Chapter 5

The future diagnosis of heart failure with normal ejection fraction: less imaging, more biomarkers?

Franssen C, Paulus WJ

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by

Constantijn Franssen, Walter J. Paulus.

From

Department of Physiology, Institute for Cardiovascular Research, VU University Medical Center, Amsterdam, The Netherlands.
INTRODUCTION

In contrast to heart failure with reduced ejection fraction (HFREF), which is easily diagnosed by clinical signs or symptoms of fluid overload in the presence of a left ventricular ejection fraction (LVEF) <35%, the diagnosis of heart failure with normal ejection fraction (HFNEF) is cumbersome as it requires three conditions to be simultaneously satisfied.¹ These three conditions consist of (i) signs or symptoms of fluid overload; (ii) an LVEF >50% and an LV end-diastolic volume index (LVEDVI) <97 mL/m²; and (iii) evidence of diastolic LV dysfunction derived either from cardiac catheterization or tissue Doppler imaging (TDI). The latter can eventually be implemented with measurements of mitral flow velocity, left atrial volume index (LAVI) or plasma natriuretic peptide levels. Due to their poor positive predictive value, natriuretic peptides are considered unable to provide stand-alone evidence for HFNEF and always need to be implemented with TDI evidence of diastolic LV dysfunction. Because of mounting evidence of TDI-derived indices failing to adequately reflect LV filling pressures² and because of emerging reports of several biomarkers being raised in HFNEF,³–⁵ the future paradigm for the diagnosis of HFNEF will probably be diverted away from elaborate imaging techniques and oriented towards the integrated use of biomarkers. Such an integrated use of biomarkers for assessing HFNEF and risk of HFNEF development is exemplified in the current issue of the European Journal of Heart Failure by the article of Collier et al.⁶

LESS IMAGING

E/E’ (ratio of early transmitial velocity to TDI mitral annular early diastolic velocity) suffers from shortcomings when used as an estimate of LV filling pressures in HFREF or in HFNEF.² The shortcomings mainly derive from questionable assumptions such as E’ solely depending on LV relaxation pressure and E’ not being affected by early diastolic load.⁷ Because of the conceptual weakness of E/E’, stand-alone diagnostic evidence for diastolic LV dysfunction is provided only by an elevated E/E’ value (E/E’>15).¹ The vast majority of HFNEF patients present with an intermediate non-diagnostic E/E’ value (8<E/E’>15) and thus require additional evidence of diastolic LV dysfunction such as abnormal mitral or pulmonary vein flow velocities, a high LAVI or elevated plasma natriuretic peptides.¹ These
drawbacks of TDI were nicely illustrated in a recent study, which evaluated several algorithms for the diagnosis of HFNEF.\textsuperscript{8} In this study, E/E’ >15 had limited sensitivity for HFNEF (35%) and a serial evaluation of E/E’, mitral or pulmonary vein flow velocities and LAVI was needed to raise the diagnostic sensitivity of the echocardiographic work-up to 77%.

Apart from LAVI, which reflects chronic diastolic LV function, all imaging-derived indices provide an estimate of instantaneous LV end-diastolic distensibility relating LVEDVI to an estimate of LV end-diastolic pressure. These indices are sensitive to the volume status of the patient and will always carry the risk of a false-negative diagnosis following diuresis and a false-positive diagnosis following fluid overload. Only an LV diastolic pressure-volume relation fitted to two or more LV end-diastolic pressure-volume points, measures intrinsic diastolic myocardial stiffness and overcomes the confounding effects of volume status. This, however, requires an intervention such as transient balloon caval occlusion or exercise. Although preliminary studies on exercise stress testing provided encouraging results for the diagnosis of HFNEF, its applicability is limited as most HFNEF patients have poor exercise capacity due to high age and debilitating comorbidities. In contrast to imaging-derived indices of LV end-diastolic distensibility, fibrosis-related biomarkers reflect a chronic cardiac process occurring in HFNEF. This process consists of myocardial fibrosis as a result of concentric LV remodelling and is not affected by the patient’s instantaneous volume status.

**MORE BIOMARKERS**

Only natriuretic peptides have so far been extensively evaluated for the diagnosis of HFNEF. Patients with HFNEF have lower plasma natriuretic peptide levels than HFREF patients\textsuperscript{9} and the levels are especially low in HFNEF patients presenting in an outpatient clinic with complaints of limited exercise tolerance.\textsuperscript{10} Natriuretic peptides were therefore judged to be of limited clinical value for the diagnosis of HFNEF and their use recommended only for exclusion of HFNEF.\textsuperscript{1} This impression was further confirmed in large HFNEF registries such as the DIAST-CHF (Diastolic Congestive Heart Failure) study\textsuperscript{5} which observed a sensitivity of 65% for the diagnosis of HFNEF when using the recommended N-terminal- pro brain natriuretic peptide cut-off value of 220 pg/mL.\textsuperscript{1} Even lower sensitivities (27 and
38%) were recently reported in a critical evaluation of diagnostic HFNEF algorithms.\(^8\)

In contrast to natriuretic peptides, fibro-inflammatory biomarkers raise high expectations for HFNEF risk assessment and for HFNEF diagnosis as illustrated in this issue of the Journal by the article of Collier et al.\(^6\) This study reported HFNEF to be associated with increased circulating biomarkers of inflammation [interleukin 6 (IL6), interleukin 8 (IL8), and monocyte chemoattractant protein 1 (MCP1)], of collagen metabolism [aminoterminal propeptide of collagen 3 (PIIINP), carboxy-terminal telopeptide of collagen 1 (CITP)], and of extracellular matrix turnover [matrix metalloproteinase 2 (MMP2) and matrix metalloproteinase 9 (MMP9)]. Apart from the inflammatory biomarkers, the present study is an extension of previous reports by the same authors\(^3\) and by other investigators\(^4,5\) evaluating the diagnostic use of fibrosis-related biomarkers in HFNEF. In a previous study, a cut-off value of 1585 ng/mL of serum MMP2 was shown to provide 91% sensitivity and 76% specificity for predicting HFNEF.\(^3\) In the present study, these results were further refined as MMP9, tissue inhibitor of matrix metalloproteinase 1 (TIMP1) and the ratio of MMP9/ TIMP1 correctly identified patients with a high LAVI. The correct identification of an enlarged left atrium is an important finding because LAVI measures chronic diastolic LV function and its correct identification therefore supports the idea that fibrosis-related biomarkers reflect chronic concentric LV remodelling and are therefore unaffected by the patient’s instantaneous volume status. The findings on TIMP1 are, however, at odds with a previous study which observed higher serum TIMP1 levels in HFNEF patients with elevated LV filling pressures\(^4\) whereas the current study observed lower serum TIMP1 levels in patients with high LAVI. Encouraging results have also been reported with another fibrosis-related biomarker namely growth differentiation factor 15 (GDF-15), which is a distant member of the transforming growth factor \(\beta\) superfamily.\(^5\) In this study, GDF-15 also related closely to LAVI again indicative of the biomarker reflecting chronic LV remodelling.

The most important finding of the present study probably relates to the significant elevation of inflammatory biomarkers in HFNEF. Inflammatory biomarkers IL6, IL8, and MCP1 were not only raised when HFNEF patients were compared with arterial hypertension patients but also elevated when arterial hypertension patients were compared with age-adjusted reference values. The latter was not observed for the fibrosis biomarkers, as PIIINP and CITP were raised
in HFNEF compared with arterial hypertension but similar to age-adjusted reference values in arterial hypertension. These findings support systemic inflammation to precede myocardial remodelling in HFNEF. A similar conclusion was also reached by the Health ABC study, which reported inflammatory biomarkers such as IL6, tumor necrosis factor α, and C-reactive protein to be strongly associated with risk of HFNEF development in older adults. Myocardial inflammation was recently also observed in endomyocardial biopsies of HFNEF patients. These biopsies contained inflammatory cells, whose number appeared to relate to collagen volume fraction and diastolic LV function. Because of production of transforming growth factor β, the inflammatory cells induced transdifferentiation of fibroblasts to myofibroblasts with high production of collagen and low expression of MMP-1. Although this study suggested the raised inflammatory biomarkers in HFNEF to result from myocardial inflammation, the reverse situation seems to be more likely with systemic inflammation instigating myocardial inflammation. Potential sources of systemic inflammation in HFNEF are obesity and diabetes mellitus. Obesity and diabetes are highly prevalent in HFNEF and are able to induce expression of E-selectin, a leukocyte-attracting protein, in the intramyocardial endothelial cells.

CONCLUSIONS

The diagnosis of HFNEF remains challenging especially when the patient presents in an outpatient setting without obvious signs of volume overload. Future diagnostic algorithms for HFNEF are likely to rely less on imaging and more on biomarkers. Most imaging indices, even those obtained with sophisticated tissue Doppler or speckle tracking imaging, provide an assessment of instantaneous diastolic LV distensibility and are therefore sensitive to the patient’s volume status. As nicely demonstrated by the article of Collier et al. in this issue of the Journal and by some other recent reports, fibroinflammatory biomarkers have the advantage of reflecting the chronic myocardial remodelling process of HFNEF and are therefore unaffected by the patient’s instantaneous volume status. Furthermore, fibroinflammatory bio-markers also provide a comprehensive picture of the initiating systemic and evolving myocardial processes occurring during HFNEF development.
FUNDING

C.F. and W.J.P. are supported by a grant from the European Commission, Research Directorate General, Brussels, Belgium (FP7-Health-2010; MEDIA-261409).

CONFLICT OF INTEREST

None declared.

REFERENCES


