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Echocardiographic Diastolic Stress Testing: What Does It Add?

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Abstract

Purpose of Review Diastolic stress echocardiography may help facilitate the attribution of exertional dyspnea to cardiac and non-cardiac disease. It represents a non-invasive hemodynamic test to assess the patients with unexplained dyspnea. It can improve the diagnosis of heart failure with preserved ejection fraction (HFpEF) or diastolic heart failure.

Recent Findings A number of studies have validated exercise E/e′ as a measure of left ventricular (LV) filling pressure against invasively measured LV filling pressure using simultaneous exercise echocardiography-catheterization studies. Addition of E/e′ during exercise echocardiography improved sensitivity for diagnosis of HFpEF compared with resting assessment alone, and its specificity can be improved if tricuspid regurgitation velocity also increases above the normal range with exercise. The independent prognostic value of exercise E/e′ has also been well delineated in a number of studies.

Summary Diastolic stress exercise echocardiography should be considered for all patients with unexplained or exertional dyspnea and normal diastolic filling pressure or grade 1 diastolic dysfunction on resting echocardiography. Addition of diastolic assessment with exercise echocardiography improves the sensitivity of the test in patients with dyspnea and there are sufficient data to integrate diastolic exercise test into our clinical practice.

Keywords Echocardiography · Stress test · Diastolic dysfunction

Introduction

A substantial subset of the patients with heart failure with preserved ejection fraction (HFpEF) have normal left ventricular filling pressure at rest that increases with exercise or stress due to diastolic dysfunction. Impaired left ventricular (LV) relaxation is one of the earliest manifestations of LV diastolic dysfunction [1]. Relaxation properties gradually decrease with aging and are also reduced in all forms of myocardial disease, including myocardial ischemia, hypertensive heart disease, and hypertrophic cardiomyopathy, and in most of HFpEF patients. The majority of people with impaired relaxation do not have symptoms or signs of heart failure (HF) at rest [2]. However, exertional dyspnea and exercise intolerance are common in these patients and therefore impaired relaxation is often a precursor to overt HF [2]. Diagnosis is challenging in this group and relies on identifying direct or indirect evidence of elevated LV filling pressure with exercise [3]. The most direct method to evaluate LV filling pressure with exercise is hemodynamic cardiac catheterization with stress [4]. However, this method has an obvious limitation and several studies have shown a good correlation between E/e′ ratio and invasively obtained LV filling pressure with exercise, as well as in the resting state. A similar correlation was obtained with pulmonary capillary wedge pressure (PCWP) and E/e′ ratio. Moreover, there is growing evidence that diastolic stress echocardiography provides important diagnostic findings that can be of value in the management of patients presenting with dyspnea of an unclear etiology [5]. With an increasing number of studies on hemodynamic validation and prognostic implications, guidelines from various societies have provided

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positive recommendations regarding the use of diastolic stress echocardiography with an emphasis on demonstrating exercise-related elevation in LV filling pressure through the measurement of exercise E/e′ ratio [6] and tricuspid regurgitation velocity. The purpose of this review is to highlight the underlying principles and diagnostic value of diastolic stress echocardiography, as well as its prognostic implications, clinical applications, and future directions.

Normal and Abnormal Diastolic Responses to Exercise

When diastolic function is normal, LV filling augments without a significant increase in filling pressure to meet bodily demands associated with stress or exertion due to appropriately facilitated myocardial relaxation and suction. In healthy subjects with normal myocardial relaxation, parameters of early diastolic function, such as early diastolic transmitral velocity (E) and early diastolic mitral annular tissue velocity (e′), were shown to increase proportionately during exercise, resulting in an unchanged E/e′ ratio [7, 8]. A normal diastolic response to exercise with Doppler echocardiography was reported by Ha et al. [7] (31 healthy subjects; mean age 59 ± 14 years) and Bruengger et al. (40 non athletic healthy subjects; mean age 29 ± 6 years) [8]. The following observations are clear in two different age groups of healthy individuals in terms of diastolic parameter response to exercise: (1) myocardial relaxation (e′) is more vigorous and augments more in younger subjects (Medial e′: 12 ± 4 vs 14 ± 2 cm/s at resting state and 15 ± 5 vs 20 ± 2 cm/s with exercise, in middle-aged vs younger normal subjects, respectively); and (2) E/e′ ratios are almost identical in these two healthy populations at rest and with exercise (E/e′ ratio: 6.7 ± 2.2 vs 6.7 ± 1.4 for resting state and 6.6 ± 2.5 vs 7.1 ± 1.1 for exercise state, in middle age vs younger normal subjects, respectively). Therefore, the same normal value of E/e′ can be used as a non-invasive estimate of LV filling pressure regardless of age. Both studies also showed that exercise diastolic parameters correlate better with exercise capacity than do resting parameters. The results of these two studies suggest that the better the myocardial relaxation (e′) at rest, the greater the expected exercise capacity.

In individuals with early diastolic dysfunction, adequate LV filling may occur with exertion—but in some cases, at the expense of increased filling pressure, resulting in dyspnea. As diastolic function worsens, LV filling becomes restrictive, resulting in even higher filling pressures. During exercise, there is less time for diastolic filling of the LV because of tachycardia. To maintain or augment the stroke volume with a shorter diastolic duration, myocardial relaxation should be faster and LV suction be augmented to maintain normal filling pressure. An analogous situation is when we evaluate patients for coronary artery disease. Normal wall motion or coronary perfusion in the resting state does not indicate there is no coronary artery stenosis. In such a situation, a stress test is performed to confirm whether there is a new wall abnormality or perfusion defect. Similarly, LV filling pressure can be determined with a form of exercise to evaluate patients with exertional dyspnea who have normal LV filling pressure, but with evidence of abnormal myocardial relaxation (grade 1 dysfunction) at rest. In subjects with diastolic dysfunction, mitral annulus e′ velocity, which reflects the degree of myocardial relaxation, is reduced at rest, and does not increase with exercise to the same extent as in normal individuals, while mitral E velocity increases due to elevated LV filling [9].

Figure 1 shows representative cases of diastolic response to exercise. On the top is an example of a normal diastolic exercise echo with proportional increase in medial mitral e′ velocity and mitral E wave with exercise. At the bottom, post exercise mitral E wave velocity, which is preload dependent, was increased while medial e′ has minimally changed, resulting in an increase in exercise E/e′ to greater than 15. The E/e′ ratio can be used as a surrogate marker to estimate left atrial or pulmonary capillary wedge pressure with exercise as well as at rest [10, 11]. Increased TR velocity with exercise is a supportive finding in the setting of diastolic dysfunction with increased filling pressure and is an integral part of diastolic exercise echocardiography [12]. The middle panel demonstrates an example of a normal diastolic exercise test in the setting of abnormal diastolic function at rest. Despite the grade 1 diastolic dysfunction at rest, the pattern does not change with exercise.

Diastolic Stress Echocardiography for the Diagnosis of Heart Failure with Preserved EF

An important role of diastolic exercise echocardiography is to provide an accurate diagnosis of diastolic heart failure, or HFpEF. It is important to remember that diastolic dysfunction is not equivalent to HFpEF. HFpEF by definition requires the presence of increased filling pressures either at rest or with exertion [13]. Although diastolic dysfunction is a central feature in HFpEF, the pathophysiology of HFpEF is complex, with variable contributions from diastolic dysfunction, impaired contractile reserve, impaired atrial function, and abnormal ventricular vascular coupling, which all contribute to the increase in pulmonary venous and left sided filling pressures [14, 15].

Recently, Obokata et al. examined the value of diastolic exercise echocardiography in patients with proven HFpEF (defined as PCWP with exercise ≥ 25 mmHg) by performing a simultaneous invasive hemodynamic-echocardiography study and comparing responses with a control group of patients with non-cardiac dyspnea [16••]. PCWP correlated with E/e′ at rest ($r = 0.63$; $p < 0.0001$) and following peak exercise

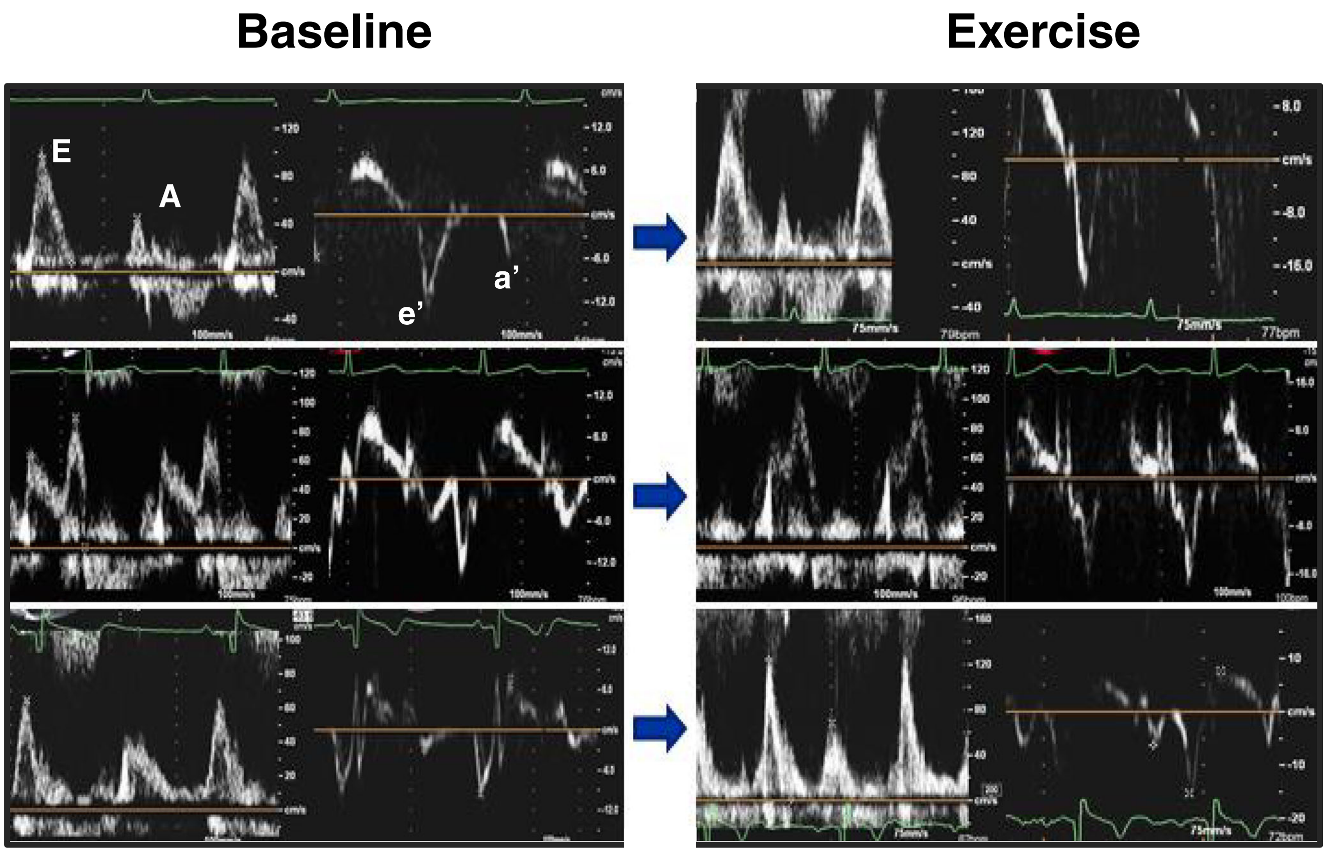

Fig. 1 Mitral inflow and medial mitral annulus velocity at rest and with exercise. Top: Normal diastolic person showed medial mitral e′ velocity also increases while mitral E wave velocity increased. Middle: Normal exercise pattern in a patient with reduced resting LV relaxation. Bottom: Post exercise mitral E wave velocity has increased while medial e′ has remained static, resulting in an increase in exercise E/e′

on a supine bicycle ($r = 0.57$; $p < 0.0001$), similar to the findings of Burgess et al. E/e′ ratio in the HFpEF group correlated with invasively measured left ventricle end-diastolic pressure (LVEDP) during exercise and approximately one-quarter of the patients manifested an elevated LV filling pressure only during exercise, whereas E/e′ did not increase significantly in the control group [17]. Moreover, it was found that even in the absence of E/e′ elevation at rest, patients with early-stage HFpEF may display hemodynamic abnormalities (elevated filling pressures) exclusively during exercise stress. In such patients, the diastolic stress test can provide additional useful information (using the non-invasive estimation of LV filling pressure by the E/e′ ratio) that might clarify the diagnosis of early-stage HFpEF. Table 1 is a compilation of invasive and echo diastolic stress test studies in HFpEF [11, 16••, 17–21]. Using PCWP as a reference, the authors showed that the addition of exercise E/e′ to resting diastolic function significantly improved the diagnostic accuracy for HFpEF. Similar to the physiology demonstrated by Borlaug et al. and Maeder et al., PCWP increased significantly from rest to peak exercise in patients with HFpEF [11, 20].

While the above studies showed a significant correlation between exercise E/e′ and LVEDP, other studies could not demonstrate a significant relationship. Some studies have raised questions about the ability of E/e′ to track changes in filling pressure during exercise, particularly because E/e′ increases far less than directly measured LV filling pressures. This is understandable, however, since the increase in pressure is related to a squared change in flow velocity (modified Bernoull equation). The relationship of E/e′ and wedge pressure is not linear and an E/e′ ratio should be looked at more in a binary fashion of normal or increased filling pressure, rather than as a parameter to estimate an exact filling pressure. Using a cutoff of greater than 15 for elevated medial E/e′ ratio with exercise, the sensitivity and specificity for predicting elevated LV filling pressure (measured invasively) was in excess of 80–85%, similar to the diagnostic accuracy for myocardial ischemia with stress echo, and quite acceptable for clinical practice [16••]. It is important to recognize that patients with dyspnea ultimately diagnosed with HFpEF frequently have normal filling pressure on rest cardiac catheterization—underscoring the importance of a stress evaluation, whether this be non-invasive or invasive. Other smaller studies have been less conclusive [20].

Kosmala et al. attempted to establish both a diagnostic and prognostic value of a strategy for the prediction of abnormal diastolic response to exercise (AbnDR) of using a combination of clinical, biochemical (especially

Table 1 Studies investigating the relationship between exercise echocardiographic parameters and/or invasively measured left ventricular filling pressures in patients with suspected HFpEF

Author	Patient's characteristic	Exercise type	Modalities during exercise	Changes of exercise hemodynamics	Conclusions/results
Burgess et al. 2006 [17]	37 patients: Unselected group undergoing left heart cath. Included patients with HFpEF	Single-leg supine bicycle	Invasive Catheterization Echocardiography	Good correlation between E/e′ and LVFP ($r = 0.37$, $p < 0.01$) at rest, and E/e′ and LVFP ($r = 0.59$, $p < 0.01$) during exercise	Positive correlations between echocardiography E/e′ and invasively measured LVFP at rest and with exercise
Talreja et al. 2007 [19]	12 patients with suspected HFpEF	Supine bicycle	Invasive Catheterization Echocardiography	Exercise E/e′ ≤ 15 identified patients with normal exercise PCWP, sensitivity 89% All patients with an exercise E/e′ > 15 had elevated PCWP (> 20 mmHg) with specificity 100%	Exercise E/′e > 15 associated with increased PCWP > 20 mmHg
Borlaug et al. 2010 [11]	55 patients Inclusion criteria: EF > 50%, exertional dyspnea, normal BNP, normal resting hemodynamics No CAD • HFpEF ($n = 32$) • Non-cardiac dyspnea ($n = 23$)	Supine cycle ergometry or outstretched arm adduction lifting of 4-lb weights (if femoral access obtained)	Invasive Catheterization	Patients with peak exercise PCWP≥ 25 mmHg were classified as having → HFpEF ($n = 32$) → LVEDP 13–> 34 mmHg PCWP < 25 mmHg → Non-cardiac dyspnea ($n = 23$) → LVEDP 12–> 14 mmHg No change	Exercise PCWP and PASP were highly correlated. An exercise PASP ≥ 45 mmHg identified HFpEF with 96% sensitivity and 95% specificity.
Maeder et al. 2010 [20]	14 patients with HFpEF Eight normal controls	Supine bicycle	Invasive Catheterization Echocardiography	Peak exercise PCWP was similar between HFpEF vs normal (23 mmHg vs. 20 mmHg; $p = 0.31$) Peak exercise E/e′ did not differ (11.1 ± 3.4 vs. 9.4 ± 3.4; $p = 0.28$).	Exercise E/e′ does not reflect LVFP increase with exercise
Obokata et al. 2017 [16••]	50 patients with HFpEF 24 patients with non-cardiac dyspnea	Supine bicycle	Invasive Catheterization Echocardiography	Correlation between exercise E/e′ and PCWP similar to rest At rest, $r = 0.63$; $p < 0.0001$ During exercise, $r = 0.57$; $p < 0.0001$	Adding of exercise E/e′ (> 14) to ESC HFpEF guideline criteria improved sensitivity (to 90%), but decreased specificity (71%). Exercise echocardiography may help rule out HFpEF
Hong et al. 2017 [21]	21 patients undergoing 1 year of routine FU CAG; no significant stenosis at FU CAG	Supine bicycle	Invasive Catheterization Echocardiography	Group I ($n = 8$) had a decrease in minimal LV pressure with exercise; Group II ($n = 13$) had an increase in minimal LV pressure with exercise LV apical back rotation parameters by speckle tracking echo at rest and during 50 W of exercise were compared.	Δ minimal LVP significantly correlated with apical back rotation at MVO ($r = -0.77$, $p = 0.009$) and minimal apical back-rotation velocity at 50 W ($r = 0.69$, $p = 0.028$). Dynamic changes in LV apical back rotation during exercise can be used as non-invasive parameters of diastolic suction during exercise.

CAG coronary angiography, *ESC* European Society of Cardiology, *HFpEF* heart failure with preserved ejection fraction; *LVEDP* left ventricular end-diastolic pressure, *LVFP*, left ventricular filling pressure, *LVP* left ventricular pressure, *MVO* mitral valve opening, *PASP* pulmonary artery systolic pressure, *PCWP* pulmonary capillary wedge pressure galectin-3, a marker of cardiac fibrosis), and resting echocardiographic markers in patients with exertional dyspnea and mild diastolic dysfunction, but resting E/e′ < 14 [22•]. Patients (171 dyspneic patients, 65 ± 8 years) were followed over 24.2 ± 4.6 months for endpoints of cardiovascular hospitalization and death. They concluded that implementation of a 2-step algorithm (Doppler echocardiographic evaluation of resting E/e′ and assessment of the biomarker galectin-3) may improve the proper diagnosis and prognostic assessment of patients with HFpEF, especially for the many patients who are unable to perform a diagnostic exercise test.

Another attempt to improve diastolic stress testing is addition of the untwisting velocity besides E/e′. Hong et al. investigated the effect of exercise on LV early diastolic function using high-fidelity LV pressure catheters in combination with echocardiography to measure e′ and untwisting velocity. LV early diastolic function can be evaluated clinically by tissue Doppler echocardiography to measure mitral annulus velocity (e′), which in principle represents LV lengthening velocity, and speckle tracking echocardiography to measure LV untwisting velocity [23]. Previous studies showed that both e′ and untwisting velocity reflect relaxation and restoring forces [24, 25]. As suggested by the study of Hong et al., untwisting velocity may help to identify patients with severely impaired diastolic function during exercise. This was, however, a study with a small number of subjects (a total of 21), with essentially a demonstration of a mechanistic principle. Whether measurement of untwisting velocity can be easily performed or has an incremental value to the current simpler method needs further clinical experience.

Prognostic Implications of Diastolic Abnormalities with Exercise

The association between abnormal exercise E/e′ and adverse medial outcomes is important clinically. Holland et al. followed 522 patients who underwent diastolic stress echocardiography [26]. At a median follow-up of 13.2 months, patients with isolated raised exercise E/e′ and isolated ischemia had similar outcomes. When patients were stratified by resting E/e′, the prognostic value of exercise E/e′ was most associated with cardiovascular hospitalization, independent of and incremental to inducible ischemia. Luong et al. at our institution examined the prognostic value of post exercise E/e′ > 15 in a large registry cohort of 14,446 patients who underwent treadmill exercise echocardiography for known or suspected coronary artery disease. Elevation in E/e′ was a strong predictor of all-cause mortality with incremental association with death independent of the presence of ischemia, age, and experience of exertional dyspnea. Patients who had both elevated E/e′ and abnormal regional wall motion abnormalities had the worst prognosis with a relative risk of death that was nearly fourfold higher than those with normal values. Furthermore, patients with post exercise E/e′ > 15 had an instantaneous risk of death that was double that of individuals with E/e′ < 15, even in the absence of ischemia [27].

Kosmala et al. reported the prognostic value of abnormal diastolic reserve (defined as exercise E/e′ > 14) and abnormal systolic response (defined as reduced global longitudinal strain rate (rest GLS)) in a characterized cohort of patients with HFpEF [28]. Both abnormal GLS and exercise E/e′ were independent predictors of outcome, and incremental to clinical variables and serum BNP levels. Importantly, the prognostic value of both abnormal exercise GLS and exercise E/e′ was superior to their prognostic value at rest. A further study was performed by Wang et al. in 80 patients with HFpEF. Abnormal LV systolic and diastolic responses to exercise assessed by LV longitudinal strain or strain rate and E/e′ have been reported to improve risk prediction compared with clinical and resting measurements in HFpEF, although this usage also requires additional confirmation in larger, multicenter studies.

Since exercise E/e′ tracks with both hemodynamics and prognosis, it suggests that it might be a useful intermediate endpoint for clinical trials. The E/e′ ratio does not change as much as filling pressures do, but a recent study demonstrated reduction in E/e′ with treatment, which was correlated with improved exercise capacity [29]. In contrast, other studies have failed to identify any changes in E/e′ with medical therapy, even as alternative measures of congestion such as natriuretic peptides or left atrial volume improved. Thus, more data on the utility of diastolic indices (including E/e′) as endpoints would also be of great interest.

Clinical Protocols and Practical Techniques and Limitations

Exercise can be performed using a supine bicycle or treadmill protocol. Dobutamine is not recommended, with its vasodilator and inotrope effect which produces a very different hemodynamic profile compared with that of exercise. Parameters obtained include mitral inflow by pulsed Doppler echocardiography at the level of the mitral tips, medial mitral annular velocities by spectral tissue Doppler echocardiography, and tricuspid regurgitation jet by continuous wave Doppler at baseline and after the termination of exercise. Diastolic function parameters can be obtained during recovery after the assessment of regional wall motion abnormalities when mitral inflow velocities become unfused, especially when an exercise echocardiogram is performed for the evaluation of dyspnea.

In patients with diastolic heart failure, left atrial pressure is increased, leading to an increase in mitral E velocity, whereas annular e′ velocity remains reduced given the limited preload effect on e′. Moreover, an increase in the pulmonary artery systolic pressure can be detected by the increase in peak velocity of the tricuspid regurgitation jet. However, the assessment of right atrial pressure during or immediately after exercise remains challenging, with limited published data. It is probable that exercise echo underestimates the degree of elevation in pulmonary artery pressure in these patients. On the other hand, in the absence of cardiac disease, e′ increases to a similar extent to the increase in mitral E velocity, and the normal E/e′ ratio is unchanged with exercise. Exercise echocardiography should also include assessment of dynamic mitral regurgitation and LV outflow tract obstruction, which may also give rise to diastolic dysfunction and symptoms, especially in patients with basal septal hypertrophy.

Summary and Future Direction

Diastolic exercise echocardiography testing provides valuable information regarding the diagnosis of HFpEF and can discriminate between cardiac and non-cardiac heart failure pathology, beyond resting images alone. Indeed, diastolic exercise echocardiography is now recommended by both the American Society of Echocardiography and the European Association of Cardiovascular Imaging in individuals with unexplained dyspnea upon exertion [6]. We now have sufficient clinical experience and data to integrate diastolic exercise echocardiography into our clinical practice [30]. Importantly, given the multiple causes of dyspnea in the elderly, conditions other than increased LV filling pressure—such as coronary ischemia, valvular disease, and constrictive pericarditis—can be diagnosed during resting and exercise echocardiography, whereas non-cardiac causes can be excluded. When patients' symptoms are exertional and remain unexplained by a resting echocardiogram, functional diagnostic testing needs to be done with exercise. Dyspnea is one of the most common referral reasons for resting as well as exercise echocardiography and was associated with the worst outcome after a stress test [31]. Unless major structural disease or hemodynamic abnormalities are suspected or found on resting echocardiography, diastolic functional evaluation with exercise is essential for comprehensive evaluation to ensure that HFpEF will not be missed. In patients who are unable to exercise sufficiently, the passive leg raise maneuver may demonstrate an increased E/e′ in patients with reduced diastolic reserve [32], but its sensitivity is low.

We acknowledge that further studies should be done to improve the diagnostic accuracy and utility of diastolic exercise echocardiography. Technical improvements that could enhance the diagnostic yield and overcome the limitation of exercise E/e′ as a measure of exercise-related diastolic dysfunction include incorporation of other novel and more sensitive markers of diastolic function into diastolic stress echocardiography protocols. These include assessment of LV long axis function with GLS, direct strain measurement of LV diastolic function, left atrial strain measurement, or measurement of early diastolic LV suction with torsion parameters. With these ongoing efforts and the recommendations from the recent guidelines, it is evident that the integration of diastolic exercise echocardiography into clinical practice will certainly add greatly our understanding of diastolic dysfunction and improve patient care.

Compliance with Ethical Standards

Conflict of Interest Kyung-Hee Kim, Garvan C. Kane, Christina L. Luong, and Jae K. Oh declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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