Invited editorial for the European Journal of Preventive Cardiology

Article: Saito et al. Prognostic Benefit of Early Diagnosis with Exercise Stress Testing in Heart Failure with Preserved Ejection Fraction

Title: Unmasking early heart failure with preserved ejection fraction: the role of exercise stress testing

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Heart failure (HF) with preserved ejection fraction (HFpEF) is a complex heterogeneous systemic syndrome which accounts for approximately half of patients with HF. Increased recognition, together with ageing of population and growing burden of comorbidities, especially diabetes, hypertension, and obesity are among the main reasons for the rising prevalence of this condition.(1)

Initially the term diastolic HF was used to address this disorder,(2, 3) drawing the attention to diastolic dysfunction as the necessary and sufficient abnormality to cause this syndrome. HFpEF is a broader term, which basically encompasses what is not (even mildly) reduced ejection fraction and includes a heterogeneous population that, besides and beyond diastolic dysfunction, may present subclinical systolic dysfunction, pericardial disease, valve diseases, right heart abnormalities, endothelial and vascular dysfunction,(4) but also specific treatable “masqueraders” that require specialized diagnostic pathways often based on multi-modality imaging.(5) Comorbidities and associated conditions, frequently present and variably combined in each patient, may be both confounders and contributing pathogenetic determinants, challenging phenotyping and classification of patients in homogeneous phenogroups.(1)

Poor understanding of the pathophysiology and, until recently, perceived dearth of treatments able to modify outcomes in HFpEF, have contributed to the scarce interest in early HFpEF diagnosis in daily clinical practice. As a result, the disease is often detected when already progressed to an advanced stage, when irreversible derangements have occurred. HFpEF diagnosis requires the presence of signs or symptoms of HF, an ejection fraction ≥50%, and documentation of increased cardiac filling pressures. While the diagnosis of HFpEF is unequivocal in the presence of overt congestion and in advanced stages, it is challenging if filling pressures are normal at rest but become pathologically elevated only during exertion. This implies the need to examine the patient with a dynamic test.

Invasive heart catheterization at rest or during stress testing allows adequate measurement of left ventricular filling pressures and is considered the gold standard for the diagnosis of HFpEF(6) and has shown prognostic utility in dyspneic patients with HFpEF.(7) However, catheterization is not universally available nor cost-effective especially considering the extensive and rising prevalence of HFpEF in the community, furthermore it lacks standardization across laboratories and carries the potential risks of an invasive exam.(8)

For these reasons, there is growing interest to accurately diagnose HFpEF by non-invasive methods in the largest possible number of patients in order to leave invasive catheterization for few selected equivocal cases. In the absence of universally accepted diagnostic criteria, multiparametric algorithms based on clinical, laboratory and echocardiography data, have been proposed by current guidelines to estimate the probability of HFpEF in patients with unexplained dyspnea.(9, 10)

In this issue of *EJPC* Saito et al.(11) conducted a retrospective study on 368 patients with exertional dyspnea and 182 were diagnosed with HFpEF applying the Heart Failure Association Pretest Assessment, Echocardiographic and Natriuretic Peptide Score, Functional Testing in Case of Uncertainty, and Final Aetiology (HFA-PEFF) algorithm. The HFA-PEFF algorithm proposed by European Society of Cardiology (ESC) consists of a stepwise approach which starts with assessment of the pre-test likelihood based on history, a second morpho-functional step, a third step to search for concealed increased filling pressures by diastolic exercise echocardiography or catheterization, and finally etiology characterization.(9)

The present study has the merit of the application of Step 3 (diastolic exercise stress echocardiography or exercise right heart catheterization), which is omitted in most studies and underused in clinical practice, and which allowed identification of 60 patients (33%) with HFpEF that would have been missed without provocative test. Authors demonstrated that patients diagnosed with HFpEF had higher rates of all-cause death and decompensated HF requiring hospitalization or iv diuretics compared with those without confirmed diagnosis. The stress testing was combined with expired gas analysis which did not add useful information.

It is well known that when HFpEF is symptomatic for congestion and requires hospitalization, the prognosis is poor,(12) at least as bad as HFrEF.(1) Of note, in the present study only 5.6% of patients with confirmed HFpEF had a history of previous HF hospitalization. This study demonstrates that early detection of HFpEF, before it becomes clinically manifest, is possible using exercise stress testing and it is important because these patients are at high risk of adverse outcomes. Stress echocardiogram was performed in all patients regardless of Step 2 score results, conversely catheterization was reserved to patients with equivocal non-invasive tests, which may reflect clinical practice. This study was not aimed to validate the algorithm.

Interestingly there was not a gradient of risk between patients who were diagnosed with HFpEF at Step 2 (with echocardiographic and biomarker data) versus patients who qualified as HFpEF only after applying Step 3 (only after provocative echocardiogram or catheterization). This indicates that these patients likely have concealed diastolic dysfunction at rest, but a similar poor prognosis and thus should receive appropriate treatment for their HFpEF.

It is conceivable that awareness of HFpEF status might have changed patient management, including but not limited to intensification of medical therapy, similarly to recently observed in a dedicated HFpEF clinic.(13) Authors concluded that the early therapy initiation improved the prognosis in these HFpEF patients. However, caution should be posed in deriving this conclusion as this is not a randomized controlled trial and therapy was initiated by referring physicians only in half of patients after the HFpEF diagnosis with no information on other non-pharmacological intervention nor if changes occurred in the control group.

The authors acknowledged that the sample size and number of events were limited, as shown by the wide confidence intervals, but there was also imbalance between groups, with HFpEF subjects being older. Finally, as far as external validity, the study was conducted at a tertiary referral center and involved patients of Asian origin, a population in whom cardiometabolic abnormalities are frequent determinants of HFpEF and can occur with normal weight and in whom sodium glucose cotransporter-2 (SGLT-2) inhibitors, the current only class IIa recommended HFpEF therapy, seem to be more beneficial then in other populations.(14) Well-designed randomized trials are needed to determine if (and which) therapy is associated with improved clinical outcomes in patients with early-stage HFpEF, yet the study by Saito et al. interestingly highlights that the focus of HFpEF research should move to the early stages of the disease.

The study by Saito et al. is notable because it underscores the importance of dynamic assessment in HFpEF and it corroborates the clinical usefulness of the ESC proposed HFA-PEFF score comprehensive of exercise testing as a diagnostic algorithm, but especially as a risk-stratification tool.

Conflicts of interest

None

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