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STATE-OF-THE-ART REVIEW

Murine Models of Heart Failure With Preserved Ejection Fraction

A "Fishing Expedition"

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SUMMARY

Heart failure with preserved ejection fraction (HFpEF) is characterized by signs and symptoms of heart failure in the presence of a normal left ventricular ejection fraction. Despite accounting for up to 50% of all clinical presentations of heart failure, the mechanisms implicated in HFpEF are poorly understood, thus precluding effective therapy. The pathophysiological heterogeneity in the HFpEF phenotype also contributes to this disease and likely to the absence of evidence-based therapies. Limited access to human samples and imperfect animal models that completely recapitulate the human HFpEF phenotype have impeded our understanding of the mechanistic underpinnings that exist in this disease. Aging and comorbidities such as atrial fibrillation, hypertension, diabetes and obesity, pulmonary hypertension, and renal dysfunction are highly associated with HFpEF, yet the relationship and contribution between them remains ill-defined. This review discusses some of the distinctive clinical features of HFpEF in association with these comorbidities and highlights the advantages and disadvantage of commonly used murine models used to study the HFpEF phenotype. (J Am Coll Cardiol Basic Trans Science 2017;2:770–89) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

UNDERSTANDING HFpEF IN HUMANS: THE REALITY OF HFpEF TODAY, PATHOPHYSIOLOGY, AND DILEMMAS

HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFpEF): THE CLINICAL ENTITY. Heart failure (HF) is characterized by dyspnea at low-normal levels of activity, and fluid and sodium retention. HF involves impaired heart function, and the percent of blood volume ejected with each beat or ejection fraction (EF), has traditionally served as an indicator of pump dysfunction (1). Decades of extensive basic and clinical research has focused on HF that involves impaired left ventricular (LV) systolic function (systolic HF), also now known as HF with reduced ejection fraction (HFrEF). However, nearly one-half of the patients with HF symptoms have a normal/preserved LVEF. Generally, an LVEF ≥50% is used as a threshold for characterizing as preserved LVEF (2,3). At present, evidence from clinical studies supports the dichotomized distinction that HFpEF and HFrEF are fundamentally and diametrically different with regard to pathophysiology and therapeutic response (4,5).

HFpEF VERSUS HFrEF: WHEN NOT ONLY EF MATTERS. HFpEF and HFrEF are fundamentally different

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beyond segregating and categorizing HF patients into more homogenous groups simply by LVEF. However, this compartmentalization not only allows HF patients with comparable hemodynamics, pathophysiologies, and unique patterns of cardiac and cellular remodeling to be clustered together but also identifies treatment responses in those specific groups (5). HFrEF can be regarded as a cardiac-centric syndrome driven by myocardial cell loss and dysfunction with the heart being subjected to higher wall stress as shown by elevated levels of brain natriuretic peptide (BNP). HFpEF, alternatively, is a systemic syndrome characterized by accumulated risk factors and comorbidities and a noncompliant and stiff heart that is exposed to lower wall stress, reflected in lower BNP levels that, although elevated, are not as high as in HFrEF (6–8). Therefore, it appears that HFrEF begins from the heart and leads to peripheral changes, whereas HFpEF starts in the periphery and culminates at the heart (4,9).

SPEAKING THE SAME LANGUAGE: THE CHALLENGE FOR TRANSLATIONAL HFpEF RESEARCHERS. Semantics related to HFpEF are a formidable task for translational researchers. Defining various terms, and therefore collecting relevant data, remains a challenge both clinically and in the preclinical area. One of the main sources of confusion lies in the distinction between diastolic dysfunction and HFpEF. These 2 terms have been used interchangeably in both the preclinical and the clinical literature. Diastolic dysfunction was widely and incorrectly touted to be the sine qua non for HFpEF but by itself is not enough to establish it. For example, normal subjects may have diastolic dysfunction, yet have no clinical features of HFpEF (10,11). Additionally, diastolic dysfunction is a common occurrence in HFrEF (12). Also, use of strain imaging with echocardiography shows subtle abnormalities in systolic function in some HFpEF populations despite preserved global LVEF (13,14). According to the 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guideline for the management of HF (3), neither LV hypertrophy nor diastolic dysfunction is required for diagnosis of HFpEF, whereas in the European HF guidelines relevant structural and/or diastolic dysfunction is a prerequisite (2). HFpEF is also a term, in the sphere of scientific literature, that is virtually nonexistent, given that the U.S. National Library of Medicine's system of medical subject headings (MeSH) still uses the outmoded terms "HF, systolic" and "HF, diastolic" to index publications. Hence, we prefer the terms HFpEF and HFrEF as they are mutually exclusive, whereas diastolic dysfunction may be present in either systolic HF (HFrEF) or diastolic HF (HFpEF). However, we acknowledge that until universally agreed definitions are adopted, translational research in the field may be hindered.

MODELING HFpEF IN THE LAB: DIFFERENT PHENOTYPES FOR A COMPLEX DISEASE

Animal models, as opposed to isolated organ and/or cell preparations, allow examination of physiological effects of cardiac function (15). However, the search for an animal model that resembles the human HFpEF phenotype is akin to "a fishing expedition" and the use and comprehensive characterization of an HFpEF animal model that recapitulates human HFpEF has hampered advancing the understanding of HFpEF. The limited number of truly authentic HFpEF animal models poses a major limitation when investigating new insights into its pathophysiology and in the development of new therapies for HFpEF (16,17). Moreover, if defining HFpEF in humans evokes controversy (18), it appears that animal models likely follow suit. Animals, unlike humans, cannot report symptoms. LVEF, diastolic dysfunction, and heart structure can be measured directly, but signs must be inferred from animal behavior. Additionally, separate from LVEF, a single measure of systolic function, there are other measures of LV systolic function such as myocardial velocities, strain, and strain rate (measures of myocardial contractility), which may be impaired in HFpEF (13,14,19). HFpEF is a complex syndrome where etiologic and pathophysiological paths, by which individual patients develop the disease, are variable (20). Specific comorbidities, as well as aging, are highly associated with the HFpEF phenotype. Given this heterogeneity, it is likely that any animal model only resembles a certain proportion of HFpEF patients. An "ideal" animal model should meet various requirements to mimic human disease, including cardiac, hemodynamic, neurohormonal, and peripheral aberrations commonly seen in HFpEF patients (21). However, similar to humans, a "one-size-fits-all" strategy is unlikely to work in animal models. That being said, the relative importance of comorbidities on the initiation, development, and treatment of HFpEF is unknown (22). A more tailored approach focusing on specific phenotypes is needed in the laboratory to understand the complex interactions underlying this disease. HFpEF in humans

ABBREVIATIONS AND ACRONYMS

AAC = ascending aortic constriction

BNP = brain natriuretic peptide

DOCA = deoxycorticosterone acetate

EF = ejection fraction

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LV = left ventricular

NaCl = sodium chloride

SAMP = spontaneous senescence prone

SAMR = spontaneous senescence resistant

SHR = spontaneously hypertensive rat

TAC = transverse aortic constriction

ZSF1 = Zucker fatty and spontaneously hypertensive heart failure rat