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REVIEW

Current Knowledge of Heart Failure with Preserved Ejection Fraction

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is the most common type of heart failure (HF) – predominantly in the elderly population – and the most difficult to treat.

The diagnosis is based, apart from clinical data, on data provided by imaging and biochemical evaluation: left ventricular (LV) diastolic dysfunction, EF ≥50% and increase of natriuretic peptide (NP). Several phenotypes of HFpEF have been identified based on etiological and pathophysiological data. Defining the phenotypes has allowed a wider knowledge of specific pathogenic mechanisms and conducting therapeutic studies with pharmacological and non-pharmacological agents – but with uncertain results.

It is currently accepted that HFpEF is a heterogenous and systemic pathological condition where the cardiac damage is secondary. The comorbidities associated with HFpEF determine a proinflammatory state, endothelial dysfunction and microvascular damage, and, as a result, morphological and functional cardiac changes and diastolic dysfunction.

Keywords: heart failure with preserved ejection fraction.

I. General data. Definitions

Heart failure with preserved ejection fraction (HFpEF) is a form (type) of heart failure (HF) that became topical in the last 5-10 years.

It is estimated that, from the total cases of HF, approximately 50% are HFpEF, 40% HFrEF and 10% are HFmEF. The prevalence of HFpEF increases with age and predominantly affects the elderly. In the US, HFpEF accounts for 2/3 of HF cases in elderly people (1).

Heart failure with preserved ejection fraction is not only commonly encountered in the population, but it also has a severe evolution and prognosis. The annual mortality caused by HFpEF ranges between 10-30%, and more than 50% of patients die with clinical signs of right heart failure.

Several considerations have led to an increased clinical and scientific interest in studying HFpEF. Thus, population studies have shown an increasing prevalence – most likely related to increased life expectancy – and a limited therapeutical effectiveness for HFpEF; the constant association of multiple comorbidities (HT, DM, obesity, chronic kidney disease) has led to formulating a new paradigm in disease pathogenesis (systemic disease) in correlation with specific risk factors; diagnostic criteria for diastolic dysfunction and HFpEF have

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been defined predominantly *via* imaging techniques; various phenotypes of HFpEF have been identified on pathophysiological and etiological bases.

Based on the above-mentioend premises, the current paper addresses: 1) the problems of defining ventricular diastolic dysfunction (DD) and HFpEF; 2) a relatively brief presentation of the pathogenesis of DD and HFpEF, considered as a systemic disease; 3) a presentation of HFpEF phenotypes on hemodynamic and etiological bases and of specific therapy elements; 4) comparative elements between HFpEF and HFrEF treatment.

HFpEF is defined as a clinical syndrome, characterized by signs and symptoms of HF, EF ≥50%, increase of natriuretic peptides (NPs), LV diastolic dysfunction (increased filling pressure), in the presence of structural or functional heart diseases (2).

The definition of HFpEF has three basic elements: EF ≥50%, LV diastolic dysfunction and increased NP levels.

LV diastolic dysfunction can be either asymptomatic or symptomatic (at rest or during exertion) but its presence is not enough for defining HFpEF. Cardiac pathology and EF ≥50% can be found in various cardiac, organic or functional conditions. LV diastolic dysfunction is present in specific pathological conditions (well defined) such as severe uncontrolled hypertension, infiltrative cardiomyopathies and ischemic cardiomyopathy with restriction (3).

It should be emphasized that not all people with diastolic dysfunction have or will develop HFpEF and not all patients with HFpEF have ventricular diastolic dysfunction. In two studies, TOPAT and CHARM, only 66% and 67% of patients with HFpEF, respectively, had diastolic dysfunction (4).

Natriuretic peptides, especially NT-proBNP, are elevated in HFpEF but their levels are lower than those commonly encountered in HFrEF; normal NP levels do not rule out the diagnosis of HFpEF. Lower levels of NP in HFpEF are mainly seen in obesity and metabolic syndrome; visceral fat could potentially increase NP clearance (5).

To summarize, HFpEF is defined by the (intercorrelated) presence of three parameters, including EF ≥50%, diastolic dysfunction (of various degrees) and high levels of NP, after the exclusion of alternative specific etiologies such as infiltrative cardiomyopathies, severe – uncontrolled – hypertension, hypertrophic cardiomyopathy (HCM), Fabry disease, ischemic cardiomyopathy (with restriction), severe valvular diseases (aortic stenosis).

TABLE 1. Echocardiographic parameters predicting HFpEF (1)

- <16% decrease in global longitudinal strain (GLS)
- Left ventricular (LV) hypertrophy
- Indexed left atrial (LA) volume >30 (34) mL/m^2
- septal e'velocity 7 cm or lateral <10 cm
- Levels of E/e' >14
- Pulmonary artery pressure ≥35 mm Hg
- Tricuspid velocity 2.8 m/sec
- TAPSE <21

Diastolic dysfunction, defined by the increased filling pressure of the LV, is usually assessed by echocardiography and multiple protocols. Cardiac magnetic resonance imaging (MRI) scan can bring additional diagnosis elements.

In clinical practice, but also in research, multiple echocardiographic parameters are used as predictors for HFpEF (Table 1).

Notes:

- LV hypertrophy with concentric remodelling is seen in <1/3 of patients with HFpEF.
- The increase of E/e' as a marker of ventricular filling pressure is relatively specific for HFpEF, when it is >13 (specificity of 86%). Lower levels of E/e' can be seen in patients with HFpEF. As with other echocardiographic parameters, the absolute E/e' value should be interpreted with a continuous scale for the estimation of the probability of HFpEF (1).

Data from guidelines prioritize four echocardiographic parameters for DD; E/e' >14; indexed LA values >34 mL/m^2; and the velocity of tricuspid regurgitation >2.8 m/sec. The increase of systolic pulmonary arterial pressure secondary to hypertension in LA is also a strong indicator for the diagnosis of HFpEF (3). ❑

II. Pathophysiology

Chronic HF in mature elderly people, accompanied by a left heart with normal volume (small heart) and arterial hypertension, was considered for a long time to be a cardiopathy related to age and/or high blood pressure levels. Echocardiographic studies that defined LV diastolic dysfunction and subsequent HF with preserved ejection fraction (≥50%) have stimulated

research on myocardial structure and function in HFpEF. Studies have shown specific changes in myocardial structure and function in patients with LV hypertrophy and diastolic dysfunction, consisting of myocyte hypertrophy and of interstitial fibrosis, and delayed LV relaxation and cardiomyocyte stiffness, respectively. The same studies reported endothelial changes in coronary microcirculation, the presence of inflammatory cells and evidence of oxidative stress (6).

In view of these data, it has been hypothesized that, in HFpEF, the myocardial damage is secondary to some pathogenic processes determined by both the associated comorbidities and age-related changes.

Paulus A. M. *et al* changed the paradigm according to which HFpEF was a systemic condition with a proinflammatory state.

Also, Paulus has described the sequence of pathogenic events that lead to the development of HFpEF (7).

1. Comorbidities (HT, DM, coronary disease, including obesity) induce a systemic proinflammatory state.
2. As a consequence of the proinflammatory state, the microvascular endothelial cells produce ROS (reactive oxygen species) that limit NO bioavailability to adjacent cardiomyocytes.
3. The decrease in NO bioavailability decreases the activity of protein kinase (PKG) in cardiomyocytes.

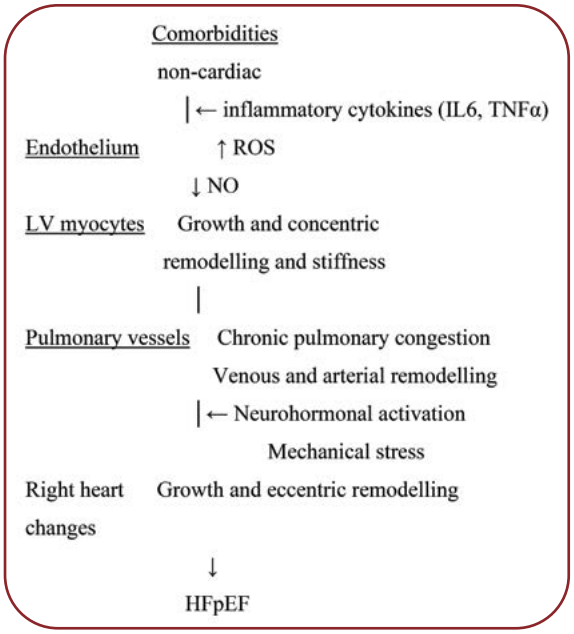

FIGURE 1. Pathophysiology of myocardial remodelling and pulmonary vessels in HFpEF (3)

4. The reduction of PKG activity leads to myocytes hypertrophy, LV concentric remodelling and cardiomyocyte stiffness.
5. Cardiomyocyte changes (stiffness) and increased collagen deposition by myofibroblasts lead to diastolic dysfunction – the major cardiac deficit in HFpEF.

Age-related physiological processes also increase the ROS expression on a microvascular level.

The set of hemodynamic and functional structural changes resulting from the pathogenic ele-

The cardiac function and pulmonary vessels
LV dysfunction (diastolic)
LV and RV dysfunction ± AFib
Pulmonary vascular dysfunction (pulmonary vasculopathy)
RV dysfunction
Hemodynamics
↑ LV filling pressure
↓ Pulmonary vasodilation during exertion
↑ LV filling pressure at rest and pulmonary HT
↑ RV filling pressure and restrictive LV filling
Extracardiac structures and functions
↑ Arterial stiffness
Endothelial and microvascular dysfunction
Vascular fibrosis

TABLE 2. Structural and functional changes in HFpEF

ments of HFpEF are summarized in Table 2 (modified after Berlaug) (1).

Clinical identification of markers of morpho-physiological changes that lead to HFpEF can be obtained by analysing the natriuretic peptides, proinflammatory markers, cardiac damage markers, and fibrosis markers.

To summarize, the pathophysiology of HFpEF starts with extracardiac factors that lead to an inflammatory state and endothelial, microvascular dysfunction and subsequently, to concentric cardiac remodelling and LV diastolic dysfunction. Thus, the myocardial damage occurs as a secondary process in HFpEF, unlike heart failure with reduced ejection fraction (HFrEF), where myocardial damage occurs primarily *via* the direct action of some cardiotropic factors, e.g., injury, ischemia, infection or toxaemia. The conceptual separation between HFpEF and HFrEF has also to be judged in terms of reality. The two types of HF share similar risk factors and common clinical and hemodynamic features. The progress from diastolic dysfunction and HFpEF to HFrEF is extremely rare, possible only *via* the intervention of coronary disease and subsequent injury. ❑

III. Phenotypes in HFpEF

While analysing the clinical and exploratory data, heart failure with preserved EF is characterised by multiple cardiac and extracardiac pathophysiological anomalies. The most important ones include LV diastolic dysfunction, LA dysfunction and remodelling, pulmonary hypertension and pulmonary vasculopathy with remodelling, pulmonary gas exchange disorders, RV and RA dysfunction and remodelling, and extracardiac damage. Thus, HFpEF can be characterized as a heterogenous syndrome, which is difficult to define as a unique type in terms of clinical aspect, hemodynamic profile and biological markers (8).

Analysis of data from trials and observations allowed the identification of several subtypes of HFpEF. Six subtypes were initially identified, among which the subtype of patients with obesity and DM and the subtype of elderly patients with high prevalence of atrial fibrillation (AFib) were the most important ones. Following the complete analysis of 375 cases of HFpEF, Shah *et al*, from Mayo Clinic, described three phenotypes (9): 1) relatively young patients, mild symptoms; NP with minimally increased levels; concentric LV hypertrophy; 2) older patients with small LV, myocardial stiffness, intermediary levels of E/e' and NP; and 3) patients with obesity, those with symptomatic diabetes, increased mass of the LV, frequent AFib and LA dilation.

The definition of the previously reported subtypes or phenotypes of HFpEF used various criteria based on etiological, clinical and imaging bases.

Currently, two etiological types and four pathophysiological types are better defined in HFpEF (4): 1) etiological phenotypes, including obesity, diabetes mellitus and coronary disease, which have different pathophysiological and clinical particularities that require different therapeutical approaches; and 2) pathophysiological phenotypes, which follow the sequence or cascade of pathophysiological processes that define each subtype; the four subtypes addressed in the present paper include: a) the phenotype of LV systolic dysfunction; b) the phenotype of LA dysfunction; c) the phenotype of pulmonary hypertension, pulmonary vasculopathy and right heart dysfunction; and d) the phenotype with chronotropic incompetence.

Discrimination between the HFpEF phenotypes allows for different therapeutical approaches.

Phenotype: LV diastolic dysfunction

Heart failure with preserved ejection fraction is the result of multiple morphological and functional myocardial changes, that involve the cardiomyocyte, the interstitial tissue, the coronary microcirculation and the epicardial coronary vessels. From a functional point of view, the delayed relaxation and increase of passive stiffness leads to LV diastolic dysfunction and EF ≥50%.

Although HFpEF has by definition LV diastolic dysfunction and EF ≥50%, some patients also develop various degrees of LV systolic dysfunction. Initially, they are asymptomatic and subsequently become symptomatic during exertion and have signs of myocardial subendocardial damage on echocardiography. 2D GLS (global longitudinal strain) is an echocardiographic parameter which reflects the function of subendocardial myocardial fibers that are more sensitive to ischemia and general stress. The decrease of GLS levels (n ≥14%–16%) shows an alteration of the cardiac function, with possible progression to systolic dys-

function and EF decline (10). Magnetic resonance imaging examination additionally defines both the myocardial damage and contractile dysfunction.

Two alterations of coronary vessels and myocardial perfusion may be found at the same time in a patient with HFpEF: coronary microvascular disease and atherosclerotic disease of epicardial coronaries. Coronary disease is frequently encountered in HFpEF and it is found in 50-60% of patients (11).

In situations of LV diastolic dysfunction, subendocardial perfusion is further limited and leads to ischemia and LV systolic function limitation (12).

The transition from HFpEF and EF ≥50% to heart failure with midrange ejection fraction (HFmrEF) and even HFrEF is very rare, possibly due to the early occurrence of pulmonary vascular disease and right heart dysfunction.

The identification of clinical and imaging elements of progressive LV systolic dysfunction in a patient with HFpEF should lead to an assessment of the permeability of epicardial coronaries (coronarography or coronary CT scan) and a possible interventional solutioning.

Phenotype: LA dysfunction

The morphological and functional aspects of LA have an important role in the development and progression of HF, both in HFrEF and in HFpEF. In normal conditions, LA has the role of conduit, reservoir and pump and modulates ventricular filling and indirectly the LV function.

In patients with HFpEF and increased ventricular filling pressure, a process of mechanical and electrical remodelling takes place in the LA. In the first stages of ventricular diastolic dysfunction, LA remodelling is moderate and contributes (if sinus rhythm is present) to the adaption of LV function to situations of rest and exertion. When the LV diastolic dysfunction progresses, LA remodelling and dysfunction increase and AFib occurs, which cancels the pumping function of the atrium. In patients with HFpEF, LA dysfunction and remodelling are frequently encountered (13).

LA dysfunction and remodelling, together with persistent or permanent AFib, is associated with an increase in atrial stiffness – resulting in an even greater increase in LA pressure – which is disproportionate to the level of filling pressure. Thus, conditions are favourable for the development of the so-called atrial myopathy (14).

Atrial remodelling, dilation and dysfunction are directly assessed by ultrasound examination and calculation of the indexed volume of LA (>30/34/mL/m^2), which basically reflects the chronic impairment of LV filling pressure (15).

The consequences of LA remodelling and dysfunction in HFpEF are manifested at three interrelated levels, including 1) increase of retrograde pressure in pulmonary and post-capillary veins – at rest and accentuated during exertion; 2) development of AFib or other atrial tachyarrhythmias; and 3) occurrence of mitral regurgitation that worsens LA remodelling and dysfunction.

Firstly, the increase of retrograde pressure at the pulmonary and post-capillary venous level and subsequently pre-capillary is the most important hemodynamic event in HFpEF. The increased pressure in pulmonary veins leads to vascular remodelling with progressive pulmonary hypertension and finally to right heart failure.

Secondly, the development of AFib, initially paroxysmal and later permanent, is followed by hemodynamic and thromboembolic risk. Uncontrolled AFib in terms of rhythm or rate decreases ventricular filling pressure, leads to progression of LA remodelling and increases the pulmonary capillary wedge pressure and pulmonary arterial pressure. In HFpEF, the increase in indexed LA volume and AFib is associated with adverse progression and risk of death (14). AFib is more frequent – 42% *vs* 26% in HFpEF than in HFrEF due to particular conditions of atrial remodelling.

Thirdly, functional mitral regurgitation in HFpEF is related to atrial remodelling and implicitly to the dilation of the mitral valve annulus (16). Generally, mitral regurgitation is mild to moderate in HFpEF, but it has a hemodynamic effect on the LA (increase in volume) and increases the risk of AFib (16). The particularities of LA dysfunction and remodelling have led to special therapeutical approaches in the LA dysfunction phenotype.

Restoring the sinus rhythm pharmacologically or *via* electric shock is necessary in order to reduce the adverse effects of atrial dysfunction. The indications for restoring the SR (rhythm control) in HFpEF are similar to those used in HFrEF.

Atrial fibrillation catheter ablation and restoring the SR may reduce the adverse consequences of Afib. A recent study has shown that catheter ablation reduced the hospitalization rate in HFpEF. Post-ablation AFib recurrence at one year had a similar incidence in HFpEF *vs* HFrEF (17). Also, a

sub-study of CABANA noted that AFib catheter ablation was associated with the reduction of a composite endpoint (mortality, debilitating stroke, severe bleeding or cardiac arrest) compared to pharmacological therapy in patients with stabilized HF, AFib and EF >50% (18).

In HFpEF, reducing the volume and pressure in LA can be obtained by using an interatrial device with left-right shunt. Functional improvement is expected by reducing the pressure volume in the LA and by increasing the pulmonary blood flow, in conditions of increased end-diastolic pressure in RV and a moderate decrease in cardiac output.

Two studies have followed the hemodynamic and functional effects of using the interatrial device in HFpEF *via* invasive monitoring at six and 12 months, respectively (8). An improvement of pulmonary vascular function at rest and during exertion was noted, without compromising the systemic perfusion. The probable explanations of the functional improvement are related to the increase in the pulmonary blood flow and to the higher content in O_2, which would modify the pulmonary vascular resistance.

Phenotype pulmonary hypertension. Pulmonary vascular disease and right heart dysfunction

The above-mentioned phenotype develops in the sequence of hemodynamic processes that follow LV diastolic dysfunction as well as LA dysfunction and remodelling. It is the most frequently seen phenotype and it is associated with a negative prognosis and risk of mortality (19).

Pulmonary hypertension type 2 is the defining stage of the phenotype. It is seen in approximately 75% of patients with HFpEF and it is usually symptomatic during exertion, in relation to the pressure level.

The hemodynamic parameters that define PH have been modified in the recent 2021 Guidelines (20) as follows: mean PAP ≥20 mm Hg; PCWP >15 mm Hg; transpulmonary gradient >12 mm Hg; and pulmonary vascular resistance >2 hW.

In the initial stages of HfpEF, the pressure in pulmonary veins increases as a result of LA remodelling and dysfunction and increased pressure in LA. Physical exertion increases the retrograde pulmonary congestion and postcapillary PH (isolated) becomes symptomatic (dyspnoea, fatigability). The progression of pulmonary venous stasis is accompanied by an increase of pulmonary wedge pressure and subsequently precapillary PH (combined), with both conditions leading to an increase in intravascular pulmonary pressure (HT).

Prolonged mechanical stress in the venous system and pulmonary arterioles, together with the proinflammatory factors of HFpEF comorbidities, lead to endothelial dysfunction and remodelling at the pulmonary venous and arteriolar levels. Morphometric studies have shown that remodelling affects the three vascular structures. At the level of the intima, the response is the thickening of the intima up to fibrosis; at the level of the tunica media, in the pulmonary arterioles, the response consists of smooth muscle cell hypertrophy, vasoconstriction and reduction of the vasodilator response (21).

A pulmonary morphometric study conducted on patients with HFpEF has shown that intima remodelling was greater at the venous level than the arteriolar level, where smooth muscle cell hypertrophy predominates, suggesting that media hypertrophy in arterioles was developing secondary to venous remodelling (21).

The narrowing of the lumen in pulmonary resistance vessels leads to an increased pulmonary vascular resistance (PVR), a stage where a pulmonary vascular disease develops. In the pulmonary microvasculature, thrombosis may develop.

The increase in PVR is mediated by vascular tone and by venous and arteriolar remodelling, both processes being determined by the imbalance between the secretion of active substances such as endothelins and vasodilator substances, e.g., NO (22).

The increase in pulmonary capillary pressures (pre- and pro-) and pulmonary vascular disease has consequences in the reduction of pulmonary gas exchange. Prolonged interstitial oedema reduces the alveolar volume, the conductance of the alveolocapillary membrane as well as the reduction of CO diffusion capacity. In patients with HFpEF, the reduction of diffusion capacity is associated with a negative prognosis and mortality (23).

The development of combined PH and PVR are the determinants of evolution and prognosis in patients with HFpEF (24).

In HFpEF, the development of PH and pulmonary vascular disease is followed by right heart dysfunction and remodelling. Changes in RV are

produced by pressure loading and other factors such as intrinsic myocardial damage by inflammation, microvascular dysfunction, chronic coronary disease, obesity and AFib (25).

The right ventricle (RV) with thin wall responds to pressure overload by dysfunction, initially systolic. During echocardiographic examination, the reduction of the longitudinal function of RV can be initially noted.

RV structure and function deteriorates even more in time, compared to the changes of the LV, which preserves its normal volume. The increase in RV pressure is accompanied by the movement of the interventricular septum to the left, affecting the LV filling (26).

The RV systolic dysfunction progression is associated with RA remodelling and dilation, which amplifies with the development of AFib and TR (tricuspid regurgitation AFib) (27). Hypertension (HT) can be a major factor for RA dilation and dysfunction, even when the RV volume is not dilated. Tricuspid regurgitation and AFib amplify the RA remodelling, RA that can appear larger than the LA on the echocardiographic examination (ultrasound aspect with bi-atrial, asymmetrical dilation) (28).

In advanced stages, HFpEF is characterized as a clinical syndrome of right heart failure and systemic congestion (including hepatic and renal congestion). In right HF, multiple mechanisms are activated, including neurohormonal and molecular activation, cytokine activation, RAAS, and the autonomous nervous system (29).

Dynamic echocardiographic examination identifies signs of loading (volume and pressure on right heart).

ECG elements – signs of overload/volume/pressure (in) RV (28)

These include RV basal end-diastolic diameter >41 mm; RV wall thickness >5 mm; IVC diameter >21 mm Hg; collapsibility <50%; regurgitation velocity tricuspid >2.8 m/sec; and TAPSE <13 mm.

On echocardiography, a decrease in TAPSE by 5 mm was reported, which was associated with an 25% increase in mortality. Besides, right HF is the main cause of mortality in HFpEF, the annual risk ranging between 10% and 30%.

Therapeutical resources for PH phenotype, pulmonary vascular disease, right HF are extremely limited.

In HFpEF, PH and pulmonary vascular disease represent a major target for pharmacological treatment. Numerous pharmacological agents recommended (within limits) in PH type 1 are used in clinical practice or are tested in clinical trials (1, 20, 29, 30).

In therapy, medications with vasodilatory and possible antiproliferative and anti-inflammatory effect, which act at the endothelial level and/or on vascular smooth muscle cells (pulmonary microangiopathy), have been studied or are being researched. This is based on the ideas that pulmonary vascular disease has a relatively fixed component (venous and arteriolar remodelling) but also a vasoconstrictive component at the pulmonary arteriolar level. Vasodilator agents could model the vasoconstrictive component and could improve symptoms and hemodynamic parameters in a HFpEF phenotype.

Clinical research has been using a wide range of therapeutic agents for PH reduction and, indirectly, for the improvement of right heart performance.

Overall, therapies with phosphodiesterase inhibitors (sildenafil), inorganic nitrites and isosorbide mononitrate, endothelin receptor antagonists, agents acting on the prostacyclin pathway showed negative or non-significant results.

Riociguat is a guanylate cuclase stimulator used in patients with HFpEF and PH, which exerted a significant effect on the intensity of pulmonary hypertension and improved the assessment of hemodynamic status as well as the echocardiographic parameters.

Most clinical trials that researched the effectiveness and the safety of vasoactive agents in PH were conducted on patients with type 1 PH. The results obtained in type 1 PH cannot be extrapolated to patients with type 2 PH or with other types, as the pathogenic mechanisms are different.

Finally, it can be concluded that medication with vasodilator effects at the level of pulmonary vessels did not have favourable results (structure, function) in this phenotype of HFpEF.

Pulmonary hypertension and pulmonary vasculopathy progression in HfpEF are associated with right heart remodelling and dilation, which extends not only to the RV but also to the RA. Thus, right HF develops, with all its clinical and hemodynamic manifestations.

Right heart global dysfunction is as difficult to treat in HFpEF as is in HFrEF. The long term means of treatment are similar (2).

Diuretic medication – especially loop diuretics – is the first treatment option: it reduces hypervolemia and improves the symptoms. During prolonged administration, it reduces the congestion, but can reduce LV efficiency and organ and tissue perfusion. In case of obesity and specific phenotype of HFpEF, weight loss and diuretic treatment can produce a significant clinical improvement.

HFpEF manifestations with right heart decompensation can be reduced by heart rate or heart rhythm control, possibly *via* catheter ablation of AFib. In extremis, the interventional treatment of tricuspid regurgitation can reduce the progression of right heart failure.

Inodilating medication *i.e.*, Levosimendan has a similar therapeutic indication in HFpEF and in HFrEF. Intravenous infusion with Levosimendan can temporarily alleviate the right heart acute decompensation, but the results are clinically and hemodynamically negative in patients with PH and pulmonary vasculopathy.

The phenotype HFpEF with chronotropic incompetence

Patients with HFpEF are mostly elderly and often have chronotropic incompetence, manifested as a limitation in the increase in heart rate (SR of AFib) during exertion. The limited chronotropic response not only reduces the ability to increase the heart output during exertion, in conditions of LV diastolic dysfunction, but also leads to an increase in LA pressure and retrograde at the pulmonary capillary level. In patients with HFpEF, fatigue and dyspnoea during exertion can be explained by chronotropic incompetence.

The mechanisms of chronotropic incompetence – sinus node dysfunction or autonomic dysfunction – are only presumed (4).

The phenotype with chronotropic incompetence poses particular problems in the treatment of HFpEF. Beta-blockers are an important pillar in the treatment of HFpEF and are also used in HFpEF for their beneficial effects on hospitalization for HF and mortality. Beta-blockers are used in up to 80% of patients with HFpEF, especially to target associated comorbidities, including HT, atherosclerotic coronary disease and AFib (2). It is considered that beta-blockers reduce the heart rate (SR of AFib) and increase the time of diastolic ventricular filling and the exercise capacity.

Is it necessary to administer beta-blockers in HFpEF and chronotropic incompetence? The answers can be obtained by interrupting the beta-blockers and by performing a general assessment of the patient. In a recent study, discontinuation of beta-blockers has improved the exercise capacity, while their use did not bring any benefit to HFpEF patients, even worsening their exercise capacity (31).

It is believed that beta-blocker administration in HFpEF patients has to be selective, especially for comorbidities. The 2021, ESC Guidelines established (mentioned) that beta-blockers had a IIb/c indication in HFpEF, similarly to HFmrEF (2).

Heart rhythm adaption and its increase in chronotropic incompetence HFpEF can be obtained by rate adapted pacing; the increase in heart rate (rhythm) is accompanied by a decrease in the ventricular filling pressure and an improvement of the functional capacity.

In the RAPID study, the use of rate adapted pacing in patients with HFpEF and chronotropic incompetence had negative results: there was no improvement in the exercise capacity of study participants, but it was associated with significant adverse effects (32).

Currently, the management of chronotropic incompetence in HFpEF remains undefined. Studies with beta-blockers interruption or rate adapted pacing had incomplete and insignificant results that cannot be used in medical practice. ❑

IV. Summary. The management of HFrEF *vs* HFpEF

The management of both types of HF (HFrEF and HFpEF) uses common therapeutical measures with proven efficiency, including: 1) diet, low sodium diet, weight loss, physical exercises and rehabilitation; 2) pulmonary or systemic congestion treatment; 3) treatment of etiological or associated comorbidities; and 4) pharmacological, interventional treatment or *via* implantable devices.

Treatment objectives, also common, include the control of HF symptoms and signs, improvement of hemodynamic conditions, reducing the morbidity and mortality and finally, improvement of the quality of life.

The pharmacological treatment of chronic or acute HF (from which the greatest efficiency is

hoped) is based, apart from diuretic medication for congestion, on a group of four types (pillars) of pharmacological agents: ACE-I or ARB; beta-blockers; mineralocorticoid receptor inhibitors (MRI); and SGLT2 inhibitors. Sacubitril valsartan is the last type of medication that acts on the SAAR mechanism, which can replace ACE-I or ARB (especially in HFrEF).

In HFrEF, according to the 2021 ESC Guidelines for HF, all four groups of pharmacological agents are recommended with a class of recommendation IA. When it comes to final effects, they reduce hospitalization (for HF worsening) and cardiovascular mortality and, to various degrees, general mortality (2).

For HFpEF, the provisions of the European and American Guidelines for HF for the pharmacological treatment are also based on the four groups (pillars) used in HFrEF. Most clinical trials and their results were conducted on patients with HFpEF ≤50% or ≥40% or, in short, HFmrEF. May these provisions be also extended for HFpEF ≥50%?

For the pharmacological treatment of HFpEF, the 2021 ESC Guidelines stipulates that the four types of pharmacological agents can be "considered" (used) for reducing the risk of hospitalization and death, with a class of recommendation II b/c. The studies based on which the provisions were developed had neutral or interpretable results as statistical significance. As a summary remark, there is little or incomplete evidence that the pharmacological treatment of HFpEF would also reduce morbidity, hospitalization and mortality (33). A probable explanation is the heterogeneity of HFpEF syndrome, with pathogenic mechanisms – partly different than those acting in HFpEF.

In the last two years, two international randomized studies, EMPEROR Preserved trial and DELIVER trial, used SGLT2 inhibitors (empagliflosine or dapagliflosine, respectively) which brought evidence of a significant reduction ($p < 0.001$) of cardiovascular death or hospitalization in HFpEF (34, 35). In both studies, most of the patients had HFmrEF or HFpEF.

The results of both studies could change the class of recommendation of SGLT2 inhibitors in the management of HFpEF.

Besides pharmacological treatment, with limited effectiveness, two special chapters are included in the management of HFpEF: 1) the control of major factors associated with HFpEF, including HT, obesity, diabetes mellitus, coronary disease, is compulsory; this type of factors are also present as risk factors in HFrEF; and 2) the phenotypes in HFpEF have particular therapeutical means for each specific type (etiological or pathophysiological); the therapeutical approach of HFpEF phenotypes may bring a plus of effectiveness for different groups of patients.

Finally, HFpEF is the predominant form of HF in the elderly, which remains relatively often underdiagnosed. Diagnosis is based on clinical manifestations of HF and DD (LV), FE ≥50% and on the increase in NP.

The development of HFpEF is the result of multiple pathogenic processes (inflammation, endothelial dysfunction, microvascular damage), which are determined by defined comorbidities.

There are many identified etiological and pathophysiological phenotypes of HFpEF that are identified and that are specific targets for treatment.

Heart failure with preserved ejection fraction is a heterogenous systemic syndrome, different from HFrEF, which is characterized by etiological conditions, pathogenic and hemodynamic mechanisms and currently limited therapeutical results. ❑

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