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► To cite this version:

Elena Galli, Corentin Bourg, Wojciech Kosmala, Emmanuel Oger, Erwan Donal. Phenomapping Heart Failure with Preserved Ejection Fraction Using Machine Learning Cluster Analysis: Prognostic and Therapeutic Implications. *Heart Failure Clinics*, 2021, 17 (3), pp.499-518. 10.1016/j.hfc.2021.02.010 . hal-03246464

HAL Id: hal-03246464

<https://hal.science/hal-03246464v1>

Submitted on 13 Jun 2023

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**Phenomapping Heart Failure with Preserved Ejection Fraction Using Machine Learning Cluster Analysis:
Prognostic and Therapeutic Implications**

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No conflict of interest for this paper, nothing to disclose for any of the authors. The authors have nothing to disclose.

KEYWORDS

Heart failure with preserved ejection fraction, machine learning, phenomapping, prognosis, precision medicine, targeted treatment

KEY POINTS

- Heart failure represents one of the main causes of morbidity and mortality worldwide
- Heart failure with preserved ejection fraction (HFpEF) is a specific entity characterized by complex pathophysiology and high heterogeneity of clinical presentations
- The application of phenomapping to a huge amount of data can disclose the intrinsic complexity of HFpEF and allows the identification of specific phenogroups of patients
- The lack of a successful therapeutical strategy for HFpEF might be strictly linked with the intrinsic complexity and heterogeneity of the disease
- Phenomapping might represent a step towards personalized medicine in HFpEF, permitting the identification of the best therapeutic options for specific phenogroups of patients

Synopsis

Heart failure with preserved Ejection Fraction (HFpEF) is characterized by a high hospitalization and mortality rate (up to 84% at 5 years), which are similar to those observed for HF with reduced EF. These epidemiological data claim for the development of specific and innovative therapies to reduce the burden of morbidity and mortality associated with this disease. Compared with HF with reduced EF, which is due to a primary myocardial damage (eg ischemia, cardiomyopathies, toxicity etc), a heterogeneous etiological background characterizes HFpEF. Initially referred to as “diastolic heart failure”, HFpEF is typified by a constellation of LV systolic and diastolic abnormalities, left atrial (LA) stiffness, pulmonary artery hypertension (PAH), vascular stiffness, impaired vasodilatation, and skeletal muscle abnormalities. We discuss these phenotypes and specificities for defining the therapeutic strategies that could be proposed according to phenotypes.

Clinic Care Points

- Description of the phenotypes and hypothesis-driven proposals for a best management and control of symptoms

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Abbreviations

AF, atrial fibrillation

BMI, body mass index

BNP, brain natriuretic peptide

CKD, chronic kidney disease

cpc-PAH, combined pre-capillary and post-capillary pulmonary artery hypertension

CPET, cardiopulmonary exercise test

CV, cardiovascular

COPD, chronic obstructive pulmonary disease

DM, diabetes mellitus

HTN, arterial hypertension

LA, left atrium

LV, left ventricle

HF, heart failure

HFpEF, heart failure with preserved ejection fraction

HFrEF, heart failure with reduced ejection fraction

IHD, ischemic heart disease

OSAS, obstructive sleep apnea syndrome

ML, machine learning

MR, mitral regurgitation

PAH, pulmonary artery hypertension

PCWP, pulmonary capillary wedge pressure

RV, right ventricle

TTE, transthoracic echocardiography

INTRODUCTION

Heart failure (HF) is a growing public health pandemic, with a prevalence of 1-2% in the adult populations of developed countries, rising to 10% in the eldest¹, and nearly 40 million individuals affected worldwide².

According to the 2016 recommendations of the European Society of Cardiology, the diagnosis of HF is based on 1) the presence of clinical sign and symptoms of the disease; 2) the elevation in natriuretic peptides, and 3) the evidence of cardiac structural abnormalities (e.g. left atrial dilatation and/or LV hypertrophy) and/or diastolic dysfunction³.

About 50% of patients with HF exhibit an LV ejection fraction (LVEF) $\geq 50\%$ - the so-called HF with preserved ejection fraction (HFpEF). Despite initially considered a relatively benign form of HF, HFpEF is characterized by a high hospitalization and mortality rate (84% and 76% at 5 years, respectively), which are similar to those observed for HF with reduced EF⁴. These epidemiological data claim for the development of specific and innovative therapies to reduce the burden of morbidity and mortality associated with this disease.

One of the main problems with HFpEF relates to the definition and identification of this entity. In a recent paper, Ho et al. have shown that the diagnostic algorithms for HFpEF proposed by the American and European scientific societies identify different clinical profiles of patients, and this heterogeneity is mirrored by diverging clinical outcomes⁵. Moreover, restrictive definitions have poor sensitivity for the detection of patients who have no or mild physiological alteration at rest and significant alterations during exercise, supporting the importance of exercise test in patients with HFpEF⁵. Accordingly, the latest diagnostic strategy-provided by the Heart Failure Association of the European Society of Cardiology included exercise echocardiography as a relevant step in the recognition of HFpEF⁶.

PATHOPHYSIOLOGY OF HFpEF

Compared with HF with reduced ejection fraction (HFrEF), which is due to a primary myocardial damage (eg ischemia, cardiomyopathies, toxicity etc) and associated with significant neurohormonal activation, HFpEF is characterized by a heterogeneous etiological background. Initially referred to as "diastolic heart failure", HFpEF is typified by a constellation of LV systolic and diastolic abnormalities, left atrial (LA) stiffness, pulmonary artery hypertension (PAH), vascular stiffness, impaired vasodilatation, and skeletal muscle

abnormalities⁷. Some of these derangements, such as the impairment in LV contractile reserve and heart rate reserve, or PAH may become evident only during exertion, which is a significant diagnostic and therapeutic challenge^{8,6}.

Patients with HFpEF are often older, with several comorbidities and cardiovascular risk factors such as ischemic heart disease (IHD), diabetes mellitus (DM), obesity, arterial hypertension (HTN), chronic obstructive pulmonary disease (COPD), obstructive sleep apnea syndrome (OSAS) and kidney failure (CKD). According to the proposed hypothesis, these pathologies are the triggers for chronic systemic inflammation⁹ which causes endothelial dysfunction and myocardial microvascular endothelial activation¹⁰, promoting myocyte hypertrophy and interstitial fibrosis. After the initial cardiovascular involvement, the next step in the progression of the disease is multiorgan involvement with development/worsening of ventriculoatrial coupling, PAH, CKD, and skeletal muscle abnormalities¹¹ (Figure 1).

The complex pathophysiology of HFpEF coupled with its highly heterogenous phenotypical presentations is the main cause of the lack of effective therapeutical strategies and of the disappointing results of recent randomized trials (eg CHARM-Preserved¹², I-PRESERVE¹³, RELAX¹⁴, NEAT¹⁵, PARAGON-HF¹⁶). The inhibition of the neurohumoral burden that is effective in improving the quality of life and in reducing the morbidity and mortality in HFrEF does not provide equivalent benefits in patients with HFpEF. The development of dedicated therapeutic strategies for HFpEF is therefore the main aim of the research in this field.

PHENOMAPPING IN HFpEF

Machine learning (ML) is focused on the application of computational algorithms to huge amounts of data to identify patterns between variables that are not disclosed by the application of standard statistical methods¹⁷. Phenomapping is a particular kind of unsupervised ML which is applied to data without *a priori* knowledge of the outcomes to uncover mathematical relationships between data and to cluster patients into different and mutually exclusive groups¹⁷.

The application of phenomapping to dense multidimensional data (clinical and biohumoral data, imaging derived features, hemodynamics variables) obtained from patients with HFpEF seems particularly

attractive, because it might solve the intrinsic heterogeneity of the syndrome, generate new pathophysiological hypothesis and prompt the application of tailored therapeutical strategies¹⁸. In 2014 Shah et al. published the first paper applying unbiased clustering to 397 patients with HFpEF¹⁹. After the exploitation of a phenotypic domain consisting of 67 continuous clinical, laboratory, ECG, echocardiographic, and hemodynamic variables, the authors were able to identify 3 separate clusters of patients with different prognosis. Interestingly, the 3 clusters corresponded to 3 potential archetypes of HFpEF which exhibited also significantly different prognosis: the natriuretic peptide deficiency syndrome (cluster 1); the obesity/cardiometabolic phenotype (cluster 2); and the right ventricular failure/cardiorenal phenotype (cluster 3)¹⁹. After this landmark work¹⁹, an increasing number of studies have been published on the application of phenomapping to different cohorts of patients with HFpEF (Table 1)^{19,20,21,22,23,24,25,26,27}. Depending on the set of input variables, various pathophysiological profiles were identified, the prognosis of which could not be effectively predicted relying exclusively on conventional risk stratification approaches.

The main issue emerging from the comparison of the different cohorts is the large heterogeneity of the included patients, with a significant difference in mean age (from 65 years in the study of Shah et al.¹⁹ to 78 years in the study of Hedman et al.²⁵), sex, clinical status, and prevalence of comorbidities. Several differences can also be found in the quality and number of selected features, which can vary from 11 to nearly 100 descriptors: some studies focused only on clinical and laboratory parameters^{20,27}, others included echocardiographic parameters obtained at rest^{19,23, 25,26}. Only a small amount of studies dealt with echocardiographic data obtained at rest and during submaximal exercise, including the evaluation of LV deformation^{21,22}. Although the assessment of LV-performance during exercise is still underused, the analysis of exercise data might provide important information. It seems particularly valuable in specific subsets of patients who have mild symptoms and modest cardiac abnormalities at rest, but might develop significant impairment of LV systolic and diastolic function and pulmonary artery hypertension (PAH) during exercise⁶. The evaluation under an exercise load can also verify the asymptomatic status of patients categorized as stage A and B HF.

The current HFA-PEFF diagnostic algorithm underscores the importance of performing cardiac catheterization for the diagnosis of HFpEF⁶. Nevertheless, only one ML study included hemodynamics parameters in the phenomapping algorithm¹⁹. Cardiac catheterization is complicated to implement in the daily routine practice of these co-morbid patients. It should be emphasized that only 4 studies among those listed in Table 1 have a validation cohort^{19,20,23,27}. The presence of an external frame of reference is fundamental in the process of strengthening and verification of machine learning-derived algorithms and has pivotal importance for their validation and future application in clinical practice.

PHENOGROUPS IN HFpEF

The heterogeneity of the investigated HFpEF populations, as well as of the applied phenotyping approaches are the reason for inconsistencies in the phenomapping outcomes, with the identified clusters differing from one study to another. Despite this variety, some phenotypes share similar characteristics and prognosis across different cohorts of patients and merit specific consideration.

Different archetypes of HFpEF

PHENOGROUP 1 includes younger, often overweight, or obese patients, with low BNP, exercise deconditioning, few signs of LV remodelling, and favourable diastolic profile.

PHENOGROUP 2 includes patients with several longstanding cardiovascular risk factors (such as DM, HTN, obesity, dyslipidaemia), severe LV myocardial remodelling (LV hypertrophy, LV longitudinal impairment and diastolic dysfunction), without significant right heart alterations.

PHENOGROUP 3 includes patients with several longstanding CV risk factors often associated with pulmonary disease (eg COPD and/or OSAS), biventricular remodelling with PAH and CKD.

PHENOGROUP 4 includes patients with few cardiovascular risk factors, lower body mass index (BMI), high prevalence of atrial fibrillation (AF), significant left atrial dilatation but modest LV remodelling.

PHENOGROUP 5 includes older patients, most often female, with lower BMI, high prevalence of AF, , severe left atrial (LA) dilatation, high prevalence of mitral regurgitation (MR), PAH, right ventricular (RV) dysfunction and CKD.

If the first three groups correspond to the classification already proposed by Shah et al¹⁹, the last two have been described in some other studies^{20,25,27,26} which included oldest patients and considered age and AF as an important factor of discrimination between phenogroups.

PATHOPHYSIOLOGY AND TREATMENT ACROSS THE PROPOSED HFPEF PHENOGROUPS

According to the simplified classification proposed above, some pathophysiological hypothesis and specific therapeutic approaches can be proposed (Figure 2, Figure 3).

Phenogroup 1: the natriuretic peptide deficiency syndrome

The **phenogroup 1** corresponds to the “natriuretic peptide deficiency syndrome” already described in literature^{19, 28}. In these patients, the combination of overweight/obesity and insulin resistance triggers the production of adipocyte-derived cell signalling molecules, which increase the activity of neprilysin and aldosterone^{29,30}. The increased BNP clearance and reduced BNP production³¹ are responsible for the reduced BNP plasma levels; whereas the elevation in aldosterone level contributes to the aggravated sodium retention and liquid expansion. These patients have often few or no symptoms at rest, but they might develop dyspnea, LV longitudinal dysfunction and eventually overt signs of cardiac dysfunction during exercise²². In this subset, weight loss, aerobic training with subsequent improvement in insulin resistance might represent a pillar of the treatment. Interestingly, the reduction of obesity either by behavioural intervention or bariatric surgery is associated with significant cardiac reverse remodelling, improvement of symptoms and an increase in BNP plasma levels, which might have beneficial effects on natriuresis^{32,33}.

The role of pharmacologic treatment to improve symptoms and the progression of the disease in these patients is an object of debate, particularly because patients in Phenogroup 1 are commonly excluded from trials on HFpEF due to their low BNP levels. Nevertheless, the increased aldosterone levels observed in obese patients might explain why in the TOPCAT trial, patients with the lowest BNP levels seemed to benefit more from spironolactone³⁴. For similar reasons, the neprilysin inhibitor Sacubitril, which has not shown benefit in an unselected HFpEF population in the PARAGON trial¹⁶, might prove beneficial in this specific subset of patients with HFpEF who have increased neprilysin activity. Neprilysin inhibitors

might have a direct natriuretic effect, but they also have pleiotropic effects by suppressing the secretion and antagonizing the effect of aldosterone³⁵, and by having a lipolytic and anti-inflammatory action^{30,36}. The sodium-glucose type 2 (SGLT-2) inhibitors might represent another therapeutic option in obese patients with HFpEF. Particularly, the SGLT-2 inhibitor empagliflozin has been reported to have favorable effects on vascular resistance³⁷ and visceral adiposity³⁸, and to reduce HF hospitalization in diabetic patients³⁹. In the EMPEROR-HF trial patients with HF and reduced LVEF taking empagliflozin 10 mg/day on the top of their medical treatment have experienced a significant reduction in HF hospitalization, death, and less renal function deterioration⁴⁰. Despite the absence of specific studies in HFpEF, empagliflozin might counterbalance the oxidative and metabolic derangements and the sodium retention observed in obese patients with HFpEF, potentially disrupting the development of the obesity-HFpEF phenotype⁴¹.

Phenogroups 2 and 3: the cardiometabolic phenotype and its evolution

These two phenogroups include patients with several cardiovascular risk factors but at different stages of the disease.

Phenogroup 2 comprises the “cardiometabolic phenotype”. This group exemplifies the effect of longstanding cardiovascular risk factors on myocyte and cardiac microcirculatory function. As well described by Paulus et al., the pro-inflammatory state caused by multiple cardiovascular risk factors is responsible for the coronary microvascular endothelial inflammation and dysfunction⁴², reduced nitric oxide bioavailability, and impaired protein kinase G activity (PKG)⁴³. This process causes T-tubule disruption in the cardiomyocytes, with a subsequent imbalance in calcium handling and impaired LV relaxation⁴⁴. Another factor contributing to myocardial stiffness and diastolic dysfunction is the increase in collagen deposition and the proliferation of myocardial fibroblasts resulting in interstitial myocardial fibrosis⁴⁵. The mechanisms provoking myocardial remodelling and dysfunction are also responsible for the development of arterial stiffness at rest^{43,46} and altered ventriculoatrial coupling during exercise⁴⁷. From a therapeutical point of view, the first approach to patients in phenogroup 2 is the management of cardiovascular risk factors. Normalization of blood pressure, calories restriction and careful control of DM

might be the key to prevent the progression of the disease. According to previous data and to a post-hoc analysis of the TOPCAT trial^{24,48}, the administration of spironolactone to patients belonging to phenogroup 2 might be considered to improve exercise tolerance⁴⁸ and survival²⁴. SGLT-2 inhibitors, given their potential to target specific pathogenetic mechanisms in HFpEF and beneficial effects found in HFrEF, might also be a useful treatment option⁴¹, however, more clinical evidence is needed. Other potential disease-modifying strategies in these patients might include drugs targeting the NO-PKG axis. Direct NO donors such as isosorbide dinitrate have already been tested in HFpEF and have proven no benefit in terms of quality of life improvement and exercise tolerance compared to placebo¹⁵. Nevertheless, in a small pilot study, intravenous administration of sodium nitrite, which is converted to NO in vivo, has shown to decrease pulmonary capillary wedge pressure (PCWP) at rest and during exercise in patients with HFpEF⁴⁹.

Phenogroup 3 corresponds to patients with longstanding cardiovascular risk factors and elevated filling pressure, who develop PAH, RV dysfunction and kidney failure.

The appearance of PAH and subsequent RV dysfunction represents a landmark in the evolution of HFpEF, because it is associated with increased hospitalization rate and poor prognosis⁵⁰.

In patients with HF, the impaired LV relaxation and chronic elevation in LV filling pressure are always the *primum movens* for the development of PAH, because it causes an elevation in LA pressure, which is transmitted back to the pulmonary circulation, causing post-capillary PAH. Importantly, nearly 12% of patients with HFpEF develop concomitant pre-capillary PAH (pcp-PAH). This is a consequence of a process involving endothelial dysfunction, smooth muscle cell proliferation and extensive remodelling of the pulmonary veins and arteries. This process is driven by the same mechanisms that are responsible for endothelial dysfunction in other vascular districts in patients with HFpEF⁵¹.

The development of PAH is often accompanied by the development of RV dysfunction, which is a predictor of poor prognosis. Nevertheless, PAH is not the only mechanism for RV impairment in HFpEF. Some recent studies have shown that in HFpEF, the RV undergoes a process of hypertrophy and fibrosis, which is like that observed in the LV. After the development of RV diastolic dysfunction, the next step in the progression of RV disease is the development of RV dilatation and systolic dysfunction⁵².

All these pathophysiological observations might have important therapeutical implications. On one hand, patients with isolated post-capillary PAH might benefit from titration of diuretics to reduce filling pressure and PAH. The use of remote pulmonary pressure monitoring systems such as the CardioMEMs® might be useful in patients with frequent HF hospitalization and/or persisting symptoms to optimize diuretics therapy and reduce hospitalization rate⁵³.

On the other hand, patients with a predominant pcp-PAH might eventually benefit from a careful administration of pulmonary vasodilators. Despite the results of a preliminary trial, showing that the inclusion of Sildenafil 50 mg thrice/day in patients with HFpEF and PAH was able to reduce PAH and improve RV dysfunction⁵⁴, the multicentric RELAX trial failed to demonstrate the benefit of sildenafil on the clinical status and exercise capacity of patients with HFpEF¹⁴. A potential explication for these findings is that the study included patients with PAH irrespectively of the evaluation of the pre-capillary or post-capillary component. One of the goals of current research in this field is therefore to improve the phenotyping of PAH in patients with HFpEF⁵⁵. Other potential therapeutical strategies may arise from new medications. For instance, the SPHERE-HF trial, a phase II study, has the objective to verify the effect of mirabegron, a β_3 -agonist, on the pulmonary hemodynamics, clinical, biochemical, and imaging parameters in patients with HF and cpc-PAH.

Another finding of phenogroup 3 is the development of kidney failure, which is a well-known predictor of poor prognosis in HF patients⁵⁶. The main pathophysiological mechanisms for the development of renal dysfunction in HFpEF is the increase in central venous pressure with a subsequent increase in renal venous pressure, which causes a substantial decrease in the glomerular pressure gradient and glomerular filtration rate, elevation in plasma renin and aldosterone activity and reduced urine output⁵⁷. CKD alters the metabolism of phosphates, causing secondary hyperparathyroidism, which might lead to increased calcium level, pulmonary vessels vasoconstriction and ectopic calcification, thus contributing to PAH and RV failure⁵⁸.

Preventing the onset and/or worsening of renal failure in HFpEF patients is fundamental to improve survival. Nevertheless, few studies have specifically addressed this issue in patients with HFpEF. The

CARESS-HF trial including patients with all EF categories has shown the benefit of stepped diuretic treatment over ultrafiltration in acute decompensated HF⁵⁹. Regarding the use of inhibitors of the renin-angiotensin-aldosterone systems, both the TOPCAT trial³⁴ and the I-PRESERVE trial have shown the detrimental effect of anti-aldosterone drugs and irbesartan on renal function in patients with HFpEF¹³. This might be since all drugs acting on the renin-angiotensin-aldosterone axis cause a significant reduction in preload. Patients with HFpEF are sensitive to preload modification because of the steep relationship between LV pressure and volume and decreased venous return might lead to a reduction in cardiac output and contribute to a deterioration of renal function.

Phenogroup 4 and 5: the atrial myopathy phenotype and its evolution

Phenogroup 4 corresponds to the recently described “Atrial fibrillation/atrial myopathy” phenotype of HFpEF. Analogous to Phenogroups 2 and 3, Phenogroups 4 and 5 probably represent 2 different phases of the same disease pathway.

Phenogroup 4 includes patients having HTN as a main cardiovascular risk factor, LA dilatation, and a high prevalence of AF. From a pathophysiological point of view, in patients with HFrEF, atrial dilatation and dysfunction are phenomena that are related to the progressive increase in LA-pressure. It pushes for the development of functional mitral regurgitation (MR). In patients with HFpEF, the LA has been initially considered as a simple bystander of the progressive exacerbation of LV stiffness and dysfunction. Nevertheless, von Roeder et al. elegantly showed that the deterioration of LA reservoir and conduit function is already evident in the initial phases of HFpEF⁶⁰. Interestingly, in a canine model of early HFpEF, Zakeri et al. demonstrated that renal induced-hypertension and aldosterone excess are associated with the development of atrial myocyte hypertrophy, titin hyperphosphorylation and microvascular dysfunction, supporting the hypothesis that a common pathophysiological process acts in all myocardial chambers⁶¹. From a functional point of view, these structural alterations are responsible for the development of impaired atrial function and associated with an impaired atrio-ventricular coupling⁶¹. There are two important consequences of the LA myopathy observed in HFpEF: the development of atrial fibrillation and the appearance of mitral regurgitation (MR). The occurrence of AF can pre-date the

diagnosis of HFpEF in 29% of patients. AF can be observed in up to 75% of patients with HFpEF in the advanced phases of the disease and is a strong predictor of morbidity and mortality⁶². Interestingly, in the Rochester Epidemiology Project, age and HTN were the main independent predictors of AF in patients with HFpEF, which exactly mirrors the clinical characteristics observed in patients belonging to Phenogroup 4. Mild-to-moderate MR is a frequent finding in patients with HFpEF and was initially considered an innocent bystander. Nevertheless, Tamargo et al. have shown that patients with HFpEF and mild-to-moderate MR have a higher prevalence of AF, more advanced diastolic dysfunction, LA functional impairment, more dilated RV, and a higher prevalence of PAH and RV dysfunction as compared to patients with HFpEF and no mitral regurgitation. All these abnormalities result in the alteration of the RV–pulmonary artery coupling and culminate in substantial impairment in cardiac output reserve with exercise⁶³.

Interestingly, Tamargo et al. also showed that mitral annulus dilatation and LA dilatation were the major determinants of mitral regurgitation in multivariable analysis⁶³. Despite it is quite difficult to establish a clear causality or sequentiality between AF and MR in HFpEF, the mutual relationship between these two entities might create a vicious circle and further promote atrial remodelling and dysfunction.

The mechanisms described above are responsible of the development of a specific, distinct etiology of mitral regurgitation, recently referred to as “atrial functional mitral regurgitation”⁶⁴. Up to 57% of patients with HFpEF might present with mild-to-moderate MR^{63,64}.

Phenotype 5 represents the natural and progressive evolution of phenotype 4.

With the ongoing disease, the severity of MR increases and patients develop PAH, overt RV dysfunction and CKD, all of which are typical for HFpEF-phenotype 5, and are associated with a very poor outcome^{20,26,65}.

The management of patients with HFpEF belonging to phenogroups 4 and 5 is not established. The control of cardiovascular risk factors, particularly HTN, which is very frequent in patients from phenotype 4 should be obtained. The inhibitors of the renin-angiotensin-aldosterone system have proven to reduce the burden of new AF episodes in patients with HFrEF, but they have not shown similar efficacy in HFpEF⁶⁶. The ongoing IMPRESS-AF trial is investigating the effect of spironolactone on the quality of life and exercise tolerance in patients with AF and HFpEF⁶⁷.

In patients with AF, the maintenance of sinus rhythm through medical therapy or transcatheter ablation could be discussed. The AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial showed that the restoration of sinus rhythm did not outperform heart rate control in terms of survival and adverse cardiovascular events. Nevertheless, the benefit of rhythm control will probably be more evident in patients in the initial phase of the disease, with mild to moderate MR and less pronounced LA remodelling⁶⁸.

All interventions aimed at reducing the load of the left atrium are also important in these patients. In addition to the optimization of diuretic therapy to reduce LA and LV pressure, MR and LA remodelling, another potential option is represented by percutaneous atrial septostomy. The initial results of REDUCE LAP-HF I trial have shown the safety of the implantation of an inter-atrial shunt device in patients with HFpEF in NYHA class II and III⁶⁹. Nevertheless, the effect of this intervention on LA size seems more evident in patients with higher LA compliance and right atrial reservoir function, which probably correspond to less advanced atrial disease⁷⁰. On the other hand, the benefit of LA unloading following the placement of a left-to-right shunt should be supported by the absence of detrimental effect on the right heart function and on PAH, which is expected to be evidenced in future studies.

The current definitions of MR severity rely upon patients with typical primary or secondary MR, with no recommendations for atrial functional MR. In a cohort of patients with severe mitral regurgitation undergoing surgery, Pimor et al. have shown that patients having atrial functional mitral regurgitation have the poorest outcome⁷¹. It is probable that in patients with HFpEF and non-compliant LV and atria, a moderate degree of MR might be sufficient to cause detrimental effects on the LA and the downstream pulmonary circulation. The optimal timing and modality of intervention for atrial functional mitral regurgitation (surgical mitral valve replacement/repair versus percutaneous mitral edge-to-edge mitral valve repair/percutaneous annuloplasty) are fundamental issues, which need to be clarified in specifically designed studies.

Prognosis across HFpEF phenogroups

All the studies on phenomapping in HFpEF consider all-cause mortality and a composite of mortality and HF hospitalization as endpoints. The intrinsic heterogeneity of the populations enrolled in the studies cited in Table 1 makes the generalization of the prognostic stratification of patients uncertain. Nevertheless, looking at the phenogroups' classification proposed above, we can identify patients in phenogroup 1 as a "low-risk" group. Patients belonging to phenogroup 3 and 5, who often has RV dysfunction, PAH, and kidney failure have the poorest prognosis and represent a "high risk" group^{20,25,26}. Finally, patients in phenogroups 2 and 4 belong to an "intermediate" risk category, who can eventually progress into a higher risk group.

CONCLUSIONS

Medicine will experience many changes in the future because of the availability of an increasing amount of digitalized data coming from electronic health records, genomic databases, medical imaging, lifestyle datasets, and wearable device. The availability of computational tools that can deal with these records will improve the characterization of patients and allow proposing specific and personalized diagnostic and therapeutical strategies, which can change current health-care systems. The striking novelty of this approach is evident by the interest developed in this field by several political and health-care institutions such as the National Institute of Health (NIH) in the USA⁷², or the European Union⁷³.

HFpEF appears to be an ideal field for the application of personalized medicine, given its heterogeneity and lack of specific therapeutic management. This individualized, high technology-based strategy might facilitate the identification of patients who can benefit from specific therapies, reduce the risk of drug side effects⁷⁴, and finally improve the quality of life and survival.

Nevertheless, several points need improvements to attend these ambitious goals:

- 1) Collection of data relying upon reliable registries and focused research trials
- 2) Development of validation cohorts to allow the verification of the algorithms proposed through different machine learning approaches

3) Design of multicenter studies to verify the efficacy of specific therapeutic strategies in distinct patient categories.

Since machine learning-based clustering does not supply specific thresholds for phenotypic data, a framework for the introduction of patient categorization into clinical practice should be developed.

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- HF, heart failure; HFpEF, heart failure with preserved ejection fraction.

Figure 1. Pathophysiological mechanisms for heart failure with preserved ejection fraction

Figure 2. Main heart failure with preserved ejection fraction clusters identified across the different studies

BNP, brain natriuretic peptide; CV, cardiovascular; CVP, central venous pressure; LV, left ventricle; PAH, pulmonary artery hypertension; DM, diabetes mellitus

Figure 3. Current proposed therapeutical approaches for the management of heart failure with preserved ejection fraction according to phenogroups.

COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DM, diabetes mellitus; HFpEF, heart failure with preserved ejection fraction; HTN, hypertension; IHD, ischemic heart disease; OSAS, obstructive sleep apnea syndrome; MR, mitral regurgitation; PDE-5, phosphodiesterase-5; SGLT-2, sodium-glucose transport protein-2;

Table Legend:

Table 1. Main studies applying phenomapping to heart failure with preserved ejection fraction

Table 1. Main studies applying phenomapping to heart failure with preserved ejection fraction

Authors	Population	Clustering	Variables	Endpoints	Clusters	Prognosis (Better to Worst)
Shah et al. Circulation, 2015 (19)	397 patients Prospective study Mean age: 64.7±13 years; Female: 63% Black: 39% LVEF: 61±7 % Validation cohort: 107 pts	Penalized model-based clustering	46 variables: clinical, laboratory, EKG, TTE, cardiac catheterization	Primary endpoint: CV hospitalization or death Secondary endpoint: HF hospitalization	(1) Younger (60.7±13.6 years), lower BNP [72 (26-161) pg/mL]. Main CV risk factors: Obesity (51%). Less electric (AF 13%) and myocardial remodelling, no hemodynamic derangement (2) Intermediate age (65.7±11.3). Several CV risk factors: Obesity (84%), DM (52%), HTN (90%), OSAS (50%). Worst LV relaxation, highest PCWP (24.6±8.3 mmHg) and PVR (2.8±4.6 WU) (3) Older (67.3±13.1 years), CKD (53%), high BNP [607 (329-1138) pg/mL]. Main CV risk factors: HTN (75%). More severe electric (AF 43%) and LV remodelling, overt diastolic dysfunction, RV remodelling and dysfunction.	1(ref) > 2 >3 for both the endpoints.
Kao et al. Eur J Heart Fail., 2015 (20)	4113 pts from the I-PRESERVED cohort Retrospective analysis Age > 60 years Female 60% LVEF: 59 (52-65) % Validation cohort: 3203 pts from the CHARM-Preserved cohort	Latent class analysis	11 variables: clinical, EKG. No imaging data.	Primary endpoint: all-cause mortality or CV hospitalization Secondary endpoint: HF hospitalization or cardiac death.	A. median age: 65 years, males: 100%. B. median age: 65 years, females: 96% A and B → Younger patients, few CV risk factors and less electrical remodelling (AF 18% and 5%, respectively). C. median age: 70 years, males: 59%. Higher prevalence of CV risk factors: obesity (75%), DM (100%), IHD (66%), CKD (63%). Moderate electrical remodelling (AF 33%). D. median age: 73 years, females: 100% women. Intermediate prevalence of CV risk factors: obesity (46%); DM (23%), CKD (36%). Moderate electrical remodelling (AF 32%). E. Older (median age: 75 years), males 100%. Main CV risk factor: IHD (62%). Significant electrical remodelling (AF 44%). F. median age: 82%, females: 78%. Lower BMI, high prevalence of CKD (80%). Marked electrical remodelling (AF 51%).	B>A(ref)>D>E>C>F
Sanchez-Martinez et al., Circ Cardiovasc Imaging. 2018 (21)	156 pts (Testing: 72 HFpEF, 33 healthy subjects; Validation: 24 HTN, 27 with non-cardiac dyspnea) from the MEDIA cohort Mean age > 60 years Females: 65% LVEF: 62.3±6.7 %	Agglomerative hierarchical clustering	22 variables from LV velocity traces acquired at rest and during exercise echocardiography.	Discriminate between healthy and HFpEF subjects and identify new descriptors to characterize HFpEF.	(1) “Healthy cluster” (2) “HFpEF”: Older (mean age: 71 years), higher NTproBNP, BMI, impaired exercise tolerance at 6MWT, LV hypertrophy, higher E/e’ ratio. Absence of significant differences in exercise-echo derived parameters	-
Przewlocka-Kosmala et al., J Am Soc Echocardiogr. 2019 (22)	228 patients (177 HFpEF, 51 asymptomatic controls) Prospective study Females: 71% LVEF > 60 %	Automated hierarchical clustering	Variables: clinical, laboratory, rest and exercise TTE, CPET.	Primary endpoint: CV hospitalization or death	(1) Normal CR/DR: mean age: 62.2±7.9 years; normal increase in HR and diastolic function during exercise. (2) Altered CR/DR: mean age: 63.9±7.9 years; decreased exercise tolerance at CPET; chronotropic incompetence and diastolic dysfunction on exercise (higher E/e’ ratio and lower LA strain values).	Normal CR/DR group > Abnormal CR/DR group

Segar et al. Eur J Heart Fail., 2020 (23)	654 pts from the TOPCAT cohort Retrospective analysis Age: 71.2±9.9 years Females: 49% Blacks: 19.4% Internal validation cohort: 1113 from the TOPCAT trial External validation cohort: 198 patients from the RELAX trial.	Finite mixture model-based clustering	61 variables: clinical, laboratory, EKG, TTE	Primary endpoint: HF hospitalisation or cardiac death Secondary endpoint: all-cause death, all-cause hospitalization, HF hospitalization, MACEs (myocardial infarction, stroke or CV death).	<ul style="list-style-type: none"> (1) older: 73 years; Males 76%. Several CV risk factors: obesity; DM (74%), HTN (91%), worse renal function. Significant LV concentric remodelling, LA dilatation, diastolic dysfunction. (2) median age: 71 years; Males 51%. Low prevalence of CV risk factors. Moderate LV concentric remodelling. Moderate LA dilatation and higher prevalence of moderate MR (24%). (3) median age: 71 years, males 52%. Intermediate burden of CV risk factors, mainly DM (44%) and HTN (91%). Moderate LV concentric remodelling and LA dilatation. 	3>2>1
Cohen et al., JACC Heart Fail., 2020 (24)	3442 pts from the TOPCAT cohort Retrospective analysis Mean age: 69±10 Females: 52% LVEF≥45%	Latent class analysis	Variables: clinical, laboratory, TTE, arterial tonometry,	Primary endpoint: CV death, HF hospitalization, aborted cardiac arrest	<ul style="list-style-type: none"> (1) Younger (61±6years), relatively preserved functional class, Main CV risk factor: smoking (24%). Low prevalence of diabetes (9%). Low prevalence of CKD (15%). Normal LV geometry. (2) Older age (77±5years), females: 56%, moderate electrical remodelling: AF 49%, high prevalence of CKD (58%), Main CV risk factor: obesity (37%). Low prevalence of diabetes (17%). LV concentric remodelling. High arterial stiffness, elevated NTproBNP. (3) Intermediate age (66±8years), females: 46%. Several CV risk factors: diabetes (88%), obesity (98%). High prevalence of CKD (57%), impaired functional class, high prevalence of depression (36%). LV concentric hypertrophy 	1>2>3
Hedman et al., Eur J Heart Fail. 2020 (25)	397 patients from the KaRen cohort. Retrospective analysis Mean age: 75.9±9.2 Females: 55.6% LVEF: 62.3±6.7 % No validation cohort	Model-based clustering	43 variables: clinical, laboratory, TTE echocardiogram + 92 plasma proteins analysis in 76 patients	Primary endpoint: all-cause death and HF hospitalization	<ul style="list-style-type: none"> (1) age: 74.0±11.0 years, Females: 50%. Several CV risk factors: HTN (100%), IHD (47%), DM (53%) and CKD (67%). Marked LV concentric remodelling, modest electric remodelling (AF 37%). (2) older, age: 78.0±8 years, Females: 45%. Main CV risk factor: HTN (83%). Significant LA dilatation and higher prevalence of RV failure. Severe electric remodelling (AF 85%). (3) younger (71.6±11.5), Females 44%. Main CV risk factor: HTN (75%). Modest LV remodelling and electric remodelling (AF 48%). (4) age: 74.4±8.0 years, females: 44%. Main CV risk factor: HTN (75%). Significant LV and atrial remodelling, highest electrical remodelling (AF 90%). (5) age: 77.5±8.5 years, female 66%. Main CV risk factor: HTN (75%), IHD (40%). Moderate LV remodelling, moderate electrical remodelling (AF 43%). (6) age: 77.6±7.2, females: 69%, low BMI (27.0±5.2). Main CV risk factor: HTN (79%). Severe LA remodelling, RV dysfunction; significant electric remodelling (AF 96%). 	2>1>6>5-4>3
Schrub et al. Arch	356 pts from the KaRen cohort	Hierarchical cluster	55 variables: clinical,	Primary endpoint: all-	(1) younger (73.8±10.3 years), males: 60%. Several CV risk factors: HTN (89%), DM (60%), obesity (BMI: 31±7 kg/m ²), CKD (60%). Less electric remodelling,	No statistical difference between

Cardiovasc Dis, 2020 (26)	Retrospective analysis Mean age: 76.1±9.3 years; Female: 56.5% LVEF> 45% No validation cohort	analysis	laboratory, EKG, TTE	cause death or HF hospitalisation Secondary endpoint: all-cause death	LV hypertrophy, lowest rate of severe MR (2%) (2) Intermediate age (76.7±9.4 years); females: 69%. Main CV risk factor: HTN (73%). Less LV remodelling, but significant LA atrial dilatation and higher severe MR rate (6%). (3) Oldest (78.3 ± 6.9 years), females: 62%. Severe electrical remodelling (AF 87%), severe LA dilatation, higher prevalence of severe MR (11%).	the 3 clusters. Tendency towards a higher long- term all-cause mortality for cluster 2 and 3 vs cluster 1.
Gu et al. Int J Cardiol. 2020 (27)	970 patients Prospective study Mean age: 70.0±6.5 years. Female: 42% LVEF> 50% Validation cohort: 290 pts	Hierarchical cluster analysis	11 variables: clinical, laboratory, EKG, TTE	Primary endpoint: all-cause death Secondary endpoint: all-cause death or HF hospitalization	(1) younger (69.3± 6.7 years), males: 59%. Main CV risk factor: HTN (72%). Less electric remodelling (AF 37%) and myocardial remodelling. (2) Older (70.9 ± 6.7 years), females: 50%. Main CV risk factor: HTN (74%). Moderate LV hypertrophy and diastolic dysfunction., and moderate electrical remodelling (AF 47%). (3) Age: 70.3±6.1 years, males: 62%. Several CV risk factors: obesity, IHD (48%), DM (39%). Less electric remodelling (AF 36%), worse LV remodelling and diastolic dysfunction.	1> 2> 3 for both the endpoints.

AF, atrial fibrillation ; BMI, body mass index; BNP, brain natriuretic peptide; CKD, chronic kidney disease; CPET, cardio-pulmonary exercise test; CR, chronotropic reserve; CV, cardiovascular; DM, diabetes mellitus; DR, diastolic reserve; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HTN, arterial hypertension; IHD, ischemic heart disease; LA, left atrium ; LV, left ventricle; LVEF, left ventricular ejection fraction; pts, patients; MACEs, major adverse cardiovascular events; MR, mitral regurgitation ; 6-MWT, six minutes walking test; OSAS, obstructive sleep apnea syndrome ; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RV, right ventricle; TTE, trans-thoracic echocardiography.

DISEASE LEADING TO HFpEF

Ageing
Obesity
Diabetes
Hypertension
CHD
COPD

SYSTEMIC
INFLAMMATION

ENDOTHELIAL
DYSFUNCTION

Overt
HFpEF

HEART AND VESSELS

Myocyte hypertrophy, fibrosis
Cardiac stiffness and hypertrophy
Vascular stiffness
Impaired ventriculo-arterial coupling

LUNG:

Pulmonary hypertension
(pre-capillary and mixed forms)

KIDNEY

Increased Central venous pressure
Glomerular dysfunction
Sodium retention
Secondary hyperparathyroidism
Cardio-renal syndrome

SKELETAL MUSCLE:

Adipose infiltration
Impaired perfusion
Impaired mitochondrial activity
↓ O₂ diffusion

HF - STAGE A

Risk factors for HF
No cardiac abnormalities
No symptoms

HF - STAGE B

Risk factors for HF
Cardiac abnormalities
No symptoms

HF - STAGE C/D

Risk factors for HF
Cardiac abnormalities
Symptoms development

Phenogroup 1 the natriuretic deficiency syndrome



Obesity
Insuline resistance
↓BNP
↑Aldosterone

Phenogroup 2 the «cardio-metabolic phenotype»



CV risk factors:
Obesity
T2DM
Hypertension

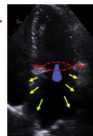
Inflammation
Endothelial
dysfunction

LV hypertrophy and
fibrosis, ↑ myocardial
and vascular stiffness,
muscular impairment

Phenogroup 4: the «atrial myopathy phenotype»



CV risk factors,
mainly arterial
hypertension



Left atrial
dilatation and
dysfunction

Atrial fibrillation

Secondary
«atrial» mitral
regurgitation

Phenogroup 3



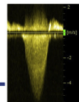
Kidney failure:

Endothelial dysfunction
↓ Cardiac output
↑ CVP



Pulmonary arterial hypertension:

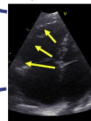
Endothelial dysfunction
Pre-capillary PAH
Post-capillary PAH



Right ventricle:

Dilatation /
Failure

Phenogroup 5



Evolution of HFpEF

Phenogroup 1

Weight control
Physical training
Others:
SGLT-2 inhibitors?
Aldosterone inhibitors?
Neprilysin inhibitors?

Phenogroup 2

Weight control
Physical training
Control of CV risk factors
(dyslipidaemia, HTN, DM)

Treatment of comorbidities
(OSAS, COPD, IHD)
Others:
Aldosterone inhibitors?
SGLT-2 inhibitors?
Neprilysin inhibitors?

Phenogroup 4

Control of CV risk factors
(particularly HTN)

Atrial fibrillation management
Rhythm control (ablation) or
Rate control

Secondary "atrial" MR
management?
Which quantification?
Percutaneous repair?
Percutaneous replacement?
Percutaneous annuloplasty?

Phenogroup 3 - Phenogroup 5

Control of CV risk factors
Treatment of comorbidities
(OSAS, COPD, IHD)

Management of congestion
Diuretics
Loops diuretics,
thyzidiques

Others:
Aldosterone inhibitors?
Remote pulmonary
pressure monitoring?

Atrial fibrillation
management
Rate control

Treatment of PAH/RV
dysfunction
Diuretics

Others:
Remote pulmonary
pressure monitoring?

PDE-5 inhibitors?
B3-agonists?

LA unloading?

Inter-atrial shunt devices?
Secondary atrial MR
management?

Management of CKD
Avoid excessive preload
reduction

Others:
Ultrafiltration?