The diagnosis of heart failure with normal ejection fraction – a demanding task!

Micha T. Maeder, Peter Ammann, Hans Rickli

Division of Cardiology, Kantonsspital St. Gallen, St. Gallen, Switzerland

With interest we have read the review article on heart failure (HF) with normal left ventricular ejection fraction (LVEF; HFNEF) by Dr Blanche and colleagues [1]. The consensus paper of the European Society of Cardiology (ESC) working group was a particular focus of this review. We feel that a few very practical aspects, regarding the tools suggested for the diagnosis of HFNEF, require a more detailed discussion.

Firstly, the authors seem to imply that left ventricular (LV) filling pressures at rest are typically elevated in HFNEF patients. This is likely to be true for patients admitted with acute pulmonary oedema, in the context of poorly controlled hypertension and perhaps rapid atrial fibrillation, who are found to have a normal LVEF [2]. However, the majority of patients with suspected HFNEF do not have symptoms at rest but suffer from exertional dyspnoea [3]. Many of these patients have a normal left ventricular end-diastolic pressure (LVEDP) or pulmonary capillary wedge pressure (PCWP) at rest [4, 5]. HFNEF is characterised by concentric LV remodelling with small LV volumes and a stiff arterial system, and LVEDP in these patients is sensitive to changes in preload and afterload [6]. Thus, filling pressures may even be low following treatment with diuretics and vasodilators. In contrast, a rapid exercise-associated increase in PCWP in the context of a non-distensible left ventricle seems to be a hallmark of HFNEF [5] (discussed in detail in [7]). Thus, diagnostic strategies aimed at identifying an elevated resting LVEDP or PCWP as a *conditio sine qua non* for the diagnosis of HFNEF might not be ideally suited to obtain the diagnosis.

The second comment refers to the role of tissue Doppler echocardiography with measurement of the ratio of peak velocity of early mitral inflow (E) to peak annular mitral velocity during early diastole (e') for the diagnosis of HFNEF. The authors state that there is a close correlation between E/e' and LVEDP [1]. In the original study by Ommen et al. [8], the correlation coefficient between E/e' (e' measured at the medial annulus) and the mean LV diastolic pressure was 0.60 in patients with LVEF <50% and 0.47 in those with LVEF >50%, indicating that 36% and 22%, respectively, of the variability of the mean LV diastolic pressure was explained by E/e'. Nague et al. [9] found a close correlation (r = 0.87) between E/e' (e' measured at the lateral annulus) and PCWP, but the performance of the E/e' ratio in patients with preserved LVEF was not reported. In a recently published, large (n = 106), real world study in patients with acutely destabilised HF and impaired LVEF, the correlation between the E/e' ratio and PCWP was weak and failed to reach statistical significance [10]. In the only study in patients with HFNEF, a good correlation between E/e' as assessed at the lateral annulus and LVEDP was found by Kasner et al. [11], but there was no significant correlation between E/e', as assessed at the medial annulus and LVEDP. Importantly, e' is higher at the lateral than at the medial annulus and thus the E/e' ratio based on an e' reading from the lateral annulus is lower. Thus, the method for the assessment of e' has to be specified for cutoffs. We do agree that E/e' (as a measure of a low e') is a good measure of LV diastolic dysfunction and possibly (owing to the relationship between e' and peak systolic mitral annular velocity [s']) also systolic dysfunction.

Finally, the role of natriuretic peptides deserves a comment. The strength of B-type natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP) in patients with possible HF lies in the high negative predictive value of these markers. However, in the algorithm, natriuretic peptides are proposed for inclusion rather than exclusion of HFNEF, with BNP and NT-proBNP cutoffs of 200 and 220 ng/l [3]. Of note, there is no published study on BNP for the prediction of invasively assessed LV diastolic function and/or LVEDP in patients with possible HFNEF. In contrast, the NT-proBNP cutoff is based on a carefully conducted invasive study [12]. However, in that study the median age was only 49 years and 55% were male, which is not typical for a HFNEF population. Given higher BNP and NT-proBNP with increasing age and female gender, the proposed cutoffs are likely to be too low and too unspecific in the more typical elderly patients (typically women) with suspected HFNEF.

We therefore think that the ESC algorithm must be applied with caution. Studies characterising haemodynamics and exercise responses of patients meeting the noninvasive criteria for HFNEF proposed in the algorithm are awaited. In addition, it should not be forgotten that for the diagnosis of HFNEF exclusion of other causes of shortness of breath is mandatory, in particular lung disease and inducible myocardial ischaemia with atypical presentation [7].

Correspondence:
Micha T. Maeder, MD
Division of Cardiology
Department of Internal Medicine
Rorschacherstrasse 95
CH-9007 St. Gallen
Switzerland
micha.maeder@bluewin.ch

References

1 Blanche C, Fumeaux T, Polikar R. Heart failure with normal ejection fraction (HFNEF):is it worth considering? Swiss Med Wkly. 2010; 140(5-6):66–72.
2 Gandhi SK, Powers JC, Nomeir AM, Fowle K, Kitzman DW, Rankin KM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med. 2001;344(1):17–22.
3 Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J. 2007;28(20):2539–50.
4 Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, et al. Role of left ventricular stiffness in heart failure with normal ejection fraction. Circulation. 2008;117(16): 2051–60.
5 Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J Am Coll Cardiol. 1991;17(5):1065–72.
6 Borlaug BA, Kass DA. Ventriculo-vascular interaction in heart failure. Heart Fail Clin. 2008;4(1): 23–36.
7 Maeder MT, Kaye DM. Heart failure with normal left ventricular ejection fraction. J Am Coll Cardiol. 2009;53(11):905–18.
8 Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation. 2000;102(15):1788–94.
9 Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol. 1997;30(6):1527–33.
10 Mullens W, Borowski AG, Curtin RJ, Thomas JD, Tang WH. Tissue Doppler imaging in the estimation of intracardiac filling pressure in decompensated patients with advanced systolic heart failure. Circulation. 2009;119(1):62–70.
11 Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K, et al. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. Circulation. 2007;116(6):637–47.
12 Tschope C, Kasner M, Westermann D, Gaub R, Poller WC, Schultheiss HP. The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements. Eur Heart J. 2005; 26(21):2277–84.

Authors' reply

Thierry Fumeaux

Service de Médecine / Soins Intensifs, GHOL – Hôpital de Nyon, Nyon, Switzerland

We thank Dr Maeder and colleagues for their attentive reading of our recent review on heart failure with normal ejection fraction (HFNEF), and for their high quality comments. As they acknowledge, our review was focused on the recent European Society of Cardiology (ESC) guidelines, and aimed to describe a practical approach for this clinical situation for the non cardiologist.

Dr Maeder et al. discuss the fact that elevated left diastolic ventricular pressure may not be present at rest in many HFNEF patients, and may only appear during exercise. We briefly discussed this point, quoting the paper by Tan et al. [1] who showed that diastolic dysfunction at rest and during exercise may differ in their mechanisms. We also acknowledge that, as discussed by Maeder et al., strategies that identify high ventricular pressure may not be adequate in many patients suspected of having HFNEF. We point out that this is also true for HF with decreased ejection fraction, in which the systolic dysfunction may not be apparent at rest and may be unmasked during exercise. As a consequence, patients who are suspected of having HF, and in whom the diagnostic strategies are not conclusive at rest must be evaluated during exercise. With regard to Dr Maeder's comments, it has to be emphasised that the title of the ESC algorithm states symptoms OR signs of HF, implying that clinical and paraclinical signs of LV dysfunction may not be present on examination. We should have pointed out this point more clearly.

Maeder et al. also discuss some pitfalls of tissue Doppler as a diagnostic technique. We did not intend to discuss detail in the evidence regarding this diagnostic method, but we appreciate the comments from our colleagues. We totally agree that cutoff values must always be interpreted with regard to the method of assessment. As for all innovative diagnostic techniques, the test of time is an important step to ascertain the real diagnostic value.

The third comment by Maeder et al. deals with the proposed cutoff values of BNP and NT-pro-BNP assays by the recent consensus statement [2]. As for all diagnostic tests, cutoff values must always be considered in the clinical context and with the knowledge of analytic characteristics. We agree that in the daily practice, these values may not be adequate for many patients, particularly for elderly woman. However, this proposal has the advantage of giving a clue as to the diagnosis and may also lead to a more systematic diagnostic approach for HFNEF. As a consequence, these cutoff values are rather intended to make physicians suspicious of HF as a potential cause of the clinical presentation, but not necessarily prove that it is responsible for it.

Finally, we agree that the ESC guidelines and algorithm are not perfect and, as for all guidelines, must be applied with caution. However, they give the opportunity to greatly improve the quality of the diagnostic and therapeutic strategies in the management of patients suspected of having HFNEF. Therefore, we think that they deserve to be known by most physicians who manage most patients with signs and symptoms of HF.

Correspondence:
Thierry Fumeaux, MD
Service de Médecine / Soins Intensifs
GHOL – Hôpital de Nyon
CH-1260 Nyon
Switzerland
E-Mail: thierry.fumeaux@ghol.ch

References

1 Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol. 2009;54(1):36–46.

2 Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J. 2007;28(20):2539–50.