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EDITORIAL

Faltering Under Pressure: Limitations to Noninvasive Diastolic Function Assessments

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Heart failure with preserved ejection fraction (HFpEF) continues to increase in prevalence, largely driven by an aging and more obese global population.[1] Although pharmacologic treatment options for HFpEF have expanded, one of the key unmet challenges is identifying patients who actually have HFpEF. Dyspnea is a common symptom among older and obese adults, and noninvasive cardiac testing often fails to adequately discriminate cardiac causes of dyspnea from noncardiac causes.[2] The gold standard for diagnosing patients with HFpEF is invasive measure of cardiac filling pressures, either at rest or during exercise.[3] In clinical practice, invasive measure of pressures is rarely done and typically reserved for patients with persistent symptoms of unexplained dyspnea. Rather, the diagnosis is based on the presence of patient symptoms, evidence for diastolic dysfunction by echocardiography, and elevated cardiac biomarkers of ventricular pressure overload. The sensitivity for this approach varies substantially, ranging from 25% to 80%.[4–6] In patients who are clinically euvolemic, mildly hypervolemic, or early in their disease state, echocardiography-based pressure and volume criteria for diastolic dysfunction may be normal or indeterminate.[7] As an example of this imprecision, the distribution of diastolic dysfunction severity in several randomized clinical trials of patients with HFpEF is highly heterogeneous, with over half of patients enrolled in these trials having either normal or mild diastolic dysfunction,[8–10] despite meeting clinical criteria for entry into the studies. With echocardiography being a core modality for diagnosis of diastolic dysfunction, understanding the causes for this heterogeneity among patients is critical.

See Article by van de Bovenkamp et al.

In 2016, the American Society of Echocardiography and the European Association of Cardiovascular Imaging released updated recommendations evaluating left ventricular (LV) diastolic function by echocardiography.[11] The revised guidelines attempted to simplify the 2009 diastolic function guidelines. Using simple 4-point diagnostic criteria, the updated algorithm was designed to improve clinical utility and interpretation by referring providers. An increased emphasis was placed on identifying LV filling pressures and, as such, markers of LV relaxation and end diastole (eg, mitral A wave and pulmonary vein atrial systolic reversal) were deemphasized, although not fully eliminated. Of the 4 current diagnostic criteria, 3 (right ventricular systolic pressure >2.8 m/s, left atrial [LA] volume >34 mL/m^2, and E/e' >14) reflect elevated pressure and remodeling associated with a chronic volume overloaded state.[11] Although these thresholds were derived from patients who had a clear diagnosis of heart failure, it is unknown how well these cut points accurately and consistently identify patients undergoing evaluation for suspected HFpEF.

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The current study by van de Bovenkamp and coauthors in this issue of the *Journal of the American Heart Association* (*JAHA*) attempts to address this important question.[12] In a retrospective evaluation of 204 patients undergoing work up for dyspnea, screened to exclude greater than moderate valvular dysfunction and depressed LV function, the authors compared the diagnostic accuracy of individual components of the updated diastolic function guidelines in identifying elevated pulmonary capillary wedge pressure (PCWP), defined as >15 mm Hg. Approximately 40% of patients had elevated PCWP, most of whom had clinical evidence for volume overload or congestion. The study authors found weak to no correlation between right ventricular systolic pressure, tissue Doppler early relaxation velocities (e'), and PCWP. There were modest correlations between LA volumes and E/e'. Approximately 25% of patients had indeterminate diastolic dysfunction. Sensitivity for the diastolic function algorithm was 35%. In contrast, NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels and H2FPEF score had higher sensitivities but lower specificities.

The study has several strengths. In addition to a relatively large sample size, PCWP was measured at end expiration, minimizing respiratory influences on hemodynamics. Echocardiographic parameters were measured blinded to the hemodynamic assessment. There are some important limitations to note. The study, similar to prior studies from other groups, was retrospective in nature. This raises the potential for residual confounding related to nonstandard algorithmic approaches to evaluating dyspnea on exertion. A prospectively-designed study with a standardized approach to evaluating dyspnea with echocardiogram, serum biomarkers, and right-sided heart catheterization may allow for more controlled patient selection and enrollment. Second, the echocardiogram and right-sided heart catheter were not performed simultaneously, with an interquartile range of −6 to 45 days between catheterization and echocardiogram. Given hemodynamic status can fluctuate day to day, a closer temporal alignment of procedures, although not always clinically practical, may have provided stronger correlation between noninvasive and invasive measurements.

With this study, van de Bovenkamp et al have added important context and additional data to the growing understanding that echocardiography is not currently suited to detect HFpEF. Although the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines do not reference the use of American Society of Echocardiography diastolic guidelines in their algorithms to diagnosis of HFpEF, the graded classification of diastolic dysfunction presented in echocardiographic reports is what most clinicians use to make decisions.[3,12]

Diastolic function is a complex and multifactorial process that combines the LV-LA pressure gradient, passive and active relaxation, ventricular restoring forces, and end-diastolic LV compliance.[13] Of these processes, the LV-LA pressure gradient is the easiest to measure (through mitral inflow velocity). Unfortunately, mitral inflow velocities do not follow a linear decline from "normal" to pathologic. The E/e' ratio has become a mainstay for the assessment of filling pressures because of its simplicity and ability to predict cardiac events in patients with established cardiac disease. Yet, E/e' is significantly less sensitive at low or moderate levels (<14) and does not track with filling pressures over time.[14,15] Finally, both LV relaxation and compliance worsen with sedentary aging, and the point at which "normal" age-related changes transition to diastolic dysfunction, resulting in pathologic increase in PCWP, is unknown.[16] Future studies of diastolic markers and algorithms must consider the influence of age and fitness on the markers themselves and independent risk of developing heart failure. For instance, e' is highly correlated with age, and many healthy seniors have e' velocities below current diastolic function thresholds (septal e' <7 cm/s, lateral e' <10 cm/s). Given HFpEF is a disease primarily of the aged, the discriminant utility for e' in differentiating HFpEF from healthy aging is negligible at >5 cm/s.[17] To date, no one marker or simple battery of markers has been successful in capturing the scope and complexity of diastolic dysfunction. In its current state, echocardiographic assessment of diastolic function is generally unable to provide diagnostic clarity in patients with undifferentiated dyspnea.

How can echocardiography become more useful for clinicians in the evaluation for HFpEF? There are 3 important unmet needs for the noninvasive assessment of patients with dyspnea: (1) improved identification of elevated resting LV filling pressures, (2) noninvasive detection of exertional increases in LV filling pressures, and (3) identification of abnormalities in diastolic relaxation. The addition of novel markers of LA function, including LA strain and volumetric changes, may improve the identification of elevated LA pressures.[18] The noninvasive "diastolic stress test" has a growing body of evidence, but further validation using invasive hemodynamic protocols is needed.[19] Diastolic stress testing also requires specialized equipment in the form of a semirecumbent cycle and an experienced sonographer. Finally, dividing diastolic relaxation into its constituent components may elucidate novel markers of structural remodeling and function. Our group has recently demonstrated the interconnectedness between systole and diastole via assessments of systolic-diastolic coupling, which describes the contribution of systolic contraction toward early diastolic recoil.[20] This relationship, driven primarily by ventricular restoring

forces, is independent of LA pressure and significantly reduced in HFpEF. Further validation is needed to determine if markers, such as systolic diastolic coupling, can detect early stages of HFpEF.

Assessment of diastolic function remains a major clinical challenge. As HFpEF continues to grow in scope, more sensitive tools to identify, phenotype, and track therapeutic improvement are needed. Detection of early-stage HFpEF, in which LV and LA structural remodeling have not become fully manifest or are relatively euvolemic, will likely continue to be problematic. A more thorough understanding of the physiological features of diastole and cardiac motion will be needed to identify and develop novel noninvasive markers. Until then, a multimodality approach to dyspnea evaluation, incorporating pretest likelihood, serum biomarkers, exercise testing, and echocardiography, is essential, keeping in mind echocardiography will be a component, and not the core determinant, of evaluation.

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