Clinical Phenotypes in Heart Failure With Preserved Ejection Fraction

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Over the past 2 decades, the syndrome of heart failure with preserved ejection fraction (HFpEF) received a lot of attention. However, little therapeutic progress was made. Among the issues that may account for the modest therapeutic progress, one appears to be overwhelming: HFpEF is not a well-defined clinical entity: It is an amalgam of cardiovascular, metabolic, renal, and geriatric conditions.

Patients diagnosed with HFpEF currently, were until few years ago managed for systemic hypertension, coronary artery disease (CAD), obesity, renal impairment, pulmonary hypertension (PH), or age-related deconditioning.

A rational approach for improving the outcome of patients with HFpEF may be to treat patients according to the conditions that led them to seek medical attention. As noted by others, a phenotype-oriented approach to heart failure (HF) and, in particular, to HFpEF is needed. The diagnosis of HFpEF rests on the presence of signs and symptoms of HF and a normal left ventricular (LV) ejection fraction. Left ventricular diastolic dysfunction (LVDD) does not establish the presence of HF and may bias toward an exclusive role for the heart in the pathogenesis of HFpEF.

As a whole, HFpEF has been extensively reviewed. The present review focuses on 4 commonly encountered clinical phenotypes of HFpEF and their comorbid conditions (Figure). Therapeutic implications are discussed.

Aging Phenotype

Pathogenesis

Hypertension and age are major risk factors for HFpEF. Community-based studies have highlighted the high incidence of HFpEF in the elderly and very elderly (≥80 years of age). Age-related systemic changes contribute to myocardial molecular dysfunction and eventually to cardiac structural alterations and HFpEF. Age-related changes comprise neurohormonal dysregulation (angiotensin II, endothelin) and a proinflammatory state (tumor necrosis factor alpha, reactive oxygen species, and monocyte chemotactant protein). Age also affects the vasculature. The major effect of age on the vasculature is systolic hypertension with widening of the pulse pressure that results from age-related increase in arterial stiffness and early wave reflections. Arterial stiffening and early wave reflections are steady vascular features in HFpEF. In the proximal arterial tree, vascular smooth cell loss of elastin increases systolic arterial pressure by lessening the “windkessel” effect. In the distal arterial tree, several pathways contribute to early wave reflections. In middle-aged and elderly subjects, when the aortic lumen is no longer enlarging, arterial stiffness clearly predicts blood pressure progression. Neuroendocrine activation (angiotensin II, aldosterone, and endothelin), metabolic alterations (insulin, hyperglycemia, and advanced glycation products), and inflammation (cytokines, oxidative stress, and nuclear factor kappa B) mediate collagen breakdown, cross-linking, and glycation that promote early wave reflections by increasing peripheral arterial resistances. Arterial stiffness is routinely assessed by carotid to femoral pulse wave velocity. Common comorbid conditions in HFpEF (obesity, hypertension, diabetes, obstructive sleep apnea [OSA], anemia, and renal impairment) are independently associated with increased arterial stiffness. However, arterial stiffness is consistently greater in HFpEF patients than in those who, with similar comorbidities, do not have HF. Thus, age-related increase in arterial stiffness is an important determinant of HFpEF.

By increasing systolic arterial pressure, arterial stiffening imposes an excessive load on the heart that leads to LVDD, ventricular-vascular uncoupling, and afterload mismatch. Aging greatly affects the efficiency of ventricular-vascular coupling during exercise. Of relevance to the preponderance of women in HFpEF, reduced efficiency of ventricular-vascular coupling with age is related to increased effective arterial elastance in women, whereas it relates to increased ventricular systolic elastance in men. With time, LVDD worsens and patients develop shortness of breath and fatigue.
Symptoms correlate with LVDD severity that, in turn, results from progressive arterial stiffening. A novel paradigm in HFpEF associates comorbid conditions to an inflammatory state that increases LV stiffness and promotes HF. The cellular and molecular mechanisms that lead from systemic inflammation to myocardial fibrosis (reduced nitric oxide bioactivity, cyclic guanosine monophosphate content, and protein kinase G) also promote arterial stiffening, with the endothelium being an essential component of vascular homeostasis. The novel paradigm broadens our understanding of the mechanisms that underlie progression of LV remodeling in HFpEF with age-related increase in arterial stiffness as the likely trigger of LV remodeling.

Therapeutic Implications

Lowering neurohormonal activation has unexpectedly failed to improve clinical outcome in large, placebo-controlled, randomized HFpEF trials. Diagnostic uncertainties may partially account for the lack of therapeutic benefit. However, the consistently neutral findings of these trials strongly suggest that neurohormonal modulation may not be beneficial in patients with HFpEF. In contrast to the well-established effect of neurohormonal modulation on LV remodeling in heart failure with reduced ejection fraction (HFrEF), it may have only modest effect on LV remodeling in HFpEF, with LV mass decreasing by \( \leq 10\% \) in hypertensive patients. Whether a modest reduction in LV mass reliably improves LVDD is unclear.

Reduced LV compliance and right ventricular (RV) remodeling are strong predictors of a poor outcome in HFpEF. Therapeutic trials in HFpEF have shown a greater prevalence of fatal outcome and HF hospitalizations than hypertension trials in elderly patients without HF. Although clinical events are clearly more prevalent when HFpEF is associated with severely reduced LV compliance and increased RV wall thickness, HFpEF may no longer be amenable to therapy at that stage. The lack of therapeutic success in patients with HFpEF suggests that the time to intervene may be earlier at the stage of preclinical diastolic dysfunction. A critical prerequisite for earlier initiation of intensive antihypertensive therapy is identification of hypertensive patients who are at risk of progressing to HFpEF.

Circulating biomarkers and direct measurement of arterial stiffness may identify hypertensive patients at risk for HFpEF. Cardiac troponin T, alone or in combination with N-terminal fragment of the prohormone of B-type natriuretic peptide (NT-proBNP), and products of collagen metabolism have been evaluated for identification of hypertensive patients at risk for HF.

Baseline high-sensitivity troponin and changes in troponin were found to be associated with incident HF or cardiovascular death in community-dwelling older adults without known HF. Elevation of troponin and NT-proBNP above the age- and sex-specific 75th percentile of the population identifies a malignant subphenotype of left ventricular hypertrophy (LVH) with high risk for progression to HF and cardiovascular death. An increase in plasma troponin and NT-proBNP by >50% in patients with low baseline levels identifies patients at risk for incident HF and cardiovascular death in the Cardiovascular Health Study.

Plasma tissue inhibitor of matrix metalloproteinase type 1 (TIMP-1) is elevated in patients with LVDD and correlates with markers of LV filling in patients with untreated hypertension. Circulating levels of carboxy-terminal propeptide of procollagen type 1, carboxy terminal telopeptide of procollagen-1, amino-terminal peptide of procollagen type III, matrix metalloproteinase (MMP)-2, and MMP-9 levels are greater in hypertensive patients with LVDD than in those without LVDD. In the Cardiovascular Health Study, the same makers of increased collagen turnover were elevated in patients with hypertension and LVDD. In 2011, a panel of 17 biomarkers, including NT-proBNP, cardioprophin, osteopontin, and soluble receptor for advanced glycation products, in addition to...
markers of collagen metabolism, was found to have a greater
discriminative value for identification of LVH and HF in
patients with hypertension than any single marker.91 More
recently, a meta-analysis concluded that circulating levels of
TIMP-1, MMP-2, and MMP-9 identify hypertensive patients
with LV remodeling, with circulating level of TIMP-1 being the
most specific for LVDD.92 In summary, serial determinations
of circulating markers of collagen synthesis/degradation may
allow identification of patients who, with preclinical diastolic
dysfunction, are at risk for HF.

An alternative approach for identification of hypertensive
patients with preclinical diastolic dysfunction or at risk for HF is
to monitor arterial stiffness by serially measuring pulse
wave velocity.93,94 Recent European Society of Hypertension
and Cardiology guidelines have endorsed this approach for
detection of subclinical target organ damage.95 Measurement
of pulse wave velocity may be technically difficult in markedly
obese patients with abundant adipose tissue over the groin.
Arterial stiffness may be indirectly monitored by measuring
circulating galectin-3 given that it correlates with pulse wave
velocity after adjustments for relevant variables.96 Circulating
levels of galectin-3 do not appear to predict outcome in
HFpEF after adjustment for age and renal function.97

Identification of patients with preclinical diastolic dysfunc-
tion or at risk for HF is needed for the design and conduct of
therapeutic interventions that may prevent/delay the develop-
ment of HFpEF in hypertensive patients. Elderly hypertens-
ive patients with preclinical diastolic dysfunction or at risk
for HF may benefit from more-intensive antihypertensive
therapy than recommended in the latest guidelines.98 A
systolic blood pressure target goal of less than 120 mm Hg
reduced the risk of incipient heart failure by 38%, as
compared to the standard goal of less than 140 mm Hg, in
the Systolic Blood Pressure Intervention Trial (SPRINT) trial.99

Obesity Phenotype

Pathogenesis

North American urban HFpEF registries have highlighted a
distinct subset of HFpEF patients.100,101 The subset consists of
African American women with hypertension and obesity
who, when diagnosed with HFpEF, are on average 10 to
15 years younger than their mainstream counterparts.100,101
Whereas the HFpEF obesity association was initially reported
in African American women, it is not specific to sex or
ethnicity.102 Obesity was reported in 34% of the Irbesartan in
Heart Failure With Preserved Ejection Fraction (I-PRESERVE)
trial and in 40% of patients who, undergoing coronary
angiography at the Mayo clinic, were found to have LV
remodeling and diastolic dysfunction without obstructive
epicardial CAD.102,103 Sex-related increase in LVH and
proximal aortic stiffness with altered ventricular-arterial
coupling partly accounts for the preponderance of women in
HFpEF.63,104–107

An elevated body mass index (BMI; kg/m²) is a recognized
risk factor for new-onset HFrEF and HFpEF.108–111 Obesity
has been associated with LVH and incipient LV dysfunction.112,113 In the Dallas Heart Study, central adiposity was
linked to concentric LVH and lower body obesity to eccentric
LVH.114 Measurement of waist circumference and waist-hip
ratio may be preferred to BMI when evaluating patients with
HFpEF and increased body weight.115,116 Besides age and
hypertension, obesity and especially central obesity is a major
determinant of arterial stiffness.117–119 In an overfed mouse
model of metabolic syndrome/obesity, weight gain precedes
the increase in arterial stiffness, which can be reversed by
caloric intake reduction and return to a normal weight.120
Increased arterial stiffness in this mouse model is related to
sympathetic nervous system activation, reduced nitric oxide
bioactivity, and inflammation. Voluntary weight loss with a
low-calorie diet for 12 weeks is associated with a decrease in
arterial stiffness in overweight/obese, middle-aged, and
elderly subjects.121 The decrease in arterial stiffness corre-
lates with a reduction in total body weight and abdominal
obesity.121 Aerobic exercise training and a low-calorie diet for
7 weeks reduces arterial stiffness to a greater extent than
diet alone in morbidly obese subjects.122 Two observations
are relevant to obesity in HFpEF: (1) Obesity correlates with
arterial stiffness in women and not in men.123 Not unexpect-
edly, obesity and arterial stiffness did not correlate in an
HFpEF population with nearly as many men as women.50 (2)
The duration of morbid obesity affects the LV response to
weight loss.124

In addition to increasing arterial stiffness, obesity is
associated with 4-fold greater prevalence of OSA, which
contributes to the pathogenesis of HFpEF through multiple
mechanisms: Sympathetic activation increases LV afterload,
hypoxic pulmonary vasoconstriction reduces LV preload,
oxidative stress stimulates inflammation, and hypoxia predis-
poses to atrial and ventricular arrhythmias.125–129

When estimated by BMI, obesity is associated with a
favorable outcome in patients with HF, a phenomenon that is
referred to as the obesity paradox.130–136 However, when
obesity is assessed by indices of visceral obesity, such as
waist circumference and waist-hip ratio, the obesity paradox
is no longer apparent.137 In the 4109 patients of the
I-PRESERVE trial, BMI and adverse clinical events were
related, with the greatest rate of adverse outcomes in the
lowest and highest BMI categories.102 The relationship
between obesity and clinical outcome has not been specif-
cally investigated in the obesity HFpEF phenotype.

Independently from body composition, African Americans
are at high risk for HFpEF.138,139 They are 2 to 3 times more

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likely to develop LVH than Caucasians. African Americans remain at higher risk to develop HF than Caucasians after adjustment for many HF risk factors. In a community-based sample of middle-aged African Americans, three quarters of ambulatory patients with HF had HFrEF. Eighty-five percent of HFrEF patients were women. The most common comorbid conditions were hypertension and obesity in 85% and 71% of patients, respectively. In summary, central obesity appears to cause premature arterial stiffening and thereby to hasten the progression to HFrEF in hypertensive patients, particularly in African American women.

**Therapeutic Implications**

Obesity-induced premature arterial stiffening is a clear target of therapy in obese patients with HFrEF. Exercise training reduces arterial stiffness. However, obese patients may not be able to exercise at sufficient workloads to reverse vascular remodeling. Sustained and substantial weight loss is more reliably attained by bariatric surgery than by lifestyle modifications and medications. Importantly, bariatric surgery improves LV relaxation and reverses concentric LV remodeling, with a substantial reduction in LV mass. In addition to decreasing arterial stiffness and blood pressure, bariatric surgery improves/cures OSA and diabetes. In the absence of evidence-based data, one cannot recommend gastric bypass surgery in obese HFrEF patients. The long-term cardiovascular effects of bariatric surgery clearly need to be assessed in obese HFrEF patients.

**PH Phenotype**

**Pathogenesis**

The diagnosis and management of PH from left heart disease-group 2 PH has been extensively reviewed. Venous (postcapillary) PH, resulting from enduring elevation in left atrial (LA) pressure, is the most common cause of PH. Functional mitral regurgitation and LVDD are associated with marked LA pressure elevation. Both are major determinants of PH in patients with HFrEF. All patients with HFrEF have some degree of functional mitral regurgitation and LVDD as their condition deteriorates. However, only 60% of patients with advanced HFrEF develop PH. Tight control of LA pressure with loop diuretic therapy, sudden death before symptomatic deterioration, or both may account for near normal pulmonary artery (PA) pressure in 40% of patients with HFrEF. On the other hand, an arterial (precapillary) component contributes to PH in 25% to 30% of patients with HFrEF. Impaired vascular reactivity with endothelin/nitric oxide imbalance, hypertrophy of vascular smooth muscle cells, extracellular matrix deposition, and genetic factors worsen precapillary PH in the setting of postcapillary PH. An elevated mean or diastolic transpulmonary pressure gradient (TPG) provides direct evidence of a precapillary component to group 2 PH. The beneficial effect of phosphodiesterase type 5 inhibition (PDE5-I) in HFrEF provides indirect evidence of a precapillary component to group 2 PH given that PDE5-I is effective in patients with arterial PH.

The prevalence of PH is slightly greater in HFrEF than in HFrEF. Not surprisingly, the severity of LVDD is as much a determinant of PH in HFrEF as it is in HFrEF. In addition, functional mitral regurgitation attributable to mitral leaflets tenting resulting from elevated LA pressure plays a role in the pathogenesis of PH in HFrEF. The contribution of functional mitral regurgitation to PH is greater in the decompensated state, when LA pressure is markedly elevated, than in the compensated state. As noted in HFrEF, patients with HFrEF may exhibit PA pressures that are “out of proportion” to LA pressures secondary to impaired pulmonary vascular reactivity and structural alterations that add a precapillary component to postcapillary PH. The diagnosis of group 2 PH rests on the documentation of mean PA pressure ≥25 mm Hg and LV filling pressure >15 mm Hg. Direct measurement of LV diastolic pressure by left heart catheterization provides a more reliable measurement of LV filling pressure than pulmonary capillary wedge pressure in patients with severe PH or tachycardia. Direct measurement of LV diastolic pressure may prevent to diagnose type II PH in a patient with type I PH. Because pulmonary blood flow affects the TPG, diastolic TPG (when pulmonary flow substantially decreases) may be preferred to mean TPG to evaluate intrinsic changes in the pulmonary vasculature. A diastolic TPG <7 mm Hg denotes isolated postcapillary PH, and a diastolic TPG ≥7 mm Hg is indicative of combined pre- and postcapillary PH.

A caveat to the hemodynamic criteria of type II PH is that severe RV failure may result in elevated LV filling pressure attributable to ventricular interdependence with enroachment of a dilated RV into the LV. In such instances, inotropic therapy may decompress the RV, thereby alleviating ventricular interdependence. The converse caveat of type II PH hemodynamic criteria is that type II PH may be missed when in patients with intravascular depletion. Fluid challenge or, preferably, supine exercise during right heart catheterization may ascertain the diagnosis. Last, when PH cannot account for the severity of RV failure, transthyretin cardiac amyloidosis should be suspected. In summary, HFrEF is a common cause of PH. When PH is “out of proportion” to the increase in LA pressure, it may be misdiagnosed as a primary arterial PH.
Therapeutic Implications
Management of PH in HFrEF presently rests on control of fluid accumulation and enhancement of LV filling. Placebo-controlled, randomized trials of endothelin antagonism with ambrisentan and bosentan have been terminated early because of poor enrollment or led to neutral findings, respectively (ClinicalTrials.gov Identifiers: NCT00840463, NCT00820352). The placebo-controlled Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) trial randomized 216 patients with HFrEF and moderate PH to PDE5-I with sildenafil. Compared to placebo, sildenafil did not significantly improve functional capacity and clinical status. Notwithstanding that PDE5-I may have failed to improve LV function, the selection of patients with moderate PH may partly account for the neutral findings of the RELAX trial.

Recently, treatment with sildenafil failed to reduce PA pressure or hemodynamic parameters in a HFrEF cohort. In contrast, a single-center, placebo-controlled, randomized trial reported significant improvements in PA pressure, RV function, and LV relaxation with sildenafil in patients with HFrEF and PH. In the absence of evidence-based data, PDE5-I cannot be recommended for the treatment of PH in HFrEF. Riociguat, a soluble guanylate cyclase stimulator that sensitizes guanylate cyclase through nitric oxide–dependent and –independent pathways, has been evaluated for the treatment of PH in HFrEF. Riociguat increases stroke volume and cardiac output without changes in pulmonary vascular resistance and TPG. The lack of US Food and Drug Administration–approved therapy makes the management of HFrEF patients with PH and particularly out of proportion PH extremely challenging. In summary, a subset of HFrEF patients seeks medical attention for PH-related symptoms. The prognosis of HFrEF patients with PH is poor because no specific therapy is presently available to alleviate the progression of PH.

CAD Phenotype
Pathogenesis
In contrast to HFrEF, where obstructive CAD is a major consideration in the evaluation and management of patients, CAD has received little attention in HFrEF. Though abnormal relaxation is the first mechanical manifestation of myocardial ischemia, acute coronary artery syndromes seldom precipitate HFrEF decompensation or present as HFrEf. The prevalence of CAD ranges from 35% to 53% in large HFrEF registries. The prevalence of CAD in HFrEF varies with the ethnic background of patients. When patients are mostly Caucasians, CAD appears to be highly prevalent and routine coronary artery angiography is recommended. Noninvasive testing fails to detect the presence of CAD in at least one third of HFrEF patients. In contrast, the prevalence of myocardial ischemia is less than 4% in a multiethnic population of patients presenting with shortness of breath and without wall motion abnormalities. Not surprisingly, patients with HFrEF and CAD experience a greater deterioration of LV function and a worse prognosis than patients with only HFrEF. However, a fatal outcome does not appear to be related to the presence of CAD in patients hospitalized for a first episode of HFrEF decompensation. Patients with HFrEF and angina are at a significantly greater risk of myocardial infarction, coronary revascularization, stroke, and death than HFrEF patients without angina.

Surgical and percutaneous coronary revascularization improves clinical outcome in patients with HFrEF and symptomatic CAD. Of note, coronary revascularization does not prevent the recurrence of flash pulmonary edema in patients with CAD and preserved LV systolic function.

In addition to epicardial CAD, coronary microvascular rarefaction has been recently reported at postmortem examination of transmural LV specimens from HFrEF patients, compared to age-appropriate control patients, who underwent autopsy after a noncardiac death. Coronary microvascular rarefaction was found to correlate with the ante mortem severity of LVH and diastolic dysfunction, as assessed by Doppler echocardiography. Whether coronary microvascular rarefaction and LV dysfunction are related in patients with HFrEF and narrow QRS has not been investigated. Microvascular dysfunction may not be limited to the myocardium given that the hyperemic response of the forearm subcutaneous microvasculature is impaired in HFrEF. In summary, when present CAD greatly affects the management and clinical course of HFrEF.

Therapeutic Implications
When HFrEF and CAD coexist, management needs to focus on CAD as well as on diuretic and antihypertensive therapy. Shortness of breath is unquestionably a cardinal symptom of HFrEF. However, when it fails to resolve with loop diuretic therapy, shortness of breath may be an angina equivalent. Focusing on HFrEF may delay stress imaging studies or coronary angiography in patients who, with HFrEF and narrow QRS, remain symptomatic because of ongoing myocardial ischemia.

Comorbid Conditions
All phenotypes of HFrEF have in common a multitude of comorbid conditions. Rare is the HFrEF patient with...
only one comorbid condition.\textsuperscript{210} Atrial fibrillation, anemia, chronic obstructive pulmonary disease (COPD) and frailty are common comorbidities of the aging phenotype. OSA, diabetes, and chronic kidney disease (CKD) are more prevalent in the obesity phenotype.

The presence of multiple comorbid conditions heavily affects the clinical course in HfPef.\textsuperscript{210–212} In an HF population of Medicare beneficiaries with a preponderance of women, comorbid conditions accounted for 45% of preventable hospitalizations.\textsuperscript{213} An even greater clinical burden of noncardiac comorbid conditions has been reported in a mostly male population of HfPef patients.\textsuperscript{210} The risk of hospitalization is closely related to the number of comorbid conditions.\textsuperscript{212} The high prevalence of comorbid conditions also affects the mode of death in HfPef patients.\textsuperscript{214} In contrast to the findings of large, randomized therapeutic trials, registries have reported a preponderance of noncardiac deaths in HfPef.\textsuperscript{215–217}

**Aging-Related Comorbid Conditions**

**Atrial fibrillation**

With hypertension as a steady background and aging as a common phenotype, atrial fibrillation (AF) is predictably a prevalent comorbid condition in HfPef.\textsuperscript{218} A history of AF was present in 29% of I-PRESERVE and Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved patients.\textsuperscript{82} The prevalence of AF reached 44% and 51% in elderly I-PRESERVE patients with a median age of 75 and 82 years, respectively.\textsuperscript{219} AF is also highly prevalent in patients hospitalized for acutely decompensated HfPef.\textsuperscript{220} Because of underlying diastolic dysfunction, AF may persist even after recovery of LV systolic function.\textsuperscript{221}

Despite some discordant findings, the presence of AF is now widely recognized to portend a poor outcome in HfPef.\textsuperscript{222–225} LA structural remodeling that provides the reentry substrate for AF clearly differs in HfPef and HFrEF.\textsuperscript{226,227} Increased LA stiffness and greater LA pulsatility may result in a higher AF burden in HfPef than in HFrEF. In brief AF, a common comorbid phenotype of HfPef, is particularly prevalent in the aging phenotype. AF increases hospitalizations and predicts a poor prognosis independent of the stroke risk.

**Anemia**

Anemia is an independent predictor of mortality in patients with HfPef.\textsuperscript{228} Its prevalence is similar to that of CKD, diabetes, and COPD.\textsuperscript{229–231} Anemia is mostly prevalent in elderly women with advanced HfPef, CKD, and diabetes.\textsuperscript{232–234} Anemia in HF has the same profile as in chronic disease with defective utilization of iron, impaired erythropoietin responsiveness, and depressed bone marrow function.\textsuperscript{232–234} Neurohormonal activation, renal dysfunction, hemodilution, and systemic inflammation contribute to the development of anemia in HfPef.\textsuperscript{232–234} Functional iron deficiency with upregulation of myocardial transferrin receptor has been reported in the absence of anemia in HfPef patients.\textsuperscript{235} The clinical implication of functional iron deficiency in HfPef is presently unclear. It does not appear to correlate with function capacity or LV stiffness.\textsuperscript{235}

A pooled analysis in a mixed population of HfPef and HFrEF patients found that iron deficiency without anemia portends a worse prognosis than anemia without iron deficiency.\textsuperscript{236} From a therapeutic standpoint treatment with erythropoietin alpha does not improve functional capacity or reduce LV mass in elderly HfPef patients.\textsuperscript{237}

**COPD**

In a mostly male elderly population of HfPef, up to 45% of patients have been reported to have COPD.\textsuperscript{210} The overall prevalence of COPD in HfPef is 30%.\textsuperscript{208} When present, COPD is an independent predictor of mortality.\textsuperscript{238} Its impact on mortality is greater in HfPef than in HFrEF.\textsuperscript{210} The link between HfPef and COPD is incompletely understood.\textsuperscript{239} The proinflammatory state associated with COPD may hasten the development of myocardial fibrosis, and COPD may directly impair LV filling.\textsuperscript{240} In patients with atrial fibrillation, COPD hastens the development of HfPef.\textsuperscript{225}

Dyspnea is the cornerstone symptom of both HfPef and COPD. A commonly faced therapeutic challenge is to determine whether dyspnea is attributable to COPD exacerbation, HfPef decompensation, or both in patients who, with known HfPef and COPD, present with symptomatic deterioration.\textsuperscript{241} Because both conditions feed on each other, an efficient approach may be to initiate aggressive treatment of both conditions on presentation.

**Frailty**

The concept of frailty refers to decreased homeostatic reserves, resulting in increased vulnerability to acute stress.\textsuperscript{242} As a concept, frailty differs from comorbidity, which is the cooccurrence of multiple conditions.\textsuperscript{243,244} Frailty can be primary as a consequence of aging or secondary attributable to the presence of comorbidity.\textsuperscript{245} However, given that the stress that reveals frailty is often the deterioration of comorbidity, one cannot, in most instances, definitely differentiate primary frailty from secondary frailty. Overall, frailty is a well-recognized component of chronic conditions, with a prevalence of 60% and 40% in obstructive pulmonary and kidney diseases, respectively.\textsuperscript{245} The prevalence of HF-related frailty is notably greater than that of age matched in community-dwelling elders.\textsuperscript{245} It
ranges from 20% to 74%, depending on age and criteria used to define frailty.\textsuperscript{245,246} When older than 70 years, 52% of patients with HF are frail compared to 30% when they are younger than 70 years.\textsuperscript{247} Frailty is more prevalent in patients with HFpEF than HFrEF given that the former patients tend to be older and have more comorbidities.\textsuperscript{246} AF, a common comorbidity of the aging phenotype of HFpEF, hastens development and progression of frailty.\textsuperscript{248} After adjustment for confounders, including comorbidities, frailty was found to be an independent predictor of visits to the emergency department and hospitalizations in ambulatory patients with HF.\textsuperscript{246} Frailty increased emergency visits by 92% and hospitalizations by 65%. In summary, frailty, which commonly occurs in HFpEF, may be particularly prevalent in the aging phenotype.

**Obesity-Related Comorbid Conditions**

**OSA**

The prevalence of OSA ranges from 40% to 62% in obese patients with HFpEF compared to 10% in nonobese HFpEF patients.\textsuperscript{249–251} Independently from hypertension and obesity, OSA impairs LV diastolic function, begets LVH, and thus may hasten HFpEF progression.\textsuperscript{126,127,252–258} Repetitive sleep arousals and hypoxic episodes heighten sympathetic activity and promote endothelial dysfunction, systemic inflammation, and arterial stiffness that may further increase blood pressure and accelerate atherosclerosis progression.\textsuperscript{128,259–265}

Continuous positive airway pressure (CPAP) is the present standard of care for OSA.\textsuperscript{128} In patients with HFrEF, CPAP improves functional class and reduces sympathetic activity, heart rate, and blood pressure.\textsuperscript{266–268} Furthermore, OSA therapy is associated with a trend toward improvement in survival.\textsuperscript{269} In contrast to HFrEF, CPAP therapy has not been extensively evaluated in HFpEF. Adherence to CPAP therapy is known to decrease systolic blood pressure, reduce arterial stiffness, and improve LV diastolic function in patients with hypertension and OSA.\textsuperscript{270–273} The effects of CPAP on morbidity and mortality have not been evaluated in large, randomized trials in patients with HFpEF. Nevertheless, because of the beneficial effect of CPAP therapy in hypertension, obese patients with HFpEF should undergo a sleep study to establish the presence of OSA and, if indicated, be initiated on CPAP therapy.

**Diabetes**

The prevalence of diabetes averages 45% in HFpEF.\textsuperscript{208} It was as high as 61% in the Urban Baltimore Community Registry.\textsuperscript{101} Diabetes hastens the transition from preclinical diastolic dysfunction to HFpEF and is associated with a nearly 2-fold increase in mortality and morbidity in HFpEF.\textsuperscript{274–277} Insulin resistance and hyperglycemia affect HFpEF patients through multiple mechanisms.\textsuperscript{278} They include increased free fatty acid concentration, mitochondrial dysfunction, abnormal calcium homeostasis, oxidative stress, and advanced glycation endproducts.\textsuperscript{278} Besides its detrimental effect on myocardial relaxation and LV ventricular stiffness, diabetes increases arterial stiffness and accelerates wave reflections.\textsuperscript{278,279} Pulse pressure is greater and renal dysfunction is more prevalent in diabetic than nondiabetic patients.\textsuperscript{279,280} Diabetes and obesity are linked; obesity compounds diabetes’ effects on the myocardium and arterial wall.\textsuperscript{278,281} Aerobic capacity and walking distance were recently reported to be lower in diabetic than nondiabetic HFpEF patients.\textsuperscript{31} A similar observation had been previously reported in HFrEF patients.\textsuperscript{282,283} As hypothesized in HFrEF patients with diabetes, skeletal muscle metabolic alterations are likely to contribute to the lower aerobic capacity of diabetic HFpEF patients.\textsuperscript{284}

From a therapeutic standpoint, a joint endocrine-HF clinic is an attractive approach given that diabetes is common in HFpEF patients who require frequent adjustments of their hypoglycemic regimen. Mitochondria-targeted antioxidants may lower oxidative stress and improve LV diastolic function.\textsuperscript{19}

**CKD**

Renal dysfunction is common in HFpEF patients and especially prevalent in elderly obese/diabetic patients with hypertension.\textsuperscript{208,285} Overall, renal dysfunction is present in 30% to 60% of patients with HFpEF.\textsuperscript{208,286,287} The prevalence of renal dysfunction is greater when defined by estimated glomerular filtration rate (eGFR) <60 mL/min/m\textsuperscript{2} and high urinary albumin creatinine ratio than by eGFR alone.\textsuperscript{288} Low eGFR and high urinary albumin creatinine ratio are associated with cardiac remodeling and subtle LV systolic dysfunction in HFpEF.\textsuperscript{288} A high urinary albumin creatinine ratio alone has been associated with RV/LV remodeling and LV longitudinal systolic dysfunction in HFpEF.\textsuperscript{289} Renal dysfunction on presentation is associated with a poor prognosis in patients who are hospitalized for a first decompensation of HFpEF.\textsuperscript{290} Patients with worsening renal function during the index hospitalization have an even poorer prognosis.\textsuperscript{290} In contrast to HFrEF, worsening renal function after angiotensin receptor blockade is associated with a poor outcome in HFpEF.\textsuperscript{291} Renal dysfunction increases the risk of adverse events during long-term renin-angiotensin system inhibition in HFpEF patients.\textsuperscript{291} Renal dysfunction may lead to loop diuretic resistance and the need for ultrafiltration.\textsuperscript{292} Besides being associated with a poor prognosis, renal dysfunction complicates the management of patients who, with HFpEF, require a tight control of fluid accumulation.
Future Directions

The large, all-inclusive, randomized, placebo-controlled therapeutic trials approach that led to great therapeutic progress in HFrEF has not worked so far in HFpEF. Such discrepancy is, in part, attributable to overt differences in the pathogenesis and progression of HFrEF and HFpEF. In that regard, marked clinical heterogeneity and multiple comorbidities argue in favor of a phenotyping approach to HFpEF.

Preliminary data derived from the I-PRESERVE trial and validated in the CHARM-Preserved trial suggest that latent class analysis can identify 6 subgroups of patients with HFpEF from 11 clinical variables. These 6 subgroups exhibited significant differences in event-free survival and, possibly, treatment response. Identification of HFpEF subgroups with different outcomes may help select specific endpoints and interventions that, in turn, will improve the likelihood of a positive treatment response. Whether latent class analysis is used to identify HFpEF subgroups or few clinical variables help define HFpEF phenotypes, delineation of the HFpEF syndrome into clinical cohorts may resolve the current therapeutic conundrum.

Conclusion

Any attempt at clinical classification is, by essence, arbitrary. Nevertheless, defining clinical phenotypes in HFpEF may help the management of patients with HFpEF and possibly lead to therapeutic progress. Elderly patients with long-standing hypertension and HFpEF are likely to benefit from a different therapeutic approach than middle-aged obese HFpEF patients. Patients who seek medical attention for PH-related symptoms are clearly in need of specific therapy. When HFpEF and CAD coexist, great attention needs to be given to both conditions. Last, HFpEF is associated with a multitude of comorbid conditions that require specific therapies.

Disclosures

None.

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Journal of the American Heart Association
Clinical Phenotypes in Heart Failure with Preserved Ejection

Samson et al


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Clinical Phenotypes in Heart Failure with Preserved Ejection

Samson et al


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Journal of the American Heart Association

13

CONTEMPORARY REVIEW
Clinical Phenotypes in Heart Failure with Preserved Ejection

Samson et al


Clinical Phenotypes in Heart Failure with Preserved Ejection
Samson et al.

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