Allen LA, Pocock SJ, Shaw LK, McMurray JJV, Pfeffer MA et al. Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke Databank. Journal of the American College of Cardiology. 2007;50(1):40–7. DOI: 10.1016/j.jacc.2007.02.067
8. Okonko DO, Mandal AKJ, Missouris CG, Poole-Wilson PA. Disordered Iron Homeostasis in Chronic Heart Failure. Journal of the American College of Cardiology. 2011;58(12):1241–51. DOI: 10.1016/j.jacc.2011.04.040
9. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B et al. Iron Deficiency Predicts Impaired Exercise Capacity in Patients With Systolic Chronic Heart Failure. Journal of Cardiac Failure. 2011;17(11):899–906. DOI: 10.1016/j.cardfail.2011.08.003
10. Förhécz Z, Gombos T, Borgulya G, Pozsonyi Z, Prohászka Z, Jánoskuti L. Red cell distribution width in heart failure: Prediction of clinical events and relationship with markers of ineffective erythropoiesis,

ISSN 0022-9040. Kardiologiia. 2022;62(4). DOI: 10.18087/cardio.2022.4.n1813

inflammation, renal function, and nutritional state. American Heart Journal. 2009;158(4):659–66. DOI: 10.1016/j.ahj.2009.07.024
11. Söderholm M, Borné Y, Hedblad B, Persson M, Engström G. Red Cell Distribution Width in Relation to Incidence of Stroke and Carotid Atherosclerosis: A Population-Based Cohort Study. PLOS ONE. 2015;10(5):e0124957. DOI: 10.1371/journal.pone.0124957
12. Patel KV, Semba RD, Ferrucci L, Newman AB, Fried LP, Wallace RB et al. Red Cell Distribution Width and Mortality in Older Adults: A Meta-analysis. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2010;65A(3):258–65. DOI: 10.1093/gerona/glp163
13. Huang S, Zhou Q, Guo N, Zhang Z, Luo L, Luo Y et al. Association between red blood cell distribution width and in-hospital mortality in acute myocardial infarction. Medicine. 2021;100(15):e25404. DOI: 10.1097/MD.0000000000025404
14. Chen X, Shen B, Zou J, Liu Z, Lv W, Cao X et al. The Prognostic Value of Red Blood Cell Distribution Width in Patients on Maintenance Hemodialysis. Blood Purification. 2016;42(4):314–21. DOI: 10.1159/000449421
15. Okonko DO, Marley SB, Anker SD, Poole-Wilson PA, Gordon MY. Suppression of erythropoiesis in patients with chronic heart failure and anaemia of unknown origin: evidence of an immune basis. International Journal of Cardiology. 2013;166(3):664–71. DOI: 10.1016/j.ijcard.2011.11.081
16. Minetti M, Agati L, Malorni W. The microenvironment can shift erythrocytes from a friendly to a harmful behavior: Pathogenetic implications for vascular diseases. Cardiovascular Research. 2007;75(1):21–8. DOI: 10.1016/j.cardiores.2007.03.007
17. Emans ME, van der Putten K, van Rooijen KL, Kraaijenhagen RJ, Swinkels D, van Solinge WW et al. Determinants of Red Cell Distribution Width (RDW) in Cardiorenal Patients: RDW is Not Related to Erythropoietin Resistance. Journal of Cardiac Failure. 2011;17(8):626–33. DOI: 10.1016/j.cardfail.2011.04.009
18. Nishiyama Y, Niiyama H, Harada H, Katou A, Yoshida N, Ikeda H. Effect of Exercise Training on Red Blood Cell Distribution Width as a Marker of Impaired Exercise Tolerance in Patients with Coronary Artery Disease. International Heart Journal. 2016;57(5):553–7. DOI: 10.1536/ihj.16-015
19. Hong S-J, Youn J-C, Oh J, Hong N, Lee HS, Park S et al. Red Cell Distribution Width as an Independent Predictor of Exercise Intolerance and Ventilatory Inefficiency in Patients with Chronic Heart Failure. Yonsei Medical Journal. 2014;55(3):635. DOI: 10.3349/ymj.2014.55.3.635
20. Van Craenenbroeck EM, Pelle AJ, Beckers PJ, Possemiers NM, Ramakers C, Vrints CJ et al. Red cell distribution width as a marker of impaired exercise tolerance in patients with chronic heart failure. European Journal of Heart Failure. 2012;14(1):54–60. DOI: 10.1093/eurjhf/hfr136