Open Access Article

THE STATE OF ENDOTHELIAL FUNCTION IN PATIENTS WITH CHRONIC HEART FAILURE WITH VARIOUS MANIFESTATIONS OF THE METABOLIC SYNDROME

Atakhodjaeva Gulchekhra Abdunabievna
DSc, Associate Professor, Department of Internal Medicine, nephrology and hemodialysis
Tashkent Pediatric, Medical Institute

Aripova Jamilya Shukhratovna
PhD, Associate Professor, Department of Internal Medicine, Nephrology and Hemodialysis
Tashkent Pediatric, Medical Institute, Tashkent Pediatric Medical Institute, Uzbekistan

The leading role in the pathogenesis of CHF is given to endothelial dysfunction. The development of severe endothelial dysfunction in CHF is due to hyperactivation of the SAS and RAAS, hyperproduction of pro-inflammatory cytokines. It consists in reducing the production of vasodilators and increasing the synthesis of vasoconstrictor substances. The main factors that disrupt EF in CHF are myocardial dysfunction, which contributes to a decrease in the hemodynamic shear stress force, neurohumoral balance, hypoxia, chronic inflammation, and intoxication [1, 4, 12, 15].

It is also necessary to note the factors that exacerbate the processes of myocardial and vascular remodeling in CHF, of which the MS components (IR, AH, DM, DLP, HTG) are significant [2,3]. Vessel remodeling in MS, on the one hand, is a consequence of the effects of IR and compensatory hyperglycemia, as well as elevated blood pressure on the vascular wall, on the other hand, it leads to the development and progression of IR and AH on its own [3, 7]. This condition is characterized by a decrease in endothelium-dependent vasodilation (EDVD) and increased adhesiveness of the endothelial lining [2, 3, 4, 7, 8].

Purpose of the research: to study the state of endothelial function in patients with chronic heart failure with various manifestations of the metabolic syndrome.

MATERIALS AND RESEARCH METHODS

To achieve the goals, 197 male patients with chronic heart failure (CHF) of ischemic genesis II-III functional class (FC) according to NYHA [11, 15, 16] were examined, aged 40-60 years with a history of myocardial infarction from 6 months up to 5 years. All patients were hospitalized in the cardiology department of the city clinical hospital No. 7 in Tashkent and were registered in the advisory polyclinic. Examination of patients was carried out on the basis of an agreement in the City Diagnostic Center of Tashkent and the RSNPMC of the Republic of Uzbekistan.

Verification of the diagnosis was carried out on the basis of the classification of the New York Heart Association (NYHA), the six-minute walk test (TSW) and the clinical assessment scale (SHS). The average TSHH was 304.2±22.13m (261-349m). Depending on the presence of MS components, 3 groups of patients were distinguished: Group I (n=70), patients without MS (CHF FC II -38, CHF FC

Received: June,13, 2022 / Revised: July ,21, 2022 / Accepted: 19,July, 2022 / Published: 13, August, 2022

About the authors：Atakhodjaeva Gulchekhra Abdunabievna
Email:

III - 32 patients); Group II (n=67) patients with various combinations of dyslipidemia (HDL-C <1.03 mmol/l; HDL-C >3.0 mmol/l) with abdominal obesity (AO), AH and hypertriglyceridemia (HTG) (CHF FC II -35 , CHF FC III - 32 patients); Group III (n=60) patients with various combinations of dyslipoproteinemia (DLP) and type 2 diabetes mellitus (DM2) with AO, AH and hypertriglyceridemia (HTG) (CHF FC II - 26, CHF FC III - 34 patients).

According to the classification of CHF (ESC 2016) [7, 12, 17], depending on the level of ejection fraction (EF), all examined patients with CHF were also divided into subgroups: with normal (preserved EF) - EF ≥50% (HFpEF) and intermediate EF (gray zone) - EF = 40-49% (HFmrEF). So, in group I patients with CHF without MS, 42 patients had preserved EF and 28 patients had intermediate EF, in group II, 39 patients had preserved EF, 28 patients with CHF had intermediate EF, and in group III, 28 x retained PV and y 32 intermediate PV.

When diagnosing MS, the criteria for diagnosing MS of the International Diabetes Federation (IDF, 2009) [2] were used. The following were considered as the main components of MS: abdominal obesity (AO) (>94 cm for men); triglyceride level (TG>1.7 mmol/l); high-density lipoprotein cholesterol (HDL-C <1.03 for men); blood pressure (SBP >130 mmHg; DBP >85 mmHg), fasting glucose (>5.6 mmol/L), or presence of type 2 diabetes [10, 78, 92, 156].

The mean age of patients in group I was 53.8±5.22 years, in group II 54.7±5.8 years and 55.6±5.33 in group III patients. The duration of the disease in patients of group I was 5.81±2.75 years; 6.6±2.33 years in group II and in patients of group III 7.16±1.92 years. The duration of myocardial infarction in group I was 4.3±3.24 years; 4.78±2.7 years in group II and in patients of group III 5.38±2.06 years. The survey did not include patients with severe CHF (CHF with low EF<40%), CHF of non-ischemic origin, with acute cerebrovascular accident, stroke, severe diabetes mellitus and insulin-dependent DM, chronic obstructive pulmonary disease, high-grade arrhythmias, liver disease, severe kidney disease.

Study of the vasomotor function of the endothelium. The state of endothelial function was assessed according to Doppler ultrasound of the brachial artery according to the method of D. S. Celemajer (1992) using a test with reactive hyperemia and nitroglycerin (in the city diagnostic center of Tashkent). Changes in the diameter of the right brachial artery were assessed using a 7 MHz linear transducer with a phase grating Acuson 128 ultrasound system (USA). PA was located in a longitudinal section 4-5 cm above the elbow bend, the image was synchronized with the ECG wave. The study was carried out in triplex mode (B-mode, color Doppler flow mapping, spectral analysis of the Doppler frequency shift).

Prior to the start of the study, the patient lay on his back for at least 10 minutes. In the initial state, the diameter of the artery and the velocity of arterial blood flow were measured using spectral analysis. Then, to obtain increased blood flow around the shoulder, a sphygmomanometer cuff was applied (above the location of the brachial artery), it was inflated to a pressure of 50 mm Hg. exceeding systolic blood pressure, and kept it for 5 minutes. The absence of PA blood flow was monitored using color Doppler flow mapping. The diameter and velocity of the PA blood flow were measured immediately after the release of air from the cuff during the first 15 seconds. and after 60 sec. Change in vascular

diameter after reactive hyperemia. The normal reaction of PA was considered to be its expansion against the background of reactive hyperemia by 10% or more of the initial diameter. A lesser degree of vasodilation and vasoconstriction was considered a pathological reaction. Shear stress on the endothelium was calculated according to the formula of O. V. Ivanova, [16,17]:

$\tau = 4 \times \eta \times V/D,$

where: — shear stress, — blood viscosity (on average equal to 0.05 Ps), V — maximum blood flow velocity in VA (cm/sec), D — VA diameter.

We used a unified indicator k - "sensitivity of PA to a change in stimulus - shear stress on the endothelium":

$$K = \frac{\Delta D / Do}{\Delta \tau / \tau_0}$$

where: ΔD - change in the diameter of the PA, D_0 - initial diameter of the PA, - change in shear stress, τ_0 - initial shear stress. The following parameters were evaluated:

- *D - Diameter of the right brachial artery (BA), cm*
- *D1- PA diameter after test with RG, cm*
- *D2- PA diameter after the test with NTG, cm*
- *VS - systolic blood flow velocity in VA, m/s*
- *VD - diastolic blood flow velocity in VA, m/s*
- *Vmean - average blood flow velocity in PA, m/s*
- *ЭЗВД= (D1- D)/ Dx100%*
- *ЭНЗВД= (D2- D)/ Dx100%*
- *K, PA sensitivity, arb. units*

Analysis of the type of distribution of the trait was carried out using the Microsoft Excel program. The normal distribution criteria were M±m. Since more than 80% of the analyzed quantitative traits were normally distributed, the statistical analysis was based on the methods of parametric statistics

The data obtained during the study were subjected to statistical processing on a Pentium-IV personal computer using the Microsoft Office Excel-2012 software package, including the use of built-in statistical processing functions. Methods of variational parametric and nonparametric statistics were used with the calculation of the arithmetic mean of the studied indicator (M), standard deviation (SD), relative values (frequency, %), the statistical significance of the measurements obtained when comparing the average values was determined by Student's t test (t) with the calculation of the error probability (R). Comparison of three or more independent groups was carried out by one-way analysis of ANOVA variations. Significance level $P<0.05$ was taken as statistically significant changes.

To establish the relationship between the components of the metabolic syndrome and indicators of cardiac and vascular remodeling, we performed a correlation analysis with the calculation of the Pearson linear relationship coefficient (r) and the subsequent determination of its significance according to the t criterion. To identify the most reliable indicators, the presence of a correlation dependence between them was determined. At the same time, the relationship was designated as having a strong relationship at r = 0.6-1, moderate - at r = 0.3-0.6, weak - at r <.

RESULTS OF THE RESEARCH

The results of the study of endothelial function showed that patients with chronic heart failure of preserved EF (HFpEF) that develops against the background of MS already differ from patients without MS according to the initial data of the blood flow velocity parameter. As can be seen from the presented data (Table 1.), the progression of MS is accompanied by a significant decrease in systolic blood flow velocity, as evidenced by a significant difference in this indicator between groups I and III of the study (12.6% P<0.05). The value of VS0 between groups I and II of the study were comparable (P>0.05).

In response to decompression in all groups, there was a statistically significant increase in systolic blood flow velocity in relation to the initial data. In groups I, II and III, the VS1 index increased by 35.5%, 40.1% and 44.3% in each group, respectively (P<0.001) in relation to the initial data. At the same time, the difference in systolic blood flow velocity after decompression between groups I, II and III of the study was not significant.

Table number 1.

Indicators of endothelial function of the PPA in patients with CHF *with preserved EF* ***(HFpEF) depending on on the representation of MS components (M±SD)***

Indicators		**1 group (n=42)**	**2 group (n=39)**	**3 group (n=28)**
D_0, mm		4,5±0,47	4,22±0,33	4,19±0,35
D_1, mm		4,96±0,42 º	4,53±0,32 *	4,49±0,44**
D_2, mm		5,01±0,40 ºº	4,72±0,38 ºº	4,66±0,39 ºº
D_3, mm		5,18±0,45 ººº	4,96±0,47 ººº	4,88±0,46 ººº
ΔD, mm		0,45±0,13	0,30±0,12**	0,30±0,10***
VS, cm/s	Under	68,61±9,12	64,7±9,6	60,93±8,69*
	15 s	93,07±9,6 ººº	90,68±12,0 ººº	88,07±13,76 ººº
VD, cm/s	Under	16,01±2,49	13,69±2,17*	11,62±2,7***▪
	15 s	20,71±2,8 ººº	17,57±2,69 ººº**	14,9±2,27ººº***▪
Vmeanc m/s	Under	33,54±4,14	30,7±3,62	28,61±4,14**
	15 s	44,83±4,34ººº	41,94±4,32 ººº	39,31±4,7ººº **
EZVD, %		10,23±3,17	7,14±1,88***	7,20±2,26***
ENZVD (NG3'),%		11,46±3,14	11,76±3,57	10,96±3,59

ENZVD (NG6'),%	15,471±4,27	17,51±4,24	16,5±4,46

Note: in relation to the data of group 1: *P<0,05; **P<0,01; ***P <0,001
with respect to post-sampling data: °P<0,05; °° P<0,01; °°° P <0,001
differences between II and III groups: ▪ P <0,05; ▪▪ P>0,01.

A similar pattern is observed in terms of diastolic (VD) and mean velocity (Vmean) of blood flow in the PPA. The difference in the initial velocity of diastolic blood flow VD0 was: in group II 16.8% (P<0.05) and in group III 37.9% (P<0.001) in relation to the data of group I. At the same time, in response to decompression in all groups, there was a statistically significant increase in diastolic blood flow velocity relative to the initial data by 29.4% in group I, by 28.3% in group II, and by 28.5% in group III (P<0.001). The indicators of the diastolic blood flow velocity of the PPA before (VD0) and after the test of reactive hyperemia (VD1) between groups II and III statistically significantly differed by 17.9% and 17.8%, respectively (P<0.05).

Comparative analysis of Vmean between groups I and III of the study also showed the presence of a statistically significant difference (17.2%; P<0.01). The difference in Vmean between groups I and II was unreliable. After decompression, there is a statistically significant increase in Vmean in all study groups by 33.7% in group I, in group II by 36.5% and in group III by 37.4% (P<0.001).

Thus, the presence of MS is accompanied by significant disturbances in blood flow velocity, which is detected in the RG test. The progression of MS negatively affects the blood flow velocity in the PPA, both systolic and diastolic, which was accompanied by a significant change in Vmean before and after the test in patients with CHF with preserved EF (HFpEF).

The results of RA Doppler ultrasound in patients with CHF of intermediate EF intermediate EF (HFmrEF) showed that patients with different representation of MS components do not significantly differ from persons in group I in the initial diameter (D0) of the RA (P>0.05). At the same time, it is important to note that in assessing the state of endothelial function, the analysis of the reaction of the vascular wall to changes in blood flow velocity is of particular importance. In response to an increase in blood flow velocity in group I, the diameter (D) of the brachial artery increased by 10.2% (P<0.05). In groups II and III, where the greatest acceleration of blood flow was observed, the VA diameter increased by 7.3% and 7.2%, respectively (P>0.05). A low fluctuation in the diameter of the PSA after a test with RG in the group of patients with MS is a manifestation of impaired endothelium-dependent vasodilation.

After the test with reactive hyperemia, significant low values of the vessel diameter (D1) were observed in groups II and III by 9.95% (P<0.05) and 10.5% (P<0.01) in relation to the data of group I. The above changes in the diameter of the PSA before and after the test with reactive hyperemia caused significant changes in the ΔD value in group II by 50% (P<0.01) and in group III by 50% (P<0.001) in relation to the data of group I patients with CHF intermediate EF (HFmrEF) without MS.

The results of measuring the diameter of the PAP before and after the test with nitroglycerin found that the changes in D2,3 in groups II and III were not significant in relation to the data of group I of the study.

In the analysis of EZVD, depending on the representation of MS components, significant differences in this parameter were revealed between groups I and II of the study by 43.3% (P<0.001), and between groups I and III by 42.1% (P<0.001). Measurement of the diameter of the VA in different groups in the test with nitroglycerin did not reveal a significant intergroup difference. As a result of this, in turn, unreliable data were obtained on changes in the index of endothelial independent vasodilation (ENVD) at the 3rd and 6th minutes after taking NTG compared with the data of group I.

Thus, the presence of MS is due to a significant decrease in vascular reactivity in patients with CHF. Of particular importance in reducing endothelium-dependent and independent vasodilation is the presence of DM2, which was reflected by more significant changes in EZVD in group III patients.

Various fluctuations in the diameter and speed of blood flow during the test with RG contributed to an increase in the resistance index (Ri) and pulsation (Pi) between groups of patients with CHF. An analysis of the Pi parameters before the test with RG between groups I and III also showed statistically significant differences by 12.8%, and after the test by 15.5%, respectively (P<0.01). The values of these parameters between groups I and II were not significant (P>0.05). The results of this analysis are presented in table 2.

Table number 2.

Indicators of shear stress and EZVD *in patients with* ***CHF of intermediate EF (HFmrEF) depending on the representation of MS components (M±SD)***

Indicators		**1 group (n=42)**	**2 group (n=39)**	**3 group (n=28)**
τ 0, dyne/cm²		61,48±9,43	54,7±9,39	51,07±9,18**
τ 1, dyne/cm²		92,2±10,54 °°°	82,12±10,03°°°*	79,12±11,95°°°**
Δτ, dyne/cm²		30,71±5,3	25,41±5,09**	24,04±5,63***
К, y.e.		0,22±0,09	0,14±0,03***	0,14±0,04***
Pi, rel units	Under	1,56±0,17	1,67±0,22	1,76±0,19**
	15 c1	1,61±0,11	1,74±0,20	1,86±0,10**
Ri, rel units	Under	0,76±0,04	0,78±0,05	0,81±0,03
	15 c1	0,78±0,03	0,8±0,04	0,83±0,02

Note: in relation to the data of group 1: *P<0,05; **P<0,01; ***P <0,001

with respect to post-sampling data: °P<0,05; °° P<0,01; °°° P <0,001

differences between II and III groups: ▪ P <0,05; ▪▪ P>0,01

The calculated data obtained indicate a decrease in the initial shear stress on the endothelium (τ0) in patients with CHF. Moreover, there is a trend towards a decrease in this indicator as the representation of MS components in sick patients increases. The decrease in the value of τ0 is determined in patients of group III by 20.4% in relation to the data of group I of the study (P<0.01).

In the test with reactive hyperemia, the shear stress on the endothelium (τ1) in all groups increases statistically significantly (P<0.001). Analysis of the shear stress on the endothelium (τ1) after the test,

depending on the representation of MS, revealed significant differences between groups I and II by 12.2% (P<0.05), between groups I and III by 16.5% (P<0 .01).

Calculating the change in shear stress (Δτ) from the difference between τ1 and τ0, which was statistically significantly lower in patients of groups II (P<0.01) and III (P<0.001) compared to group I, and also knowing the pressure difference (ΔD) in PA (tab. 1. and 2.) you can calculate the ability of PA to vasodilate (K). A comparative analysis of the sensitivity of PA to shear stress in relation to group I showed a decrease in this indicator by 57.1% (P<0.001) in groups II and III of the study.

During the analysis of the results of the ED study, a significant moderate correlation was found between Δτ and LDL (r= -0.38; P<0.05); negative correlation between Δτ and OT (r= -0.34; P<0.05); moderate correlation between ΔD and HDL (r=0.37; P<0.05); moderate negative correlation between ΔD and TG (r= -0.35; P<0.05); moderately high negative correlation between ΔD and OT (r= -0.58; P<0.001); negative correlation between K and SBP (r= -0.39; P<0.05); K and OT (r= -0.33; P<0.05); EZVD and DBP (r= -0.32; P<0.05). A high negative correlation was found between K and DBP (r= -0.61; P<0.001) in Group I patients with CHF without MS before treatment.

In group II patients with CHF and DLP + AO + HTG + AH before treatment, a moderate correlation was noted between Δτ and cholesterol; ΔD and cholesterol, ΔD and OT (r= -0.32; r= -0.33; r= -0.35, respectively; P<0.05). There was a moderate correlation between the sensitivity of PA to shear stress - K and TG (r= -0.40; P<0.05); EVD and TG (r= -0.43; P<0.01); EVD and SBP (r= -0.40; P<0.05); EZVD and DBP (r= -0.38; P<0.05)).

When evaluating the correlation relationships between MS components and ED parameters in the group of patients with CHF and DM2, there is a negative correlation between ΔD and WC, EZVD and WC (r= -0.30 and r= -0.33, respectively (P<0.05) , Δτ and fasting blood glucose (r= -0.34; P<0.05), EVD and SBP (r= -0.49; P<0.01), EVD and DBP (r= -0.49 ; P<0.01), as well as between EVD and fasting blood glucose (r= -0.37; P<0.05).

CONCLUSIONS: In patients with CHF, which develops against the background of various combinations of MS components (II and III groups), inadequate vasodilatation is observed in response to a significant increase in the stimulus. Despite a significant acceleration of blood flow after the test with RG, their diameter was inferior to the diameter of the vessels of group I.

The results of the studies found that patients with CHF have ED, the severity and nature of this dysfunction depends on the presence and nature of the representation of MS components. We found that CHF without MS proceeds with less pronounced manifestations of ED. In contrast to patients with MS, in response to a slight acceleration of blood flow after decompression, a statistically significant increase in the diameter of the VA is observed, which is somewhat inferior to that of group I patients with CHF without MS. However, despite this and close initial values of shear stress on the endothelium, after decompression, this indicator statistically significantly decreases in comparison with group I. A significant deterioration in EF in patients with CHF without MS is also confirmed by a statistically significant low index of PA sensitivity to shear stress (K).

BIBLIOGRAPHY:

1. Agostoni P, Paolillo S, Mapelli M, et al. Multiparametric prognostic scores in chronic heart failure with reduced ejection fraction: a long-term comparison. European Journal of HeartFailure. 2018;20:700-10. doi:10.1002/ejhf.989.
2. Atakhodjaeva G., Mizaeva B., Aripova J., Abdulatipov A., Valiev A. The effectiveness of the treatment of heart failure metabolic syndrome on the parameters of post infarct remodeling and functional state of the left ventricle in patients with metabolic syndrome. Chin J Ind Hyg Occup Dis, 2021, Vol.39, No.13 P. 382-392. https://doi.org/10.5281/zenodo.5593953
3. Бардымова Т.П., Потасов К.В., Цыретова С.С., Донирова О.С. Сахарный диабет 2-го типа и ишемической болезнь сердца. // Бюллетень ВСНЦ СО РАМН. – 2017. – Т2. №1(113). – С.100-108.
4. Душина А.Г., Лопина Е.А., Либис Р.А. Особенности хронической сердечной недостаточности в зависимости от фракции выброса левого желудочка. *Российский кардиологический журнал*. 2019;(2):7-11. https://doi.org/10.15829/1560-4071-2019-2-7-11
5. Душина А.Г., Лопина Е.А., Либис Р.А. Особенности хронической сердечной недостаточности в зависимости от фракции выброса левого желудочка. *Российский кардиологический журнал*. 2019;(2):7-11. https://doi.org/10.15829/1560-4071-2019-2-7-11
6. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2016 The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2016 of the European Society of Cardiology. Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. // Eur. Heart J. - 2016. - Vol. 10. - P. 1093-1128.
7. Fomin IV. Chronic heart failure in Russian Federation: what do we know and what to do.Russian journal of cardiology. 2016;8:7-13. doi:10.15829/1560-4071-2016-8-7-13.
8. Галявич А.С., Мингалимова И.М., Галеева З.М., Балеева Л.В. Оценка риска отдаленного летального исхода у госпитализированных пациентов с постинфарктной хронической сердечной недостаточностью. *Российский кардиологический журнал*.2020;25(1):3671. https://doi.org/10.15829/1560-4071-2020-1-3671
9. Gheorghiade M., Vaduganathan M., Fonarow G. et al. Rehospitalization for Heart Failure Problems and Perspectives // J Am CollCardiol. – 2013. – Vol. 61, №4. – P. 391-403.
10. Habal M. V., Liu P. P., Austin P. C. et al. Association of heart rate at hospital discharge with mortality and hospitalizations in patients with heart failure. // Circ Heart Fail. – 2014. - №7. – P.12-20.
11. Kamilova U., Abdullaeva Ch., Atakhodjaeva G., Beknazarova S., Masharipova D., Ikramova F. Disorders of kidney function in chronic heart failure. Indian Journal of Forensic Medicine and Toxicology Vol. no. 15 issue no. 4 October-December 2021.P.1547-1552. http://www.ijfmt.com/scripts/IJFMT_October-December%202021%20(1).pdf
12. Клинические рекомендации 2020. Российское кардиологическое общество (РКО)Хроническая сердечная недостаточность. Российский кардиологический журнал 2020; 25 (11) https://russjcardiol.elpub.ru ISSN 1560-4071 (print) doi:10.15829/1560-4071-2020-4083

13. Kurlykina NV, Seredenina EM, Orlova YaA. Use of loop diuretics in heart failure: Current aspects. Terapevticheskiy arkhiv. 2017;89(9):115-9. (InRuss.) doi:10.17116/terarkh2017899115-119.

14. Mareev V, Fomin I, Ageev F, et al. Russian Heart Failure Society, Russian Society of Cardiology. Russian Scientific Medical Society of Internal Medicine Guidelines for Heart failure: chronic (CHF) and acute decompensated (ADHF). Diagnosis, prevention and treatment. Kardiologiia. 2018;58(6S):8-158. (In Russ.). doi:10.18087/cardio.2475.

15. MareevVYu, Fomin IV, Ageev FT, et al. Clinical guidelines. Chronic heart failure (CHF). Russian Heart Failure Journal. 2017;18(1):3-40.. doi:10.18087/rhfj.2017.1.2346.

16. Ponikowski P, Voors AA, Anker SD, et al. ESC Guidelines for the diagnosis and treatmentof acute and chronic heart failure. European Heart Journal. 2016;37(27):2129-200.doi:10.1093/eurheartj/ehw128.

17. Ponikowski P, Voors A, Anker S, et al. 2016 ESC Guidelines for the diagnosis and treatmentof acute and chronic heart failure: The Task Force for the diagnosis and treatment of acuteand chronic heart failure of the European Society of Cardiology (ESC). Developed with thespecial contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail.2016;18:891-975. doi:10.1093/eurheartj/ehs104.

18. Tereshchenko SN, Zhirov IV. Chronic heart failure: new challenges and new perspectives. Therapeutic archive. (InRuss.) 2017;9:4-9. doi:10.17116/terarkh20178994-9.