JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 75, NO. 11, 2020

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

A Biomarker Approach to Understanding HFpEF*

Dalane W. Kitzman, MD,[a] Bharathi Upadhya, MD,[a] G. Michael Felker, MD[b]

Heart failure with preserved ejection fraction (HFpEF) is the most common form of heart failure (HF) in the community; its prevalence is increasing, and prognosis has not improved and may be worsening. After HF hospitalization, 5-year survival of HFpEF is a dismal 35%, worse than many cancers. Despite the strong public health importance of HFpEF, our understanding of the pathophysiology of HFpEF is incomplete, and drug development has proved immensely challenging. A broad array of interventions proven to be resoundingly successful in HF with reduced ejection fraction have now been formally tested in numerous randomized controlled clinical trials targeting neurohormonal inhibition, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-adrenergic inhibitors, and mineralocorticoid receptor antagonists; however, none have been shown to be clearly effective in reducing mortality and other key clinical outcomes in HFpEF. Those disappointing findings suggest a need for a reassessment of our presumptions regarding the pathophysiology of HFpEF and potential therapeutic targets.

A key emerging concept is that HFpEF is actually a systemic progressive disorder, influenced by aging, driven partly by multiple key comorbidities, especially obesity, that induce a systemic proinflammatory state leading to myocardial remodeling and dysfunction through incompletely defined mechanisms (1). Adiposity-induced inflammation has wide-ranging adverse effects, including endothelial dysfunction, capillary rarefaction, and mitochondrial dysfunction in both the cardiac and systemic beds (2). The concept of HFpEF as a systemic syndrome is supported by multiple lines of evidence, including: 1) high prevalence of multiple comorbidities and their surprisingly strong impact on outcomes; 2) failure of cardiac factors alone to fully explain HFpEF symptoms and outcomes (3); 3) strong contributions of extracardiac factors, including vascular, kidney, skeletal muscle, and adipose tissue; and 4) typical cardiac features of HFpEF can be produced through perfusion of young hearts with blood from older animals, and that such features can be reserved in old heart and skeletal muscle by perfusion with blood from young animals (4). All of this evidence implies a metabolic and systemic origin of HFpEF.

If HFpEF is indeed a syndrome that is initiated, promoted, and progressed via factors circulating in systemic blood, it follows that analysis of blood-based factors has the potential to provide badly needed insights into the pathogenesis and pathophysiology of HFpEF. Discovery of novel biomarkers may allow for: more precise diagnosis and prevention by identifying individuals who are at highest risk; improved prognosis; identification of novel surrogate endpoints; selection of therapeutic targets; and development and evaluation of new therapies (5).

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the [a]Sections on Cardiovascular Medicine and Geriatrics, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina; and the [b]Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina. This work is supported in part by National Institutes of Health grants R01AG18915, R01AG045551, U24AG05964, UL1TR001420, W81XWH-15-1-0574, R01 HL122393, P30AG12232; and the Kermit Glenn Phillips II Chair in Cardiovascular Medicine. Dr. Kitzman has served as a consultant for AstraZeneca, Bayer, Novartis, Merck, Pfizer, Boehringer Ingelheim, AbbVie, DCRI, and Corvia; has received grant support from AstraZeneca, Bayer, and Novartis; and has stock in Gilead. Dr. Upadhya has received grant support from Corvia. Dr. Felker has received grants from the National Heart, Lung, and Blood Institute, American Heart Association, Amgen, Merck, Cytokinetics, and Roche Diagnostics; and has served as a consultant to Novartis, Amgen, Bristol-Myers Squibb, Cytokinetics, Medtronic, Cardionomic, Relypsa, V-Wave, Myokardia, Innolife, EBR Systems, Arena, Abbott, Sphingotec, Roche Diagnostics, Alnylam, LivaNova, Windtree Therapeutics, Rocket Pharma, and SC Pharma.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2020.01.020

In this issue of the *Journal*, Chirinos et al. (6) sought to exploit this opportunity to advance our understanding of HFpEF using an elegant and sophisticated approach. The investigators examined a

SEE PAGE 1281

large number of reasonable candidate biomarkers, employed machine learning to interrogate the data, and evaluated a validation cohort. The investigators measured 49 pre-selected soluble proteins with multiple biological roles using a multiplex assay in a subset of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial) participants (n = 379) to derive clusters of soluble proteins to potentially explain mechanisms of action of HFpEF. Next, the investigators identified biomarkers predicted the combined endpoint of all-cause death and HF-related hospitalization using advanced statistical modeling to develop a multimarker predictive model. This work produced multiple valuable findings. Two large and tightly related, dominant biomarker clusters were identified, which included biomarkers of fibrosis/tissue remodeling, inflammation, renal injury/dysfunction, and fibrosis. Multiple biomarkers predicted incident death and HF hospitalization. A machine-learning derived model using a combination of biomarkers was strongly predictive of the risk of death and HF-hospitalization (hazard ratio [HR]: 2.85; 95% confidence interval [CI]: 2.03 to 4.02; $p < 0.0001$) and markedly improved the risk prediction when added to the MAGGIC (Meta-Analysis Global Group in Chronic HF) risk score. The predictive model was then validated in the HFpEF portion of the Penn Heart Failure Study, and they found similar results. Altogether, the authors present a compelling case that unbiased biomarker analysis has the promise of identifying fundamental biological signals that can reflect both clinical and subclinical pathophysiology with potential implications for early diagnosis and therapy.

Previous studies using multiplex analyses of soluble proteins representing potential mechanistic domains combined with network analysis, which also identified biomarker profiles that were relatively specific for HFpEF, were generally related to inflammation and extracellular matrix remodeling. Although the clustering is interesting, the present data would be even more informative if there were a comparison group of age-/sex-matched subjects without HF. In addition, the present study focused only on HF hospitalizations plus all-cause mortality. However, in community-based studies, only about 17% of rehospitalizations after an initial hospitalization for acute HFpEF are for HF, and the majority are for noncardiac causes (7). These non-HF hospitalizations produce a heavy burden for patients and increase health care costs. Thus, future work in this area should also examine all-cause hospitalizations, because that better assesses the overall patient experience in this systemic disorder.

The present study evaluating potential novel biomarkers builds on the relatively sparse published data regarding biomarkers and their utility in HFpEF. Increased natriuretic peptide levels are strongly associated with increased mortality in HFpEF; however, in TOPCAT, there was a conceptually paradoxical inverse relationship between natriuretic peptide levels and benefit from spironolactone. Tumor necrosis factor, C-reactive protein, soluble ST2, galectin-3, and pentraxin-3 are increased in HFpEF (8–10), and TNF levels correlate with mortality in HFpEF (8). In HFpEF patients with elevated C-reactive protein levels indicative of systemic inflammation, IL-1 blockade with anakinra reduced systemic inflammation and improved exercise capacity (11).

Given that HFpEF is a complex syndrome with multiple pathophysiological mechanisms contributing to varying degrees within individual patients, the use of multimarker arrays to understand pathophysiology, classify patients into appropriate subtypes, and identify potential individualized treatments is inherently appealing (5). Such approaches have been limited by challenges due to lack of specificity, complexity, multiplicity, and interpretation (12). The present results from Chirinos et al. (6) provide hope that newer, sophisticated techniques, perhaps also including other types of biomarkers (such as cellular, exosomal, miRNA, and bioenergetic) will overcome these barriers and help advance our understanding of the pathogenesis and treatment of the large and growing population of patients with HFpEF.

ACKNOWLEDGMENT The authors thank Dr. Thomas Register for critical review/editing.

ADDRESS FOR CORRESPONDENCE: Dr. Dalane W. Kitzman, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, North Carolina 27157-1045. E-mail: dkitzman@wakehealth.edu. Twitter: @wakeforestmed.

JACC VOL. 75, NO. 11, 2020
MARCH 24, 2020:1296–8

REFERENCES

1. Paulus W, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013; 62:263–71.

2. Kitzman DW, Shah SJ. The HFpEF obesity phenotype: the elephant in the room. J Am Coll Cardio 2016;68:200–3.

3. Upadhya B, Pisana B, Kitzman DW. Evolution of geriatric syndrome: pathophysiology and treatment of heart failure with preserved ejection fraction. J Am Geriatr Soc 2017;65:2431–40.

4. Rando TA, Finkel T. Cardiac aging and rejuvenation—a sense of humors? N Engl J Med 2013; 369:575–6.

5. Allen LA, Felker GM. Multi-marker strategies in heart failure: clinical and statistical approaches. Heart Fail Rev 2010;15:343–9.

6. Chirinos JA, Orlenko A, Zhao L, et al. Multiple plasma biomarkers for risk stratification in patients with heart failure and preserved ejection fraction. J Am Coll Cardiol 2020;75:1281–95.

7. Dunlay SM, Redfield MM, Weston SA, et al. Hospitalizations after heart failure diagnosis: a community perspective. J Am Coll Cardiol 2009; 54:1695–702.

8. Manzano-Fernandez S, Mueller T, et al. Usefulness of soluble concentrations of interleukin family member ST2 as predictor of mortality in patients with acutely decompensated heart failure relative to left ventricular ejection fraction. Am J Cardiol 2011;107:259–67.

9. Matsubara J, Sugiyama S, Nozaki T, et al. Pentraxin 3 is a new inflammatory marker correlated with left ventricular diastolic dysfunction and heart failure with normal ejection fraction. J Am Coll Cardiol 2011;57:861–9.

10. van Kimmenade RR, Januzzi JL Jr., Ellinor PT, et al. Utility of amino-terminal pro-brain natriuretic peptide, galectin-3, and apelin for the evaluation of patients with acute heart failure. J Am Coll Cardiol 2006;48:1217–24.

11. Van Tassell BW, Arena R, Biondi-Zoccai G, et al. Effects of interleukin-1 blockade with anakinra on aerobic exercise capacity in patients with heart failure and preserved ejection fraction (from the D-HART pilot study). Am J Cardiol 2014;113:321–7.

12. Parikh KS, Sharma K, Fuzat M, et al. Heart failure with preserved ejection fraction expert panel report: current controversies and implications for clinical trials. J Am Coll Cardiol HF 2018; 6:619–32.

KEY WORDS aging, biomarkers, comorbidities, fibrosis, HFpEF, inflammation, kidney, liver, obesity