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Opinion

Being in Two Minds—The Challenge of Heart Failure with Preserved Ejection Fraction Diagnosis with a Single Biomarker

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Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous disorder developing from multiple etiologies with overlapping pathophysiological mechanisms (Fig. 1). HFpEF accounts for a substantial proportion of patients diagnosed with HF, and according to latest data, the lifetime risk for HFpEF at any given index age is approximately 1 in 10 for both men and women (1, 2). Tackling HFpEF has become the focus of cardiovascular research since the 5-year mortality rate after HFpEF hospitalization remains unacceptably high (between 50%–75%), and existing therapies are generally ineffective in treating this disorder (3). Noncardiac comorbidities are thought to play a more prominent role in HFpEF pathogenesis than cardiac comorbidities, and a contemporary view is that HFpEF is a multiorgan disorder leading to the disruption of homeostasis of the cardiovascular system (4).

Currently, there are 2 HFpEF diagnostic algorithms in use. The Heart Failure Association (HFA)-PEFF algorithm developed by Pieske and colleagues on behalf of the European Society of Cardiology (5) uses a stepwise approach to diagnosing HFpEF, and focuses more on echocardiographic examination. HFpEF is considered when an individual with signs and symptoms of HF, and with typical risk factors/comorbidities, has *cardiac* structural or functional abnormalities in the setting of a normal left ventricular ejection fraction >50% during echocardiographic examination. Furthermore, the 2016 European Society of Cardiology guidelines on diagnosis and management of HF state that increased natriuretic peptides must be present as a part of the definition of HFpEF (6). By contrast, the H_2FPEF score developed by Reddy and colleagues (7) does not include natriuretic peptide testing, and places more emphasis on non-echocardiographic parameters. Using this approach, an obese, elderly individual (>60 years) with paroxysmal or persistent atrial fibrillation, but with normal echocardiographic parameters, would already have a 75%–80% probability of HFpEF. Although both these approaches essentially identify individuals with HFpEF from those having noncardiac dyspnea, they do not provide any information on underlying pathophysiological mechanisms leading to this heterogeneous syndrome. This is clearly reflected in the limited therapeutic success once a diagnosis of HFpEF is established. A pathophysiological basis for identification and classification of HFpEF is therefore warranted.

Circulating biomarkers reflect cardiac as well as noncardiac abnormalities, and their measurements often provide insights into pathophysiological processes associated with HF (Fig. 1). Nevertheless, the clinical uptake of biomarkers for diagnosing HFpEF has generally been poor, with only cardiac natriuretic peptides (NPs) having emerged as clinically relevant (6). Specifically, higher NP concentrations favor a diagnosis of HFpEF, whereas low NP concentrations rule out acute decompensated HFpEF. The value of NPs in ruling out HFpEF in the non-acute setting, however, remains controversial (5). For instance, the performance of NPs to diagnose HFpEF in the outpatient clinic is expected to be lower compared with an analogous setting in HF with reduced ejection fraction. This is because cardiac wall stress, a key trigger for NP release, may not always be increased in individuals with subclinical HFpEF under normal resting conditions due to prevalence of concentric left ventricular (LV) hypertrophy. Interestingly, even among patients with proven HFpEF (i.e., increased LV filling pressures during invasive hemodynamic measurements) around 20%–30% have NPs below the recommended diagnostic thresholds (5). Furthermore, obesity is a common comorbidity in patients with HFpEF, and obese individuals, despite having increased LV end diastolic pressures, present with substantially lower NP concentrations compared with non-obese counterparts (8). Therefore, the concept that *"low NP levels equate with low cardiovascular risk"* needs to be reconsidered in HFpEF, and the latest consensus is that low NP concentrations do not exclude a diagnosis of HFpEF in the non-acute setting (5).

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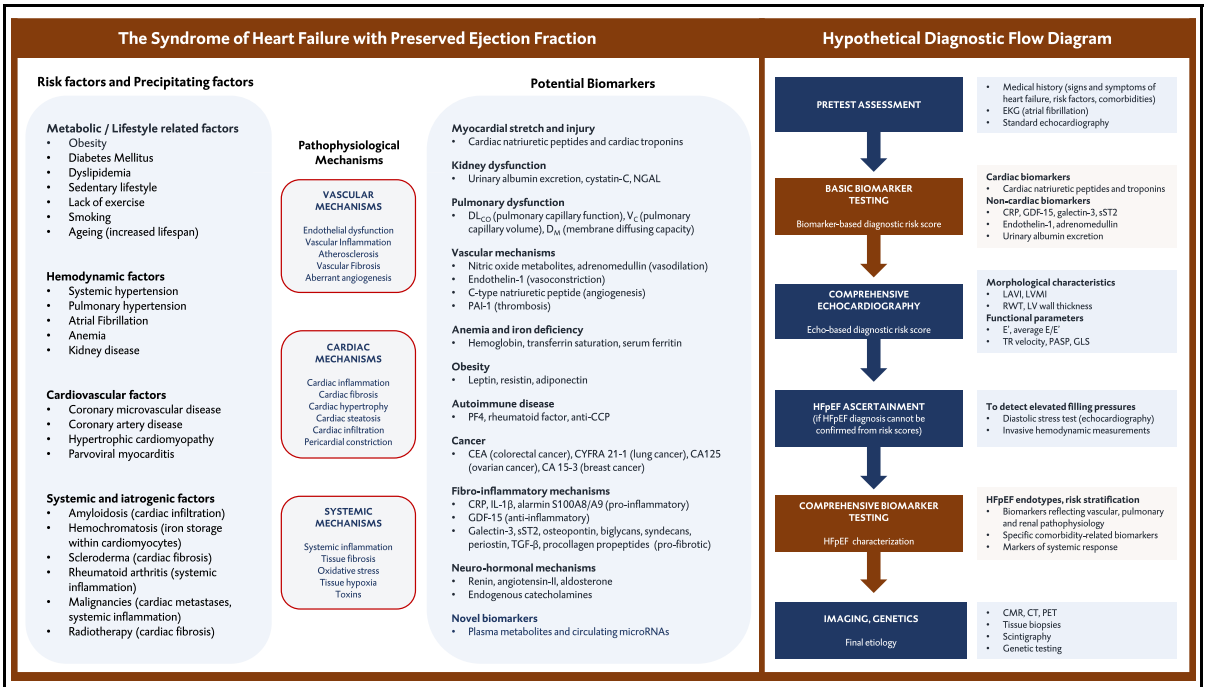

Fig. 1. A multi-marker approach to diagnose and characterize HFpEF.
Abbreviations: NGAL, neutrophil gelatinase-associated lipocalin; DLCO, diffusing capacity for carbon monoxide; PAI-1, plasminogen activator inhibitor-1; PF4, platelet factor 4; anti-CCP, anti-cyclic citrullinated peptide; CEA, carcinoembryonic antigen; CYFRA 21-1, cytokeratin 19 fragment; CA125, cancer antigen 125; CA 15-3, carcinoma antigen 15-3; CRP, C-reactive protein; IL-1β, interleukin-1β; GDF-15, growth differentiation factor-15; sST2, soluble interleukin-1 receptor-like-1; TGF-β, transforming growth factor-β; EKG, electrocardiogram; LAVI, left atrial volume index; LVMI, left ventricular mass index; RWT, relative wall thickness; LV, left ventricle; TR, tricuspid regurgitation; PASP, pulmonary artery systolic pressure; GLS, global longitudinal strain; CMR, cardiac magnetic resonance; CT, computed tomography; PET, positron emission tomography.

Certainly, there is a clinical need to look for biomarkers offering additional information above and beyond NPs in the diagnostic work-up of HFpEF. Cardiac troponins (cTns) indicate myocardial injury due to any cause (e.g., ischemia, inflammation, infiltration, cardiotoxicity), and are promising biomarkers in HF management. They strongly predict HFpEF in the general population, and even minor increases in plasma cTn concentrations signify cardiovascular risk (9). There is a strong rationale to include cTns in HFpEF diagnostic protocols, particularly in obese individuals. This is because obesity is associated with higher circulating cTn concentrations (10), and theoretically obese individuals with HFpEF would have a higher probability of having increased cTn concentrations—even if NP concentrations would fall below the diagnostic threshold. We, therefore, propose that cTns should be included along with NPs in future HFpEF diagnostic algorithms.

Although blood tests for NPs and cTns would be a good starting point in diagnosing HFpEF, cardiac biomarkers provide information primarily on the *'reactive cardiac component'* of HFpEF phenotype. A comprehensive echocardiographic examination, which would be the next (and a more decisive) step in the diagnostic protocol for HFpEF (5), also provides more detailed *'cardiac-specific'* information (i.e., evidence of diastolic dysfunction or increased LV filling pressures at rest or with exercise). We would like to point out that a cardiocentric approach to identifying individuals with HFpEF has two major drawbacks. First, it does not provide any information on the degree of systemic inflammation—which is thought to be the driving factor (i.e., causative factor) for multiorgan dysfunction, including LV diastolic dysfunction (11). For instance, systemic and organ-specific inflammation due to adiposity may be better reflected by inflammatory biomarkers rather than cardiac-specific biomarkers during early phases of HFpEF progression. Second, it overlooks noncardiac pathophysiology—particularly vascular, pulmonary, and renal dysfunction. Besides sustaining and perpetuating preexisting systemic inflammation, these

systemic perturbations also contribute to cardiac dysfunction and to the overall symptomatic burden through multiple mechanisms (4). In this regard, several noncardiac biomarkers, which are currently not considered, may have a more prominent role in (early) diagnosis and characterization of HFpEF (12).

Keeping these aspects in mind, we propose a hypothetical algorithm that also integrates multimarker testing into the existing diagnostic protocol for HFpEF (Fig. 1). For practical purposes, a *"core biomarker panel"* including biomarkers reflecting key pathophysiologic domains could first be measured in individuals with a clinical suspicion of HFpEF, before performing a comprehensive echocardiographic examination. For instance, C-reactive protein and growth differentiation factor can serve as markers of systemic inflammation; galectin-3 concentrations would indicate ongoing tissue fibrosis (e.g., pulmonary, hepatic, renal, and cardiac fibrosis); soluble interleukin-1 receptor-like 1, adrenomedullin, and endothelin-1 concentrations may aid in identifying pulmonary/tissue congestion and endothelial dysfunction; increased urinary albumin excretion would indicate renal dysfunction; and increased NPs and cTns indicate abnormal cardiac stretch and myocardial injury, respectively. The above-mentioned biomarkers can easily be integrated into clinical care since they have been extensively studied, can be measured using standardized assays, and are relatively inexpensive. However, specific studies examining the value of including these biomarkers in HFpEF diagnosis need to be conducted (e.g., derivation and validation of a multimarker HFpEF probability score), and it would be particularly important to establish population-specific predictive/diagnostic cutpoints for individual biomarkers.

As a further step, a more comprehensive multimarker approach may be used to characterize specific HFpEF phenotypes/endotypes for optimizing therapy, and to stratify risk (13, 14). This would include i) *organ-specific biomarkers* focusing on the vasculature (C-type natriuretic peptide, nitric oxide metabolites, plasminogen activator inhibitor-1, fibrinogen), lungs (pulmonary diffusion, pulmonary capillary volume, membrane diffusing capacity), and kidneys (cystatin-C, neutrophil gelatinase-associated lipocalin, urinary albumin excretion), ii) *comorbidity-specific biomarkers*, for example, anemia (hemoglobin), iron deficiency (serum ferritin, transferrin saturation), obesity (resistin, leptin, adiponectin), autoimmune diseases (platelet factor 4, anti-scl-70 antibodies, rheumatoid factor, anticyclic citrullinated peptide), and cancer (carcinoembryonic antigen, cytokeratin fragments, cancer antigen 125, carcinogen antigen 15-3, carbohydrate antigen 19-9, human epididymis protein 4), iii) *markers of systemic response* (i.e., fibroinflammatory and neurohormonal mechanisms). A particularly interesting group of markers are alarmins, which may not only serve as biomarkers but also as therapeutic targets in HFpEF, and iv) *novel markers* including plasma metabolites and circulating microRNAs. However, for the sake of efficiency in resource allocation, we suggest that a comprehensive multimarker approach should be considered only after a definitive diagnosis of HFpEF has been reached based on advanced echocardiographic evaluation or invasive testing (Fig. 1).

In summary, we believe that a pathophysiological basis for identification and classification of HFpEF based on a multimarker strategy is urgently needed. From a practical point of view, a cardiac centered approach to HFpEF diagnosis using NPs and cTns would be a good starting point. However, from a holistic and futuristic point of view—there are several biomarkers that provide information on *noncardiac components* of the HFpEF syndrome. Although, at present, these biomarkers do not directly aid in the diagnosis of HFpEF, they would still be useful in classification of HFpEF phenotypes/endotypes—which may "guide" patient selection in HFpEF trials. It is also likely that specific individual marker characterization of HFpEF cases will become increasingly clinically relevant for monitoring of treatment efficacy, as pathway specific therapies such as anti-inflammatory approaches (exemplified by Canakinumab in CANTOS trial) become further tested and established in cardiovascular settings including HFpEF. The fact that some of the noncardiac biomarkers, including markers of fibrosis (15), may also serve as biotargets in the treatment of HFpEF should also be carefully considered.

Supplemental Material

Supplemental material with additional references to support these arguments is available at *Clinical Chemistry* online.

Nonstandard Abbreviations: cTNs, cardiac troponins; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle; NP, natriuretic peptides.

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