Heart failure remains a leading cause of morbidity, mortality, and healthcare expenditure, both nationally and worldwide [1, 2]. In the current era of cardiovascular disease, heart failure with preserved ejection fraction (HFpEF) is recognized to be a clinical entity with equal prevalence and similar morbidity and mortality rates to the traditional syndrome of heart failure with reduced ejection fraction (HFrEF), yet with distinct differences. The HFpEF phenotype presents many challenges, beginning with accurate diagnosis, because the differential diagnosis for patients with symptoms of dyspnea in the context of a normal ejection fraction remains very broad. Moreover, although numerous medical and device-based therapies have been identified in the past several decades to improve clinical outcomes in HFrEF, treatment options for HFpEF with similar efficacy are lacking. Familiarity with the current understanding of the underlying pathophysiology of HFpEF can aid in overcoming some of these challenges, although the mechanisms resulting in HFpEF and the proper therapies remain incompletely defined.

The overall prevalence of HFpEF and HFpEF related hospitalizations in the United States have increased over the past 20 years; moreover, the proportion of all heart failure admissions due to the preserved ejection fraction phenotype is rising and is projected to become more common than HFrEF among hospitalized patients [1, 2]. Examination of the risk factors for HFpEF development clearly indicate that this disease entity is characterized, and potentially even caused, by the adverse pathophysiologic effects of multiple comorbidities. These comorbidities include hypertension, diabetes, obesity, chronic obstructive pulmonary disease, and chronic kidney disease. Noncardiovascular death rates are significantly higher in HFpEF than HFrEF, and the risk of mortality rises with the number of the aforementioned comorbidities.

The diagnosis of HFpEF is not straightforward. Although an initial suspicion should arise in patients with signs and symptoms of heart failure and an ejection fraction exceeding 50%, using additional diagnostic tools is important to distinguish true HFpEF from similarly presenting conditions, including infiltrative cardiomyopathies, group 1 pulmonary hypertension, chronic obstructive pulmonary disease, constrictive pericarditis, and deconditioning. Assessment for patients with suspected HFpEF should include a detailed history and physical examination, paying close attention to the presence or absence of systemic comorbidities; electrocardiography; chest radiography; transthoracic echocardiography; measurement of serum natriuretic peptide levels; and, in some cases, invasive hemodynamic measurement by right heart catheterization. If echocardiographic assessment of diastolic function is indeterminate, an invasive right heart catheterization should be done to document elevation in cardiac filling pressures, which is a hallmark of HFpEF and the primary mechanism of symptoms. Several key clinical pearls regarding the available diagnostic tools must be remembered...
to avoid overdiagnosis of HFpEF and failure to recognize the disease when it is actually present.

Patients with HFpEF, in contrast to those with HFrEF, have lower average natriuretic peptide levels even after adjustment for other markers of congestion and disease severity [3]. This is likely related to lower degrees of left ventricular wall stress caused by the structural changes of HFpEF relative to those seen in HFrEF, as well as the relatively high rate of obesity in HFpEF patients, which is known to falsely lower natriuretic peptide levels because of adipose tissue is the primary site of natriuretic peptide metabolism. Natriuretic peptide levels can be elevated in numerous other conditions beyond heart failure, including atrial fibrillation, chronic renal insufficiency, pulmonary embolism, sepsis, and anemia.

The identification of diastolic dysfunction by transthoracic echocardiography is helpful when present; however, a substantial number of echocardiographic studies, when interpreted according to the guidelines, yield indeterminate diastolic function assessments, owing to inadequate or conflicting indices of diastolic function [4, 5]. Newer echocardiographic imaging techniques, specifically myocardial strain imaging, can increase the sensitivity for HFpEF diagnosis [6].

When invasive hemodynamics is measured, remembering that at-rest hemodynamics in patients with HFpEF may be normal is important; therefore, an exercise right-heart catheterization can greatly improve the diagnostic accuracy of this test in identifying patients with HFpEF [7].

Patients with a syndrome of HFpEF who lack any of the existing comorbidities known to be strongly associated with HFpEF, particularly if the presentation is severe, should undergo evaluation for possible infiltrative cardiomyopathies and, more importantly, cardiac amyloidosis.

The management of HFpEF is tightly connected to the underlying pathophysiology of this disease, which remains incompletely understood. The link between systemic comorbidities and diastolic dysfunction has been a topic of intense research. The pathophysiologic model of myocardial dysfunction and remodeling caused by excessive afterload was the basis for initial theories regarding the underlying mechanisms that lead to HFpEF [8]. However, the identification of cellular pathways linking the proinflammatory state to coronary microvascular dysfunction and consequent impairment in diastolic function has become more widely accepted over the simpler concept in which HFpEF is merely a manifestation of hypertensive heart disease [9]. This “multimorbidity theory” described by leading authors in the field is crucial to remember, because it identifies numerous targets for therapy in patients with HFpEF that are not necessarily specifically directed at the myocardium. Several therapies, despite not having been studied in large multi-center randomized trials, have been aimed at optimizing comorbidity status and have shown promise of benefits and improved quality of life in patients with HFpEF. These therapies include pursuing a rhythm control strategy in all patients with HFpEF and atrial fibrillation when feasible, percutaneous coronary revascularization if obstructive coronary artery disease is present and amenable to intervention, and management of obstructive sleep apnea with nocturnal continuous positive airway pressure [10–12].

Specific pharmacologic therapies with evidence of benefit in HFpEF are scarce but include the aldosterone antagonist spironolactone, which decreases hospitalization rates and potentially mortality [13–15]. Spironolactone has direct effects on the myocardium, by decreasing fibrosis, and also is a diuretic that can ameliorate congestive symptoms in HFpEF. Clinicians must remember that a risk of hyperkalemia exists with spironolactone use, and that spironolactone must be avoided if the serum potassium level is above 5 mEq/L or the serum creatinine level is above 2.5 mg/dL.

The guidelines for pharmacologic management of HFpEF also include the use of angiotensin receptor blockers, which have been associated with a decrease in hospitalization rates [16].

The sodium/glucose cotransporter 2 (SGLT2) inhibitors dapagliflozin and empagliflozin are now a key part of the guideline-directed pharmacotherapies for HFrEF [16]. Although no clear evidence has indicated improvement in clinical outcomes of HFpEF with SGLT2 inhibitor use, data have indicated improvements in myocardial cellular energetics [17]. SGLT2 inhibitors are commonly used in patients with HFpEF because of the high prevalence of diabetes in this population, and have been part of the drug strategy for maintaining euvolemia, because of their diuretic effects.
The use of invasive hemodynamic monitoring devices is an area of growing interest in HFpEF treatment. Data have indicated that, with continuous pulmonary artery pressure monitoring, the onset of cardiopulmonary congestion can remain subclinical for as many as 5 days before the manifestation of overt heart failure symptoms. Therefore, the ability to detect asymptomatic changes in hemodynamics through the use of implantable devices (e.g., CardioMEMS) can be used to tailor medical therapy (e.g., diuretics, vasodilator doses, etc.), prevent clinical heart failure decompensation, and decrease hospitalization [18].

HFpEF is a disabling condition with rising prevalence, yet incompletely understood disease mechanisms, pathophysiology, and treatment. Efforts to better characterize underlying causes and optimal management strategies are rapidly evolving, and must continue to decrease the staggering morbidity and mortality rates created by this disease. Although evidence suggests that several options may benefit every patient, HFpEF truly appears to be an entity in which an individualized approach to the comorbidity profile of each patient is likely to have the highest likelihood of treatment success.

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REFERENCES