REVIEW ARTICLE

Functional reserve in heart failure with preserved ejection fraction: what can the six-minute walk test add?

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous clinical syndrome in which preserved left ventricular ejection fraction does not necessarily indicate normal cardiovascular performance during physical exertion. Younger men may present with clinical and metabolic characteristics that differ from the conventional HFpEF profile, although the existence of a distinct phenotype in this population remains unproven. This review critically examines age- and sex-related heterogeneity in HFpEF, the limitations of resting echocardiography in assessing functional reserve, and the potential role of exercise-based phenotyping. Evidence from exercise hemodynamic studies, stress echocardiography, and cardiopulmonary exercise testing indicates that exercise intolerance may arise from diverse mechanisms, including impaired diastolic reserve, chronotropic incompetence, right ventricular–pulmonary arterial uncoupling, and reduced peripheral oxygen extraction. The six-minute walk test (6MWT) offers an accessible means of assessing integrated functional capacity; however, walking distance is influenced by demographic characteristics, physical fitness, comorbidities, and noncardiac factors. Although reduced six-minute walk distance is associated with adverse outcomes in established HFpEF, its ability to detect early disease in younger men has not been established. An integrated approach combining clinical risk factors, echocardiographic findings, and individualized responses to the 6MWT may help identify functionally distinct patient subgroups and guide further investigation. Prospective studies are needed to validate this approach and determine its incremental diagnostic and prognostic value. Until such evidence is available, the 6MWT should be regarded as a potential initial tool for functional stratification rather than a stand-alone diagnostic test.

Keywords: *heart failure with preserved ejection fraction; functional reserve; exercise intolerance; six-minute walk test; cardiopulmonary exercise testing; phenotyping.*

MAIN TEXT

Introduction

A preserved ejection fraction does not necessarily imply that the heart retains its ability to meet the demands of physical exertion. This paradox is particularly relevant in younger men with

heart failure with preserved ejection fraction (HFpEF), whose clinical profiles may differ substantially from the conventional presentation of an older patient with multiple comorbidities [1–5]. Findings from age-stratified analyses and machine learning studies suggest that HFpEF encompasses distinct clinical and pathophysiological phenotypes; however, the existence of a distinct phenotype specific to younger men has yet to be established [1, 2]. Moreover, relatively modest abnormalities on resting echocardiography (Echo) do not necessarily indicate that the cardiovascular system (CVS) can respond adequately to increasing physiological demands [3–7]. In some cases, functional impairment may become apparent before unequivocal structural abnormalities develop, although this hypothesis requires direct investigation. Exercise stress echocardiography and cardiopulmonary exercise testing (CPET) can help elucidate the mechanisms underlying exercise intolerance, but their availability is limited. In contrast, the six-minute walk test (6MWT) offers a simple means of quantitatively assessing overall functional capacity [6–11]. However, a reduced six-minute walk distance (6MWD) is nonspecific, and its established prognostic value in patients with diagnosed HFpEF does not, in itself, demonstrate its ability to detect early disease in younger men [11–15].

The aim of this review is to critically evaluate age- and sex-related heterogeneity in HFpEF, the potential for phenotyping based on responses to physical exertion, and the prospects for using the 6MWT as an initial tool for functional risk stratification. Particular emphasis is placed on distinguishing established evidence from hypotheses that require further investigation.

HFpEF in Younger Men: A Distinct Phenotype or a Diagnostic Blind Spot?

The conventional clinical profile of a patient with heart failure with preserved ejection fraction (HFpEF) can be both useful and limiting: it facilitates the recognition of typical cases but may also lead to insufficient attention being paid to patients whose characteristics do not fit the expected profile. Younger men are of particular interest because their clinical features may differ from the traditional disease model.

In the age-stratified analysis of the CHART-2 study, younger patients with HFpEF, particularly men under 65 years of age, were more likely to have an elevated body mass index (BMI) and inadequately controlled diabetes mellitus (DM). In older age groups, women and patients with an accumulated burden of comorbidities, including coronary artery disease (CAD), arterial hypertension (AH), chronic kidney disease (CKD), and atrial fibrillation (AF), accounted for a greater proportion of the population [1]. Thus, substantially different clinical profiles may exist under the same diagnostic label.

However, the most important issue is not the existence of these differences per se, but their clinical significance. Do they merely reflect age-related variations in risk factors (RFs), or do they

indicate distinct pathways in the development of HFpEF? Observational data do not provide a definitive answer, but they make the latter possibility worthy of further investigation.

Further evidence of disease heterogeneity comes from a machine learning study that identified a phenogroup consisting predominantly of younger men with unhealthy lifestyles, hyperlipidemia, and impaired liver function, but comparatively less pronounced abnormalities in cardiac structure and function [2]. This finding is particularly noteworthy: in this group, adverse clinical and metabolic features were not accompanied by an equally pronounced cardiac substrate, as observed in some other patients with HFpEF [16].

Nevertheless, it is important not to draw conclusions that extend beyond the available evidence. A cluster identified by a statistical algorithm is not necessarily equivalent to a distinct pathophysiological phenotype. It may reflect an early stage of the same underlying disease, a specific combination of RFs, or characteristics of the study population. To establish a distinct HFpEF disease trajectory, the reproducibility of the phenotype must be confirmed, its physiological characteristics must be defined, and its independent clinical or prognostic significance must be demonstrated [2].

One possible explanation is that, in some younger men, the key distinction lies not in the absence of cardiac pathology, but in a mismatch between the severity of metabolic abnormalities and the extent of changes detectable at rest. This remains a hypothesis, but it provides a basis for a more productive research question: should the assessment of these patients focus solely on established cardiac remodeling, or should it also evaluate how effectively the cardiovascular system (CVS) responds to functional demands?

Diagnostic algorithms for HFpEF integrate clinical features, natriuretic peptides, and echocardiographic parameters to estimate the probability of disease and determine whether additional functional testing is warranted [3]. However, studies investigating sex-related differences suggest that the diagnostic performance of these algorithms may not be equivalent in men and women. In a study involving two independent cohorts of patients with unexplained dyspnea, the discriminatory performance of the HFA-PEFF algorithm, the H_2FPEF score, and the 2016 European Society of Cardiology (ESC) criteria was numerically lower in men than in women, although the differences did not reach statistical significance [4, 17, 18].

These findings do not establish that HFpEF is systematically underdiagnosed in men. They nevertheless highlight a more subtle issue: an algorithm that performs well in the overall clinical population may not be equally effective across all phenotypic subgroups. Male sex itself should not be considered a cause of an unfavorable disease course; rather, it may be associated with particular combinations of metabolic, vascular, and other RFs whose significance varies with age [1, 5].

This leads to a fundamental shift in how the problem is framed. The question is no longer simply whether HFpEF occurs in younger men, but whether the condition is recognized too late in some of these patients because diagnostic assessment focuses primarily on established disease rather than early manifestations of functional impairment. Testing this hypothesis requires an integrated assessment of patients' clinical profiles, objective measures of cardiac function, and responses to physical exertion.

Preserved Left Ventricular Ejection Fraction, Occult Dysfunction, and Functional Reserve: What Does Resting Echocardiography Fail to Reveal?

Left ventricular ejection fraction (LVEF) is one of the most familiar parameters in cardiology. However, in heart failure with preserved ejection fraction (HFpEF), a preserved LVEF may create a false impression of normal functional capacity. An LVEF of ≥50% does not exclude substantial abnormalities in hemodynamic adaptation and, on its own, cannot determine how effectively the cardiovascular system (CVS) can increase cardiac output during physical exertion [3, 6]. Therefore, the fundamental question is not only how the heart functions at rest, but also what happens when its compensatory capacity is challenged.

During exercise, heart rate (HR), venous return, and tissue oxygen (O_2) demand increase. An adequate response requires a coordinated increase in cardiac output, maintenance of acceptable filling pressures, enhanced peripheral oxygen delivery, and an appropriate response of the pulmonary vasculature. In HFpEF, impairment of one or more of these mechanisms may limit exercise capacity even when resting parameters are relatively preserved [6, 10, 19].

Exercise hemodynamic data are particularly informative in this regard. A systematic review and meta-analysis of 27 studies involving 2,180 patients with HFpEF and 682 control participants found that mean pulmonary artery wedge pressure (PAWP) at peak exercise was approximately 30 mmHg in patients with HFpEF, compared with 16 mmHg in the control group [7]. However, substantial variability in absolute values was observed across studies. A more consistent distinguishing feature was the steeper slope of the relationship between PAWP and cardiac output in patients with HFpEF [20, 21].

The physiological implications of this finding are more important than the absolute values themselves. In some patients, filling pressures may remain relatively low at rest but rise disproportionately to cardiac output as venous return increases. In other words, the problem lies not only in the baseline state but also in the inability of the cardiovascular system to adapt adequately to increasing demands. Exercise hemodynamic measurements can therefore reveal abnormalities that remain inconspicuous during standard resting assessments [6, 7].

Nevertheless, it would be misleading to reduce functional reserve solely to the left ventricle's (LV) ability to accommodate an additional volume of blood. Exercise intolerance in

HFpEF may result from chronotropic incompetence, an inadequate increase in stroke volume, right ventricular (RV) dysfunction, impaired right ventricular–pulmonary arterial coupling, increased vascular stiffness, or reduced skeletal muscle oxygen extraction [8–10, 22]. Depending on the individual patient, one mechanism or a combination of several mechanisms may predominate.

Studies using exercise stress echocardiography confirm that HFpEF encompasses distinct functional profiles. In a study by Saito et al., cluster analysis of clinical, echocardiographic, and exercise-related parameters identified three phenogroups: one with relatively preserved biventricular reserve, another characterized predominantly by impaired right ventricular–pulmonary arterial coupling, and a third characterized by increased ventricular and vascular stiffness and impaired LV diastolic reserve [8]. These phenogroups differed in exercise tolerance and clinical outcomes.

These findings support an important conclusion: an identical LVEF does not guarantee equivalent physiological capacity. Two patients may have similar resting measurements yet differ substantially in the effectiveness of their cardiovascular response to exercise. Accordingly, HFpEF phenotyping should consider not only structural abnormalities and diastolic function but also the capacity to recruit functional reserve.

Chronotropic incompetence—an inability to increase HR adequately during physical exertion—provides a particularly clear illustration of this principle. In a study by Yuasa et al., chronotropic incompetence was identified in 41% of patients with HFpEF and was associated with a smaller increase in cardiac output, lower peak oxygen uptake (VO_2), and poorer exercise tolerance [22]. Resting measurements alone did not necessarily reflect the full extent of this limitation [23].

Importantly, functional impairment may also arise from mechanisms beyond the heart itself. A study by Skow et al. demonstrated that peripheral limitations to exercise, associated with impaired oxygen delivery and utilization by skeletal muscles, play a substantial role in some patients with HFpEF [9]. Consequently, reduced exercise capacity should not automatically be interpreted as a direct manifestation of LV dysfunction.

A broader perspective is provided by the study of De Schutter et al., which combined cardiopulmonary exercise testing (CPET) with stress echocardiography to identify five distinct exercise response patterns: predominant diastolic dysfunction, impaired peripheral oxygen extraction, impaired right ventricular–pulmonary arterial coupling, reduced LV systolic reserve, and chronotropic incompetence [24]. Three patterns were associated with a higher incidence of an adverse composite outcome than the group characterized predominantly by moderate diastolic dysfunction. All five patterns were reproduced in an independent validation cohort.

This represents an important step from a static description of HFpEF toward dynamic phenotyping. The response to exercise may reflect not merely disease severity but also its functional

organization—that is, the specific mechanisms limiting the body's ability to meet increasing metabolic demands.

Nevertheless, exercise testing should not be regarded as infallible. Results depend on the testing protocol, exercise intensity, body position, physical fitness, age, comorbidities, and current treatment. Furthermore, reduced exercise capacity is nonspecific: similar clinical presentations may occur in pulmonary disease, anemia, obesity, muscle weakness, and physical deconditioning [6, 7, 10]. Even the most informative methods require interpretation within the broader clinical context.

Resting echocardiography and functional testing should therefore be viewed as complementary rather than competing approaches. Resting echocardiography characterizes the structural and functional substrate, whereas exercise testing demonstrates how that substrate manifests under increasing physiological demands. This combination is of particular interest in younger men with a suspected early or atypical HFpEF phenotype, although current evidence is insufficient to conclude that functional abnormalities systematically precede structural changes in this population.

The key question is now not only how to detect occult functional limitation but also how to assess it using an accessible and reproducible method. Exercise stress echocardiography and CPET provide detailed insights into the underlying physiological mechanisms, but their resource-intensive nature limits their widespread use. This raises the next question: can the six-minute walk test (6MWT) serve as an initial level of functional stratification without replacing comprehensive diagnostic assessment?

The Six-Minute Walk Test: A Simple Distance or a Window into Functional Reserve?

Compared with more complex exercise-based diagnostic methods, the six-minute walk test (6MWT) appears deceptively simple: patients walk as far as possible in six minutes, and the result is expressed in meters. However, this distance reflects an integrated physiological response to physical exertion involving the cardiovascular system (CVS), lungs, skeletal muscles, and mechanisms of oxygen (O_2) delivery and utilization. This is why the 6MWT is of interest for functional stratification in heart failure with preserved ejection fraction (HFpEF), although it should not be regarded as a direct measure of cardiac reserve or a stand-alone diagnostic test [6, 10, 11].

The key challenge lies in interpreting the distance achieved. The same six-minute walk distance (6MWD) may have different implications depending on age, sex, height, body mass, and physical fitness. A systematic review of reference values for standardized walking tests confirmed the importance of age and sex in predicting functional performance [25]. Consequently, an absolute distance interpreted without individual context may obscure a relative reduction in functional

capacity, particularly in younger individuals from whom a higher level of physical performance would generally be expected [26].

The prognostic significance of the 6MWT in HFpEF is supported by clinical studies. In a study by Scrutinio et al., a shorter 6MWD was associated with increased three-year mortality. Normalization of the result according to clinical characteristics also retained prognostic value in patients with substantial functional limitations [12]. In the FRAGILE-HF study, a shorter walking distance was associated with a poorer prognosis in older patients hospitalized for worsening heart failure (HF), and the inclusion of this measure improved the prognostic model [13].

However, a fundamental distinction must be made between established evidence and a proposed application. An association between 6MWD and prognosis in patients with established HFpEF does not mean that the 6MWT can detect early disease in younger men. A reduced walking distance may reflect established functional impairment, multimorbidity, or noncardiac causes. Therefore, the test's prognostic value cannot automatically be extrapolated to early disease detection.

Why not use cardiopulmonary exercise testing (CPET) from the outset? CPET enables the assessment of peak oxygen uptake (VO_2), ventilatory efficiency, and various mechanisms of exercise limitation, providing substantially more detailed physiological phenotyping [6, 10]. In the ExIC-FEp study and the subsequent meta-analysis, the 6MWT demonstrated a moderately good ability to identify substantial reductions in functional capacity as defined by CPET. However, its accuracy was insufficient for it to replace CPET fully, and optimal threshold values remained uncertain [11].

Accordingly, these methods are better viewed as complementary levels of assessment rather than competing alternatives. CPET helps explain why exercise capacity is impaired, whereas the 6MWT provides a simpler means of assessing the extent of that impairment and monitoring changes over time. This accessibility may be a substantial advantage in preventive medicine, provided that the results are not interpreted in isolation.

Standardization is equally important. The 6MWD is influenced by corridor length, instructions, verbal encouragement, the use of assistive devices, and the effects of repeat testing. International technical standards developed by the European Respiratory Society and the American Thoracic Society (ERS/ATS) emphasize the need for standardized administration of field walking tests and careful consideration of their measurement limitations [27, 28]. Without such standardization, changes in performance may reflect differences in testing conditions rather than genuine changes in the patient's clinical status [29].

Perhaps the greatest opportunity to improve the clinical utility of the 6MWT lies not in identifying a universal distance threshold but in broadening the interpretation of its results. Two

patients may cover the same distance yet differ in their heart rate (HR) response, blood pressure (BP), oxygen saturation, severity of dyspnea, and rate of recovery. These parameters cannot independently establish the underlying mechanism of HFpEF, but they may enrich the functional assessment and help identify patients who require more comprehensive evaluation.

This leads to a research hypothesis: can the combination of individually interpreted 6MWD, clinical characteristics, and physiological responses to exercise identify functional profiles that are not apparent on resting echocardiography? This question is particularly relevant to younger men with a suspected early HFpEF phenotype. However, it remains unproven that such an approach can specifically identify cardiovascular dysfunction rather than general physical deconditioning.

Therefore, the 6MWT should be considered not a simplified substitute for CPET or exercise stress echocardiography, but a potential first-line tool for functional stratification. Its scientific value depends not only on the distance covered but also on how accurately that result is interpreted in relation to the patient's individual characteristics and other clinical findings.

From Functional Assessment to Phenotyping: A Hypothesis Requiring Validation

Viewing heart failure with preserved ejection fraction (HFpEF) through the lens of functional reserve provides an opportunity to integrate three levels of assessment: the patient's clinical profile, the structural and functional characteristics of the heart, and the response to physical exertion. Each captures a different aspect of the disease, but their combined assessment may reveal differences that remain undetected when left ventricular ejection fraction (LVEF) or six-minute walk distance (6MWD) is considered in isolation [3, 6, 8, 24].

In younger men, a particularly interesting scenario is one in which metabolic risk factors (RFs) are already prominent, resting echocardiographic abnormalities are minimal, yet functional performance is lower than expected given the individual's characteristics. Such a profile may warrant further investigation; however, it does not, in itself, establish a diagnosis of HFpEF. A similar pattern may occur in individuals with low physical fitness, obesity, anemia, or other noncardiac conditions [6, 10, 25].

The working hypothesis is that combining clinical RFs, echocardiographic parameters, and an individualized interpretation of the response to the six-minute walk test (6MWT) may help identify functionally heterogeneous subgroups of patients with suspected HFpEF. It is essential, however, to distinguish between identifying reduced functional capacity and establishing its underlying cardiovascular mechanism. The former can be assessed using relatively simple methods. The latter requires comparison with more specific investigations, including cardiopulmonary exercise testing (CPET), exercise stress echocardiography, and, in selected cases, invasive hemodynamic assessment [6, 7, 11].

Testing this hypothesis will require prospective studies involving younger men and appropriately matched control groups. In addition to standardized 6MWD measurements, investigators should assess heart rate (HR), blood pressure (BP), oxygen saturation, and symptoms during exercise, relating these findings to clinical characteristics, biomarkers, and echocardiographic parameters. It is particularly important to account for alternative causes of reduced exercise capacity and to determine whether comprehensive functional assessment provides incremental prognostic information beyond established clinical measures.

The key outcome of such research should not simply be the identification of an arbitrarily defined “low” walking distance, but rather the determination of whether an integrated functional profile can identify clinically meaningful risk groups and predict subsequent outcomes. Until such evidence becomes available, the use of the 6MWT for early HFpEF phenotyping in younger men should be regarded as a promising research direction rather than a validated diagnostic strategy.

Conclusion

A preserved ejection fraction does not guarantee preserved functional reserve, and relatively unremarkable findings on resting echocardiography do not exclude limitations that become apparent during physical exertion. This discrepancy is particularly relevant in younger men with heart failure with preserved ejection fraction (HFpEF), whose clinical profiles may differ from the typical disease phenotype. However, the existence of a distinct phenotypic subgroup of younger men has yet to be established [1, 2, 6, 8].

The six-minute walk test (6MWT) is an accessible tool for the quantitative assessment of functional capacity, but its diagnostic capabilities should not be overstated. A reduced six-minute walk distance (6MWD) is nonspecific, and the established prognostic value of the test in patients with diagnosed HFpEF does not, in itself, demonstrate its effectiveness for early disease detection in younger men [11–13].

A promising direction is not the search for a universal 6MWD threshold, but rather the interpretation of functional performance in the context of each patient's clinical and structural-functional profile. Further research is needed to determine whether this approach can identify clinically meaningful phenotypes, guide decisions regarding more comprehensive diagnostic assessment, and improve outcome prediction.

Ultimately, the central research question is not how many meters a patient with suspected HFpEF can walk, but whether their functional response is appropriate for their individual characteristics and which mechanisms account for any observed discrepancy. Answering this question may represent a step toward a more individualized approach to HFpEF assessment, provided that the proposed concept is validated in prospective studies.

Additional information

Author contributions. All authors contributed to the compilation and layout of this material.

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