Research Letter

Coronary Microvascular Dysfunction and Clinical Outcomes in Patients With Heart Failure With Preserved Ejection Fraction

Although heart failure with preserved ejection fraction (HFpEF) has similarly poor outcomes as HF with reduced ejection fraction,[1] the etiology of HFpEF is less clearly understood. A current hypothesis is that comorbidities associated with HFpEF contribute to inflammation and coronary microvascular dysfunction (CMD).[2] CMD can be quantified using invasive techniques that measure coronary flow reserve (CFR) and the index of microvascular resistance (IMR), both more common in patients with HFpEF than in controls.[3] We sought to determine the association between abnormal CFR and IMR, and outcomes in patients with HFpEF.

Materials and Methods

This prospective, observational, two-center study, outlined previously,[3] used a combined death or HF hospitalization (HFH) at 1 year, collected via phone call or office visit as the primary outcome. For HFH, Framingham criteria must be satisfied[4] and HF must have been the primary reason for hospitalization. HFpEF patients were grouped into 2 coronary physiology groups based on presence or absence of overt CMD, defined as having both abnormal CFR and IMR with cutoffs of $\leq$2.0 for CFR and $\geq$23 units for IMR.[3]

Continuous baseline parameters were expressed as means $\pm$ standard deviations or medians with interquartile ranges and compared between patients with and without overt CMD using either Student's *t* tests or Mann−Whitney *U* (Wilcoxon) tests depending upon normality as determined by Shapiro−Wilk tests. Categorical baseline parameters were expressed as relative counts and percentages and compared with Chi-square tests of association or Fisher's exact tests. Kaplan−Meier time-to-event analysis was performed for the primary outcome with log-rank to determine differences between CMD groups without correction for multiple tests. Univariate logistic regression was performed to determine the relevant clinical, laboratory, echocardiographic, and hemodynamic parameters associated with the primary outcome. Analyses were performed using Stata MP 15.0 (StataCorp LP).

Results

There were 32 patients with HFpEF and 16 control patients. Of the HFpEF patients, there were 9 (28%) with normal CFR and IMR, 9 (28%) with normal CFR and abnormal IMR, 3 (9%) patients with abnormal CFR and normal IMR, and 11 (34%) with overt CMD. On average, HFpEF patients with overt CMD had more comorbidities, higher E/e′, diastolic dysfunction grade, and mean pulmonary artery (PA) pressure than those without overt CMD, with a similar pattern comparing HFpEF patients to controls (Supplementary Table 1). HFpEF patients had lower survival free of HFH compared with control patients (69% vs 100%, 10 events vs 0 events, $P = .015$; Fig. 1), as did HFpEF patients with overt CMD compared with all other HFpEF patients (45% vs 81%, 6 events vs 4 events, $P = .039$; Fig. 1) and HFpEF patients with abnormal CFR compared with HFpEF patients with normal CFR (50% vs 83%, 7 events vs 3 events, $P = .038$; Fig. 1). There was a trend toward HFpEF patients with abnormal IMR having lower survival free of HFH than patients with normal IMR (60% vs 82%, 8 events vs 2 events, $P = .17$; Fig. 1). Overt CMD (odds ratio [OR] 1.63, 95% confidence interval [CI] 1.02−3.24, $P = .047$), male gender (OR 1.63, 95% CI 1.02−3.24, $P = .047$), weight (OR 1.05, 95% CI 1.01−1.09, $P = .02$), pulse (OR 1.07, 95% CI 1.01−1.14, $P = .02$), septal wall thickness (OR 4.9, 95% CI 1.32−9.5, $P = .04$), PA pressure (OR 1.11, 95% CI 1.01−1.21, $P = .03$), pulmonary capillary wedge pressure (OR 1.17, 95% CI 1.01−1.33, $P = .04$), and cardiac index (OR 1.54, 95% CI 1.10−2.98, $P = .04$) were associated with the primary outcome after univariate logistic regression.

Discussion

In this follow-up study to previous work,[3] we show that CMD is associated with poor outcomes in patients with HFpEF. Comorbidities contribute to poor outcomes in HFpEF,[5–7] however, HFpEF patients have outcomes out of proportion to the comorbidities.[8] Our HFpEF patients with overt CMD had higher number of comorbidities than those without overt CMD; however, the number of comorbidities was not a predictor of the primary outcome. Septal wall thickness and elevated PA pressure were among predictors of the primary outcome in univariate analysis, consistent with a prior study.[9] PA pressure was elevated in overt CMD patients, and further investigation is needed to evaluate the relationship between pulmonary hypertension and CMD.

A recent study demonstrated a high prevalence of abnormal CFR (defined as CFR <2.5) as measured by echocardiography in HFpEF patients.[10] We chose a cutoff CFR of $\leq$2.0 to increase the specificity of the

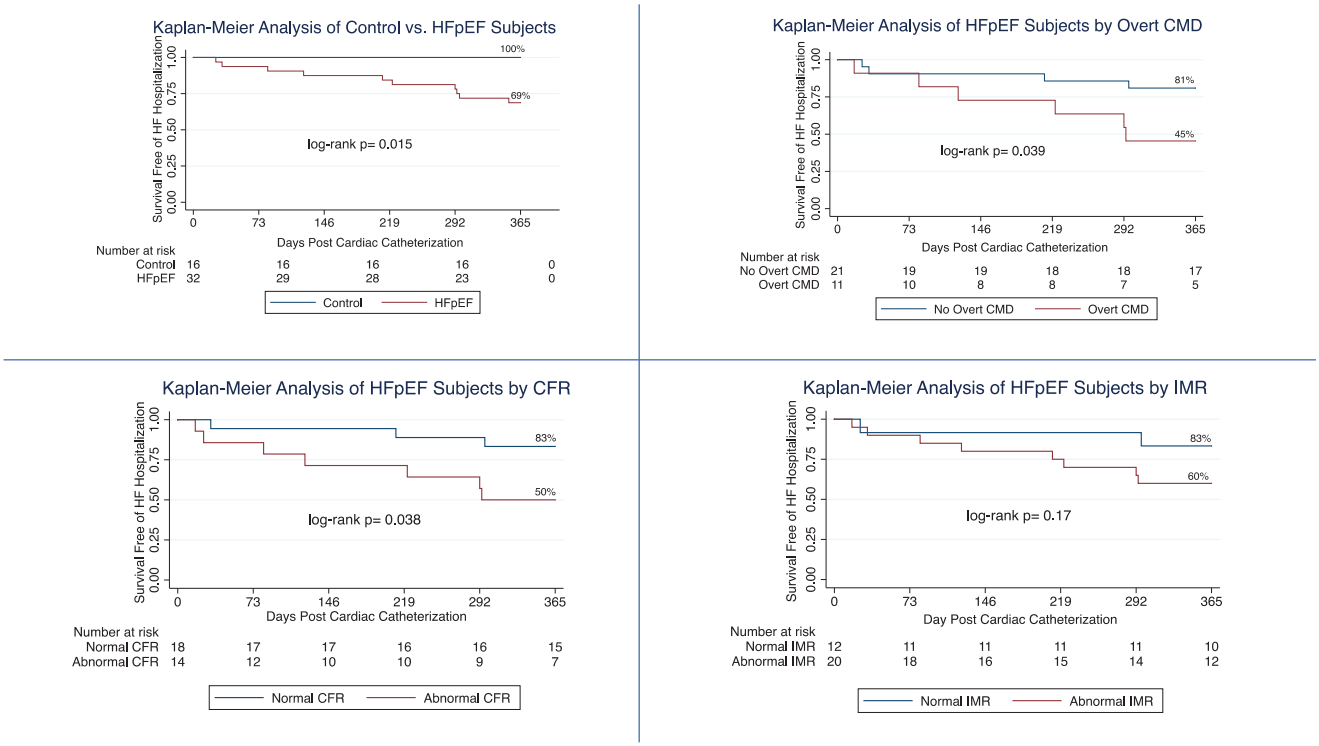

Fig. 1. Kaplan–Meier analysis. Top left, Control versus HFpEF. Top right, HFpEF subjects by overt CMD. Overt CMD = abnormal CFR and abnormal IMR; No overt CMD = normal CFR and normal IMR or abnormal CFR or IMR alone. Bottom left, HFpEF subjects by CFR. Bottom right, HFpEF subjects by IMR.

measurement. To our knowledge, this is the first study to correlate invasively-determined CFR and IMR with outcomes in patients with HFpEF. Given our small sample size, results must be interpreted with caution. We identify a group of high-risk HFpEF patients in which therapies targeted at CMD may be used in future clinical trials.

Disclosures

None.

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Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.cardfail.2019.08.010.

Tess Allan, BA[1]
Kathryn Dryer, MD[1]
William F. Fearon, MD[3]
Sanjiv J. Shah, MD[2]
John E.A. Blair, MD[1]
[1]*Section of Cardiology, Department of Medicine, University of Chicago, Pritzker School of Medicine, Chicago, Illinois*
[2]*Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois*
[3]*Division of Cardiology, Department of Medicine, Stanford University, Stanford, California*

E-mail address: jblair2@bsd.uchicago.edu (J.E.A. Blair).

References

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–9.
2. Paulus WJ, Tschöpe 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.
3. Dryer K, Gajjar M, Narang N, Lee M, Paul J, Shah AP, et al. Coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction. Am J Physiol Heart Circ Physiol 2018;314:H1033–42.
4. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971;285:1441–6.
5. Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in heart failure: a community perspective. Circ Heart Fail 2008;1:91–7.
6. Edelmann F, Stahrenberg R, Gelbrich G, Durstewitz K, Angermann CE, Düngen H-D, et al. Contribution of comorbidities to functional impairment is higher in heart failure with preserved than with reduced ejection fraction. Clin Res Cardiol 2011;100:755–64.
7. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population

with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol 2012;59:998–1005.
8. Mohammed SF, Borlaug BA, Roger VL, Mirzoyev SA, Rodeheffer RJ, Chirinos JA, et al. Comorbidity and ventricular and vascular structure and function in heart failure with preserved ejection fraction: a community-based study. Circ Heart Fail 2012;5:710–9.
9. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Anand IS, O'Meara E, et al. Cardiac structure and function and prognosis in heart failure with preserved ejection fraction: findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. Circ Heart Fail 2014;7:740–51.
10. Shah SJ, Lam CSP, Svedlund S, Saraste A, Hage C, Tan R-S, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. Eur Heart J 2018;39:3439–50.

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