HFpEF etiology – can focus on sex-specific mechanisms deliver insights for all?

Delbridge LMD[1,2], Bell JR[1,3], Weeks KL[1,4,5], Raaijmakers AJA[1,3], Mellor KM[2,1,6]

[1] Department of Anatomy & Physiology, University of Melbourne, Australia
[2] Department of Physiology, University of Auckland, New Zealand
[3] Department of Microbiology, Anatomy, Physiology & Pharmacology, La Trobe University, Australia
[4] Baker Department of Cardiometabolic Health, University of Melbourne, Australia
[5] Department of Diabetes, Monash University, Australia
[6] Auckland Bioengineering Institute, University of Auckland, New Zealand

Keywords: heart failure with preserved ejection fraction, diastolic function, sex differences

Word count: 811
References: 10

Corresponding author:
Prof Lea MD Delbridge
Cardiac Phenomics Laboratory
Department of Physiology,
University of Melbourne, Australia.
lmd@unimelb.edu.au

Dear Editor,

In considering the heart failure with preserved ejection fraction (HFpEF) conundrum, the standard and disturbing preamble is almost ubiquitous: HFpEF has overtaken heart failure with reduced ejection fraction (HFrEF) as the major form of new failure diagnosis, incidence is escalating alarmingly, and there is no specific therapy for HFpEF. The historical perspective on the emergence of HFpEF has been elegantly chronicled [1]. It seems that achieving a definitive HFpEF diagnosis has always been problematic. Symptomatic HF, initially described as featuring diastolic 'stiffness' (high filling pressures) was termed HFpEF, to distinguish the condition from the more common state of failure involving diminished ejection fraction. It was noted early that the cardiac signs, symptoms and co-morbidities were variable: usually hypertrophy, often hypertension, commonly natriuretic factor elevation, possibly fibrosis, maybe minor dilation [2]. Over time the constellation of comorbidities has expanded and includes more generalized metabolic and vascular components. Recently there has been considerable progress in 'sub-phenotyping' or clustering various HFpEF types using clinical measures and more lately innovative machine-learning algorithms [3]. Present indications are that a single heroic discovery of the HFpEF mechanism and cure is unlikely.

Integral to the clinical HFpEF narrative is observation of gender disparity. Screening studies have reported that in both women (82%) and men (65%) HFpEF is the most prevalent failure type [4]. Women significantly outnumber men, with a gender distribution ratio of approximately 2:1 in HFpEF [5]. Women with HFpEF have diastolic dysfunction more frequently than men (52.8% versus 32.0%) and this condition has been independently associated with adverse clinical events (female comorbidity odds ratio of 2.84) [6]. The risk of HFpEF increases with age, and the aging female demography confers an elevated burden of disease on women even when the risk-adjusted incidence is similar in women and men [7]. Diagnostic guidelines include minimal recognition that female and male HFpEF may be different entities - the only gender-specific content of an ESC Guideline [8] is that the risk criterion for women identifies a more aged cohort and lower cardiac weight/dimension indices.

Despite major professional society and funder mandates for more than a decade, and publisher policies to promote sex/gender inclusiveness, the vast majority of pre-clinical work (primarily rodent) is still limited to males or unspecified sex. While the limited extent of female HFpEF under-

investigation (clinical and pre-clinical) is an ongoing issue, a more positive perspective could be that this situation offers unexploited opportunity to deliver new mechanistic insights relating to HFpEF diagnoses for all genders.

It is noteworthy that HFpEF has prompted a unified clinician call to pre-clinical colleagues for the collaborative development of new animal models to provide HFpEF disease mechanism insight. While this has been challenging, given that there are many HFpEF sub-phenotypes, the response in terms of model novelty has been disappointing. In general, models nominated as HFpEF have been HFrEF derivative, relying on titrated treatments or investigative timing to capture a transitory point in disease development where diastolic dysfunction is evident, and systolic dysfunction yet to emerge. Clinically HFpEF mortality has been refractory to HFrEF interventions, but even so the majority of animal model approaches have related to the renin-aldosterone-angiotensin-system axis, and/or with nitric oxide bioavailability manipulation. Biomarker profiling in female murine metabolic models exhibiting HFpEF phenotype has been informative [9], and suggests more specific and novel work to link biomarkers with functional deficit is required.

Some new findings indicate that HFpEF (in male rodents) has an underlying cardiomyocyte hypercontractility component [2]. This contrasts dramatically with the HFrEF phenotype, of hypocontractility associated with activator Ca^{2+} deficiency, and requires multi-model exploration. The clinical importance and gendered characteristics of diastolic dysfunction identify this feature as a key pre-clinical investigative focus. Diastolic 'stiffness' pathology is frequently attributed to extracellular matrix/fibrotic abnormality. Comparisons of matrix morphology in male and female matched models of varying phenotypes is required. A potentially more significant source of myocardial stiffness resides within the cardiomyocyte. Sex-specificity of titin involvement needs further exploration, and a multitude of other sarcomeric proteins subject to post-translational modification have potential to contribute to cardiomyocyte stiffness in a sex-specific way. In the therapeutic pre-clinical development pipeline it is a common route to move from rodents to 'large animal' models. For HFpEF this offers a potentially interesting model default reversal as these models are mostly female (i.e. porcine, ovine).

The epidemiologic findings that consistently identify the two-fold increase in HFpEF female vs male incidence are remarkably reminiscent of the seminal findings reported from Framingham four decades ago. Heart failure risk (before HFrEF/HFpEF era) was found to be doubled for those

with diabetes, and for women this risk was re-doubled [10]. In retrospect the question arises - is this a double jeopardy or the same vulnerability refined more specifically? A molecular mission which focuses on functional sex/gender contrast for any one HFpEF phenotype, with a specific emphasis on diastolic dysfunction will provide new insights for other pheno-forms of HFpEF.

Funding

L.M.D.D., J.R.B and K.L.W are supported by funding from the National Health and Medical Research Council of Australia (2013650), the National Heart Foundation of Australia (105683), and the Diabetes Australia Research Program. K.L.W is supported by a National Heart Foundation of Australia Future Leader Fellowship (102539). K.M.M. is supported by funding from the Health Research Council of New Zealand (19/190) and the Marsden Fund of New Zealand (19-UOA-268).

Disclosures

The authors have no disclosures to declare.

References

[1] S. Mishra, D.A. Kass, Cellular and molecular pathobiology of heart failure with preserved ejection fraction, Nat Rev Cardiol. 18 (2021) 400–423. https://doi.org/10.1038/s41569-020-00480-6.

[2] C.L. Curl, V.R. Danes, J.R. Bell, A.J.A. Raaijmakers, W.T.K. Ip, C. Chandramouli, T.W. Harding, E.R. Porrello, J.R. Erickson, F.J. Charchar, A.R. Kompa, A.J. Edgley, D.J. Crossman, C. Soeller, K.M. Mellor, J.M. Kalman, S.B. Harrap, L.M.D. Delbridge, Cardiomyocyte Functional Etiology in Heart Failure With Preserved Ejection Fraction Is Distinctive-A New Preclinical Model, J Am Heart Assoc. 7 (2018). https://doi.org/10.1161/JAHA.117.007451.

[3] F.R. Heinzel, S.J. Shah, The future of heart failure with preserved ejection fraction : Deep phenotyping for targeted therapeutics, Herz. 47 (2022) 308–323. https://doi.org/10.1007/s00059-022-05124-8.

[4] A.R. de Boer, I. Vaartjes, A. Gohar, M.J.M. Valk, J.J. Brugts, L.J.M. Boonman-de Winter, E.E. van Riet, Y. van Mourik, H.-P. Brunner-La Rocca, G.C.M. Linssen, A.W. Hoes, M.L. Bots, H.M. den Ruijter, F.H. Rutten, Heart failure with preserved, mid-range, and reduced ejection fraction across health care settings: an observational study, ESC Heart Fail. 9 (2022) 363–372. https://doi.org/10.1002/ehf2.13742.

[5] F. Duca, C. Zotter-Tufaro, A.A. Kammerlander, S. Aschauer, C. Binder, J. Mascherbauer, D. Bonderman, Gender-related differences in heart failure with preserved ejection fraction, Sci Rep. 8 (2018) 1080. https://doi.org/10.1038/s41598-018-19507-7.

[6] Y. Sotomi, S. Hikoso, D. Nakatani, H. Mizuno, K. Okada, T. Dohi, T. Kitamura, A. Sunaga, H. Kida, B. Oeun, T. Sato, S. Komukai, S. Tamaki, M. Yano, T. Hayashi, A. Nakagawa, Y. Nakagawa, Y. Yasumura, T. Yamada, Y. Sakata, PURSUIT-HFpEF Investigators, Sex Differences in Heart Failure With Preserved Ejection Fraction, J Am Heart Assoc. 10 (2021) e018574. https://doi.org/10.1161/JAHA.120.018574.

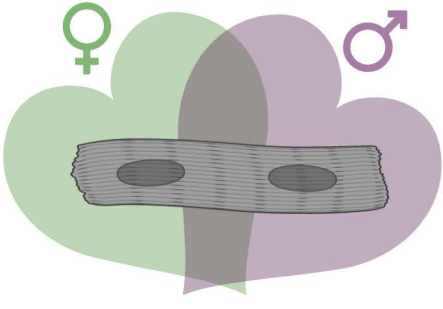
[7] S.M. Dunlay, V.L. Roger, M.M. Redfield, Epidemiology of heart failure with preserved ejection fraction, Nat Rev Cardiol. 14 (2017) 591–602. https://doi.org/10.1038/nrcardio.2017.65.

[8] B. Pieske, C. Tschöpe, R.A. de Boer, A.G. Fraser, S.D. Anker, E. Donal, F. Edelmann, M. Fu, M. Guazzi, C.S.P. Lam, P. Lancellotti, V. Melenovsky, D.A. Morris, E. Nagel, E. Pieske-Kraigher, P. Ponikowski, S.D. Solomon, R.S. Vasan, F.H. Rutten, A.A. Voors, F. Ruschitzka, W.J. Paulus, P. Seferovic, G. Filippatos, How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC), Eur J Heart Fail. 22 (2020) 391–412. https://doi.org/10.1002/ejhf.1741.

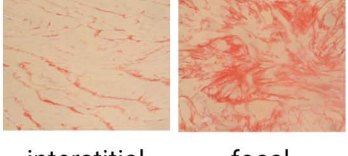
[9] C. Withaar, L.M.G. Meems, G. Markousis-Mavrogenis, C.J. Boogerd, H.H.W. Silljé, E.M. Schouten, M.M. Dokter, A.A. Voors, B.D. Westenbrink, C.S.P. Lam, R.A. de Boer, The effects of liraglutide and dapagliflozin on cardiac function and structure in a multi-hit mouse model of heart failure with preserved ejection fraction, Cardiovasc Res. 117 (2021) 2108–2124. https://doi.org/10.1093/cvr/cvaa256.

[10] W.B. Kannel, D.L. McGee, Diabetes and cardiovascular disease. The Framingham study, JAMA. 241 (1979) 2035–2038. https://doi.org/10.1001/jama.241.19.2035.

HFpEF Mechanisms
Myocardial & Cardiomyocyte Stiffness

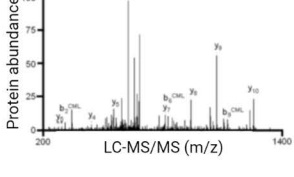


Extracellular matrix & fibrosis

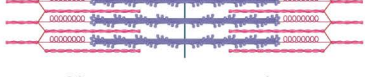


interstitial focal

Post-translational modifications



Sarcomeric structural proteoforms



myofilament/cyto-architecture