Decoding the Diagnostic Dilemmas of Heart Failure with Preserved Ejection Fraction: Applying the Universal Definition for Enhanced Diagnosis Standardization

Renato A. Hortegal

Instituto Dante Pazzanese de Cardiologia, São Paulo, SP – Brazil

Heart Failure (HF) is a clinical syndrome in which the heart is unable to meet the metabolic demands of the body at normal level of filling pressures, whether at rest or while exercising. Traditionally, HF is classified based on the left ventricular ejection fraction (LVEF), which measures the percentage of the left ventricular end diastolic volume ejected during each contraction. Whereas a normal LVEF is established as ≥50%, it is worth noting that approximately half of all HF patients display values within this normal range.

HF with Preserved Ejection Fraction (HFpEF) and HF with Reduced Ejection Fraction (HFrEF) are distinct diseases characterized by different underlying mechanisms, diagnostic workup and treatment approaches. Moreover, diagnosing HFpEF in clinical practice is often more challenging due to the lack of standardized criteria in clinical trials and guidelines, as well as complexities arising from the heterogeneity of the HFpEF syndrome. In an attempt to standardize the diagnosis of HF, a universal definition and classification of HF were proposed, encompassing the diverse spectrum of HF phenotypes based on LVEF.

According to this guideline, a diagnosis of HF requires the presence of past or current symptoms and/or signs of HF caused by structural/functional cardiac abnormalities and corroborated by at least one of the following: 1) elevated natriuretic peptides (NP); or 2) objective evidence of cardiogenic pulmonary or systemic congestion.

Nevertheless, how can we apply these universal HF criteria to the unique intricacies of diagnosing HFpEF?

Implementing the Universal Definition of HF for HFpEF Diagnosis

The clinical diagnosis of HFpEF is straightforward when a patient presents with typical symptoms and signs of left and/or right congestive HF with LVEF ≥50%, along with echocardiographic abnormalities and elevated NP.

However, patients with HFpEF may not display this classical HF presentation. Indeed, a significant proportion of patients (~50%) will only display symptoms during exertion, without current or previous evidence of fluid overload on clinical examination or prior hospitalization for decompensated HF (Figure 1). This exercise-induced left atrial hypertension phenotype makes diagnosis challenging in clinical practice, with the Framingham criteria showing limited sensitivity.

Moreover, some HFpEF patients may lack detectable structural abnormalities in imaging studies. For instance, Ho et al. found that in a cohort of 243 patients with an invasive diagnosis of HFpEF, 59% lacked left atrial enlargement, 73% lacked LV hypertrophy, and 29% had no abnormalities in resting echocardiography. Similarly, functional abnormalities may not be evident, leading to low sensitivity of these features for HFpEF diagnosis.

Elevated NP are commonly observed in patients with HFpEF, as demonstrated in the DELIVER trial, where the median NT-proBNP was 1011 pg/mL. However, it is important to note that patients with HFpEF can definitely display normal NP levels, yet they still face a threefold increase in mortality rates compared to patients without HF.

In such cases, the guideline recommends investigating objective evidence of cardiogenic pulmonary or systemic congestion using diagnostic modalities such as chest radiography or elevated filling pressures on echocardiography, or even invasive hemodynamic measurements (e.g., pulmonary artery catheter) at rest or during exercise.

Echocardiographic Assessment of Diastolic Dysfunction to Diagnose HFpEF

Echocardiography is the main diagnostic tool for evaluating patients suspected of having HFpEF. Nonetheless, what the current evidence-based arguments support the predictive capabilities of echocardiographic parameters and its diastolic indexes in assessing cardiac filling pressures or establishing a formal diagnosis of HFpEF?

In 2016, the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) jointly updated their recommendations, combining the best evidence with expert opinions, and endorsed the algorithm “B” for assessing filling pressures. Nevertheless, it is worth noting that, despite this endorsement, at least three significant studies showed conflicting results regarding the performance of the ASE 2016 algorithm to predict filling pressures, raising concerns about its external validity.

Initially, HFpEF was described as “diastolic HF,” but this terminology is no longer recommended. While echocardiography remains as a key diagnostic tool for assessing HFpEF, it is crucial to recognize that diastolic dysfunction observed...
Decoding diagnostic dilemmas of HF with HFpEF

**Editorial**

Hortegal

Applying the Criteria of Universal Definition of HF for HFpEF diagnosis. HFpEF: HF with Preserved Ejection Fraction; RV: right ventricle; LV: left ventricle; LA: left atrium; RHC: right heart catheterization; PAWP: pulmonary capillary wedge pressure.

Figure 1 – Applying the Criteria of Universal Definition of HF for HFpEF diagnosis. HFpEF: HF with Preserved Ejection Fraction; RV: right ventricle; LV: left ventricle; LA: left atrium; RHC: right heart catheterization; PAWP: pulmonary capillary wedge pressure.

Universal Definition Criterion: Symptoms and/or signals of HFpEF

Three Phenotypes of Clinical Presentation:
- Congestive HF (fluid overload signs)
- Right Ventricular Failure with Pulmonary Hypertension (predominant signs of RV failure)
- Exercise-Induced Left Atrial Hypertension (no overt signs of fluid overload on examination)

Universal Definition Criterion: Structural Abnormalities

- 59% may have no left atrium enlargement on echocardiography
- 73% may have no LV hypertrophy
- 29% has no structural abnormalities on echocardiography

Universal Definition Criterion: Functional Abnormalities

- Comprehensive echocardiographic evaluation of diastolic function is crucial, but the evidence of diastolic dysfunction is not specific nor sufficient for making HFpEF diagnosis
- E/e' may exhibit a false-positive rate of 29%, and its measurement may not be feasible in 20% of cases during exercise
- LA reservoir strain is a promising parameter

Universal Definition Criterion: Natriuretic Peptides

- Normal in 20-35% of all HFpEF patients

Universal Definition Criterion: Right side and left side filling pressures

- Diastolic Dysfunction assessed by echocardiography has limited predictive capacity in evaluating filling pressures
- RHC: PAWP ≥15mmHg (rest) or ≥25mmHg (exercise) defines HFpEF, even though there are some controversies about which the exact point of measurement is.
- RHC combined with Cardiopulmonary Exercise Test (iCPET) is the gold standard test to evaluate the different causes of exercise intolerance, but it demands complex setup and specialized expertise

**Universal Definition Criterion: Structural Abnormalities**

- 59% may have no left atrium enlargement on echocardiography
- 73% may have no LV hypertrophy
- 29% has no structural abnormalities on echocardiography

**Universal Definition Criterion: Functional Abnormalities**

- Comprehensive echocardiographic evaluation of diastolic function is crucial, but the evidence of diastolic dysfunction is not specific nor sufficient for making HFpEF diagnosis
- E/e' may exhibit a false-positive rate of 29%, and its measurement may not be feasible in 20% of cases during exercise
- LA reservoir strain is a promising parameter

**Universal Definition Criterion: Natriuretic Peptides**

- Normal in 20-35% of all HFpEF patients

**Universal Definition Criterion: Right side and left side filling pressures**

- Diastolic Dysfunction assessed by echocardiography has limited predictive capacity in evaluating filling pressures
- RHC: PAWP ≥15mmHg (rest) or ≥25mmHg (exercise) defines HFpEF, even though there are some controversies about which the exact point of measurement is.
- RHC combined with Cardiopulmonary Exercise Test (iCPET) is the gold standard test to evaluate the different causes of exercise intolerance, but it demands complex setup and specialized expertise

One of the main echocardiography parameters used is the E/e’ ratio, which is associated with mean left atrial pressure. Bovenkamp et al. demonstrated that E/e’ >9 had sensitivity of 78% and specificity of 59%, whereas a cut of E/e’>14 had lower sensitivity (38%), but higher specificity (89%). However, the reliability of the E/e’ ratio may be compromised in various clinical scenarios, including mitral annulus calcification, conduction delay, regional wall motion abnormalities, and high output state.

In the diastolic stress test during exercise, the measurement of E/e’ may be challenging, with approximately 20% being unfeasible during peak exercise and a false-positive rate at approximately 29%.

Left atrial reservoir strain (LArS) is a promising parameter for HFpEF diagnosis. LArS ≤18% or ≤24% is associated with increased filling pressures. However, this parameter, along with other new parameters derived from speckle tracking demand further research to evaluate its performance in less selected populations.

Using the recently proposed HFpEF and HFA-PEF scores for suspected HFpEF can be valuable in balancing clinical, echocardiographic, and NP parameters in the diagnostic workup (Figure 2). The HFpEF score, proposed by the Mayo Clinic group in 2018, provides a probability
of HFpEF for individuals with unexplained dyspnea and has been validated using invasive measurements of pulmonary capillary wedge pressure (PAWP). It is important to note that the prevalence of HFpEF in this study population was 64%, which may lead to selection bias.20

In 2019, the European Society of Cardiology published a consensus recommendation proposing a stepwise approach to evaluate patients with suspected HFpEF. After excluding other conditions that may mimic HFpEF in the pre-test assessment (Step “P”), they suggested a scoring system (Step “E”) to classify patients as having low, intermediate, or high probability of HFpEF.2 This scoring system was subsequently prospectively validated.21

While validation studies generally demonstrate good overall performance for both score systems, some inaccuracies have been identified. For example, false negative rates of 25% (23 out of 91 cases) and 28% (14 out of 50 cases) were reported for patients classified as low probability (score) or 1) by HFAPEFF and H₂FPEF, respectively.22

Furthermore, recent data suggest that applying these scores to less selected populations may result in high prevalence of intermediate scores,23,24 requiring additional tests such as exercise right heart catheterization (RHC).

Exercise RHC for the Diagnosis of HFpEF

Exercise RHC is the gold standard for diagnosing HFpEF as it directly measures PAWP. In reference centers, simultaneous measurement of VO₂ (Invasive CardioPulmonary Test) allows estimation of the kinetics of all components of the Fick equation through the different stages of exercise.

A PAWP ≥15mmHg at rest or ≥25mmHg during exercise defines HFpEF.25-27 Additionally, the increase in PAWP indexed to change in cardiac output (PAWP slope/Cardiac Output>2) has been proposed as a diagnostic criterion to define HFpEF.28

However, conducting RHC requires a complex setup and demands specialized expertise for data acquisition and interpretation. Moreover, there are notable variations in protocols (upright vs. supine) and standardization methods for measuring PAWP, such as the reference point (mid-A wave end of expiration vs. mean during the respiratory cycle).29

Despite those limitations, exercise RHC is a highly accurate approach to fulfill the criteria for objective evidence of pulmonary congestion as stipulated by the universal definition of HF. Furthermore, it not only provides insights into the mechanisms underlying exercise limitation, but also enables prognostication of patients diagnosed with HFpEF.

**Figure 2 – Current recommendations for the diagnostic approach of patients with suspected HFpEF. HFpEF: Heart Failure with Preserved Ejection Fraction; *Exercise Test encompasses both Diastolic Stress Echocardiography and Exercise RHC. #Preload Challenge refers either to infusion of normal saline or passive leg raising maneuver during RHC.**

### References


This is an open-access article distributed under the terms of the Creative Commons Attribution License