# Phenotyping in heart failure with preserved ejection fraction: A key to find effective treatment

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## Abstract

Heart failure with preserved ejection fraction (HFpEF) is an increasingly widespread medical condition, with excessive morbidity and mortality. Recently, for the first time in HFpEF, a reduction in the primary composite outcome of cardiovascular death or HF hospitalization was shown with empagliflozin. The failure of previous clinical trials in HFpEF might have resulted from suboptimal patient selection and inclusion of patients without "true" or clinically significant HFpEF. Another important factor might be the heterogeneity of HFpEF, and thus there is a growing interest in HFpEF phenotyping. This phenotyping can be based on clinical presentation (e.g., subtypes with predominant atrial fibrillation, obesity, pulmonary hypertension and right ventricular failure, coronary artery disease (CAD), or noncardiac comorbidities), but also on HFpEF etiology. Specific therapies, such as tafamidis in transthyretin-related amyloidosis (ATTR) or mavacamten in hypertrophic cardiomyopathy, have demonstrated their efficacy. However, pathomechanisms leading to the development of different phenotypes of HFpEF seem more complex and subtle. Machine learning and neural network models might help identify specific subgroups within the HFpEF population that either cluster patients with similar genetic, biochemical, echocardiographic or clinical characteristics, or respond similarly to a given treatment. Herein, we review different approaches to HFpEF phenotyping and present some distinct HFpEF subtypes.

**Key words:** diastolic dysfunction, phenotype, artificial intelligence, heart failure with preserved ejection fraction

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## Introduction

Heart failure with preserved ejection fraction (HFpEF) constitutes as much as half of all heart failure (HF) cases.[1] However, the diagnosis of HFpEF is challenging, and no simple, unified definition of HFpEF exists (Table 1).[1–4] Furthermore, until recently, no treatment was available to improve outcomes in HFpEF – in contrast to HF with reduced EF (HFrEF). Even the latest 2021 guidelines of the European Society of Cardiology (ESC) provide only 2 recommendations regarding HFpEF therapy, i.e., diuretics for decongestion and symptomatic relief, and adequate treatment of comorbidities.[5] These ESC guidelines were released during the 2021 ESC Congress. At the same congress, the results of the EMPEROR-Preserved trial were announced, showing, for the first time in HFpEF, a reduction in the primary composite outcome of cardiovascular death or HF hospitalization with empagliflozin compared to placebo.[1] Thus, empagliflozin becomes the first drug with proven benefits in HFpEF. The DELIVER trial, with results expected in 2022, will show whether another sodium-glucose co-transporter-2 (SGLT2) inhibitor, dapagliflozin, is also beneficial in HFpEF.[6] The most recent 2022 American guidelines recommend SGLT2 inhibitors in the treatment of HFpEF.[4] However, the fact that after years of extensive research there is potentially only 1 effective drug class for HFpEF (compared to the broad armamentarium of drugs for HFrEF) is somewhat disappointing. The failure of previous clinical trials in HFpEF might be, at least in part, attributable to the heterogeneity of HFpEF and thus, there is a growing interest in HFpEF phenotyping.

## Pathogenesis and phenotypes

Pathogenesis of HFpEF is complex and multifactorial, and involves not only left ventricle (LV) diastolic dysfunction (impaired relaxation and increased stiffness) due to LV hypertrophy in course of arterial hypertension, but also subtle impairment of LV systolic function, coronary and peripheral microvascular dysfunction, oxidative stress, myocardial fibrosis, metabolic disturbances, skeletal muscle pathology, and systemic low-grade inflammation mediated through tumor necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β) and interleukin 6 (IL-6).[7,8] Microvascular dysfunction and inflammation precede symptomatic myocardial diastolic dysfunction.[9–11] Those mechanisms seem to be mediated by micro ribonucleic acids (miRNA).[5,12–14] The HFpEF hearts also have significantly higher calcium ion levels ($Ca^{2+}$) than those with HFrEF.[15] Furthermore, extracardiac comorbidities are extremely frequent in HFpEF, and may add to the development of the disease.

The multiplicity of pathomechanisms leading to HFpEF results in its heterogeneous manifestations, and might also provide an explanation for failure of most hitherto

**Table 1.** Diagnosis of HFpEF and recommended HFpEF treatment in European and American guidelines and consensus documents

| Guidelines/consensus documents | HFpEF diagnostic criteria | HFpEF treatment |
|---|---|---|
| AHA/ACC/HFSA 2022 guidelines[4] | LVEF ≥ 50% + symptoms ± signs<br>+ evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated NPs, noninvasive and invasive hemodynamic measurement) | # diuretics for symptom control (strong recommendation)<br>$ SGLT2i<br>& ARNI, MRA, ARB |
| ESC 2021 guidelines[1] | LVEF ≥ 50% + symptoms ± signs<br>+ objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including elevated NPs*, concentric LVH, left atrial enlargement*, increased E/e' ratio and/or elevated estimated systolic pulmonary artery pressure | # diuretics for symptom control (class I recommendation)<br># treatment of etiologies and CV and non-CV comorbidities (class I recommendation) |
| HFA-PEFF score 2019[2] | HFpEF diagnosis in a symptomatic patient with preserved LVEF: 5–6 points in the HFA-PEFF score<br>0–2 points in each of the 3 domains:<br>1) functional (reduced e' velocity, increased E/e' ratio, elevated estimated systolic pulmonary artery pressure, reduced GLS);<br>2) morphological (left atrial enlargement*, concentric LVH);<br>3) biochemical (elevated NPs*). | N/A |
| ASE/EACVI diagnostic algorithm 2016[3] | Echocardiographic diagnosis of diastolic dysfunction (not overt HFpEF) in a patient with LVEF ≥ 50% – over half of the following criteria positive:<br>1) reduced e' velocity;<br>2) increased E/e' ratio;<br>3) left atrial enlargement;<br>4) elevated estimated systolic pulmonary artery pressure. | N/A |

* cutoffs based on presence or absence of atrial fibrillation; # – therapies with strong or class I recommendation; $ – moderate recommendation; & – weak recommendation. ACC – American College of Cardiology; AHA – American Heart Association; ARB – angiotensin receptor blocker; ARNI – angiotensin receptor-nephrilysin inhibitor; ASE – American Society of Echocardiography; CV – cardiovascular; EACVI – European Association of Cardiovascular Imaging; ESC – European Society of Cardiology; GLS – global longitudinal strain; HFA – Heart Failure Association; HFpEF – heart failure with preserved ejection fraction; HFSA – Heart Failure Society of America; LVH – left ventricular hypertrophy; LVEF – left ventricular ejection fraction; MRA – mineralocorticoid receptor antagonist; NPs – natriuretic peptides; N/A – not applicable; SGLT2i – sodium-glucose co-transporter-2 inhibitor.

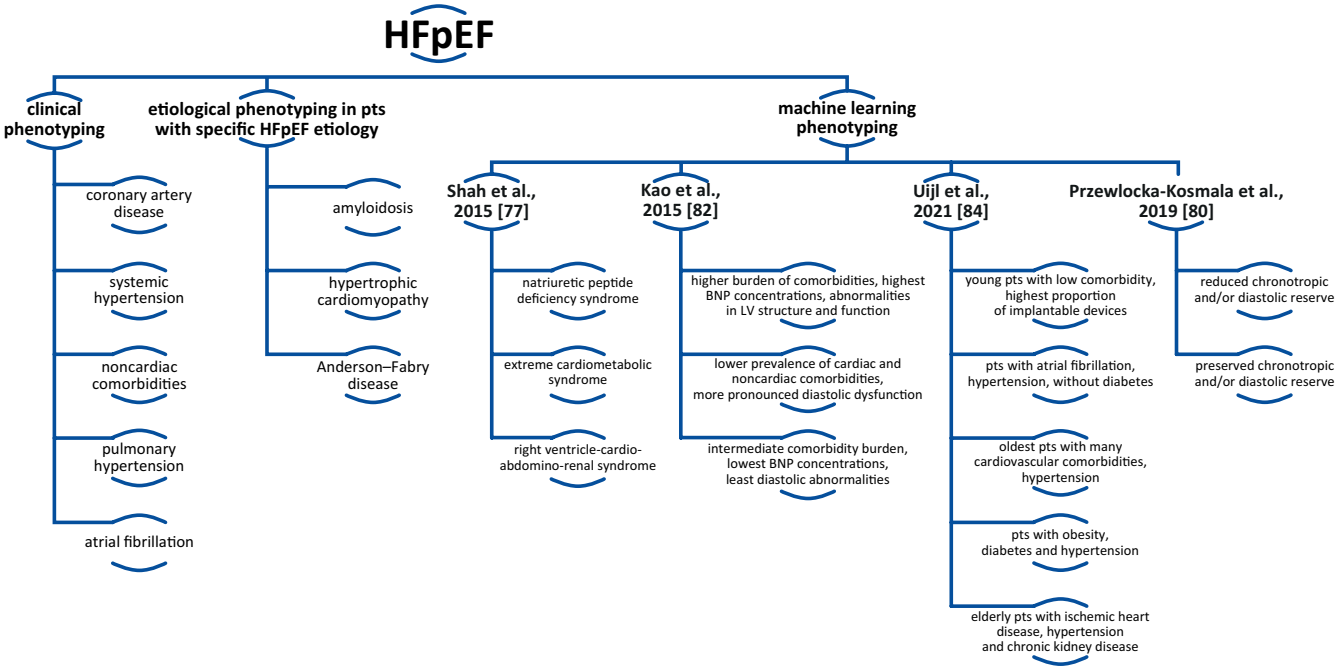


**Fig. 1.** Phenotyping of heart failure with preserved ejection fraction (HFpEF)

BNP – B-type natriuretic peptide; LV – left ventricle; pts – patients.

HFpEF trials. Appropriate phenotyping of HFpEF might help to guide its treatment.[16] Such phenotyping might be based on clinical presentation, etiology, but also phenomapping with the help of machine learning and artificial intelligence (Fig. 1).

## Clinical phenotyping

The HFpEF is characterized by polimorbidity, and in a single HFpEF patient, different cardiac and noncardiac diseases usually coexist. Still, distinct clinical phenotypes can be identified based on the domination of a given pathology and clinical presentation (Table 2).[15,17–22]

## Systemic hypertension

Arterial hypertension, especially long-standing and untreated or poorly controlled, leads to arterial stiffness, LV hypertrophy due to increased afterload, and multiorgan inflammatory response. As such, hypertension plays a crucial role in HFpEF pathogenesis and should be controlled from the early onset, as normalization of blood pressure prevents structural changes in myocardium and blood vessels, and improves outcomes.[23–25] The landmark Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that well-controlled hypertension reduces hospitalizations and the incidence of new-onset HFpEF.[26] In patients with symptomatic HFpEF and uncontrolled hypertension, adequate hypotensive treatment, including a diuretic, results in relief of dyspnea and decongestion.[27]

## Pulmonary hypertension

Pulmonary hypertension (PH) can occur in the majority of HFpEF patients at rest, and even more so with exercise.[28–30] Pulmonary artery endothelial dysfunction was reported in an animal model of HFpEF with coexisting normal aortic endothelial function and intracardiac pressures.[31] This suggests that pulmonary vascular endothelial dysfunction might precede the onset of systemic endothelial dysfunction, explaining the observed high prevalence of PH in HFpEF. Normally, pulmonary arteries are not subjected to high pressures, in contrast to systemic arteries. Therefore, pulmonary circulation is more prone to oxidative stress and inflammatory reaction in response to increased pressures. In obese hypertensive rats with HFpEF, in which vascular endothelial growth factor (VEGF) receptors were blocked, oral nitrites prevented the development of new-onset PH. However, they did not reverse the already preexisting PH.[32–34] Patients with HFpEF and PH may develop right ventricular dilation and dysfunction, tricuspid regurgitation, and, ultimately, symptoms of right ventricular HF, which may dominate the clinical presentation of those patients.

## Atrial fibrillation

Atrial fibrillation (AF) can cause HF symptoms such as dyspnea and impaired exercise capacity, but also lead to the development of tachycardia-induced cardiomyopathy and HFrEF.[1] On the other hand, AF often develops in patients with HF, as a consequence of elevated left

**Table 2.** Key concepts and therapies in different clinical phenotypes of HFpEF

| Clinical phenotype | Key concepts | Therapy |
|---|---|---|
| Ischemic heart disease | In HFpEF pts, angina is often caused by CMD. The CMD affects arterioles and capillaries (<200 µm in diameter).[39] Impaired coronary flow reserve in the absence of obstructive CAD is present in up to 3/4 of HFpEF pts. In pts with the metabolic syndrome, systemic inflammation and oxidative stress cause endothelial dysfunction with decreased nitric oxide availability, leading to both CMD with subendocardial ischemia, and impaired lusitropy – hallmarks of CMD-HFpEF phenotype. | So far, studies targeting the cGMP pathway (e.g., the RELAX trial with sildenafil[19]) did not meet their primary endpoints in HFpEF. New studies targeting the nitric oxide-cGMP pathway are warranted. |
| | Obstructive CAD (atherosclerosis of epicardial coronary arteries). | Statins, antiplatelets, ACE inhibitors, β-blockers and other antianginal drugs; coronary revascularization if needed. |
| Systemic hypertension | Systemic hypertension plays a central role in HFpEF pathogenesis through the development of concentric hypertrophy and diastolic dysfunction. The ALLHAT showed that well-controlled hypertension reduces HF hospitalizations and new HFpEF cases. | Antihypertensive treatment decreases dyspnea and congestion. |
| Noncardiac comorbidities | Both a study by Kapłon-Cieślicka et al. and an analysis by Chioncel et al. recorded that: 1) almost 1/2 pts with HFpEF have T2DM and >1/2 are obese; 2) approx. 1/4 suffer from CKD; 3) 1/5 of pts are recorded to have COPD; 4) circa 5% of all pts suffer from sleep apnea as well.[21,22] | Treatment of concomitant noncardiac diseases (in particular T2DM, obesity, pulmonary diseases) remains the mainstay of HFpEF therapy. |
| Pulmonary hypertension | Pulmonary vascular endothelial dysfunction precedes systemic endothelial dysfunction, explaining high prevalence of PH in HFpEF. In obese hypertensive rats with HFpEF with blocked VEGF receptors, oral nitrates prevented PH. | So far, treatment with sildenafil was ineffective in HFpEF-PH.[20] |
| Atrial fibrillation | The prevalence of AF in HFpEF is estimated at 45–60% and is higher than in HFpEF. | Oral anticoagulation in all HFpEF pts with AF. Rate compared to rhythm control (in HFpEF, there is a paucity of data regarding advantage of any strategy (rate compared to rhythm control), or any drug class (e.g., β-blockers) for rate control).[1] |

ACE – angiotensin-converting enzyme; AF – atrial fibrillation; ALLHAT – Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial; cGMP – cyclic guanosine monophosphate; CMD – coronary microvascular disease; cGMP – cyclic guanosine monophosphate; COPD – chronic kidney pulmonary disease; CAD – coronary artery disease; CKD – chronic kidney disease; VEGF – vascular endothelial growth factor; T2DM – type 2 diabetes mellitus; HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction; PH – pulmonary hypertension; pts – patients.

atrial pressure. The prevalence of AF in HFpEF is estimated at 40–65%,[35] and is higher than in HFrEF,[36] which might be attributable to the fact that HFpEF not only leads to an increase in left atrial pressure, but also shares common risk factors with AF (hypertension, obesity, metabolic syndrome).[37] In a patient with HF symptoms, AF and preserved EF, it might be difficult to both diagnose HFpEF (given left atrial dilation and elevation of natriuretic peptides in AF even in the absence of HF) and determine whether the symptoms are attributable to AF or HFpEF. Whether patients with HFpEF and concomitant AF would benefit from rhythm control strategy remains to be determined. Even in patients with preserved EF, AF may lead to the development of functional mitral regurgitation, related to atrial and annular dilation (so-called functional atrial mitral regurgitation). On the other hand, severe primary mitral regurgitation often results in AF. Recently, the Atherosclerosis Risk in Communities (ARIC) study showed that in the setting of HFpEF with concomitant significant mitral regurgitation, AF is associated with increased mortality.[38]

## Coronary artery disease

Although coronary artery disease (CAD), especially in patients after myocardial infarction (MI), is commonly related to HFrEF, it may also lead to HFpEF. In a substantial proportion of HFpEF patients, angina is caused by the dysfunction of coronary microcirculation rather than by the disease of the epicardial coronary arteries.[39,40] This is often referred to as ischemia with no obstructive coronary artery disease (INOCA).[41] Coronary microvascular dysfunction (CMD) can account for up to 2/3 of all ischemic clinical conditions with chest pain symptoms but without atherosclerosis in coronary arteries.[41] The CMD cannot be diagnosed with classic computed tomography coronary angiography (CTCA) or invasive coronary angiography, as it mainly affects arterioles and capillaries (<200 µm in diameter).[42] Nondirect invasive methods for CMD diagnosis include the assessment of 1) delayed flow of contrast, 2) coronary flow reserve and 3) index of microvascular resistance, all measured during invasive coronary angiography.

## Noncardiac comorbidities

Almost half of patients with HFpEF have type 2 diabetes mellitus (T2DM) and over half of them are obese.[43] These proportions have grown in the last decade. Recently, a new group of DM drugs, SGLT2 inhibitors, has been investigated in HF, including HFpEF, showing an improvement

in prognosis even in non-DM patients.[43–48] Apart from obesity, metabolic syndrome and DM, other common noncardiac comorbidities in HFpEF include chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, and anemia. The treatment of concomitant diseases remains the mainstay of HFpEF therapy.[8,10]

## Etiological phenotyping

While in most patients with HFpEF, its development is multifactorial and related to older age, hypertension, obesity, metabolic syndrome, T2DM, and other noncardiac comorbidities, in some, HFpEF occurs due to a specific condition which, in some cases, may be a subject to a targeted treatment (Table 3). This has been recently referred to as "secondary" HFpEF. Important causes of such "secondary" HFpEF include restrictive and infiltrative cardiomyopathies (with amyloidosis being the most common), as well as hypertrophic cardiomyopathy, but also other conditions with HF symptoms and preserved EF but with no permanent damage to the left ventricular myocardium (such as mitral stenosis, pericardial diseases, acute tachyarrhythmias, or high-output HF in patients with severe anemia, fever/sepsis, thyreotoxicosis, or large arteriovenous fistulas).[49] Below, we decided to focus on those "secondary" HFpEF causes that are related to permanent diastolic dysfunction of the LV.

## Amyloidosis

Amyloidosis in myocardium is in most cases caused by immunoglobulin light chain amyloid (AL) or transthyretin amyloid (TTR). The latter causes transthyretin-related amyloidosis (ATTR), which may be of particular interest since specific treatment of cardiac ATTR has been recently introduced. Amyloidosis is an increasing cause of HFpEF, might constitute up to 15% of HFpEF cases, and should be excluded during differential diagnosis of HF, especially in elderly patients without typical risk factors for HFpEF (hypertension, obesity, T2DM) and in those with amyloidosis "red flags".[50,51] The ATTR may be either hereditary – caused by autosomal dominant mutations in the TTR gene, or acquired – due to the aggregation of wild-type transthyretin. Amyloid is deposited in the myocardium and/or peripheral nervous system. The most common cardiac symptoms are dyspnea, angina, edema, and syncope.[50–53] Noncardiac manifestations, often referred to as "red flags", include peripheral neuropathy, neuropathic pain, numbness, and loss of muscle strength in the lower extremities. Gastrointestinal symptoms such as diarrhea and weight loss can be a consequence of autonomic neuropathy. Other autonomic manifestations include erectile dysfunction, orthostatic hypotension and neurogenic bladder.[50,53–55] Biopsy used to be required for the diagnosis of amyloidosis as a gold standard. Congo red or Direct Fast Scarlet 4BS staining binds to amyloid fibrils and creates characteristic apple-green birefringence under polarized light microscopy. However, genetic testing and innovative imaging techniques are becoming vital in the diagnostic process.[53,56–59] Echocardiography is used as the first diagnostic step, and some indicators, such as 1) thickened LV wall with granular sparkling appearance, with concomitant thickening of the atrial septum; 2) free right ventricle (RV) wall and valves; 3) atrial enlargement; 4) restrictive LV filling pattern; 5) pericardial effusion, and; 6) reduced LV strain with relative apical sparing pattern might hint towards amyloidosis.[56,58,59] Compared to a similar degree of LV wall thickening due to hypertrophy, the QRS amplitude is smaller, and natriuretic

**Table 3.** Key concepts and recommended therapies for proposed etiological phenotypes of HFpEF

| Etiological phenotype | Key concepts | Recommended therapy |
|---|---|---|
| Amyloidosis | Amyloidosis might constitute up to 15% of HFpEF cases. | Tafamidis is recommended in pts with ATTR (hereditary or wild-type) with cardiac involvement and NYHA class I or II symptoms to improve prognosis (class I recommendation)[1]; maintenance of euvolemia; diuretics if needed (with caution due to orthostatic hypotension). |
| Hypertrophic cardiomyopathy | LVH leads to diastolic dysfunction. LVOTO in HOCM additionally impairs hemodynamics. LVOTO occurs due to asymmetric LVH, SAM of the mitral leaflet and dyssynchrony. Apart from those anatomic macroscopic abnormalities, functional changes at the level of the sarcomere (an increased number of actin-myosin crossbridges) are also responsible for LVOTO. | In symptomatic HOCM:<br>– β-blockers/verapamil/diltiazem ± disopyramide;<br>– septal reduction therapy;<br>– sequential pacing;<br>– as per ESC guidelines.[63]<br>Mavacamten is a new drug that decreases the number of actin-myosin crossbridges leading to an improvement in LVOTO and symptoms.[68–70] |
| Anderson–Fabry disease | Thickening of LV wall in AFD leads to restrictive cardiomyopathy, and vascular dysfunction – to CAD. | Enzyme replacement therapy; chaperone therapy (for pts with *GLA1* gene mutation). |

AFD – Anderson–Fabry disease; ATTR – transthyretin-related amyloidosis; CAD – coronary artery disease; ESC – European Society of Cardiology; HFpEF – heart failure with preserved ejection fraction; HOCM – hypertrophic obstructive cardiomyopathy; LV – left ventricle; LVH – left ventricular hypertrophy; LVOTO – left ventricular outflow tract obstruction; NYHA – New York Heart Association; pts – patients; SAM – systolic anterior motion.

peptides concentrations are higher in amyloidosis. Cardiac magnetic resonance is indicated in patients suspected of cardiac amyloidosis. For the diagnosis of AL amyloidosis, laboratory tests for the detection of monoclonal light chains in serum and/or urine are performed. In ATTR, nuclear imaging techniques using technetium-99m ($^{99m}$Tc) provide relatively high sensitivity (>90%) and specificity (86%), yet are noninvasive in comparison to classic biopsy and histopathological assessment. High uptake of $^{99m}$Tc in the cardiac muscle area in comparison to bones and other peripheral structures suggests ATTR cardiomyopathy and might substitute as a diagnostic method in the future.[50,56,58,59] Genetic testing can prove hereditary ATTR. Recently, an oral medication, tafamidis, previously used for the treatment of ATTR neuropathy, has proven effective in the treatment of ATTR cardiomyopathy. Tafamidis binds to transthyretin, preventing tetramer dissociation and amyloid genesis. Studies such as ATTR-ACT show that tafamidis is a safe oral medication that reduces mortality and morbidity, and improves New York Heart Association (NYHA) class in patients with HF caused by both hereditary and wild-type ATTR.[60–62] Thus, the new 2021 ESC guidelines on HF, recommend treatment with tafamidis in patients with ATTR (hereditary or wild-type) with cardiac involvement and NYHA class I or II symptoms to improve prognosis (class I recommendation).[10]

## Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease. It affects people of all ages and with different comorbidities.[63] Its phenotypic expression ranges from mild symptoms and almost standard life-length expectancy up to sudden cardiac death (SCD) in seemingly healthy young people.[64–66] Hypertrophic cardiomyopathy is characterized by LV muscle hypertrophy which is not secondary to increased afterload (i.e., with no identifiable cause). Histopathological findings are myocytes hypertrophy, disarray and fibrosis. Common symptoms are dyspnea at rest, ventricular tachycardia and syncope. The first symptom may be SCD in young adults and adolescents.[64,67,68] In patients with symptomatic hypertrophic obstructive cardiomyopathy (HOCM), hitherto pharmacotherapy, based on β-blockers or non-dihydropyridine calcium channel blockers with or without disopyramide, is often inadequate, poorly tolerated and not disease-specific.[67,68] Mavacamten is a cardiac myosin inhibitor. In HOCM, diastolic dysfunction and hypercontractility with left ventricular outflow tract obstruction (LVOTO) result not only from anatomic, macroscopic abnormalities (asymmetric left ventricular hypertrophy), but also from functional changes at the level of sarcomeres: an increased number of actin-myosin crossbridges. Mavacamten is a cutting-edge allosteric inhibitor of cardiac-specific myosin adenosine triphosphatase, reducing the number of actin-myosin crossbridges. Its use in HOCM results in normalized contractility, improved relaxation and improved myocardial energetics.[69–73] In the EXPLORER-HCM trial, in HOCM, mavacamten, compared to placebo, alleviated the symptoms and exercise capacity, reduced LVOTO and natriuretic peptides, and consequently received a "breakthrough therapy designation" from the American Food and Drug Administration (FDA).[69,70] The VALOR-HCM trial, whose results were recently announced during the American College of Cardiology's 71$^{st}$ Scientific Sessions, showed that mavacamten alleviated the symptoms and significantly reduced the need for septal reduction therapy among symptomatic patients with HOCM who were on maximally tolerated medical therapy.

## Anderson–Fabry disease

Anderson–Fabry disease (AFD) is a genetic storage disorder. It is caused by X-linked mutations in the *GLA* gene, resulting in deficiency of the enzyme alpha-galactosidase A, which should metabolize neutral glycosphingolipids.[74,75] The increased amount of those molecules leads to their accumulation in various tissues including vascular endothelium, kidneys, heart, eyes, skin, and nervous system.[76] The AFD causes thickening of LV wall, which leads to restrictive cardiomyopathy and vascular dysfunction, in consequence leading to CAD. Common symptoms and complications include HF symptoms, angina, arrhythmias, chronotropic incompetence, and SCD. Early AFD diagnosis enables timely introduction of enzyme replacement therapy. In recent years, a new form of treatment was introduced – chaperone therapy. However, it is reserved only for patients with *GLA1* gene mutation.[74]

## Machine learning phenotyping

Artificial intelligence, machine learning and the use of complex algorithms are more and more frequently applied in medicine. Recently, new phenotypes have emerged in HFpEF using machine learning to identify specific subgroups, and helping to stratify risks and predict outcomes (Table 4).

The study using phenomapping led by Shah et al. has collected data from 420 prospectively enrolled, symptomatic HFpEF patients, including: 1) demographic and clinical characteristics; 2) blood laboratory measurements; 3) electrocardiographic (ECG) features; and 4) echocardiographic measurements.[77] Data were systematically inserted into a specially designed computer algorithm called support vector machines (SVM), which identifies a separation boundary between classes of interest in a much higher dimensional feature space. The SVM is a robust nonlinear algorithm that can be used for classification or regression.[78]

**Table 4.** Key concepts in machine-learning phenotyping of HFpEF

| Study name | Phenotype | Key concepts |
|---|---|---|
| Shah et al. 2015[77] | natriuretic peptide deficiency syndrome | This phenogroup had the least visible electric and myocardial remodeling, although 65% of pts had at least grade 2 diastolic dysfunction. In long-term follow-up, pts had the lowest risk of cardiovascular hospitalization or death. |
| | extreme cardiometabolic syndrome | This phenogroup pts with comorbidities (i.e., obesity, T2DM and obstructive sleep apnea) had the highest fasting glucose levels. Patients had the most impaired LV relaxation (lowest e' velocity) on echocardiography and the highest pulmonary capillary wedge pressure and pulmonary vascular resistance on invasive hemodynamic testing. |
| | right ventricle-cardio-abdomino-renal syndrome | This phenogroup consisted of the oldest pts who were most likely to have CKD (highest serum creatinine concentration and the lowest GFR). They had the most severe electric and myocardial remodeling with the longest QRS duration, highest LV mass index, worst RV function, and highest BNP concentrations. This phenogroup also had the highest mortality risk measured using MAGGIC risk score. In long-term follow-up, phenogroup 3 had the highest risk of cardiovascular hospitalization or death. |
| Segar et al. 2019[82] | higher burden of comorbidities, highest BNP concentrations, abnormalities in LV structure and function | Phenogroups from the TOPCAT-subanalysis did not differ with respect to age. Phenogroup 1 had higher risk for all adverse clinical events, including all-cause death and HF hospitalization. |
| | lower prevalence of cardiac and noncardiac comorbidities, more pronounced diastolic dysfunction | Phenogroup 2 had higher risk of HF hospitalization but lower risk of atherosclerotic event (MI, stroke or cardiovascular death), and comparable risk of death. Patients had lower LV mass and intermediate burden of diastolic function abnormalities compared with other groups. |
| | intermediate comorbidity burden, lowest BNP concentrations, least diastolic abnormalities | Patients in phenogroup 3 had the lowest E/e' ratio on echocardiography. |
| Uijl et al. 2021[84] | young pts with low comorbidity, highest proportion of implantable devices | This cluster had the best prognosis. Patients had the lowest BNP levels and the lowest number ofźpts had NYHA class III–IV. |
| | pts with AF, hypertension, without T2DM | Patients in this cluster most often had implantable devices, AF prevalence and were most likely to use RAS inhibitors, β-blockers and diuretics. |
| | oldest pts with many cardiovascular comorbidities, hypertension | Together with cluster 2, pts in cluster 3 were most likely to use RAS inhibitors, β-blockers and diuretics. The majority of measured parameters oscillated on medium levels. |
| | pts with obesity, T2DM and hypertension | Patients had higher systolic blood pressure levels and the highest prevalence of DM. |
| | elderly pts with ischemic heart disease, hypertension and CKD | This cluster had the worst prognosis. Patients were often prescribed diuretics. Patients had the highest BNP levels and most pts had NYHA class III–IV. |
| Przewłocka-Kosmala et al. 2019[80] | reduced chronotropic and/or diastolic reserve | Hierarchical clustering was used on continuous variables obtained from resting and post-exercise echocardiography. Patients in this subgroup had a higher risk of 1) HF hospitalization and 2) cardiovascular hospitalization or death during a 2-year follow-up. |
| | preserved chronotropic and/or diastolic reserve | Patients in this subgroup had a lower risk of 1) HF hospitalization and 2) cardiovascular hospitalization or death during a 2-year follow-up. |

AF – atrial fibrillation; BNP – B-type natriuretic peptide; CKD – chronic kidney disease; T2DM – type 2 diabetes mellitus; GFR – glomerular filtration rate; LV – left ventricle; RV – right ventricle; HF – heart failure; MI – myocardial infarction; HFpEF – hear failure with preserved ejection fraction; NYHA – New York Heart Association; pts – patients; RAS – renin-angiotensin system; TOPCAT – Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist.

A total of 67 phenotypical variables were found, which then scientists blinded to the agenda of this trial merged into bigger subgroups using hierarchical clustering methods. That led to the extraction of 3 main phenogroups using Gaussian distribution for values calculated with the program. The final cohort included 397 HFpEF patients (mean age 65 years, 62% female) with complete data. Of those, 216 patients had additional data from invasive hemodynamic testing. Phenogroup 1 included younger HFpEF patients with the lowest B-type natriuretic peptide (BNP) levels. This HFpEF phenogroup had the least visible electric and myocardial remodeling, although 65% had at least grade 2 diastolic dysfunction. Phenogroup 2 included HFpEF patients with the highest burden of HF-associated comorbidities, such as obesity, T2DM and obstructive sleep apnea, and the highest fasting glucose levels. This HFpEF phenogroup was characterized by the most impaired LV relaxation on echocardiography (lowest e' velocity) and the highest pulmonary capillary wedge pressure and pulmonary vascular resistance on invasive hemodynamic testing. Phenogroup 3 included the oldest HFpEF patients who were most likely to have CKD (with the highest serum creatinine concentration and the lowest estimated glomerular filtration rate (eGFR) compared to the other 2 phenogroups). Phenogroup 3 had the most severe electric and myocardial remodeling, with the longest QRS duration, highest LV mass index, highest E/e' ratio, worst RV function, and highest BNP concentrations. This phenogroup also had the highest mortality risk using the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk

score.[79] In long-term follow-up, HFpEF phenogroup 1 had the lowest, and phenogroup 3 – the highest risk of cardiovascular hospitalization or death.[78] These results were then replicated in a prospective validation cohort consisting of 107 HFpEF patients.[78]

In a study by Przewlocka-Kosmala et al., hierarchical clustering was used on continuous variables obtained from resting and post-exercise echocardiography in 177 patients with HFpEF.[80] This led to the identification of a subgroup of HFpEF patients with impaired chronotropic and/or diastolic reserve who had a higher risk of 1) HF hospitalization and 2) cardiovascular hospitalization or death during a 2-year follow-up.

A different approach was used by Kao et al., who applied latent class analysis allowing to include not only continuous, but also categorical variables.[81] In 4113 HFpEF patients enrolled in the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE), 6 subgroups were identified with significant differences in an event-free survival. Observations were then validated in 3203 patients from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved study. A different type of phenomapping analysis based on a dataset from another randomized controlled trial, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT), was performed by Segar et al.[82] Using unsupervised cluster analysis on 61 phenotypic variables in 654 HFpEF patients (TOPCAT participants enrolled in the Americas, who had available echocardiographic data), 3 mutually exclusive phenogroups were identified: phenogroup 1 had higher burden of comorbidities, the highest BNP concentrations, and abnormalities in LV structure and function; phenogroup 2 had lower prevalence of cardiac and noncardiac comorbidities but more pronounced diastolic dysfunction; and phenogroup 3 had intermediate comorbidity burden, the lowest BNP concentrations, and the least diastolic abnormalities (including the lowest E/e' ratio) on echocardiography.[83] Interestingly, in contrast to the previous study by Shah et al., the 3 phenogroups from the TOPCAT subanalysis did not differ with respect to age.[78] In comparison to phenogroup 3, phenogroup 1 had higher risk for all adverse clinical events including all-cause death and HF hospitalization, and phenogroup 2 had higher risk of HF hospitalization but a lower risk of atherosclerotic event (MI, stroke or cardiovascular death), and a comparable risk of death.[82]

Other distinct HFpEF phenogroups were identified in different HFpEF cohorts depending on the type of analysis used.[84,85] In 6909 HFpEF patients from the Swedish Heart Failure Registry (SwedeHF), latent class analysis identified 5 phenogroups: cluster 1 (10% of patients) – young patients with a low comorbidity burden and the highest proportion of implantable devices; cluster 2 (30%) – patients with AF and hypertension, without T2DM; cluster 3 (25%) – the oldest patients with many cardiovascular comorbidities and hypertension; cluster 4 (15%) – patients with obesity, T2DM and hypertension; and cluster 5 (20%) – elderly patients with ischemic heart disease, hypertension and CKD, who were most often prescribed diuretics. Those clusters were externally validated in a cohort of 2153 patients from the Chronic Heart Failure ESC-guideline based Cardiology practice Quality project (CHECK-HF) registry. Patients in cluster 1 had the most favorable prognosis, and those in clusters 3 and 5 – the worst prognosis.[84]

## Conclusions

Recent studies have demonstrated the importance of identifying subgroups among HFpEF patients. Phenotyping based on HFpEF etiology (such as amyloidosis or hypertrophic cardiomyopathy) may guide the choice of specific treatment. Clinical HFpEF phenotyping (with division into patient subgroups with prevailing, e.g., hypertension, noncardiac comorbidities, CAD, or AF) can also point towards preferred therapies. In contrast to that "traditional", clinical phenotyping, phenomapping based on machine learning enables clustering of common clinical and/or laboratory characteristics, leading to the identification of less obvious or "predictable" HFpEF subgroups. These subgroups were shown to have different prognosis. In future, machine learning phenotyping might change our approach to HFpEF treatment.

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