Ageev F. T.[1], Ovchinnikov A. G.[1, 2]

[1] Chazov National Medical Research Center of Cardiology, Moscow, Russia

[2] Evdokimov Moscow State University of Medicine and Dentistry, Moscow, Russia

Heart Failure With Low and Preserved Left Ventricular Ejection Fraction – are These Two Different Independent Diseases or One Disease, but at Different Stages of its Progression? How Does This Affect the Choice of Therapy and Its Effectiveness?

The article discusses the question of whether it is possible to conclude that any heart failure (HF), throughout the entire range of left ventricular ejection fractions (LVEF), is a single holistic disease, based on the «external» similarity of treatments for reduced (HFrEF) and preserved (HFpEF) LVEF, and that positioning HFpEF and HFrEF as separate independent diseases is not valid.

Keywords Heart failure with preserved ejection fraction; HFpEF; treatment of HFpEF

For citation Ageev F. T., Ovchinnikov A. G. Heart Failure With Low and Preserved Left Ventricular Ejection Fraction – are These Two Different Independent Diseases or One Disease, but at Different Stages of its Progression? How Does This Affect the Choice of Therapy and Its Effectiveness? Kardiologiia. 2023;63(10):4–8. [Russian: Агеев Ф.Т., Овчинников А.Г. Сердечная недостаточность с низкой и с сохраненной фракцией выброса левого желудочка – это два разных самостоятельных заболевания или одно заболевание, но на разных этапах своего развития? Как это влияет на выбор терапии и ее эффективность? Кардиология. 2023;63(10):4–8].

Corresponding author Ageev F. T. E-mail: ftageev@gmail.com

Question

Treatment of patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) include almost the same recommended drugs: diuretics, sodium-glucose cotransporter type 2 (SGLT2) inhibitors, valsartan/sacubitril (ARNIs), mineralcorticoid receptor antagonists (MRAs). Does this mean that any heart failure is a single holistic disease and the recognition of HFpEF as a separate independent disease is not eligible?

Answer

Two main concepts of the onset and development of CHF syndrome are currently discussed. According to the first concept, CHF is a spectrum of phenotypes on different tracks of a single process without categorizing patients to independent phenotypes HFrEF and HFpEF [1]. The disease starts with the loss of some healthy cardiomyocytes (more often in myocardial infarction) and is accompanied by cardiac remodeling with a gradual reduction in left ventricular ejection fraction (LVEF) as a longitudinal unifying hemodynamic indicator and, which is crucial, a compensatory reaction of neurohumoral systems. At the same time, the neurohormonal hyperactivation is considered the main driving force for the development of heart failure. Another concept offers two pathogenetically independent phenotypes of CHF: HFrEF and HFpEF [1]. The mechanism of HFrEF corresponds to the first concept, and the HFpEF phenotype develops in a different way. The root cause of HFpEF is not the partial loss of the functioning myocardium, but a low-intensity pro-inflammatory condition affecting the myocardium and inherent with comorbidities such as obesity, diabetes, arterial hypertension with LV hypertrophy, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), etc. The driving force of the process is low-intensity inflammatory damage to cardiomyocytes and excessive collagen deposition in the intercellular space (myocardial fibrosis), which collectively leads to increased chamber stiffness, the development of diastolic dysfunction and a typical clinical picture of CHF. At the same time, neurohumoral activation makes minimal contribution in the development of heart failure, which is usually limited only by excess aldosterone (Table 1).

Thus, when choosing pathogenesis-based therapy for patients with dyspnea, edema, etc., we deal with fundamentally different concepts: neurohumoral response in HFrEF and inflammatory/fibrous process in HFpEF. So the obvious question is why an externally similar therapy is recommended in both cases?

The similarity is in fact only external. The 2022 AHA/ACC/HFSA guidelines [2] stipulate that the treatment of patients with HFrEF (LVEF < 40%) is based almost exclusively on the redundancy of the neurohumoral response (central figure). All neurohumoral modulators of the renin-angiotensin-aldosterone system (RAAS), including angiotensin-converting enzyme (ACE) inhibitors, angiotensin

ISSN 0022-9040. Kardiologiia. 2023;63(10). DOI: 10.18087/cardio.2023.10.n2553

Central illustration. Fundamental similarities and differences in the recommended treatment of heart failure for patients with reduced (≤ 40 %) and preserved (≥ 50 %) left ventricular ejection fraction in accordance with the 2022 AHA/ACC/HFSA guidelines [2]

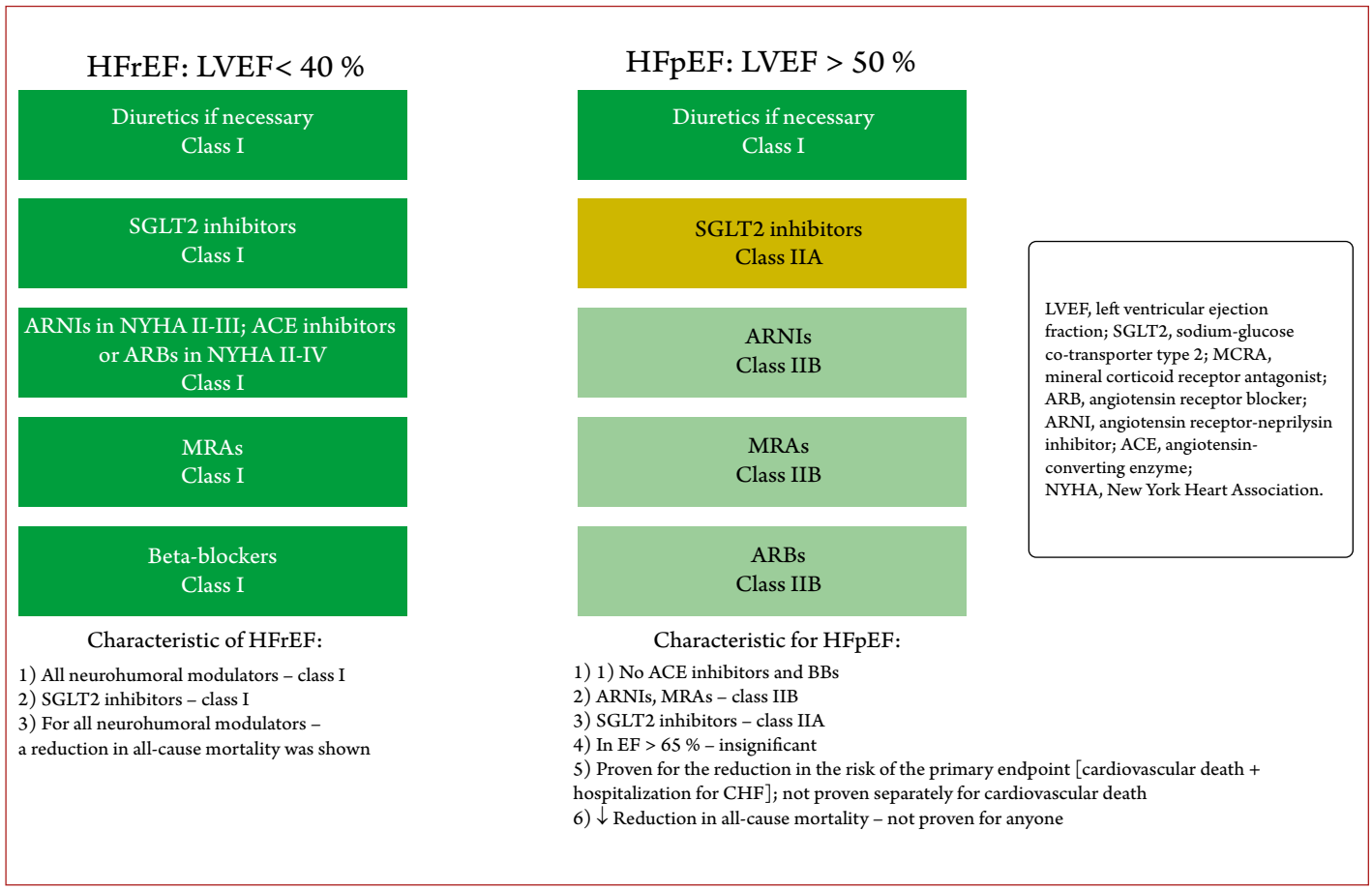

Table 1. Morphological and neurohumoral differences underlying the pathogenesis of heart failure with reduced ejection fraction and heart failure with preserved ejection fraction

Parameters	LVEF ≥ 50 % (HFpEF)	LVEF < 50 % (HFrEF)
Pathogenetic mechanisms	MS inflammation	Cardiomyocyte death
LV structure/function		
LV volume	↔	↑
Wall thickness	↑	↔
Remodeling	Concentric	Eccentric
LVEF	↔	↓
LV stiffness	↑	↓
Hormone activation		
RAS	+/–	+++
SAS	+/–	+++
NUP	+/–	+++
Aldosterone	++	+++
Fibrosis	Interstitial/reactive	Focal/replacement

receptor blockers (ARBs), ARNIs (valsartan/sacubitril), and sympatho-adrenal system blockers (beta-blockers, BB) and MRAs are highly effective and reduce all cardiovascular indicators and all-cause mortality (class I, level of evidence A).

The treatment of patients with HFpEF (LVEF > 50%) based on the neurohumoral concept does not look so rousing and convincing. ACE inhibitors and BB are not mentioned at all for lack of evidence of their efficacy, ARNIs and MRAs are only class IIb with a low level of evidence. We are talking here about the composite primary endpoint (cardiovascular death + hospitalization for decompensated CHF) rather than separate cardiovascular mortality and even all-cause mortality, as for patients with LVEF < 40%. SGLT2 inhibitors stand out as they are quite effective in patients with HFrEF and HFpEF. However, they have the highest class and level of evidence IA only for HFrEF and only IIA for HFpEF[1]. It should be added that none of the therapies recommended for HFpEF had no

[1] By the time when this article was published, the 2023 Focused Update of the ESC Guidelines for the diagnosis and treatment of heart failure for patients with HFpEF [3] came out, in which SGLT2 inhibitors were assigned the level and class of evidence IA instead of IIA as in the previous version. This change is associated with more than convincing results of the DELIVER study of dapagliflozin in patients with CHF and LVEF > 40 % [4] and the findings of the EMPEROR preserved study of empagliflozin [5] allowed increasing the class and level of SGLT2 inhibitors in the treatment of HFpEF.

significant direct positive effect on the prognosis for patients with LVEF > 60–65%.

Thus, despite some similarities in the treatments, the differences in efficacy are more obvious, which does not confirm the concept of CHF being a single holistic disease and rather speaks in favor of the concept of two independent phenotypes of CHF.

Nevertheless, what may be the reason for the identified similarities and differences in the treatment responses? In particular, how to explain some success of classical neurohumoral modulators (ARNIs, ARBs and MRAs) in patients with inflammatory/fibrotic HFpEF, and what is the phenomenon of SGLT2 inhibitors, which are effective in all phenotypes of CHF? First, given the heterogeneity of HFpEF origin, the presence of a neurohumoral component in the development of the disease cannot be excluded in all patients with LVEF > 50%, which explains some partial positive effect if ARNIs and ARBs in at least within LVEF up to 60–65%.

Second, myocardial fibrosis, both interstitial in HFpEF and focal inherent with HFrEF, is sensitive to MRAs. Third, it was proved with regard to the SGLT2 inhibitor phenomenon that they had their own hemodynamic and neurohumoral effects [6, 7] and the ability to directly positively affect cardiomyocytes, which is extremely important in myocytic deficiency associated with HFrEF and microinflammation and reactive interstitial fibrosis in HFpEF. Due to the activation of intracellular processes of autophagy, gliflozins build resilience of cardiomyocytes to oxidative stress and provide favorable conditions for the repair of damaged cellular organelles; mobilize the heart cell energy resources lost during the pathological process by restoring the suppressed processes of mitochondrial respiration [8, 9]. The unique dual mechanism of action allows gliflozins to effectively work both in the neurohumoral storm setting and on the inflammatory/fibrotic track of the disease development. It is not surprising that SGLT2 inhibitors are listed first in the recommendations for the treatment of both HFrEF and HFpEF.

This dualism also applies to ARNIs, yet to a lesser extent: valsartan present in the molecule of this complex provides neurohumoral modulation, which is more in demand in HFrEF, and neprilysin inhibitor sacubitril enhances neurohumoral support and produces the anti-inflammatory/antifibrotic effect necessary for HFpEF.

In other words, patients with HFrEF are in more need of neurohumoral effects, and patients with inflammatory/fibrotic HFpEF require anti-inflammatory and antifibrotic effects inherent with these drugs to varying degrees.

Although the concept of two independent phenotypes of CHF (neurohumoral phenotype characteristic of HFrEF and inflammatory/fibrous phenotype characteristic of HFpEF) is very convincing, there is one contradiction that requires a special explanation: neither neurohumoral modulators, including ARNI, nor SGLT2 inhibitors were shown to be able to reliably affect the prognosis for CHF patients with LVEF > 60–65% [10].

This fact became a stumbling block for both concepts of CHF development and the subject of a more detailed study. One of the popular explanations is that the neurohormonal influence in the pathogenesis of CHF extends above the level of LVEF 50%, but gradually decreases with higher LVEF and disappears at LVEF > 60–65% [10]. The contribution of the inflammatory/fibrotic mechanism, on the contrary, gradually increases and becomes predominant in LVEF > 60–65%, changing the hemodynamic relief of the heart function, which requires a different therapeutic approach and drugs with a different mechanism of action to be considered. What actually goes on with hemodynamics and the heart in patients with CHF and LVEF beyond > 60–65% is the subject of heated discussions and more detailed studies [11]. But it is this view of the changes in the efficacy of conventional CHF therapy along the entire track of LVEF that further leads experts to the conclusion that it is necessary to redefine the absolute role of LVEF as a comprehensive longitudinal factor of heart failure in general and the need to shift to the right of its norm up to 60–65%, in particular [10]. A detailed review of opinions on the normal values of LVEF has been published in our journal in issue #6 of this year [12].

It should be noted in conclusion that the analysis of the recommended therapy for patients with HFrEF and HFpEF showed that there are more differences than similarities, but most importantly, these differences being of pathogenetic nature are deeper in meaning. The question posed revealed a more significant problem – the one of modern understanding of the very nature of heart failure syndrome, specific developmental mechanisms, and the role of LVEF in the diagnosis and ranking of patients with CHF.

No conflict of interest is reported.

The article was received on 04/07/2023

REFERENCES

1. Ageev F.T., Ovchinnikov A.G. Diastolic heart failure: 20 years later. Current issues of pathogenesis, diagnosis and treatment of heart failure with preserved LVEF. Kardiologiia. 2023;63(3): 3–12. [Russian: Агеев Ф.Т., Овчинников А.Г. Диастолическая сердечная недостаточность: 20 лет спустя. Актуальные вопроса патогенеза, диагностики и лечения сердечной недостаточности с сохраненной ФВЛЖ. Кардиология. 2023;63(3):3-12]. DOI: 10.18087/cardio.2023.3.n2376

ISSN 0022-9040. Kardiologiia. 2023;63(10). DOI: 10.18087/cardio.2023.10.n2553

2. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. Journal of the American College of Cardiology. 2022;79(17):e263–421. DOI: 10.1016/j.jacc.2021.12.012
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2023;ehad195. [Epub ahead of print]. DOI: 10.1093/eurheartj/ehad195
4. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. New England Journal of Medicine. 2022;387(12):1089–98. DOI: 10.1056/NEJMoa2206286
5. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. New England Journal of Medicine. 2021;385(16):1451–61. DOI: 10.1056/NEJMoa2107038
6. Packer M. Molecular, Cellular, and Clinical Evidence That Sodium-Glucose Cotransporter 2 Inhibitors Act as Neurohormonal Antagonists When Used for the Treatment of Chronic Heart Failure. Journal of the American Heart Association. 2020;9(16):e016270. DOI: 10.1161/JAHA.120.016270
7. Bosch A, Poglitsch M, Kannenkeril D, Kolwelter J, Striepe K, Ott C et al. Angiotensin pathways under therapy with empagliflozin in patients with chronic heart failure. ESC Heart Failure. 2023;10(3):1635–42. DOI: 10.1002/ehf2.14313
8. Packer M. Critical Reanalysis of the Mechanisms Underlying the Cardiorenal Benefits of SGLT2 Inhibitors and Reaffirmation of the Nutrient Deprivation Signaling/Autophagy Hypothesis. Circulation. 2022;146(18):1383–405. DOI: 10.1161/CIRCULATIONAHA.122.061732
9. Braunwald E. Gliflozins in the Management of Cardiovascular Disease. New England Journal of Medicine. 2022;386(21):2024–34. DOI: 10.1056/NEJMra2115011
10. Packer M. A reclassification of heart failure based on recognition of heart failure with normal to supernormal ejection fraction, a clinically common form of cardiac contracture, with distinctive pathophysiological and therapeutic features. European Journal of Heart Failure. 2023;25(5):669–72. DOI: 10.1002/ejhf.2849
11. Rosch S, Kresoja K-P, Besler C, Fengler K, Schöber AR, von Roeder M et al. Characteristics of Heart Failure With Preserved Ejection Fraction Across the Range of Left Ventricular Ejection Fraction. Circulation. 2022;146(7):506–18. DOI: 10.1161/CIRCULATIONAHA.122.059280
12. Ageev F. T., Ovchinnikov A. G., Ageeva S. F., Mareev V. Yu. What is "normal left ventricular ejection fraction" and its relationship with the pathogenesis and effectiveness of the treatment of heart failure. Kardiologiia. 2023;63(6):69–74. [Russian: Агеев Ф.Т., Овчинников А.Г., Агеева С.Ф., Мареев В.Ю. Что такое «нормальная фракция выброса левого желудочка» и ее связь с патогенезом и эффективностью лечения сердечной недостаточности. Кардиология. 2023;63(6):69-74]. DOI: 10.18087/cardio.2023.6.n2404

ISSN 0022-9040. Kardiologiia. 2023;63(10). DOI: 10.18087/cardio.2023.10.n2553