

EDITORIAL COMMENT

# Diastolic Function in Heart Failure With Reduced Ejection Fraction



## The Overlooked Prognosticator?\*

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The prevalence of heart failure (HF) in the U.S. population is rapidly increasing, and although evidence-based HF therapies have improved the prognosis, the rate of adverse events remains high. Several factors have been shown to be predictive of increased morbidity and mortality in patients with HF and include, but are not limited to, age, sex, body mass index, diabetes, renal function, New York Heart Association (NYHA) functional class, and ejection fraction (EF) (1). In addition to risk prediction, EF is also important for distinguishing between the 2 main HF classifications: heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction. Therefore, there is an inherent emphasis on the evaluation of left ventricular (LV) systolic function during the initial HF presentation. However, diastolic dysfunction is also present to varying degrees in both HF subtypes. In most patients with HF, abnormalities of systolic and diastolic dysfunction coexist, regardless of EF, yet the impact of diastolic dysfunction on prognosis among patients with HFrEF is less well studied than other risk predictors. As a result, diastolic dysfunction is rarely factored into the initial assessment of disease severity or prognosis in patients with HFrEF.

Diastolic dysfunction results from impaired LV relaxation, LV chamber stiffness, and ultimately, increased cardiac filling pressures. The most recent American Society of Echocardiography guidelines for

diastolic function emphasize the fact that patients with HFrEF have at least some degree of diastolic dysfunction that can be divided into severity grades (2). The key variables recommended for grading LV diastolic function include early and late transmitral inflow velocities (E and A velocities, respectively), mitral annular tissue velocities ( $e'$ ), the E/ $e'$  ratio, tricuspid regurgitation peak velocity, and left atrial maximum volume index (2). These variables are incorporated into an algorithm to determine the severity of diastolic dysfunction. More severe diastolic dysfunction is associated with worse clinical outcomes. Both diastolic grade and individual diastolic variables have been shown to have prognostic potential, but previous studies have been conducted in a relatively small number of patients with HFrEF, and questions remain about the generalizability and applicability to the larger HFrEF population.

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In this issue of *JACC: Heart Failure*, Benfari et al. (3) report on a large, single-center cohort in which 12,421 patients who received their initial HFrEF diagnosis between 2003 and 2011 were examined for an association between the severity of diastolic dysfunction and mortality. The study population consisted predominantly of men (68%) with an average age of 69 years; 41% had previously undergone coronary revascularization, and 63% were considered to be in NYHA functional class I or II at study entry. The average EF was  $36 \pm 10\%$ ; the E/ $e'$  ratio was  $17.2 \pm 9.4$ ; and moderate-to-severe secondary mitral regurgitation (MR) was present in 32% of subjects. Concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP) was only available in 16.4% of subjects upon initial HF presentation. A majority of patients were taking beta-blockers (83%)

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and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) (78%) at the time of diagnosis, but the use of mineralocorticoid receptor antagonists was low (16%). Medical management of HF therapies, average drug doses, and adherence to guideline-directed medical therapy were not assessed during follow-up. The mortality rate at 5 years was 42%.

This retrospective cohort study evaluating the association between diastolic dysfunction and mortality in patients with HFrEF is the largest reported to date. This study confirms that worsening diastolic dysfunction severity is associated with an increased risk of death. Furthermore, the single diastolic parameter of  $E/e'$  was associated with short- and long-term mortality, particularly when stratified by  $E/e'$  severity groups (<8, 8 to 14, >14 to 20, and >20). This is important because unlike systolic dysfunction, which can be characterized by a single variable such as EF, the assessment of diastolic dysfunction typically requires the integration of multiple parameters. However, this study suggests that the initial  $E/e'$  ratio alone may be the most predictive diastolic prognosticator in the initial HFrEF presentation.

Elevated filling pressures are a hallmark of HF and can be measured invasively to assess HF severity and evaluate response to treatment. The early transmitral flow velocity-to-early diastolic mitral annulus velocity ( $E/e'$ ) ratio correlates with invasive LV filling pressures in patients with HFrEF. An  $E/e'$  value of <8 is usually associated with normal LV filling pressures and a ratio >14 has high specificity for increased filling pressures (2). In small previous studies of patients with HFrEF, higher  $E/e'$  values have been shown to predict HF hospitalization and cardiac death (4,5). Similarly, but in a larger and more heterogeneous cohort, Benfari et al. (3) has shown that, even after comprehensive adjustment for multiple covariates, an elevated  $E/e'$  ratio at the time of first HF diagnosis is associated with increased mortality. The association of elevated  $E/e'$  with mortality was significant with  $E/e' >14$  but most predictive when  $E/e'$  was >20 (hazard ratio [HR]: 1.21; 95% confidence interval [CI]: 1.07 to 1.37);  $p = 0.003$ ). The magnitude and significance of the association decreased with decrementing  $E/e'$  groups.

Another important observation from the study by Benfari et al. (3) was the utility of  $E/e'$  in predicting LV filling pressures in the setting of secondary MR, which is primarily due to LV myocardial dysfunction in patients with HFrEF. Previous studies in a small number of patients with HFrEF have demonstrated that, even in the presence of moderate-to-severe secondary MR, an  $E/e'$  ratio >15 predicted an

elevated LV end-diastolic pressure with 80% sensitivity and 100% specificity and was associated with increased HF admissions and cardiac death (6,7). The study by Benfari et al. (3) builds on this work by showing that an increasing  $E/e'$  ratio is associated with decreased survival in patients with no or mild MR, as well as in patients with moderate or severe secondary MR. Therefore, although the interaction between  $E/e'$  and secondary MR was significant ( $p = 0.04$ ), the results suggest that the  $E/e'$  ratio is informative and useful despite the severity of secondary MR.

The findings by Benfari et al. (3) are insightful, but a considerable knowledge gap remains because neither previous studies nor the current study examined the change in diastolic function or  $E/e'$  over time. Diastolic variables are affected by loading conditions, patient hemodynamics and are subject to measurement variability. Additionally,  $E/e'$  can vary extensively with the application of guideline-directed medical therapy and the extent of LV remodeling (adverse or beneficial). Further study is needed to assess how  $E/e'$  changes over time with HF therapies and the extent to which these changes in  $E/e'$  reflect response to therapy and predict future outcomes. It is also unclear if  $E/e'$  would retain predictive significance when adjusted for more objective HF biomarker levels, such as the natriuretic peptides BNP and NT-proBNP, which are profound prognostic indicators in HFrEF and are subject to less measurement variability than  $E/e'$ . Higher natriuretic peptide levels independently indicate a worse prognosis in patients with HFrEF, and conversely, lower biomarkers are associated with improved clinical outcomes (8). The  $E/e'$  ratio may have independent prognostic value in addition to other known HF prognosticators, but it is reasonable to ask if we need another prognostic measurement in HFrEF when so many already exist. However, if the  $E/e'$  ratio could be used not only for initial prognostication but also to guide clinical care, it would be of considerable value to the HF field. Further study is needed to assess whether adverse outcomes can be attenuated by decreasing  $E/e'$  through optimized medical management.

The study by Benfari et al. (3) provides the most comprehensive assessment of diastolic function at initial HFrEF presentation and subsequent mortality risk. Furthermore, the simplicity of using  $E/e'$  rather than multiple diastolic parameters is appealing for practical application in clinical care. Quantifying a patient's survival prospects based on their presenting risk profile can help identify those patients in need of more intensive HF monitoring. This study assesses diastolic dysfunction, a

prognosticator often overlooked at the time of HF diagnosis, and its influence on subsequent survival; however, future work is needed to know how best to leverage this information to improve patient management and reduce adverse outcomes.

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