Title: **Diagnosing heart failure with preserved ejection fraction – what´s the score?**

Authors: Søren Lund Kristensen, MD PhD[1,2], John JV McMurray[1]

Affiliations: [1]BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; [2]Department of Cardiology, Rigshospitalet University Hospital, Copenhagen, Denmark

Correspondence: Professor John J.V. McMurray,
British Heart Foundation Cardiovascular Research Centre,
University of Glasgow, 126 University Place,
Glasgow, G12 8TA, United Kingdom.
Tel: +44 141 330 3479
Fax: +44 141 330 6955
Email: john.mcmurray@glasgow.ac.uk

Definitive diagnosis of heart failure with preserved ejection fraction (HFpEF) remains a challenge in the absence of invasive haemodynamic measurements.[1,2] In part, this is because indirect measures of raised intracardiac increased filling pressures are imprecise and, in the case of natriuretic peptides may be influenced by comorbidities such as obesity (associated with lower concentrations) and chronic kidney disease and atrial fibrillation (associated with elevated concentrations). Moreover, left ventricular filling pressure may be normal at rest in patients with HFpEF, especially in individuals taking a diuretic, and only rise to abnormally high levels during exercise. [1,2]

Recently, two scores have been developed to help diagnose HFpEF. Reddy et al derived and validated a predictive model in two cohorts of patients referred for investigation of possible HFpEF, all of which underwent invasive haemodynamic exercise testing.[3] Six variables were independent predictors of HFpEF: age >60 years, body mass index >30 kg/m2, hypertension treated with ≥2 antihypertensive medications, atrial fibrillation, Doppler echocardiographic E/e' >9, and pulmonary artery systolic pressure >35 mm Hg (Table). The resultant total H2FPEF score ranges from 0 to 9 with the scores <2 and scores ≥6, respectively, reflecting a low or high likelihood of HFpEF. Individuals with an intermediate score (between 2 and 5) require further investigation e.g. invasive haemodynamic assessment. Of note, natriuretic peptides were not found to be predictive and are not included in this score. Unfortunately, as is often the case with scores of this type, an external validation raised doubts about its usefulness in less selected cohorts.[4]

Recently, the Heart Failure Association of the ESC published a 4-step algorithm for the diagnosis HFpEF, based upon expert consensus.[5] The suggested approach also uses a score, the HFA-PEFF score. Step 1 is assessment of the pre-test likelihood of HFpEF. Step 2 involves scoring based on major (2 point) and minor (1 point) criteria in three categories: function, morphology and biomarker. The resultant score includes some of the same variables as in the H2FPEF score, such as

average E/e' and tricuspid regurgitation-velocity, but is considerably more complex (Table). The pre-test probability step in the HFA-PEFF score includes consideration of some of the demographic/comorbidity variables in the H2FPEF score but does not allocate points for these.

In the HFA-PEFF score, echocardiographic measurements are used to provide the supporting functional and morphological evidence and a natriuretic peptide (BNP or NT-proBNP) measurement the biomarker evidence in support of the diagnosis. Combined, the major and minor criteria yield a HFA-PEFF score of between 0 and 6 points (the maximum score allowed in each category is 2 points). An overall score of <2 points means HFpEF is unlikely. A score of 2-4 points indicates that a diagnosis of HFpEF is possible, but further work-up is needed, and a score of ≥5 points that HFpEF is confirmed. The fourth and final step is an optional one where the goal is to define the specific aetiology.

In this issue of the *Journal*, Barandiarán Aizpurua and colleagues have examined the performance of the second step in the HFA-PEFF algorithm in an important validation study in two single-centre patient cohorts.[6] The Maastricht cohort included 270 patients referred with suspected HFpEF, the diagnosis of which was confirmed in 228. The Chicago cohort comprised only patients with confirmed diagnosis of HFpEF, all of which had been hospitalized previously. It is important to note that the final clinical diagnosis against which the score was compared included haemodynamic measurements during rest and exercise in only half of the Chicago cohort and none of the Maastricht cohort, yet this is arguably the gold standard against which any new test should be compared. As a result, the present study compared the HFA-PEFF score against a diagnosis of HFpEF made by experts using the same variables as those included in the score. Moreover, the ratio of HFpEF 'cases' to non-HFpEF 'controls' was very high. These two factors may have led to overestimation of the performance of the HFA-PEFF score. These caveats need to be taken into account when considering the apparently excellent results of the 'rule-in approach' with a

specificity of 93%. Only 13 (3%) individuals from the Northwestern cohort and 3 (1%) from the Maastricht cohort had a diagnosis of HFpEF but a HFA-PEFF score of ≤1 point. Similarly, the performance of the score used as a 'rule-out' test, where a score of <2 had a sensitivity of 99% in the Maastricht cohort, may be overoptimistic, especially with the small number of non-HFpEF controls.

Barandiarán Aizpurua and colleagues also suggest simplifications of the algorithm and, interestingly, found that natriuretic peptides had a similar performance to the total score. Although potentially very valuable, we cannot draw definitive conclusions about these observations in the present cohorts, because of the limitations discussed above. However, should natriuretic peptides be confirmed as useful as the HFA-PEFF score, clinical practice could be simplified greatly.

The present report by Barandiarán Aizpurua and colleagues is a very welcome first step in evaluating the HFA-PEFF score and hopefully more investigators will evaluate this and the H2FPEF score in further cohorts of less selected patients, including a larger proportion of patients without a final diagnosis of HFpEF. An evaluation of both scores simultaneously in the same cohort will be particularly important given the simplicity of the H2FPEF score, should it perform as well as the HFA-PEFF score. Although difficult, it will be particularly important to test both scores against the gold standard of invasive measurements of filling pressures, including pressure during exercise. Which if any of these two scores will prove useful in the longer term remains to be seen and further iterations of this type of approach may emerge as a result of future investigation. Ultimately, any validated aid to the diagnosis of HFpEF will be a big step forward.

Table: Comparison of the H_2FPEF and HFA-PEFF scores

	H_2FPEF	**HFA-PEFF (Step 2)***
Variables included (points)		
Demographics	Age >60 years **(1)** Body mass index >30 kg/m^2 **(2)**	-
Co-morbidity	Hypertension treated with ≥2 antihypertensive medications **(1)** Atrial fibrillation **(3)**	-
Cardiac morphology	-	LAVI >34 ml/m^2 **(2)** or LVMI >149/122 gm^2 (m/w) and RWT >0.42 **(2)** LAVI 29-34 ml/m^2 **(1)** or LVMI >115/95 gm^2 (m/w) **(1)** or RWT >0.42 **(1)** or LV wall
Cardiac function/ non-invasive haemodynamics	Average E/e' x9 **(1)** TR velocity >2.8 m/s (PASP >35 mm Hg) **(1)**	Average E/e' ≥15 **(2)** or septal e' <7cm/s **(2)** or lateral e' <10cm/s **(2)** or TR velocity >2.8 m/s (PASP >35 mm Hg) **(2)**
Natriuretic peptides	-	NT-proBNP >220 pg/ml **(2)** or BNP >80 pg/ml **(2) [AF:** NT-proBNP >660 pg/ml **(2)** or BNP >240 pg/ml **(2)]** NT-proBNP 125-220 pg/ml **(1)** or BNP 35-80 pg/ml **(1) [AF:** NT-proBNP 365-660 pg/ml
Scores	**<2** low (HFpEF unlikely) **2-5** intermediate (further investigation) **≥6** high (confirmed)	**<2** low (HFpEF unlikely) **2-4** intermediate (further investigation) **≥5** high (confirmed)

H_2FPEF: **H**eavy [body mass index >30 kg/m2, 2 points], **H**ypertension [≥2 antihypertensive agents, 1 point], atrial **F**ibrillation [3 points], **P**ulmonary hypertension [right ventricular systolic pressure >35 mm Hg, 1 point], **E**lder [age >60 years, 1 point], **F**illing pressure [Doppler E/e' x9, 1 point]

***HFA-PEFF**: Maximum of 2 points per category (morphology, function or natriuretic peptides)

AF = atrial fibrillation RWT = relative wall thickness LAVI = left atrial volume index LVMI = left ventricular mass index BNP = B-type natriuretic peptide NT-proBNP = N-terminal prohormone of BNP TR = tricuspid regurgiation PASP = pulmonary artery systolic pressure

REFERENCES

1. Obokata M, Reddy YNV and Borlaug BA. Diastolic Dysfunction and Heart Failure With Preserved Ejection Fraction: Understanding Mechanisms by Using Noninvasive Methods. *JACC Cardiovasc Imaging*. 2020;13:245-257.
2. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Dungen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP, Investigators P-H and Committees. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *The New England journal of medicine*. 2019.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P and Authors/Task Force M. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European heart journal*. 2016;37:2129-200.
4. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology F and American Heart Association Task Force on Practice G. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. 2013;62:e147-239.
5. Paulus WJ and Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *Journal of the American College of Cardiology*. 2013;62:263-71.