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Deliberating the Diagnostic Dilemma of HFpEF

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Abstract

There is a lack of consensus on how we define heart failure with preserved ejection fraction (HFpEF), with wide variation in diagnostic criteria across society guidelines. This lack of uniformity in disease definition stems in part from an incomplete understanding of disease pathobiology, phenotypic heterogeneity, and natural history. We review current knowledge gaps and existing diagnostic tools and algorithms. We present a simple approach to implement these tools within the constraints of the current knowledge base, addressing separately (1) hospitalized individuals with rest congestion, where diagnosis is more straightforward, and (2) individuals with exercise intolerance, where diagnosis is more complex. Here, a potential role for advanced or provocative testing, including evaluation of hemodynamic responses to exercise is considered. More importantly, we propose focus areas for future studies to develop accurate and feasible diagnostic tools for HFpEF, including animal models that recapitulate human HFpEF, and human studies that both address fundamental understanding of HFpEF pathobiology as well as new diagnostic approaches and tools. In sum, there is an urgent need to more accurately define the syndrome of HFpEF, in order to inform diagnosis, patient selection for clinical trials, and ultimately future therapeutic approaches.

Keywords

Heart failure with preserved ejection fraction (HFpEF); Diagnosis; Exercise Testing

Introduction

Both the prevalence and incidence of heart failure with preserved ejection fraction (HFpEF) are rising relative to HF with reduced ejection fraction,¹⁻³ yet there is continued lack of consensus on how we define HFpEF across various society guidelines and clinical trials. While most criteria rely on the presence of clinical symptoms and preserved ejection fraction (with variable cut-points), there is substantial variation regarding the use of biomarkers, abnormal cardiac structure and function ascertained by echocardiography, and previous hospitalizations to define HFpEF.³⁻⁵ In a recent study, the application of existing HFpEF criteria to 461 individuals with chronic dyspnea and preserved ejection fraction with extensive clinical, biochemical, and hemodynamic assessment resulted in anywhere between 12% to 90% of individuals being classified as having HFpEF using various society guideline criteria. Concomitantly, this diverse range in individuals labeled as having HFpEF had widely variable future cardiovascular events.⁶ While this prior study highlighted the lack of consensus around disease definition, it was suggested that the findings could be better understood within the context of the natural history of HFpEF.⁷

We examine existing pragmatic approaches to the diagnosis of HFpEF, recognizing that the lack of uniformity in disease definition stems in part from an incomplete understanding of disease pathobiology, and more importantly highlight current knowledge gaps with the goal of motivating future research. At the heart of the matter is the urgent need to more accurately define the syndrome of HFpEF, in order to inform patient selection, diagnosis and ultimately future therapeutic approaches.

Recognizing the Heterogeneity of Clinical Presentation in HFpEF

Unlike other diseases within cardiovascular medicine such as atrial fibrillation or hypertension where definitions are centered around a specific diagnostic test, HFpEF is a clinical syndrome for which we rely on a constellation of symptoms, signs, and other manifestations. As a clinical syndrome, the complexity of defining HFpEF arises in part from considerable heterogeneity in patients' clinical presentation on multiple levels: (1) comorbidities i.e. co-existing conditions that modify clinical symptoms and signs; (2) organ system involvement, which may include both cardiac and non-cardiac manifestations; and (3) subset or stage of disease, where different phenotypes or stages of HFpEF may present with non-uniform clinical symptoms and signs.

Understanding HFpEF within the Context of Comorbidities

It is increasingly recognized that there is heterogeneity with respect to comorbid diseases upon HFpEF presentation ("HFpEF predisposition", Figure 1). For example, while HFpEF was first recognized among elderly individuals with longstanding hypertension, more contemporary HFpEF samples include younger, predominantly obese individuals with cardiometabolic disease, characterized by lower natriuretic peptide levels and distinct exercise physiology.^{8,9} Recent data in Asian cohorts demonstrate that clustering of multimorbidities in both HFpEF and HFrEF relates differentially to patient quality of life and clinical outcomes.¹⁰ In this study, latent class analysis identified three HFpEF-predominant phenotypes, namely 'Elderly/AF' (older, high prevalence of atrial fibrillation);

‘Metabolic’ (obese, high prevalence of diabetes and hypertension) and ‘Lean diabetic’ (high prevalence of diabetes in absence of obesity).

Understanding HFpEF within the Context of Organ System Involvement

Further heterogeneity exists across HFpEF phenotypic manifestations (“HFpEF manifestations”, Figure 1) with evidence of both cardiac and extra-cardiac organ system involvement, including contributions from right ventricular dysfunction, left atrial predominant myopathy, arterial stiffness, pulmonary hypertension, impaired peripheral oxygen extraction, skeletal muscle sarcopenia, and abnormal kidney function.^{11–15} While multiple physiologic abnormalities likely contribute to exercise intolerance in a given patient, significant variation in defects along the O₂ pathway are also thought to underlie disease heterogeneity.¹⁶ In considering the many extracardiac manifestations and comorbidities among patients with HFpEF, it is not surprising that non-cardiovascular outcomes outweigh cardiovascular disease endpoints.¹⁷ Indeed, this diversity in clinical presentations has prompted proposals for HFpEF phenotype-guided approaches to treatment.^{18,19}

Understanding HFpEF within the Context of Natural History

Even in the absence of heterogeneity in comorbidities or organ system involvement, disease severity or expression as manifested by symptoms and signs are inextricably linked to our ability to diagnose the clinical syndrome of HFpEF. For example, the sensitivity and specificity of detecting jugular venous distention to make a diagnosis of HFpEF will be greater in those with overt rest congestion and “more severe” disease compared with physical examination findings among patients “early” in the disease process. Thus, in addition to heterogeneity in comorbidities or organ system involvement, the natural history of the disease (or disease severity) must also be considered.

This concept is illustrated by our recent study where the definition of HFpEF was established based on the presence of elevated left ventricular (LV) filling pressures at rest or with exercise using invasive hemodynamic measurements during cardiopulmonary exercise testing (CPET).²⁰ Among this physiologically-defined HFpEF sample, 91% of individuals met American College of Cardiology / American Heart Association (ACC/AHA) HFpEF diagnostic criteria, whereas only 17% met HFSA criteria. Notably, the application of HFSA criteria enriched for individuals with 4 times the event rate compared with the ACC/AHA sample, suggesting more advanced disease. These data indicate that ACC/AHA criteria are sensitive but non-specific, whereas HFSA criteria are highly insensitive for diagnosis but identify a high risk HFpEF phenotype. In addition, heterogeneity in outcomes among different HFpEF definitions may represent successive stages in disease progression.⁷ Notably, disease severity or stage may determine responsiveness to therapy, as illustrated in two large HFpEF trials where treatment benefit was observed among patient subgroups with lower natriuretic peptide levels in post-hoc analyses.^{21,22} Hence, it is essential that we understand HFpEF diagnosis within the context of its natural history or disease severity.

In contrast to HFrEF, where disease progression from risk factor to asymptomatic LV remodeling and clinically overt disease is relatively well understood and conceptualized

within the framework of the ACC/AHA HF stages (A: risk factors, B: remodeling, C: clinical HF, D: end-stage HF),³ much remains to be uncovered about progression from HFpEF predisposing factors to overt disease.²³ For example, pre-clinical diastolic dysfunction may precede HFpEF,^{24,25} yet many cardiac and extra-cardiac comorbidities also influence disease propensity and trajectory.^{26–28} Furthermore, once HFpEF is clinically recognized, non-cardiovascular comorbidities contribute significantly to outcomes including hospitalization and mortality.^{17,29} Lastly, whether different HFpEF subphenotypes are characterized by distinct disease trajectories remains unknown. For example, individuals with normal rest but abnormal exercise pulmonary capillary wedge pressure (PCWP, “early disease”) have lower exercise capacity,³⁰ may develop exercise-induced pulmonary congestion,³¹ and are clearly at higher risk for future cardiovascular events including HF hospitalizations,⁶ yet progression to rest congestion may not be predestined.

In light of major knowledge gaps in disease heterogeneity and determinants of disease trajectory, we examine current approaches to HFpEF diagnosis. We acknowledge that disease definitions vary widely – for purposes of this paper, we will rely on the classic physiologic definition of HFpEF put forth by Dr. Eugene Braunwald as “the hearts inability to meet the metabolic demands of the body, or to do so at the expense of elevated filling pressures”, and we extend this to states of rest and exercise as has been embraced by a number of studies.³² It is clear that further research is needed in order to illuminate the use of specific diagnostic criteria that may in the future be tailored toward distinct HFpEF subphenotypes and/or disease stages.

A Practical Approach to HFpEF Diagnosis

Within the framework of the natural history of HFpEF, we can broadly divide patients into non-hospitalized HFpEF, where the main clinical manifestation is that of dyspnea on exertion and HF admission is rare, and hospitalized HFpEF marked by rest congestion (Figure 1D). Whether individuals with exercise intolerance and abnormal exercise reserve necessarily progress to rest congestion is unclear, though current data suggest greater future risk of HF hospitalizations even among the former group.^{6,33} In either case, a preserved LV ejection fraction > 50% must also be confirmed to rule out HFrEF. We will outline currently available diagnostic approaches based on this dichotomy (Figure 2), acknowledging that individuals with HFpEF and exercise intolerance have a higher likelihood to progress to rest congestion:

- 1. Rest congestion (hospitalized HFpEF):** The diagnosis of HFpEF among individuals hospitalized for rest congestion is more straightforward and can be made entirely based on a careful history and physical examination to elicit classic signs and symptoms of volume overload in the setting of preserved ejection fraction (Figure 1). Here, confirmatory or supportive evidence includes the use of natriuretic peptides, chest radiography, and echocardiography. Although these supportive objective tests are very helpful for ruling in the diagnosis in an overtly decompensated patient, there are notable exceptions. For example, up to 3 in 4 individuals with known HFpEF may not have LV hypertrophy on echocardiography.^{31,34–36} Similarly, 29% of obese individuals

with HFpEF had normal natriuretic peptide levels despite the presence of clinically overt HF with elevated PCWP.³⁷ Lastly, while routine invasive hemodynamic assessment via right heart catheterization is not recommended for the diagnosis of HFpEF,³ it provides definitive characterization of HFpEF when the history and physical examination or other testing prove ambiguous or at odds with one another. Diagnostic tools and specific cut-points and test characteristics are summarized in Table 1.

- 2. Exercise intolerance (non-hospitalized HFpEF):** The diagnosis of HFpEF in patients without overt rest congestion is more complex. While exercise intolerance can severely limit quality of life, the etiology of breathlessness can be multifactorial, and the physical examination may be normal in the setting of normal LV filling pressures at rest.^{33,38} In the absence of rest congestion and with the high prevalence of obesity, it is not surprising that natriuretic peptide levels may not be elevated (mean N-terminal pro B-type natriuretic peptide [NT-proBNP] 104 pg/mL in the study by Borlaug et al).³⁸ Supportive information may include the presence of other HFpEF predisposing factors or other manifestations such as atrial fibrillation, or the presence of structural heart disease on echocardiography.

The Role of Advanced or Provocative Testing

It is crucial to recognize that exercise intolerance is the defining symptom of HFpEF in this group of patients.³⁹ As such, evaluation at rest may be normal, and exercise testing may be needed to unmask abnormal cardiovascular reserve in the absence of apparent volume overload.^{33,38,40} In a recent pooled analysis, one of the most significant impairments in exercise reserve among HFpEF patients was an exaggerated increase in PCWP with exercise.⁴¹ Noninvasive CPET can confirm limitations in overall exercise capacity, with peak oxygen consumption (VO_2) being similarly prognostic among patients with HFpEF and HFrEF.⁴² Further, impaired peak VO_2 is directly correlated with elevated LV filling pressures with exercise in HFpEF, although discrimination from non-cardiac causes of dyspnea using peak VO_2 alone remains challenging.³⁰ Thus, CPET or 6-minute walk testing can help to define limitations in functional capacity among individuals with suspected HFpEF, though they do not provide definitive diagnostic information or evaluation of multi-organ system abnormalities.

Noninvasive evaluation of LV diastolic performance

Beyond functional capacity, evaluation of LV diastolic performance during exercise can be assessed non-invasively using echocardiography with ascertainment of the mitral early inflow to mitral annular early diastolic velocity ratio (E/e' ratio) and tricuspid regurgitation velocity at rest and with each stage of exercise.^{43,44} In this setting, exercise E/e' ratio has been shown to correlate with invasively measured PCWP during exercise, improving sensitivity of HFpEF diagnosis when compared with invasive hemodynamic measures. It is notable that the association of E/e' and invasively measured LV filling pressures is not consistently shown across studies.^{45,46} Further, widespread ascertainment of exercise diastolic function by echocardiography may be limited, with undetectable tricuspid

regurgitation jet velocity in half of individuals, and ~20% without obtainable E/e' ratio.⁴⁴ In this context, diastolic stress testing with echocardiography may be considered in experienced echocardiography laboratories, though the gold standard for advanced evaluation remains exercise testing with invasive hemodynamic evaluation.

Invasive evaluation of LV diastolic performance

Invasive CPET allows for direct evaluation of LV hemodynamic exercise responses, recognizing that individuals with HFpEF may have normal rest PCWP, with “unmasking” of abnormal LV responses with exercise. It is important to note that reference values to define abnormal exercise PCWP remain uncertain, and both methods outlined below are used. A number of prior studies have used a single cut-point of peak exercise PCWP ≥ 25 mmHg, which has been linked to worse lung congestion.^{31,38} Other studies have indexed PCWP to cardiac output (CO) or work in order to account for variable “doses” of peak exercise achieved. This allows a relatively effort-independent assessment of LV hemodynamic responses and predicts clinical outcomes.^{6,47} This method involves serial hemodynamic measures of PCWP and CO throughout the duration of exercise to estimate PCWP/CO slope, with a steep PCWP/CO slope >2.0 mmHg/L/min indicative of HFpEF.³³ This is analogous to recent consensus that increases in pulmonary artery pressure indexed to increases in CO are preferable to an absolute cut-point to define abnormal exercise pulmonary artery pressure responses.^{48,49} Among a sample of 461 individuals with dyspnea on exertion, we found that 129 (28%) had elevated rest PCWP, and 114 (25%) had normal rest but abnormal PCWP/CO slope with exercise, substantiating the importance of provocative testing to uncover abnormal exercise responses as outlined in other studies.^{20,38,41} Further, exercise provocation appears to be better than volume challenge or leg raise maneuvers in unmasking abnormal hemodynamic responses using provocative testing.^{38,50} It is important to acknowledge that advanced testing with hemodynamic assessment during exercise (either invasively or noninvasively) may not be widely available, and validation of more widely applicable noninvasive correlates for exercise diastolic function represents an important area for future study.

HFpEF Diagnostic Algorithms

Two recent diagnostic algorithms have emerged that incorporate multiple diagnostic tools to help guide HFpEF diagnosis. Both approaches leverage non-invasive data to identify low- or high-risk individuals, with additional testing recommended among patients with intermediate probability. For example, the H₂FPEF score developed by Reddy et al incorporates six clinical and echocardiographic criteria to estimate a probability of HFpEF among patients with unexplained dyspnea (Table 1). When compared with HFpEF diagnosis based on invasive hemodynamic measure, the score had good discrimination (area under the receiver operator characteristic curve 0.84).⁵¹ While the score enables discrimination of HFpEF from non-cardiac causes of dyspnea, it is important to remember that the prevalence of HFpEF among the derivation and validation sample was high (64% and 61%). In this setting, the application of this score to broader samples with lower pre-test probability of HFpEF needs to be interpreted with caution. Studies examining the applicability of the H₂FPEF score to external samples are emerging. For example, within the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial,

the H₂FPEF score was higher among participants from Americas vs. Russia/Georgia, identified patients at higher risk of adverse clinical events.⁵² Within the Alberta Heart Failure Etiology and Analysis Research Team sample, a H₂FPEF score of > 2 had a sensitivity of 89–90% to detect clinically-adjudicated HFpEF and a H₂FPEF score < 6 had a specificity of 82% to rule out HFpEF. However, it is important to acknowledge that HFpEF adjudication in this study was not validated against invasive hemodynamic assessment, limiting the conclusions that can be drawn.⁵³

Second, the European Society of Cardiology recently proposed a stepwise algorithm to aid in HFpEF diagnosis that extended and updated previous approaches.^{54,55} This algorithm incorporates multiple diagnostic tools in a sequential approach to generate the HFA-PEFF score (HFA-PEFF; Heart Failure Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional Testing, Final Etiology). This step-wise approach includes (1) pre-test assessment based on HFpEF predisposing and comorbid factors, (2) a score based on echocardiographic (structure and function) and natriuretic peptide levels separating patients into those with high scores (definite HFpEF), low (unlikely HFpEF), or intermediate scores (diagnostic uncertainty), with (3) further evaluation in those with diagnostic uncertainty, including functional testing with an exercise stress echocardiogram or invasive hemodynamic measurements at rest or with exercise. Initial validation of the HFA-PEFF score has been performed within the Maastricht cohort which included patients with suspected HFpEF (cases and non-cases), and the Northwestern (Chicago) HFpEF cohort (cases only).⁵⁶ A high HFA-PEFF score (5–6 points) was shown to diagnose HFpEF with high specificity (93%), whereas a low HFA-PEFF score (0–1 points) ruled out HFpEF with a sensitivity of 99%; however a large proportion of 36% of patients fell in the intermediate category.

With respect to current validation efforts for both diagnostic approaches, it is notable that validation studies to date have largely relied on expert consensus drawing from various clinical, echocardiographic, and biomarker data for case definitions. In this context, future data with validation against invasive hemodynamic criteria as the “gold standard” are needed to complement current efforts. Further, how these multi-pronged approaches will aid in HFpEF diagnosis among broader at-risk samples remains to be seen and will be an important area of future research.

What is not considered HFpEF?

Many other conditions may lead to volume overload with preserved LV function, and potential “secondary HFpEF” causes are important to consider as this may lead to specific therapies (Figure 2). This includes underlying cardiac conditions (valvular heart disease, pericardial disease, pure right-ventricular failure, primary cardiomyopathies including amyloidosis), high-output states (anemia, thyroid disease), and fluid overload from kidney or liver disease. It is important to acknowledge that each of these secondary etiologies may warrant specific clinical management considerations. Therefore in this paper, we refer to HFpEF as “garden variety HFpEF”, whereby secondary conditions have been ruled out and the clinical presentation of HF in the setting of preserved EF has not been attributed directly to these other specific etiologies.

HFpEF Diagnosis: Major Knowledge Gaps and Unanswered Questions

HFpEF remains challenging to diagnose despite advances in cardiac biomarkers, noninvasive imaging modalities, and provocative testing. Fundamentally, it is important to recognize that part of the problem is that HFpEF is a clinical syndrome with a multitude of contributing risk factors, etiologies, and phenotypic manifestations.¹⁸ In order to address current knowledge gaps (outlined in Figure 1), we propose the following focus areas for future research:

- Animal models that recapitulate human HFpEF: The search for preclinical models that resemble the complex human clinical phenotype of HFpEF has been challenging.⁵⁷ While specific models focused on aging, obesity, or hypertension mimic certain aspects of disease, a recent ‘two-hit’ mouse model combining both metabolic and mechanical stress may most closely capture both systemic and cardiac manifestations arising on a background of multiple comorbidities in human disease.⁵⁸ Future research should leverage such preclinical models to better understand disease pathogenesis, diverse disease manifestations, and natural history, in parallel with human studies, as fundamental understanding of disease biology will inform diagnostic approaches.
- Human studies that address (1) careful phenotyping to untangle disease heterogeneity; (2) determinants of HFpEF disease progression and clinical trajectories; (3) the potential role of biomarkers (circulating, urinary, imaging) to distinguish HFpEF from non-cardiac causes of dyspnea or comorbidities including novel methods such as exercise-induced pulmonary B-lines; (4) the potential role of hemodynamic and/or activity monitors (invasive or non-invasive) in aiding the diagnosis of HFpEF or its pre-test probability; (5) prospective validation of any proposed diagnostic algorithm against “gold standard” invasive hemodynamic assessment in diverse populations, with particular attention to diagnostic accuracy in HFpEF patients with only exercise induced hemodynamic abnormalities.

Of the focus areas above, we would like to highlight that something as fundamental as the natural history of HFpEF remains largely understudied – future insights will inform approaches to diagnosis and therapies. Given heterogeneity in comorbid burden and disease manifestations, the determinants of disease trajectory may be unique for a given phenotype or underlying biological pathway with disease progression marked by distinct clinical manifestations. For example, progressive right ventricular dysfunction may occur in a subset of individuals with HFpEF and portends worse outcomes, whereas the development of LV systolic dysfunction remains rare over time.^{59,60} It also is unclear whether disease trajectories are invariably linear (progressing canonically from one predominant stage to the next) or non-linear. Do “early” manifestations of exercise intolerance lead to greater physical inactivity, which in turn may drive skeletal sarcopenia and impaired peripheral oxygen extraction as shown in many patients with HFpEF?^{12,61,62} Is there a subset of patients with a predisposition to pulmonary vascular dysfunction which may lead to predominant right ventricular failure later in the course?^{9,63} Do hypertension and chronic kidney disease perhaps lead to greater cardiac fibrosis and arterial stiffness as the predominant clinical

feature in a subset of HFpEF?^{64,65} And is the ‘elderly with atrial fibrillation’ phenotype fundamentally different in clinical presentation and disease trajectory compared to the ‘young obese’ phenotype? How does inflammation relate to different phenotypes, and are there potential therapeutic implications?^{66,67}

In sum, we highlight important knowledge gaps and challenges in HFpEF diagnosis and present an approach to implement available tools within the constraints of the current knowledge base. More importantly, we emphasize that further studies to develop accurate and feasible diagnostic tools for HFpEF are urgently needed. While invasive hemodynamic testing remains the gold standard, it is not yet accessible for all patients and a stepped invasive approach as outlined here may help identify indeterminate patients for referral. Further, academic institutions with capacity for advanced diagnostic testing including invasive evaluation of LV diastolic performance should prioritize research into development of novel diagnostic tools for HFpEF.

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Non-standard Abbreviations and Acronyms

ACC/AHA	American College of Cardiology / American Heart Association
CO	cardiac output
CPET	cardiopulmonary exercise testing
E/e' ratio	mitral early inflow to mitral annular early diastolic velocity ratio
HFA-PEFF	Heart Failure Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional Testing, Final Etiology algorithm
HFpEF	heart failure with preserved ejection fraction
LV	left ventricular
NT-proBNP	N-terminal pro B-type natriuretic peptide
PCWP	pulmonary capillary wedge pressure

TOPCAT	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
VO₂	oxygen consumption

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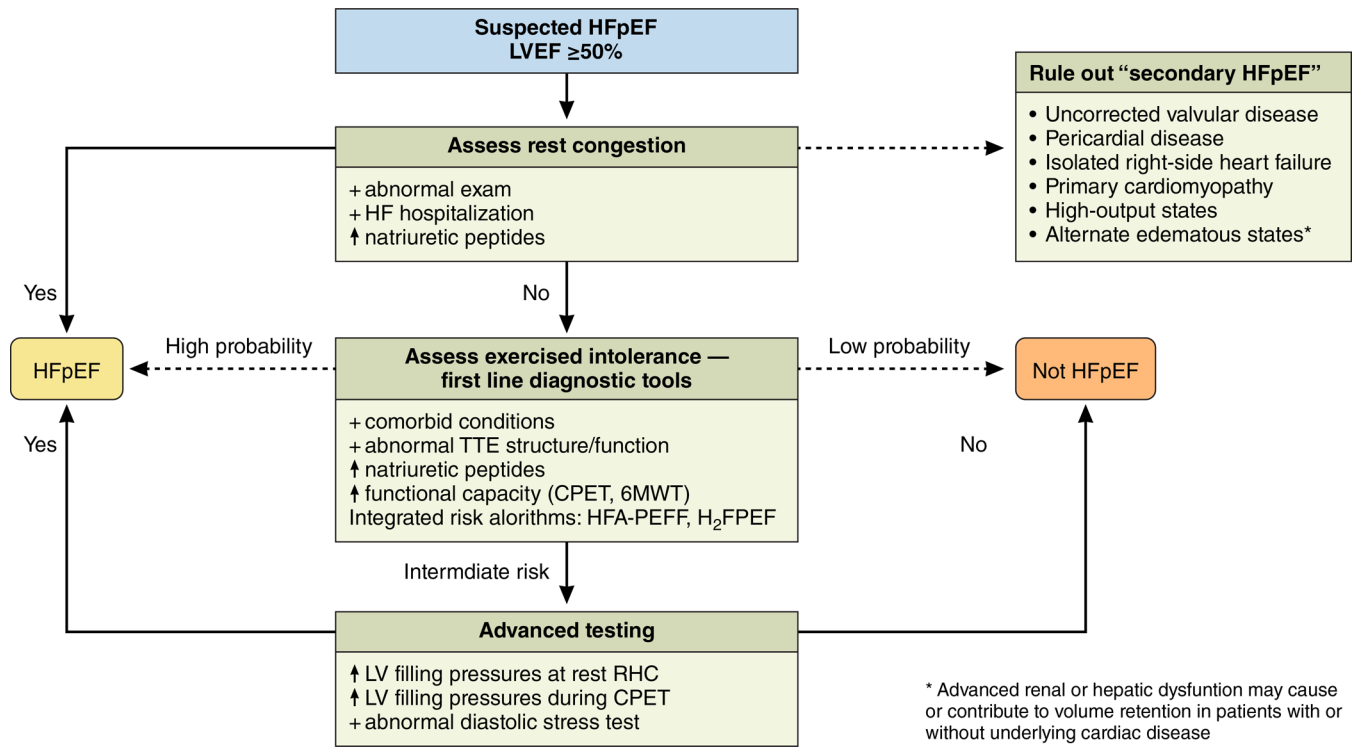


Figure 1. Contributors to diagnostic dilemma of HFpEF and summary of diagnostic tools. We place HFpEF diagnosis within the context of the natural history of the disease (**panel A**). We recognize limited understanding with respect to factors driving progression of cardiac remodeling and extracardiac involvement (**panels B and C**). Broadly, we propose to categorize individuals with HFpEF into non-hospitalized individuals with exercise intolerance vs hospitalized individuals with rest congestion in order to examine relevant diagnostic tools and approaches (**panel D and E**). Central to this conceptual framework is the recognition of major current knowledge gaps (right-hand side of figure).

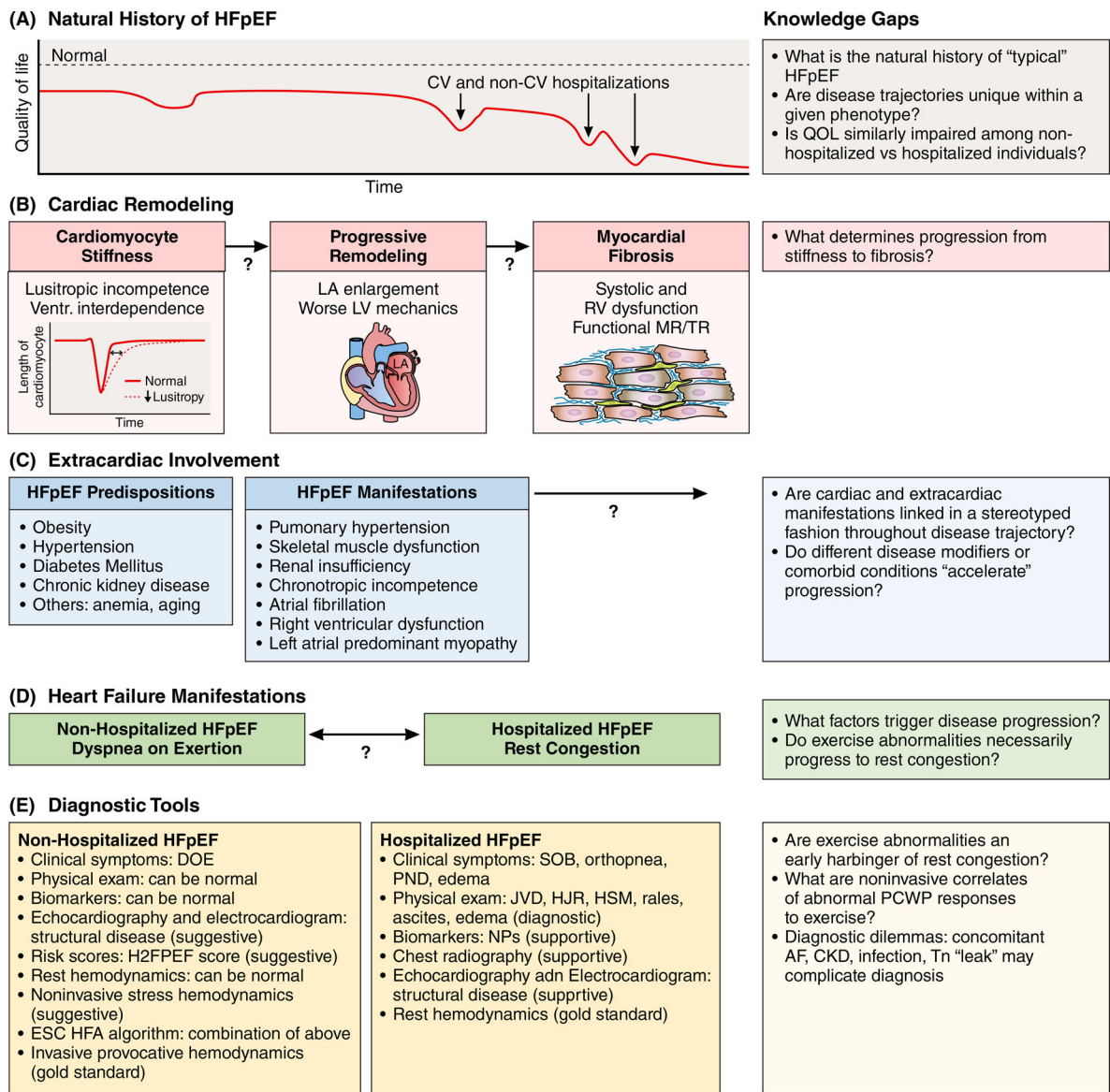


Figure 2. Practical approach to diagnostic tools.

In individuals suspected to have HFpEF, first steps include evaluating for rest congestion and consideration of potential secondary causes. If no diagnosis has been made, first-line diagnostic tools include echocardiography, natriuretic peptide levels, and objective assessment of functional capacity. Algorithms including HFA-PEFF and H₂FPEF may be helpful in estimating probability of HFpEF. In individuals where diagnosis remains unclear, advanced testing can be considered including rest and exercise invasive hemodynamic measures, and diastolic stress testing in experienced centers.

Table 1.

Diagnostic Tools for HFpEF

	Non-hospitalized HFpEF	Hospitalized HFpEF	Criterion	Comments	Test Characteristics
History	Dyspnea on exertion	Rest congestion	Orthopnea		
Physical exam	May be normal	Diagnostic	JVP Rales Peripheral edema Third heart sound		
Natriuretic peptides	Supportive	Supportive	Major ESC criterion: NT-proBNP > 220 (660 in AF); minor ESC criterion: > 125 (375 in AF) ⁵⁴	Natriuretic peptides are 3–3.5 fold higher in AF compared with sinus rhythm ⁶⁸ and may be falsely low in obese individuals with HF ³⁷	High negative predictive value for overall HF ² although NPV less robust in HFpEF. Up to 20% with invasively-proven HFpEF have low NT-proBNP (<125) ^{38,44,69} ; >125 cut-point: sensitivity 77% specificity 53% ⁵¹
Echocardiography	Supportive	Supportive	Diastolic function: Tissue Doppler of mitral septal and lateral e' and E/e' ratio	ESC criteria: septal e' < 7 or lateral e' < 10 (< 75 yrs); septal e' < 5 or lateral e' < 7 (75 years); E/e' ratio 15 (major), 9–14 (minor). ⁵⁴	Septal e' < 7: sensitivity 46%, specificity 76%; E/e' ratio > 9: sensitivity 78%, specificity 59% ⁵¹ . Systematic review: E/e' correlated with invasive LV filling pressures with summary r 0.62 in 9 studies ⁷⁰
			TR jet velocity	ESC criteria: TR velocity > 2.8 m/s or PASP > 35 mmHg ⁵⁴	PASP > 35: sensitivity 46%, specificity 86% ⁵¹
			Left atrial enlargement	ESC criteria advocate for separate cutpoints in sinus vs atrial fibrillation: Major - LAVI > 34 (sinus), > 40 (AF); minor - LAV 29–34 (sinus), 34–40 (AF) ⁵⁴	LAVI > 30 sensitivity 70%, specificity 71% ⁵¹
			Left ventricular hypertrophy	ESC criteria emphasize concentric remodeling: Major - LVMI >= 149 (men), >= 122 (women) and relative wall thickness > 0.42; minor - LVMI 115 (men), 95 (women) or relative wall thickness > 0.42 or wall thickness 12 mm ⁵⁴	Can be normal. LVH sensitivity 26% specificity 88% ⁵¹
Invasive hemodynamics	May be normal	Confirmatory / diagnostic	Pulmonary capillary wedge pressure or left ventricular end-diastolic pressure	High filling pressure defined as LVEDP 16 or PCWP 15 mmHg	Diagnostic
Echocardiographic stress test	Suggestive		Exercise measures of diastolic function and TR velocity	Ideally semi-supine bicycle test with imaging during exercise, however universal protocols are lacking. Limited published data. TR velocity measurable in only about 50% of individuals with HFpEF ⁷⁴	Addition of exercise average E/e' > 14 or septal E/e' > 15 to ESC algorithm improved sensitivity (90% from 60% for ESC alone) with similar specificity (71% from 75%) but higher false-positive rate to 29% ⁴⁴

	Non-hospitalized HFpEF	Hospitalized HFpEF	Criterion	Comments	Test Characteristics
Noninvasive CPET	Suggestive		Surrogate markers of cardiac functional limitation: peak VO_2 , VE/VCO_2 slope	Mean peak VO_2 in HFpEF is decreased relative to normals, however in intermediate range, shares overlap with non-cardiac dyspnea ^{1,51}	Peak $\text{VO}_2 < 14$ discriminates HFpEF from non-cardiac dyspnea with sensitivity 91%, specificity 51% ³⁰
Invasive CPET (RHC)	Confirmatory / diagnostic		Exercise measures of pulmonary capillary wedge pressure	Universal protocols are lacking. Can use single cutpoint of peak PCWP $> 25 \text{ mmHg}$ ^{1,34} versus change in PCWP indexed to change in flow (cardiac output) ³³	Diagnostic