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EDITORIAL

Do Existing Definitions Identify Subgroup Phenotypes or Reflect the Natural History of Heart Failure With Preserved Ejection Fraction?

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Over the last decennium, the definition of heart failure with preserved ejection fraction (HFpEF) has remained problematic, with lack of consensus between and among societal organizations and large outcome trials. In this issue of *Circulation*, the challenge of a satisfactory HFpEF definition is highlighted by the application of 7 existing HFpEF definitions to a single-center study sample of patients presenting with dyspnea (New York Heart Association class II–IV) and preserved left ventricular (LV) ejection fraction (>50%).[1] The 7 existing definitions included 3 societal HFpEF definitions based on expert consensus (American College of Cardiology/American Heart Association [ACC/AHA] 2013, European Society of Cardiology 2016, and Heart Failure Society of America 2010) and 4 sets of HFpEF trial entry criteria geared mostly toward maximizing outcome events (I-PRESERVE [Irbesartan in Heart Failure With Preserved Ejection Fraction Study], RELAX [Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure With Preserved Ejection Fraction], TOPCAT [Treatment of Preserved Cardiac function in Heart Failure With Aldosterone Antagonist], PARAGON [Prospective Comparison of ARNI With ARB Global Outcome in HF With Preserved Ejection Fraction]). Given the uncertainties and controversies on how to define HFpEF, the authors also included a pathophysiological approach with HFpEF defined by elevated LV filling pressures during exercise. The authors defined HFpEF as elevated pulmonary artery wedge pressure at rest or during exercise, thus complementing the 7 existing HFpEF definitions with thorough hemodynamic data. The authors are to be commended for their efforts.

CLINICAL, ECHOCARDIOGRAPHIC, AND LABORATORY CHARACTERISTICS: UNEQUAL DISEASE SEVERITY OR DISTINCT PHENOTYPES?

Among the clinical features reported by Ho et al,[1] body mass index (BMI) is comparable in all 7 populations at ≈30 kg/m^2, the cutoff value for obesity. Despite comparable BMI, high-sensitivity C-reactive protein varied considerably from 1.9 to 4.8 mg/L in the ACC/AHA and TOPCAT populations, respectively. This finding illustrates evolution to metabolically unhealthy obesity to be multifactorial and to depend not only on BMI but also on overall comorbidity profile.[2] In this respect, abdominal obesity would have been a more appropriate measure of metabolic risk than BMI.[3]

Among the echocardiographic variables reported by Ho et al, the constancy of LV ejection fraction (LVEF) is remarkable in all 7 HFpEF populations (64%–66%). The comparable LVEF in the populations argues against transition over time from HFpEF to other heart failure phenotypes. Minimal transition (1.6%) from HFpEF to heart failure

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with reduced ejection fraction was indeed observed in a recent prospective study.[4] Higher transition frequencies have been reported, but these studies were hampered by short observation periods, retrospective analysis, high prevalence of coronary artery disease, or low HFpEF cut-off value (LVEF, 40%).[5]

Despite the constancy of some variables across the various HFpEF definitions, other characteristics suggest that the 7 definitions used to identify populations with different disease severities do not correspond to distinct disease phenotypes,[6] as depicted in the Figure (B). The prevalence of left atrial enlargement (LAE) and prior atrial fibrillation (AF) varied widely in the 7 HFpEF populations, with the ACC/AHA population consistently having the lowest value for both variables and the TOPCAT population having the second highest value for these variables after I-PRESERVE for LAE and the Heart Failure Society of America for AF. LAE is closely related to the presence of AF. Indeed, a high frequency of prior AF was observed in the 3 HFpEF populations with the highest prevalence of LAE and reached staggering proportions of 51% in the Heart Failure Society of America report, 50% in TOPCAT, and 45% in I-PRESERVE. These numbers confirm a recent study reporting that in patients with AF and dyspnea, the odds ratio for having HFpEF is 38.6 for permanent AF and 7.9 for paroxysmal AF.[7] In addition, NT-proBNP (N-terminal pro-B-type natriuretic peptide) plasma levels were lower in ACC/AHA and higher in the 3 trial populations with the poorest outcome (TOPCAT, PARAGON, I-PRESERVE), providing an important clue to the mechanism linking diastolic LV stiffness to outcome, namely myocardial fibrosis. In the MESA study (Multiethnic Study on Atherosclerosis), a close relationship was observed in a community-based population between log NT-proBNP and myocardial fibrosis measured by T1 mapping.[8] A similar relationship, which correlated with outcome, was observed in clinical HFpEF and in at-risk preclinical HFpEF.[9] Taken together, the distinct values of LAE, AF, and NT-proBNP in the 7 HFpEF populations support worsening of diastolic LV stiffness and increasing LV endomyocardial fibrosis to determine the natural history of HFpEF. NT-proBNP reflects the central cardiac nature of HFpEF even in the presence of multimorbidity, being tightly linked to diastolic LV stiffness and myocardial fibrosis and to right ventricular dysfunction (Figure [B]). This latter aspect is not accounted for in the article by Ho et al but is probably also relevant for the natural history of HFpEF.[10]

CARDIOPULMONARY EXERCISE TEST AND REST/EXERCISE HEMODYNAMICS: DO THEY PROVIDE ADDITIONAL INFORMATION?

Despite invasive hemodynamics being considered the pathophysiological gold standard for the diagnosis of HFpEF (Figure [B]), in daily clinical practice, procurement of invasive hemodynamic data remains cumbersome. It is time consuming, not universally available, requires a special expertise, and has unknown reproducibility, all aspects that are difficult to reconcile with the epidemiology of a highly prevalent disease. Moreover, the upper limit of normal for left heart filling pressures is not only flow (cardiac output) dependent but also related to age, sex, BMI, and body position (supine in the catheterization laboratory versus upright in the cardiorespiratory laboratory).[11] Finally, the prevalence of abnormal pulmonary artery wedge pressure at rest or during exercise was roughly 75% to 80% in most of the definitions, with the notable exception of the ACC/AHA criteria (only ≈55% of patients with abnormal pulmonary artery wedge pressure at rest or during exercise).

Despite LV stiffness being an important determinant of the natural history of HFpEF, diastolic stiffness appears to be unrelated to the pulmonary artery wedge pressure value at rest or during peak exercise because these remained nearly equivalent across the different HFpEF definitions. This again challenges the utility of hemodynamic phenotyping for prognostic assessment in that several noninvasive prognostic markers varied widely in the 7 HFpEF populations (Figure [A]), with the ACC/AHA definition and HFpEF defined by elevated LV filling pressures during exercise consistently presenting on average low-risk prognostic markers.

Oxygen consumption at peak exercise, as well as its determinant, cardiac output reserve, progressively decreased from the ACC/AHA definition to I-PRESERVE and PARAGON. Ventilatory inefficiency, that is, the slope of the relationship between minute ventilation and carbon dioxide production, which is tightly correlated with hemodynamic disturbances[12] but also with neurohumoral imbalance, presented a similar but inverse relationship, being lower in ACC/AHA and higher in I-PRESERVE and PARAGON.

HETEROGENEITY OR NATURAL HISTORY

A remarkable finding in the study by Ho et al was the close relationship between size and outcome of the 7 HFpEF populations. The close tracking of sample size and outcome suggested that existing definitions identify patients at different stages of the natural history of HFpEF. The further on the timeline an HFpEF definition recruits patients, the smaller the patient population will be, and the more likely it is that patients will have unfavorable outcome events. This is illustrated in the Figure (C), which shows a schematic of an HFpEF survival curve using data from a recent prospective study.[4] This study followed up patients with HFpEF over a 1-year period and observed minimal mortality initially that in-

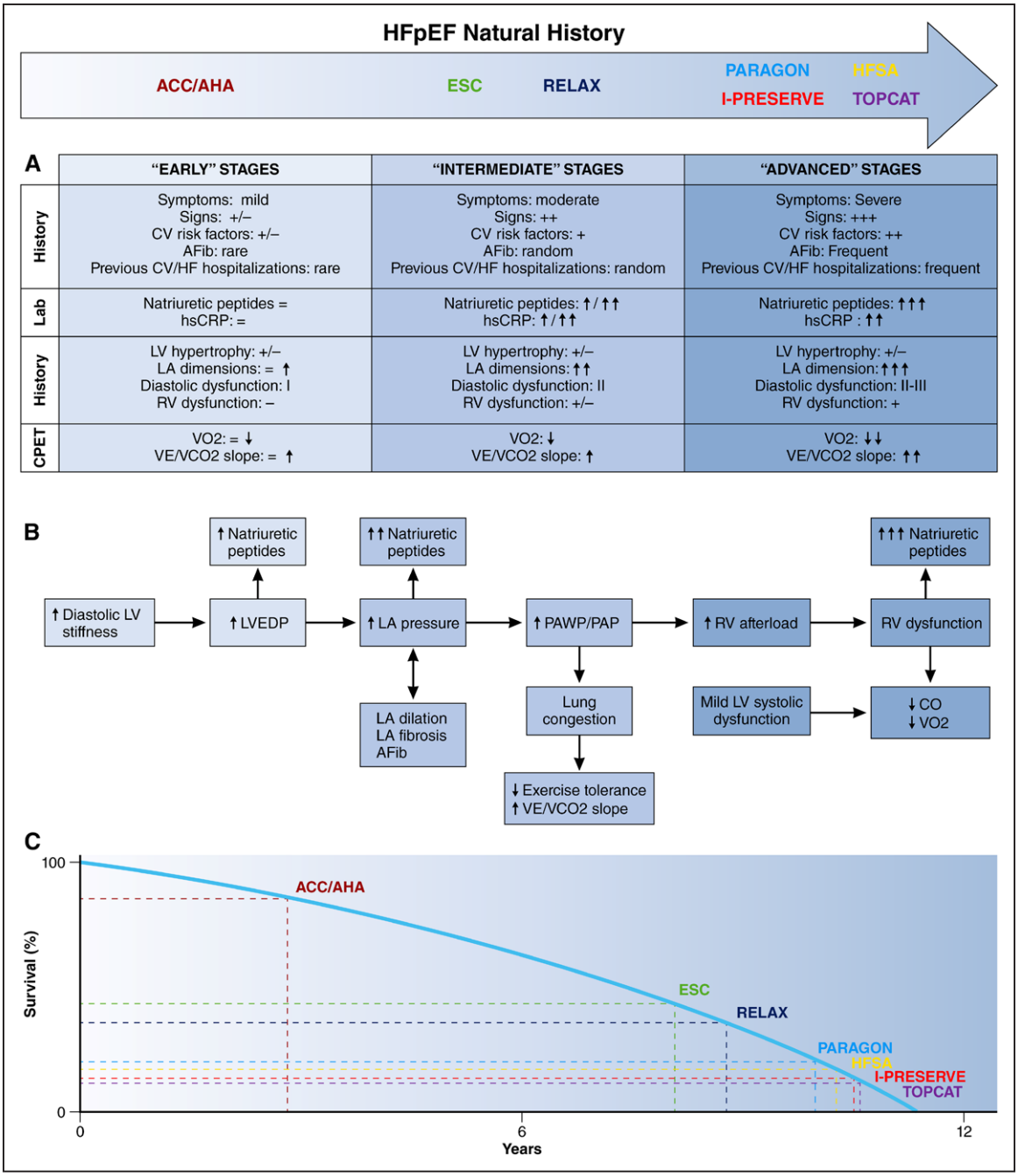

Figure. Natural history of heart failure with preserved ejection fraction (HFpEF).
A, Successive stages of disease severity can be described on clinical basis according to a noninvasive multiparametric assessment (clinical history, blood tests, echocardiography, cardiopulmonary exercise test [CPET]). **B**, Pivotal role of diastolic stiffness and associated hemodynamic disturbances in initiating and driving the natural history of the disease. **C**, Schematic survival curve of HFpEF according to 7 existing definitions of the disease. Mortality rates equal the slope of the tangents to the survival curve and decline from TOPCAT (Treatment of Preserved Cardiac function in Heart Failure With Aldosterone Antagonist) to American College of Cardiology/American Heart Association (ACC/AHA). AFib indicates atrial fibrillation; CO, cardiac output; CV, cardiovascular; ESC, European Society of Cardiology; HF, heart failure; HFSA, Heart Failure Society of America; hsCRP, high-sensitivity C reactive protein; I-PRESERVE, Irbesartan in Heart Failure With Preserved Ejection Fraction Study; LA, left atrial; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; PAP, pulmonary artery pressure; PARAGON, Prospective Comparison of ARNI With ARB Global Outcome in HF With Preserved Ejection Fraction; PAWP, pulmonary artery wedge pressure; RELAX, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure With Preserved Ejection Fraction; RV, right ventricle; V_E/V_{CO_2}, minute ventilation over carbon dioxide production; and V_{O_2}, oxygen consumption.

creased afterward and reached 89% after 11 years. The study also revealed phenotypic persistence in HFpEF, with 89% of patients with HFpEF retaining the HFpEF phenotype (LVEF >50%). In the Figure (C), the 7 HFpEF populations were ranked along the HFpEF survival curve in accordance with sample size. Mortality rates for the 7 HFpEF populations equal the slope of the tangents to the survival curve and decline from TOPCAT to ACC/

AHA. This decline corresponds to the death incidence rates of the 7 HFpEF populations reported by Ho et al (Table 4), with TOPCAT having the highest (6.56 per 1000 person-years), ACC/AHA the lowest (0.46 per 1000 person-years), and the 5 other HFpEF populations intermediate values. From the Figure (C), it becomes evident that the 7 populations assess HFpEF at different time points along the HFpEF timeline, with ACC/AHA at the earliest and TOPCAT at the most advanced time. This is again confirmed by Ho et al (Table 2), who reported a preceding heart failure hospital admission in 8% and 71% of the ACC/AHA and TOPCAT populations, respectively, and a preceding cardiovascular hospital admission in 36% and 96% of the ACC/AHA and TOPCAT populations, respectively. The more advanced position along the HFpEF timeline of TOPCAT, I-PRESERVE, and PARAGON compared with RELAX results from trial design, with the first 3 trials favoring outcome events such as death or heart failure hospitalization and RELAX looking at exercise tolerance.

In conclusion, existing definitions of HFpEF using a multiparametric assessment correspond to successive stages along the HFpEF timeline. The shared and distinctive characteristics of the different populations resulting from these definitions provide valuable insight into the natural history of HFpEF. This is especially relevant when solving the jigsaw puzzle of HFpEF disease severity, which applies to risk assessment in daily practice and to the design of future clinical trials.

ARTICLE INFORMATION

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Disclosures

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