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

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

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

DIASTOLIC HEART FAILURE: 20 YEARS LATER.
Current issues of pathogenesis, diagnosis and treatment of heart failure with preserved LVEF

This review analyzes results of studies of the recent decade that focus on epidemiology, mechanisms of development, diagnostic methods, and treatments of heart failure with preserved ejection fraction (HFpEF). As expected, the prevalence of HFpEF continues to increase due to the growing contribution of comorbidities to the structure of causes for chronic heart failure (CHF), such as arterial hypertension with left ventricular hypertrophy, obesity, chronic kidney disease, as well as due to ageing of the population and decreased contributions of ischemic heart disease and myocardial infarction. Concomitant diseases are a source of low-intensity microvascular inflammation, which is currently assigned a role of a trigger mechanism eventually provoking energy deficiency, disorders of cardiomyocyte relaxation, and diffuse myocardial fibrosis. Both these processes lead to increased heart muscle rigidity and abnormally high left ventricular filling pressure (LVFP). High LVFP is associated with the development of pulmonary venous congestion and impairment of alveolar blood oxygenation, which form the clinical picture of HFpEF. Detecting high LVEF with tissue Doppler echocardiography by the E/e' value became the instrumental basis for the HFpEF diagnostics. Recognition of inflammation and fibrosis as the key pathogenetic factors marked the main vector of modern therapy for HFpEF (anti-inflammatory and antifibrotic). The best implementation of this vector became possible with the advent of drugs from the class of angiotensin receptor and neprilysin inhibitors (ARNI), sodium-glucose cotransporter type 2 (SGLT2) inhibitors, and aldosterone antagonists. However, the efficacy of such treatments is evident only with the LV EF <60–65% while at higher values, the efficacy substantially decreases. This limitation may result from the heterogenous nature of the disease and requires more advanced methods for verification of HFpEF clinical phenotypes. Among such methods, transcriptomic, metabolomic, and proteomic approaches are considered. With the use of capabilities of the «machine learning» and the artificial intelligence, these approaches can become a new frontier in research to represent an important step towards personalized medicine for patients with HFpEF.

Keywords Heart failure with preserved ejection fraction (HFpEF); microvascular inflammation; myocardial fibrosis; ARNI; SGLT2 inhibitors

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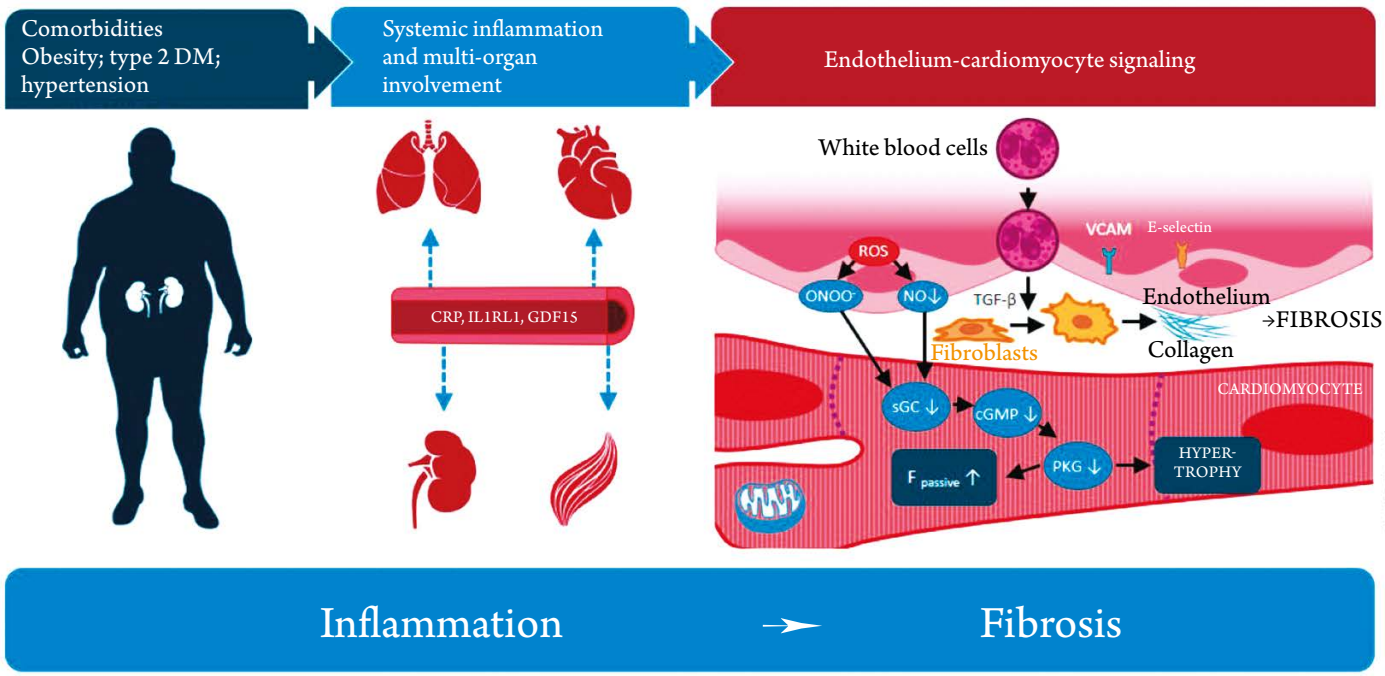
Corresponding author Ageev F.T. E-mail: ftageev@gmail.com

It has been over 20 years since our journal published in 2010 article, Meet Diastolic Heart Failure [1], and 10 years since article, Diastolic Heart Failure: 10 Years of Acquaintance» [2], which ended with the following questions: What new transformation awaits heart failure? How soon will the problem of heart failure with preserved ejection fraction (HFpEF) be solved? Will they (new treatments) be effective?» The past decade did see revolutionary changes in our perceptions of what this form of chronic heart failure (CHF) is, what its pathogenesis is, and what are ways of diagnosis and treatment given a new understanding of the development mechanisms

Definition

This form is formally determined by a single term, «heart failure with preserved ejection fraction (HFpEF)», which reflects the main distinguishing characteristic of this phenotype of CHF, namely, left ventricular ejection fraction (LVEF) ≥50%. Other previously proposed terms «preserved LV systolic function» and «diastolic heart failure» are no longer used since they do not fully reflect the full scope of this CHF phenotype and can even be misleading. It is incorrect to refer to «preserved systolic function» just based on LVEF≥50%, as this indicator only indirectly and very loosely represents the contractility and systolic function of the myocardium. More sensitive techniques, such as magnetic resonance imaging (MRI) or assessment of left ventricular global longitudinal strain (GLS) in 2D echocardiography, which are used to evaluate myocardial contractility and systolic function, show that decreased myocardial contractility is observed in patients with CHF with any LVEF. That is, the LVEF value≥50% performs an exclusively distinguishing function in the CHF classification, between different CHF phenotypes, but is not a longitudinal indicator of myocardial contractility. Moreover, there is a serious discussion at present regarding the definition of the «normal» LVEF. The level of≥50% is not recognized by all experts as «normal», that is «preserved» [3].

Figure 1. Low-level systemic microvascular inflammation, a universal contribution to the development of HFpEF



CRP, C-reactive protein; IL1RL1, interleukin 1 receptor-like 1; GDF15, growth differentiation factor; ROS, reactive oxygen species; ONOO-, peroxynitrite; NO, nitric oxide; sGC, soluble guanylate cyclase; cGMP, cyclic guanyl monophosphate; PKG, protein kinase G; TGF-β, transforming growth factor; VCAM, vascular cell adhesion molecule; F passive, passive cardiomyocyte stiffness.

The term «diastolic heart failure» was not officially recognized, since signs of impaired diastolic filling of the heart can be observed in patients without obvious clinical signs of heart failure, for example, in the elderly and senile patients, and diastolic dysfunction is an almost obligatory feature of any heart failure phenotype, including the phenotype with predominant systolic dysfunction.

Epidemiology, clinical picture, prognosis

The last decade has not seen any fundamental changes in our understanding of the epidemiology, clinical picture, or prognosis of patients with HFpEF. As expected, the prevalence of HFpEF among CHF patients increases from year to year and already exceeds 50%, according to various authors [4]. This trend is expected due to the increasing contribution to the list of CHF causes of the diseases such as arterial hypertension (AH), obesity, type 2 diabetes mellitus (DM), chronic kidney disease (CKD), as well as a decrease in the contribution of coronary artery disease and myocardial infarction. The assessment of the clinical picture and prognosis in HFpEF also did not change significantly. Survival of patients with HFpEF is relatively higher than that of patients with reduced LVEF, but this difference does not seem significant [5].

Perspectives on the pathogenesis of HFpEF

The understanding of the HFpEF mechanisms underwent key changes. Two main concepts are currently discussed. Concept 1: HFpEF is an independent disease other than HF with reduced LVEF (HFpEF), and the root cause of HFpEF is a low-level pro-inflammatory state rather than a partial loss of the functioning myocardium (Figure 1). Concept 2: CHF is a single unimodal disease with many development paths from HFpEF to HFrEF (Figure 2).

The concept of an independent pro-inflammatory model of the HFpEF development is based on the idea that concomitant diseases, most particularly, obesity and hypertension, as well as DM, chronic obstructive pulmonary disease (COPD), CKD, anemia, are accompanied by systemic low-level inflammation of the coronary microvascular endothelium. Endothelial inflammation leads to the formation of reactive oxygen species and reduces the bioavailability of NO. This, in turn, results in a decrease in the level of cyclic guanosine monophosphate and a reduction of the activity of protein kinase G. Reduced activity of this enzyme increases rest stress (passive stress) of cardiomyocytes due to hypophosphorylation of titin and reduce inhibition of pro-hypertrophic stimuli that cause cardiomyocyte hypertrophy.

Moreover, microinflammation in endothelial cells is accompanied by the expression of adhesion molecules (VCAM and E-selectin), which contributes to the migration of monocytes into the subendothelial space. Transforming growth factor (TGF-b), released by the monocytes, stimulates the conversion of fibroblasts into myofibroblasts,

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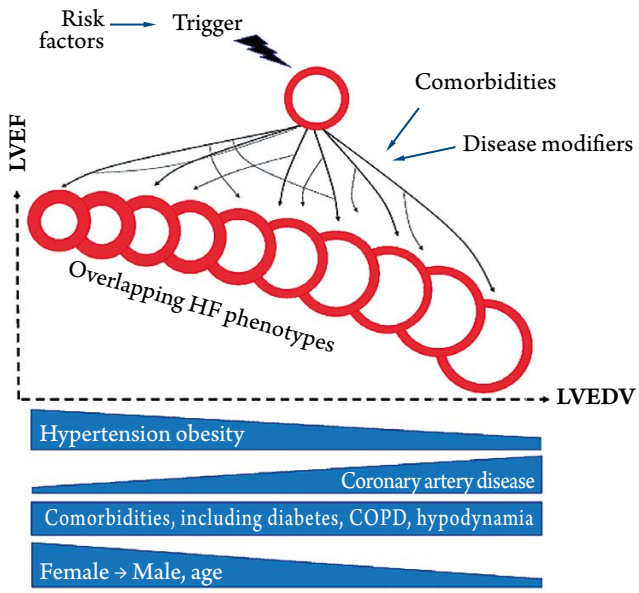
Figure 2. CHF is a spectrum of different phenotypes on different paths of a single process; adapted from Filippos Triposkiadis et al. [7]



LVEF, left ventricular ejection fraction; HF, heart failure; LVEDV, left ventricular end-diastolic volume; COPD, chronic obstructive pulmonary disease.

which, when in excess, deposit collagen in the interstitial space causing the development of clinically significant myocardial fibrosis. The diastolic dysfunction (DD) and ventricular rigidity (chamber stiffness) are increased as a result of changes in the diastolic characteristics of cardiomyocytes and excessive collagen matrix (fibrosis). Increasing DD and higher chamber stiffness complicate LV diastolic filling. This complication is initially compensated by higher left atrial (LA) filling, and when the LA compensatory resource is exhausted, an adequate filling of LV is provided by higher pressure gradient between the LA and the LV (LV filling pressure (LVFP)). The increase in LVFP is the main hemodynamic constant that determines the presence of DD as a possible cause of the CHF clinical signs. The mechanism of the transformation of high LVFP into clinical signs of CHF (dyspnea at rest or during exercise, weakness, fatigue) is implemented through a deterioration of the outflow from the pulmonary veins to the overloaded LA and the development of venous and later mixed (reactive) pulmonary hypertension (PH). Venous PH is accompanied by complicated lymphatic drainage of pulmonary tissue, edema of the alveolar walls with a worsening of transient properties and a drop in blood oxygenation, which is inevitable in this situation. Hypoxia and the associated clinical signs (dyspnea, weakness, etc.) most clearly manifest during physical exercise, even insignificant, since the rigid collagen matrix does not allow the complete implementation of the Frank-Starling mechanism: cardiac output (CO) does not increase to ensure the load because cardiomyocytes cannot additionally stretch in diastole to enhance systolic contraction. When arteriolar (reactive) PH comes into venous PH, the mechanism of right ventricular insufficiency is initiated, the congestion of the systemic circulation develops, and the renal component of CHF joins the process.

It is obvious that the mechanisms of the DD formation are more diverse and not limited only to microvascular inflammatory processes and myocardial fibrosis. Among them, the tachy component, the right ventricular influence, the state of the pericardium, the extracardial environment, infiltrative processes in the myocardium and some other components are considered. Nevertheless, the inflammatory mechanism of the development of HFpEF is regarded as a priority and the most common, which is confirmed by the positive outcomes of clinical studies in such patients receiving drugs that have anti-inflammatory and antifibrotic properties, e.g, statins, valsartan+sacubitril and sodium-glucose cotransporter type 2 (SGLT2) inhibitors [6].

The pro-inflammatory/fibrotic concept of the pathogenesis explains why HFpEF, despite having similar clinical picture with the «classic» form of CHF with reduced LVEF, can be considered as an independent disease. The main difference is the trigger mechanism (Table 1), which is low-level microvascular inflammation in HFpEF and the death of cardiomyocytes in myocardial ischemia (most often in acute myocardial infarction, less often in chronic ischemia or toxic effects) in HFrEF. Morphological and functional differences include thickening of the LV walls with its normal volume (concentric remodeling), high myocardial stiffness, and preserved LVEF in HFpEF; and dilatation of the LV cavity with the same wall thickness (eccentric remodeling), reduction of LVEF with unchanged stiffness of the walls in HFpEF. Myocardial fibrosis is present in both mechanisms of CHF development, but it is diffuse (interstitial) in HFpEF, and in HFpEF, it has focal and replacement nature (for example, in the area of ischemic damage) more often. The neurohormonal response to exposure in the principal difference. In HFrEF caused by the death of some potent cardiomyocytes, the mechanism of stimulation of the remaining alive cardiomyocytes is triggered to maintain the same level of cardiac output (CO) by activating the sympathoadrenal system (SAS) and renin-angiotensin-aldosterone system (RAAS). In HFpEF, all cardiomyocytes are alive and do not need stimulation, therefore, significant activation of SAS and RAAS is not observed in this form of CHF. The first phenotype can be designated as cardiac disorder with systemic manifestation, the second one as systemic disorder with cardiac manifestation. The difference in the development mechanisms of these two phenotypes of CHF explains different responses to neurohumoral

modulators: ACE inhibitors, beta-blockers are effective in HFrEF and ineffective in HFpEF.

The second concept of CHF development is the concept of a single disease with numerous development paths. According to Triposkiadis et al. [7], CHF is a spectrum of various phenotypes (Figure 2) on different paths of a single process. Each phenotype is the result of an individual patient path, in which the heart is remodeled either toward concentric hypertrophy (the beginning of the path) or eccentric hypertrophy (the end of the path), or a combination of both (the middle of the path). The onset of the process and the subsequent path depend on the risk factor (s), concomitant pathology, and disease modifiers. Risk factors are diseases that always precede the development of HF: the more risk factors, the higher the incidence of HF. Concomitant diseases (usually 2 or more) can precede HF or develop against its background and coexists. Finally, modifiers are specific characteristics of the patient that contribute to the development of the initial phenotype and the progression of HF in one or another path. Hypertension, obesity, as well as female sex and advanced age, turn the path towards the concentric type of remodeling, and ischemic heart disease changes the path towards eccentric remodeling. The path turns towards eccentric remodeling against the background of acute damage or overload (AMI, toxic effects), and towards concentric remodeling against the background or when AH, DM, obesity, hypothyroidism join. Despite the quantitative differences between the leftmost and the rightmost sides of the spectrum, there is an important overlap between the phenotypes across the spectrum. Any division of the spectrum according to any criterion (e.g., LVEF) is artificial.

Table 1. The main differences in the development mechanisms, hormone activity, and the nature of fibrosis in heart failure with preserved and reduced left ventricular ejection fraction

Parameter	Heart failure with preserved ejection fraction (HFpEF)	Heart failure with reduced ejection fraction(HFrEF)
Pathogenic trigger mechanism	Microvascular inflammation	Cardiomyocyte death
LV structure/function		
LV volume	↔	↑
Wall thickness	↑	↔
Remodeling	Concentric	Eccentric
LVEF	↔	↓
LV stiffness	↑	↓
Hormone activation		
Renin-angiotensin system	+/–	+++
Sympathoadrenal system	+/–	+++
Aldosterone	++	+++
Fibrosis	Interstitial/reactive	Focal/replacement

LV, left ventricle; LVEF, left ventricular ejection fraction

What LVEF should be considered preserved (normal) or reduced?

The traditional view of LVEF as the main determinant of the LV systolic function and a factor dividing CHF to systolic and diastolic has recently come under justified criticism. Sixty years ago, Folse and Braunwald [8] reported a radioisotope method for determining the fraction of the left ventricular (LV) end-diastolic volume ejected during the cardiac cycle. Their work set the stage for the use of LVEF in clinical practice and shaped decades of subsequent cardiovascular research. LVEF remains to this day the indicator of ventricular contractility dominating the minds of physicians, bearing information relevant to the diagnosis, treatment, and prognosis of almost all cardiovascular diseases.

The value of 50% was chosen as the cut-off point between normal and reduced LVEF based on the database of the 7 largest American population-based studies performed using the echocardiographic indicators [9]. The median LVEF in the healthy (non-AH, DM, CKD) population, irrespective of age, race, and height/weight, was 62% with a range of two standard deviations (2σ): 52–72% for male patients and 64% with a range of 54–74%, respectively, for female patients, who cover 95% of the total healthy population in a single-modal distribution. Therefore, the choice of LVEF 50% virtually guarantees that any LVEF below this value will is «reduced», and LVEF≥50% is preserved. This figure has become the basis for the accepted division of patients with CHF into subgroups with reduced (< 40%), mid-range (41–49%), and preserved (≥ 50%) LVEF. It would seem that the mortality of CHF patients is higher, the lower is the level of LVEF. However, studies conducted in recent years with the correlation of the prognosis for cardiovascular patients to LVEF in its entire range (and not only LVEF<50%) showed that LVEF 60–65% rather than 50% is the break point (mortality nadir) [10, 11]. CHF patients with a so-called abnormal LVEF≥60–65% also show a progressive increase in mortality, as do those who have LVEF<60% (Figure 3). A comparative study of HFpEF patients with LVEF 50–60% and LVEF>60% showed their heterogeneity, e.i., they differed significantly from each other in the main hemodynamic and morphological characteristics [12–14]. The fact that the cohort of CHF patients with LVEF≥50% is heterogeneous in form and content is confirmed by different reactions to the same therapy: treatment with

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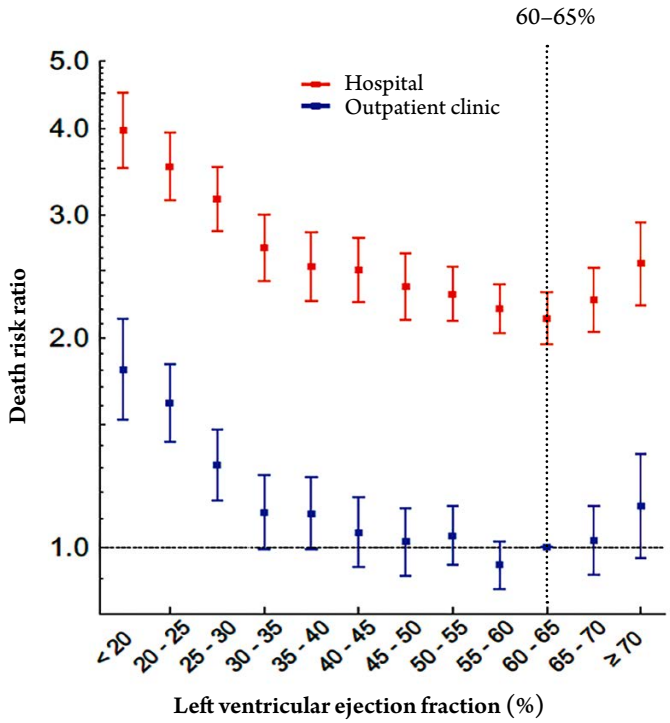
Figure 3. Relationship between left ventricular ejection fraction and survival in a heterogeneous clinical cohort*



* adapted from Gregory J. Wehner et al. [11]

valsartan+sacubitril or SGLT2 inhibitors is effective in LVEF from 50% to about 60%, and its effect weakens in LVEF>60% [15, 16]. The only reasonable conclusion from this phenomenon is that the unification of all patients with CHF into one group based om LVEF≥50% is not correct, and the level of LVEF≥50% itself cannot serve as a criterion for the normality or preservation of LVEF, and its threshold should be reconsidered to higher level of 60–65% [14, 17].

Treatment of patients with HFpEF: revolution

The main events of the last decade were associated with the development of new drug treatment approaches for the effective management of patients with HFpEF. After the relatively unsuccessful completion of randomized clinical trials (RCTs) of ACE inhibitors (PEP-CHF) and sartans (I-PRESERVE, CHARM-preserve) [18–20], several more tests of «non-neurohumoral exposure» were conducted using rhythm-reducing drug ivabradine [21], alagebrium acting against the end products of glycation [22], and a number of others. However, none of them showed a satisfactory effect. High expectations were associated in the TOPCAT mega-project with the mineralcorticoid receptor antagonist spironolactone, but the result was neutral in this study, although the post-hoc analysis showed a significant improvement in the primary endpoint in patients with baseline NT-proBNP>360 pg/mL [23].

In 2019, multicenter, randomized, double-blind phase III study (PARAGON – HF) was complete and it was the closest to the topic of HFpEF at that moment; valsartan+sacubitril was compared with active valsartan in patients with LVEF≥45% and elevated NT-proBNP [15]. Although the result was not statistically significant (the odds ratio of developing a primary composite endpoint (cardiovascular death or HF hospitalization) was 0.87, p=0.059), the subsequent post-hoc analysis showed a significant positive effect of the therapy in the subgroup of patients with LVEF 45–57%, which was a kind of precursor of changing perspectives of the effective treatment of patients with LVEF.

Some progress on this issue was achieved in 2021 after the completion of the EMPEROR-preserved study of empagliflozin [16], in which the reduction in the risk of the primary composite endpoint was 21% (p<0.001) and was very significant in the LVEF range of 40–60%. A year later, the DELIVER study of another SGLT2 inhibitor, dapagliflozin, was completed, the results of which built more confidence in glyphlozins: the reduction in the risk of the primary composite endpoint was 18% (p=0.0008) and was reliable in the subgroups of patients with LVEF above or below 60% [24]. The results of this study series of spironolactone, ARNI, SGLT2 inhibitor gave rise to a widely discussed concept of the efficacy of treating patients with CHF with any LVEF or without taking into account LVEF, which is convincing, though not flawless, since there is still no unambiguous solution of problems of the efficacy of treating patients with abnormal LVEF ≥60–65% [25, 26]. Nevertheless, the current drug master files for valsartan +sacubitril, empagliflozin, and upcoming dapagliflozin, state that these drugs can be used in heart failure irrespective of the LVEF value.

Those RCTs also clearly confirmed the concept of heterogeneity of HFpEF patients: such patients do have similar symptoms and signs of heart failure, but they represent an extremely heterogeneous group with various etiological and pathogenic mechanisms of the disease development. Thus, attempts to treat all patients with HFpEF under the same umbrella, that is, without considering their individual characteristics, are doomed to failure. One cannot but agree with the opinion of Shah S., according to whom, the modern trend towards a personalized approach to the treatment of cardiovascular diseases is most illustratively exemplified by HFpEF [27]. Such a personalized approach is based on the identification of clearly defined phenotypes of HFpEF, each with a specific set of demographic, pathogenic, and clinical characteristics [28–30]. Only a few HFpEF phenotypes are currently distinguished (Table 2) [31], the most prevalent of which are the brain natriuretic peptide (BNP) deficiency phenotype, which is more frequently observed in patients with AH and left ventricular hypertrophy, and the

Table 2. Clinical phenotypes of HFpEF and treatment modalities, adapted from Ageev F.T., Ovchinnikov A.G. [31]

	Phenotype	Peculiarities	NT-proBNP	Preferred treatment
1	BNP deficiency syndrome	AH+LVH ± fibrosis (± CAD, COPD, CKD, obesity)	from ↔ to ↑	V+S* ± spironolactone*
2	Cardiometabolic syndrome	Obesity, DM (± CAD, AH, COPD, CKD)	↑↑	SGLT2 inhibitor* (empagliflozin, dapagliflozin)+statins
3	With mixed PH and RV failure ± cardiorenal syndrome	↑ CVP, congestion in the systemic circulation, PASP≥40 mm Hg, severe course	more often ↑↑↑	Sildenafil**, torasemide***
4	Cardiac amyloidosis (more common than ATTR-CM)	More often male patients of 60 years and older, with EF of 60% and higher	more often ↑↑↑	Transthyretin stabilizers

* the combination V+S, an SGLT2 inhibitor, and spironolactone can be considered in phenotypes 1, 2, and 3;
** in the presence of invasively confirmed mixed pulmonary hypertension; *** – torasemide is preferred in congestion.
BNP, brain natriuretic peptide; CAD, coronary artery disease; AH, arterial hypertension; LVH, left ventricular hypertrophy: COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease, V+S, valsartan+sacubitril; SGLT2 sodium glucose co-transporter type 2; DM, diabetes mellitus; PH, pulmonary hypertension; RV, right ventricle; CVP, central venous pressure; PASP, pulmonary artery systolic pressure; ATTR-CM, transthyretin amyloid cardiomyopathy; EF, ejection fraction.

cardiometabolic phenotype, which is prevalent in patients with abdominal obesity, metabolic syndrome, DM. It should be recognized that certain features of different phenotypes intersect and can change as the disease progresses. This understanding of the development mechanisms justifies the combination therapy for patients with HFpEF with the accentuated use of SGLT2 inhibitor and valsartan+sacubitril supplemented with mineralocorticoid receptor antagonists. This combination of three drug classes seems to be the most promising approach for the treatment of most patients with HFpEF [32].

Diagnosis of HFpEF: Are we ready?

The habit of focusing on LVEF as a determinant of heart failure prevented the adequate diagnosis of LVEF for a long time. For example, linking the diagnosis of HFpEF exclusively to the presence of clinical signs and LVEF>50% in some registers and epidemiological studies inevitably led to underdiagnosis or overdiagnosis of HFpEF [33, 34]. Therefore, the understanding of the main mechanism of the HFpEF development and the introduction of the evaluation methods for this mechanism into routine practice have become the most important achievements of the past decade.

The main hemodynamic mechanism determining the presence of HFpEF is increased left ventricular filling pressure (LVFP), and high LVFP plays a key role in the diagnosis of LVEF, being a kind of analogue of reduced LVEF for systolic HF. LVFP can be directly measured by cardiac catheterization, which is still the gold standard for the diagnosis of HFpEF, but this complex invasive procedure is not suitable for routine practice. Tissue Doppler imaging (TDI) is an integral part of the diagnosis of HFpEF. It includes the estimation of the E/e' ratio, a key non-invasive parameter, which is closely correlated with LVFP and allows quickly and accurately assessing LVFP [35]. Non-invasive assessment of LVFP by E/e' is included in all current HFpEF diagnosis algorithms developed by experts of the European Society of Cardiology (HFA – PEFF) and American experts (H2FPEF) [36, 37].

Returning to the issue of verifying the diagnosis of HFpEF in the current Russian setting, it should be recognized that there is no alternative to fully equipping hospitals and outpatient clinics with modern ultrasound devices with the tissue Doppler function and training physicians in current algorithms for HFpEF diagnosis [38].

Conclusion: What is next?

When explaining the reasons for the disappointing results of the I-PRESERVE study, M. Packer said in 2008: «…perhaps we should understand what we are studying; we do not understand this disease (HFpEF – author's note) at all…» [39]. The next 15 years of target research allowed provided insight into the disease and allowed formulating the main working concept: HFpEF is a consequence of low-level systemic multi-organ microvascular inflammation accompanied by a violation of cardiomyocyte energy supply and a deterioration of the relaxing properties of the heart and an increase in intercellular fibrosis. The inevitable increase in the myocardial stiffness, when these processes occur together, is compensated by a pathological increase in LVFP, the detection of which at rest or during exercise is a key diagnostic criterion for HFpEF. The non-invasive determination of LVFP using tissue Doppler imaging by E/e' in combination with other clinical and biochemical signs makes it possible to easily verify the diagnosis of HFpEF with high sensitivity and specificity.

The mechanisms of DD formation are not limited only to microvascular inflammatory processes and myocardial

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СЕРДЦА ПАЦИЕНТОВ В ВАШИХ РУКАХ

Гипертрофия левого желудочка сегодня может привести к ХСН завтра[1]

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fibrosis and include an intricate mosaic of cardiac and non-cardiac components, which necessitates forming delineated phenotypes of the disease, each of which is characterized by a set of predominant characteristics and is sensitive to certain treatments.

The choice of treatment based on this understanding has already shown its viability: the use of ARNI, SGLT2 inhibitors, mineralocorticoid receptor antagonists, and their combinations in the phenotypes of HFpEF patients with a predominance of AH, LV hypertrophy, obesity, DM made it possible to succeed for the first time – the risk of cardiovascular death and hospitalization for HF was reduced, at least within the limits of LVEF<60%.

But most importantly, the lack of a convincing effect of this therapy in patients with LVEF >60–65% once again reminds of the heterogeneous nature of the disease and requires the use of more advanced methods for verifying its phenotypes, such as transcriptomic, matobolic, and protobolic analyses, which can become the next frontier in the research of HFpEF representing an important step towards personalized medicine [40]. The first pilot studies on the isolation of responsible proteins in the cohort of HFpEF patients [41] showed the presence of stable networks of certain groups of inflammatory proteins with hemodynamic parameters, and the different expression of a small group of circulating intracellular proteins that enhance autophagic processes, prevent oxidative stress and inflammation, and contribute to the restoration and renewal of cardiac and renal cells [42]. These findings broaden the horizons in the phenotyping of HFpEF and the personalized approach to treatment decision making.

So, in what direction will the HFpEF science and practice develop further? Obviously, the nearest future should be devoted to the implementation of the gained knowledge in real-world clinical practice. It should be brought home to physicians that HFpEF is an individual disease, which, despite having a similar clinical picture, develops according to its own pathophysiological laws, which are different from HFrEF. Increasing efforts should be made to introduce HFpEF diagnostic algorithms into routine practice, which are based on the available measurement of LVFP, such as implementing the echocardiogram protocol with the estimation of E/e'. It should be implemented in the treatment of HFpEF patients what has been proven during the RCTs and stated in the Guidelines [43] – the use of a drug complex, the best of which at the moment are ARNI, SGLT2 inhibitors, spironolactone.

Given the heterogeneity of HFpEF pathogenesis, the treatment efficacy of these patients will depend on the accuracy of determining the clinical phenotype (personification), and to increase the accuracy, more productive and multivariate methods should be introduced, such as transcriptomic, metabolic, and proteomic analyses. The sharp increase in the number of analyzed parameters in the new techniques will require changes in the entire analytical apparatus and the use of a new, so-called machine learning data processing system [44]. The use of artificial intelligence, which is likely to become the main direction of HFpEF research in the coming years, should be a great help for physicians in this situation.

Whether it will or not, we will discuss, following tradition, in our journal in 10 years.

No conflict of interest is reported.

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