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What Are HFpEF Mimics and What Are They Mimicking? Insights Into Our Conceptualization of Heart Failure With Preserved Ejection Fraction as a Disease

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Abstract

During the initial workup of a patient with chronic heart failure, increased left ventricular (LV) filling pressures at rest or during exercise, and a LV ejection fraction $\geq 50\%$, physicians are expected to exclude the presence of established diseases that masquerade as heart failure with preserved ejection fraction (HFpEF), referred to as “HFpEF mimics”. These diseases include (1) cardiac amyloidosis; (2) hypertrophic cardiomyopathy; (3) infiltrative, restrictive and inflammatory cardiomyopathies (sarcoidosis, hemochromatosis, Fabry’s disease, and radiation- and chemotherapy induced restrictive disorders); (4) hemodynamically significant valvular heart disease; (5) pericardial diseases (particularly constrictive pericarditis); (6) high-output heart failure; and (7) end-stage kidney disease. These diseases were recognized long before HFpEF was defined as a disorder, have specific targeted treatments, and have generally been excluded from randomized controlled trials of new drugs for HFpEF. Interestingly, following the exclusion of HFpEF mimics, patients demonstrate the typical clinical and pathophysiological features of cardiometabolic HFpEF, with an exceptionally high prevalence of central adiposity, dysglycemia, hypertension and systemic inflammation — even though large-scale trials did not require participants to have any feature of a cardiometabolic disorder. The homogeneity of the phenotypic presentations of these patients is consistent with the lack of observed heterogeneity in the responses to broad-based treatments (i.e., sodium-glucose cotransporter 2 inhibitors, finerenone and incretins). Importantly, many patients with adiposity-related HFpEF were not permitted to participate in large-scale trials, which excluded patients with severe obesity, lower natriuretic peptides and without manifest echocardiographic diastolic filling abnormalities. In conclusion, the exclusion of HFpEF mimics from the broad population of patients with left-sided heart failure and an ejection fraction $\geq 50\%$ yields a relatively homogeneous patient population with the features of adiposity-related HFpEF.

When physicians encounter a patient with chronic heart failure, symptoms, signs or laboratory evidence of congestion, increased left ventricular (LV) filling pressures at rest or during exercise, and a LV ejection fraction $\geq 50\%$, they are reminded, first and foremost, to consider and to exclude the presence of established diseases that present in a manner akin to patients with heart failure and a preserved ejection fraction (HFpEF). These diseases include (1) cardiac amyloidosis; (2) hypertrophic cardiomyopathy; (3) infiltrative, restrictive and inflammatory cardiomyopathies (sarcoidosis, hemochromatosis, Fabry's disease, endomyocardial fibrosis, and radiation- and chemotherapy-induced restrictive disorders); (4) hemodynamically significant valvular heart disease; (5) pericardial diseases (particularly constrictive pericarditis); (6) high-output heart failure; and (7) end-stage kidney disease. By convention, these diseases are referred to as “HFpEF mimics”, “HFpEF mimickers” or “HFpEF masqueraders”.¹⁻⁴ Other diseases that are characterized by exertional dyspnea, LV ejection fraction $\geq 50\%$ but have normal LV filling pressures or LV morphology (e.g., pulmonary arterial hypertension, chronic lung disease, severe anemia, rapid atrial fibrillation, deconditioning) can be grouped together as “non-left-heart HFpEF mimics”, and they are not considered further in this perspective.

At first, the use of the term “HFpEF mimic” might seem to represent a highly unusual and inexplicable naming convention. Why are diseases that mimic HFpEF referred to as “HFpEF mimics”? What are “HFpEF mimics” actually mimicking?

HFpEF Mimics Were Recognized as Diseases Before HFpEF Was Defined

When the modern era of heart failure emerged in the 1970s, trials focused on patients with systolic dysfunction, generally defined at the time as an ejection fraction $\leq 35\%$ or meaningful LV enlargement, typically caused by an ischemic or nonischemic dilated cardiomyopathy. In the 1980s, it was recognized that some patients with heart failure did

not exhibit substantial systolic dysfunction.⁵⁻⁷ With the advent of routine laboratory tests, echocardiography, cardiac catheterization and myocardial biopsy, clinicians were able to identify patients with cardiac amyloidosis, hypertrophic, infiltrative, restrictive and inflammatory cardiomyopathies, hemodynamically significant valvular heart disease, constrictive pericarditis, high-output heart failure, and end-stage kidney disease, and these diseases were recognized as specific causes of heart failure in patients without a low ejection fraction. Such patients were excluded from participation in trials of direct-acting vasodilators, positive inotropic agents, angiotensin converting-enzyme inhibitors, beta-adrenergic blockers and mineralocorticoid receptor antagonists, which focused on patients with heart failure and a reduced ejection fraction (HFrEF).

Interestingly, a few early trials allowed the enrollment of patients with an ejection fraction > 35%. The V-HEFT and V-HEFT II trials (carried out from 1980 to 1991) enrolled a few hundred patients with a LV ejection fraction of > 35%,⁸ but the patients did not appear to respond favorably to hydralazine and isosorbide dinitrate. The number of patients with a LV ejection fraction of $\geq 50\%$ in these two trials is not known, but were likely to be few, since all patients were required to have meaningful LV enlargement. In the DIG trial (carried out from 1991-1995), a small minority of patients — 719 of the 7788 patients (9.2%) — had an ejection fraction $\geq 50\%$,⁹ and they did not exhibit a favorable effect of digoxin on cardiovascular death or heart failure hospitalization.

The Emergence and Design of Large-Scale Trials Dedicated to HFpEF

In 1999, the CHARM investigators first proposed the term HFpEF as identifying patients with heart failure who had a LV ejection fraction > 40%,¹⁰ but this numerical threshold represented an arbitrary value. The CHARM trials studied heart failure with a broad spectrum of ejection fractions, and the HFpEF and HFrEF trials were run in parallel.¹¹

Given the expected variance in ejection fraction measurements, the investigative sites likely had some discretion as to whether to enroll patients into one trial or the other. Subsequent work demonstrated that the pathophysiological features of patients with an ejection fraction of 41-49% (i.e., those with mildly reduced ejection fraction) resembled that seen in patients with heart failure and an ejection fraction of $\leq 40\%$ (i.e., HFrEF).¹² As a result, the universal definition of HFpEF currently defines HFpEF as requiring a LV ejection fraction $\geq 50\%$.³

The first stand-alone trials of patients with HFpEF with >1000 patients were the I-PRESERVE trial (initiated in 2002)¹³ and the TOPCAT trial (initiated in 2006);¹⁴ these trials enrolled patients with a LV ejection fraction of $\geq 45\%$ and specifically excluded HFpEF mimics, i.e., those with cardiac amyloidosis, hypertrophic and restrictive cardiomyopathies, hemodynamically significant valvular heart disease, constrictive pericarditis, and end-stage kidney disease, as well as those with chronic lung disease or cor pulmonale. All HFpEF trials initiated since 2002 specified eligibility criteria that excluded the participation of patients with HFpEF mimics. These large-scale trials subsequently demonstrated the efficacy of sodium-glucose cotransporter 2 inhibitors, mineralocorticoid receptor antagonists and incretin drugs.¹⁵⁻¹⁹ Trials with similar exclusion criteria also reported the lack of efficacy of angiotensin receptor blockers and drugs that dilate peripheral veins and the pulmonary vasculature through a nitric oxide-cyclic guanosine monophosphate mechanism.²⁰⁻²⁷ Ongoing prospective observational studies of HFpEF involving deep phenotyping are also excluding HFpEF mimics.²⁸

Therefore, HFpEF has been defined operationally by the criteria that were used to define patient eligibility into placebo-controlled trials that have established the evidence base for our treatment of the disease. Accordingly, true HFpEF is defined by symptoms and signs of heart failure, a LV ejection fraction $\geq 50\%$, and objective evidence of hemodynamic

congestion, usually reflected by LV diastolic filling abnormalities, increased natriuretic peptides or increased LV filling pressures at rest or exercise, excluding HFpEF mimics.

HFpEF Mimics Are Diseases With Their Own Defined Treatments

Why have patients who had HFpEF mimic diseases been excluded from participation in HFpEF trials? HFpEF mimics are well-defined disorders with a rich clinical history dating back for decades (and preceding the delineation of HFpEF as a clinical entity), a defined pathogenesis, and (most importantly) highly effective disease-specific treatments. Cardiac amyloidosis results from the infiltration of amyloid fibrils, and transthyretin forms respond favorably to treatment with drugs that suppress amyloid synthesis or stability.^{29,30} Hypertrophic cardiomyopathy is frequently a monogenetic, polygenetic or epigenetically-driven disease that benefits symptomatically from cardiac myosin inhibitors.^{31,32} Sarcoidosis is treated with immunosuppressive agents;³³ hemochromatosis responds to phlebotomy or iron chelation therapy;³⁴ and Fabry's disease is managed with enzyme replacement and pharmacological chaperone therapies.^{35,36} High-output heart failure responds to cause-specific treatments (e.g., thiamine and arteriovenous shunt revisions);^{37,38} the cardiac abnormalities of end-stage kidney disease are reversed following renal transplantation;^{39,40} and constrictive pericarditis and severe valvular disease benefit from surgical or device interventions that alleviate the primary hemodynamic derangement.^{41,42} The established benefits of disease-specific treatments make it unethical to withhold treatment and randomize patients to placebo or an intervention being evaluated for the management of true HFpEF (**Figure 1**).

The proportion of patients with heart failure, increased left ventricular filling pressures and an ejection fraction $\geq 50\%$ who have a disease classified a HFpEF mimic is not known. Cohort studies have not defined the prevalence of HFpEF mimics in any representative

patient population that presents to a clinician with complaints of exertional dyspnea and is found to have heart failure and an ejection fraction $\geq 50\%$ on their initial assessment. Two-dimensional Doppler echocardiography, when performed and interpreted with experience and when considered together with other features (age and accompanying conditions), should be able to identify most patients with HFpEF mimics. However, many patients do not undergo additional definitive diagnostic testing for cardiac amyloidosis or sarcoidosis. The medical literature is replete with reports of patients with HFpEF mimics who were initially diagnosed and treated as if they had true HFpEF⁴²⁻⁴⁴ — an unfortunate occurrence since HFpEF mimics require disease-specific treatments.

It should be noted that some patients with coronary artery disease experience exertional dyspnea (rather than angina) as the primary symptom of effort-induced ischemia. These patients likely represent a very small minority of patients with epicardial artery disease, and there is no noninvasive test that can reliably elucidate the potential contribution of ischemia to complaints of exertional dyspnea. At the present time, such patients can only be defined retrospectively, based on the observation that coronary revascularization has led to resolution of symptoms of effort-induced breathlessness in an individual patient. However, in general, the completeness of coronary revascularization (when applied routinely) has not been associated with improved exertional dyspnea and a reduced risk of heart failure hospitalizations among patients with heart failure and an ejection fraction $\geq 50\%$.⁴⁵ In light of these diagnostic difficulties and therapeutic uncertainties, patients with exertional dyspnea as the primary symptom of effort-induced ischemia were not excluded from participation in large-scale trials. Therefore, we have not included this disorder in our listing of HFpEF mimics, a decision that is aligned with an identical decision made by scientific statements, consensus documents and guidelines.

Interestingly, a similar exclusionary principle has been applied to trials of HFrEF. For most of the past 40 years, trials of new agents for HFrEF have typically excluded patients with reversible causes or requiring disease-specific interventions. These have included drug-related cardiomyopathies; tachycardia-induced cardiomyopathy; malignant hypertension; hyper- or hypothyroidism; acute myocarditis or peripartum cardiomyopathy; nutritional deficiencies (thiamine, selenium, etc.); cardiac amyloidosis with a reduced ejection fraction; or cardiomyopathy potentially related to acute ischemia or hibernating myocardium. These disorders were generally excluded from large-scale trials of HFrEF; they have disease-specific treatments; and the role of neurohormonal activation and the efficacy of neurohormonal antagonism in these disorders is not known.

Patient Characteristics and Treatment Responses in Dedicated HFpEF Trials

What are the features of the trial participants that have been enrolled in randomized controlled trials in HFpEF? Nearly all the patients have had abdominal obesity^{46,47} and a history of hypertension; >80% have been overweight or had obesity; half have had type 2 diabetes,¹⁵⁻¹⁷ with dysglycemia and insulin resistance in $\approx 75\%$;^{48,49} and the vast majority have had evidence for systemic inflammation.^{15-17,50} These features correspond closely to what has been referred to as “cardiometabolic HFpEF”, an endotype that has been causally linked to the upstream influence of excess and dysfunctional visceral fat.^{51,52} According to the 2023 American College of Cardiology Scientific Statement on HFpEF,³ the vast majority of patients with HFpEF can be considered to have “cardiometabolic HFpEF”. Aging (through its effects to promote visceral adiposity), hypertension (mediated through adiposity-related arterial stiffness), and atrial fibrillation (through adiposity-mediated atrial myopathy) may be considered components of adiposity-related HFpEF (**Figure 1**). The mechanistic importance of these pathophysiological derangements (independent of adiposity) remains to be demonstrated.^{53,54}

The homogeneity of the cardiometabolic features of patients enrolled in HFpEF trials is consistent with the lack of heterogeneity in the observed treatment responses in these studies. In the patients enrolled in the DELIVER and EMPEROR-Preserved trials (which studied SGLT2 inhibitors), the FINEARTS-HF trial (which studied finerenone) and the incretin trials (which studied semaglutide and tirzepatide), patients showed consistent responses across all prespecified and post hoc subgroups.¹⁵⁻¹⁹ Patients with coronary artery disease, atrial fibrillation or elevated blood pressure (with presumed arterial stiffness) did not show differential responses to treatment, even though they were well-represented in the trials and have been hypothesized (by some) to produce HFpEF by cardiometabolic- and adiposity-independent pathways. It is noteworthy that SGLT2 inhibitors, mineralocorticoid receptor antagonists and incretin drugs reduce visceral adiposity and mute the activation of deleterious molecular signaling pathways that accompany an expansion of visceral fat mass.⁵² However, the degree to which these actions contribute to their clinical benefits in patients with HFpEF has not been defined.

Lack of Full Representation of Adiposity-Related HFpEF in Large-Scale Trials

Even though patients with HFpEF who have been eligible for clinical trials have had all the typical features of a cardiometabolic disorder, it should be noted that large-scale trials did not require participants to have any feature of an adiposity-related disease. In fact, the eligibility criteria of these trials systematically excluded many patients with adiposity-related HFpEF. In most trials, patients were not permitted to participate if they had a body mass index > 40 - 45 kg/m² or if they did not have meaningfully elevated levels of natriuretic peptides.¹³⁻¹⁸ Suppression of circulating natriuretic peptides is a typical feature of obesity-related HFpEF.^{55,56} In addition, many trials required patients to have evidence of diastolic filling abnormalities on echocardiography, but this finding is present in a minority of

patients who have demonstrable HFpEF.⁵⁷ The SUMMIT trial did not restrict the participation of patients with marked obesity and did not require patients to have diastolic filling abnormalities or a threshold level of natriuretic peptides, and it reported striking clinical benefits following a treatment with a drug that caused meaningful decreases in body weight and metrics of central adiposity.¹⁹ The exclusion of patients with marked adiposity may have attenuated the reported magnitude of clinical benefit in large-scale trials.^{46,58-60}

Summary and Conclusions

The term “HFpEF mimics” refers to a group of distinct diseases that have pathophysiological mechanisms and therapeutic responses that are fundamentally different from true HFpEF. HFpEF mimics refers to specific disorders that were recognized long before HFpEF was defined as a clinical entity, should be identified during a patient’s initial clinical evaluation, and have their own disease-specific treatments. Importantly, such patients have been systematically excluded from large-scale placebo-controlled trials of therapeutic interventions for HFpEF for the past 20-25 years.

Following the exclusion of HFpEF mimics, the patients who remained eligible for participation in large-scale HFpEF trials showed the characteristic features of adiposity-related HFpEF — even though the eligibility criteria for these trials did not require patients to have any cardiometabolic feature. Importantly, these trials demonstrated clinical benefits of drugs that are known to favorably influence adipose tissue biology — without evidence for heterogeneity of the treatment benefit across subgroups.

Therefore, the exclusion of HFpEF mimics from the broad population of patients with heart failure and an ejection fraction $\geq 50\%$ yields a relatively homogeneous patient population

with the clinical and pathophysiological features of a cardiometabolic- and adiposity-related disorder, even though these trials generally excluded many patients with severe adiposity. Patients with adiposity-related HFpEF — referred to as “true HFpEF” — have dominated participation in trials that established the efficacy of SGLT2 inhibitors, finerenone and incretin drugs. Diseases that are grouped together as “HFpEF mimics” are singled out, because they masquerade as adiposity-related HFpEF.

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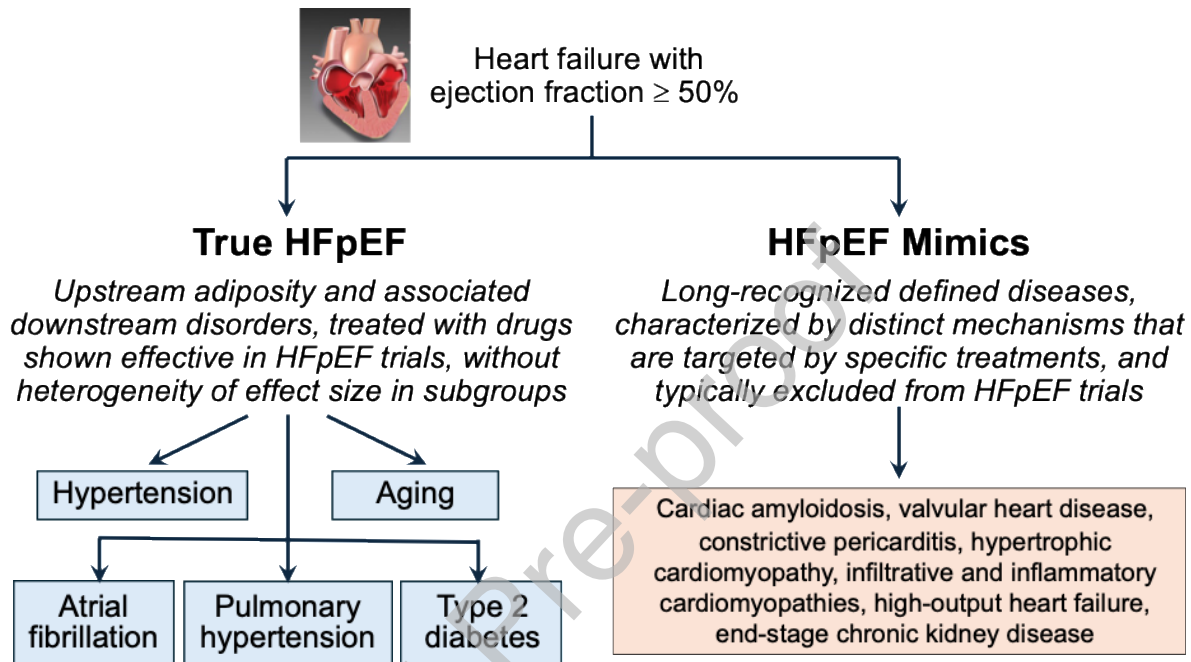
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Figure 1

Clinical, Pathophysiological and Therapeutic Features That Distinguish HFpEF Mimics From Patients With True HFpEF



Legend: Patients with heart failure, increased left ventricular filling pressures and an ejection fraction $\geq 50\%$ can be grouped into those with (1) "true HFpEF", which is generally characterized by the presence of central adiposity (and associated [typically downstream] cardiometabolic disorders) and whose participation has dominated large-scale trials that demonstrated the efficacy of sodium-glucose cotransporter 2 inhibitors, finerenone and incretin drugs, without evidence of heterogeneity of the treatment benefit across subgroups; and (2) "HFpEF mimics", which comprise defined diseases, recognized long before HFpEF was identified as a clinical entity, with distinct pathophysiological mechanisms, and which respond favorably to targeted disease-specific treatments. Because of the need to provide disease-specific treatments that were expected to provide considerable benefits, patients with HFpEF mimics were generally not allowed to be recruited into large-scale HFpEF trials. The patients who participated in these trials had all the features of an adiposity-related disorder, even though the eligibility criteria for these trials did not require patients to have any cardiometabolic abnormality. Interestingly, many patients with adiposity-related HFpEF were also not allowed to participate in large-scale trials, because these trials excluded patients with severe obesity or who did not have meaningful increases in natriuretic peptides.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Milton Packer reports a relationship with 89bio, Abbvie, Actavis, Altimune, Alnylam, Amgen, Ardelyx, ARMGO, AstraZeneca, Attralus, Biopeutics, Boehringer Ingelheim, Caladrius, Casana, CSL Behring, Cytokinetics, Daiichi Sankyo, Imara, Lilly that includes: consulting or advisory. Milton Packer reports a relationship with Medtronic, Merck, Moderna, Novartis, NovoNordisk, Pharmacocosmos, Regeneron, Roche, Salamandra, v-Wave that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



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