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How to diagnose? How to treat? Dilemmas of the HFpEF

Piotr Hoffman

Department of Congenital Heart Diseases, National Institute of Cardiology, Warsaw, Poland

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Heart failure (HF) is defined as a clinical syndrome in which typical symptoms such as breathlessness, fatigue and others accompanied by signs of pulmonary and/or peripheral congestion resulting from structural and/or a functional cardiac abnormality leading to reduced cardiac output and/or elevated intracardiac pressures at rest or during exertion [1]. Clinical presentation of HF should be confirmed by transthoracic echocardiography (TTE) which reveals cardiac morphology, function and allows the calculation of ejection fraction of the left ventricle (LVEF). Low ejection fraction (EF) corroborates HF diagnosis, nevertheless in a substantial number of patients with obvious clinical HF manifestation LVEF remains within the normal range (≥ 50%). The latter group constitutes a separate category of HF patients — with preserved ejection fraction of the left ventricle (HFpEF) which differs in many aspects from those with reduced EF (HFrEF). These differences mainly include risk factors, comorbidities, patient demographics, diagnostic algorithm and evidence-based treatment.

Heart failure with preserved ejection fraction of the left ventricle has become a preponderant form of HF in western countries accounting for > 70% amongst patients > 65 years and is constantly growing with every decade of life and the gap between HFpEF and HFrEF is getting wider [2]. This is caused by growing number of obese, diabetic individuals, with metabolic syndrome living a sedentary life who are at risk of a progression to symptomatic HFpEF if left untreated. The difference in LVEF which defines both groups results from an entirely distinct cardiac pathophysiology leading to a decrease in overall ventricular performance which is described by left ventricular (LV) pressure/volume relationship. If dominant functional abnormality in HFrEF is diminished LV contractility defined by a decrease in the slope of the end-systolic pressure-volume relationship (systolic elastance), the HFpEF exhibits increase in LV diastolic stiffness causing an upward and leftward shift of the diastolic pressure-volume relationship [3]. In some individuals this may occur only on exertion. Invasive evaluation of the filling pressures remains the gold standard of diagnosing HFpEF and currently is the only method which unequivocally proves or refutes its pathophysiology.

For years HF was diagnosed on the grounds of clinical findings known as the Framingham criteria which suffer from poor sensitivity [2]. In particular, well compensated patients with HFpEF who develop symptoms only by exertion may go unrecognized. Although invasive assessment may confirm increased diastolic filling pressures during exercise this method cannot be applied as widely as required for obvious reasons. Alternatively, echocardiography is widely utilized to discover LV diastolic dysfunction. Elevation in the E/e' indicating higher LV filling pressures as well as increased estimated systolic pulmonary artery pressure represents the most robust indicators of HFpEF [4]. TTE also uncovers other structural (LV hypertrophy, higher left atrial volume) and functional (RVFAC, TAPSE) abnormalities associated with HFpEF. Recently, speckle tracking echocardiography has become a promising tool which exhibits

Address for correspondence: Prof. Piotr Hoffman, Department of Congenital Heart Diseases, National Institute of Cardiology, ul. Alpejska 42, 04–628 Warszawa, Poland, tel: +48 22 343 44 00, e-mail: phoffman@ikard.pl

subtly diminished ventricular systolic function in a subclinical phase of the disease when EF remains normal. Most of TTE parameters are specific but not sensitive enough to rule out the absence of HFpEF. American Society of Echocardiography/ /European Association of Cardiovascular Imaging recommendations provide meticulous algorithms for studying and interpreting LV diastolic performance both in patients with reduced and preserved EF. Of utmost importance is ability of echocardiography to rule out secondary HFpEF due to valvular disease, pericarditis and other conditions requiring specific diagnostic and therapeutic strategies. Further, TTE enables noninvasive evaluation during exercise which may unmask diastolic dysfunction in case of normal parameters at rest [5].

Owing to the difficulties and doubts concerning the diagnosis of the HFpEF two comprehensive diagnostic scores integrating clinical and echocardiographic variables were recently proposed in order to appreciate the risk of HFpEF. For patients with unexplained dyspnea Reddy et al. [4] developed H_2FPEF composite score which assesses the probability of HFpEF. Importantly, HFpEF as established by H_2FPEF was verified by means of invasive hemodynamic exercise testing in every patient [4]. Utilization of the score enables the Bayesian approach in which only patients with intermediate pre-test probability are referred for a definitive test including exercise testing. A similar score was proposed as a consensus expert statement (HFA-PEFF) which, thus far, has not been verified by means of invasive tests [6]. The latter score adds a concentration of N-terminal-pro--B-type natriuretic peptide, more echocardiographic morphological and functional parameters as well as exercise echocardiography. An intermediate probability is an indication for subsequent hemodynamic exercise testing.

Despite diagnostic uncertainties, many symptomatic patients worldwide are diagnosed as having HFpEF and are subsequently treated. However, contrary to HFrEF, large-scale clinical trials did not provide firm clues concerning treatment despite testing many hypotheses, drugs from various classes and non-pharmacological strategies. Considering the variety of etiologies and pathophysiologies, it seems to be justified to categorize HFpEF patients into more homogeneous phenotypes which may lead to better characterization of the entire HFpEF cohort. Various features and parameters modifying such a phenotype include comorbidities, cardiac and pulmonary vascular function, hemodynamics, extracardiac structure, function and biomarkers [2]. Obokata et al. [7] proposed obese, ischemic, and cardiometabolic phenotypes as three major categories of HFpEF pointing to essential differences among them and their preferred therapeutic options. It is conceivable that one therapeutic strategy may turn out valuable only in a given well-defined HFpEF phenotype and not in others. However, there are still many more issues to be addressed with regard to pathophysiology, definition, diagnostic algorithms and therapies since HFpEF encompasses various hemodynamic and cellular mechanisms [8]. With respect to noninvasive assessment of HFpEF, diastolic stress echocardiography remains the only tool which is capable of recognizing patients with symptoms solely with exercise. Nonetheless, a lot of effort has to be made to refine and standardize its methodology. On the other hand, simplification of a diagnostic approach should be sought for such as combination of simple TTE parameters and biomarkers as well as selection of simple highly reproducible parameters used for community based epidemiological studies and screening performed in populations at risk [9, 10]. Another important diagnostic issue concerns the potential role for other noninvasive imaging modalities in diagnosing HFpEF. From a therapeutic standpoint the question remains unanswered — which pathophysiological pathways should be modified in order to slow down or to stop the disease. Is there one leading pathway eventually resulting in HFpEF, or is it a mixture of interacting mechanisms?

Heart failure with preserved ejection fraction of the left ventricle became a dominant form of HF worldwide and is associated with high morbidity and mortality. Despite enormous scientific effort there are still many clinical doubts regarding this clinical syndrome. Therefore, one has to appreciate an excellent review on this topic prepared by Club 30 of the Polish Cardiac Society published in current issue of "Cardiology Journal" [11]. Indeed, a guide to the guidelines is still needed while dealing with HFpEF and its dilemmas.

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