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Diastolic Stress Testing Along the Heart Failure Continuum

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Abstract

Purpose of Review This review summarizes recent developments highlighting the clinical utility of diastolic stress testing along the heart failure continuum.

Recent Findings Invasive hemodynamic assessment of cardiac filling pressures during physiological stress is the gold-standard technique for unmasking diastolic dysfunction. Non-invasive surrogate techniques, such as Doppler ultrasound, have shown excellent agreement with invasive approaches and are now recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging. While cycle exercise is often advocated, recent evidence supports the use of isometric handgrip as a viable alternative stressor.

Summary Diastolic stress testing is a powerful tool to enhance detection of diastolic dysfunction, is able to differentiate between cardiac and non-cardiac pathology, and should be incorporated into routine clinical assessment.

Keywords Diastolic stress testing · Heart failure · Exertional dyspnea · Isometric handgrip · Cycle exercise

Introduction

Normal left ventricular (LV) diastole requires the coordination of several physiological processes which allow the heart to fill sufficiently under low filling pressures. As systole ends, LV elastic recoil and active relaxation gives rise to an abrupt decline in LV pressure until the mitral valve opens, and blood flows along a pressure gradient toward the apex. Upon pressure equilibration between the left atrium and the LV (i.e., diastasis), the final component of ventricular filling occurs when the atrium contracts and systole resumes. Impairment of any one of these processes can result in a rise in LV filling pressure that is transmitted to the left atrium and pulmonary veins, and can be associated with pulmonary edema and dyspnea [1]. Progression along the American College of Cardiology/American Heart Association (ACC/AHA) heart failure continuum from stage A (presence of cardiovascular risk factors with no structural adaptations) to stage C (structural adaptation and symptoms of heart failure) is associated with graded levels of diastolic dysfunction.

Conventional resting measures of diastolic function, particularly Doppler derived mitral inflow and annular tissue velocities, are both prognostic and predictive of events in overt heart disease (e.g., stage C) [2–4]. However, when disease is less advanced (e.g., stage A) and/or when the diagnosis remains equivocal, diastolic stress testing may be indicated to differentiate cardiac vs. non-cardiac pathology. Indeed, over the past decade, assessment of diastolic function during physiological stress, termed "diastolic stress testing," has emerged as a powerful tool to enhance detection of diastolic dysfunction as the etiological feature of exertional dyspnea [5]. As a result, diastolic stress testing is now recommended by both the American Society of Echocardiography and the European Association of Cardiovascular Imaging [2, 3, 6].

This article reviews the evolution of diastolic stress testing, current practices, and procedures, and discusses the potential for diastolic stress testing across the heart failure continuum.

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Pathophysiology of Diastolic Dysfunction

Diastole is a complex process governed by multiple factors that regulate active LV pressure decay and passive LV diastolic stiffness (Fig. 1). Determinants of active LV pressure decay include oxygen delivery and intracellular calcium handling. Indeed, diastole is a highly energy-dependent process, requiring sufficient delivery of oxygen for the generation of adenosine triphosphate (ATP). Unlike systole, which only requires ATP for the removal of troponin-C from actin, diastole requires ATP for the (1) reuptake of calcium into the sarcoplasmic reticulum via the sarco-endoplasmic reticulum calcium ATP-ase (SERCA), (2) dissociation of actin and myosin, and (3) uncoupling of calcium from troponin-C [7]. In addition to these direct consequences, oxygen deprivation also contributes to diastolic dysfunction by shifting substrate utilization away from fatty acid metabolism toward glucose metabolism [8–10].

Impaired intracellular calcium handling has also been implicated as a primary mechanism driving diastolic dysfunction. For example, excess calcium entry through L-type calcium channels, over activity of calcium-release-activated calcium channels (such as Orai-1), impaired sodium-calcium exchanger pumps, calcium reuptake and leaky ryanodine receptors have each been implicated in a variety of conditions associated with diastolic dysfunction, including heart failure with preserved ejection fraction (HFpEF) [11–15]. These detrimental molecular processes ultimately impair actin-myosin cross-bridge cycling and lead to a stiff ventricle.

In addition to the contributions from active LV pressure decay, diastolic dysfunction is also associated with increased passive LV stiffness. Expansion of the extracellular matrix

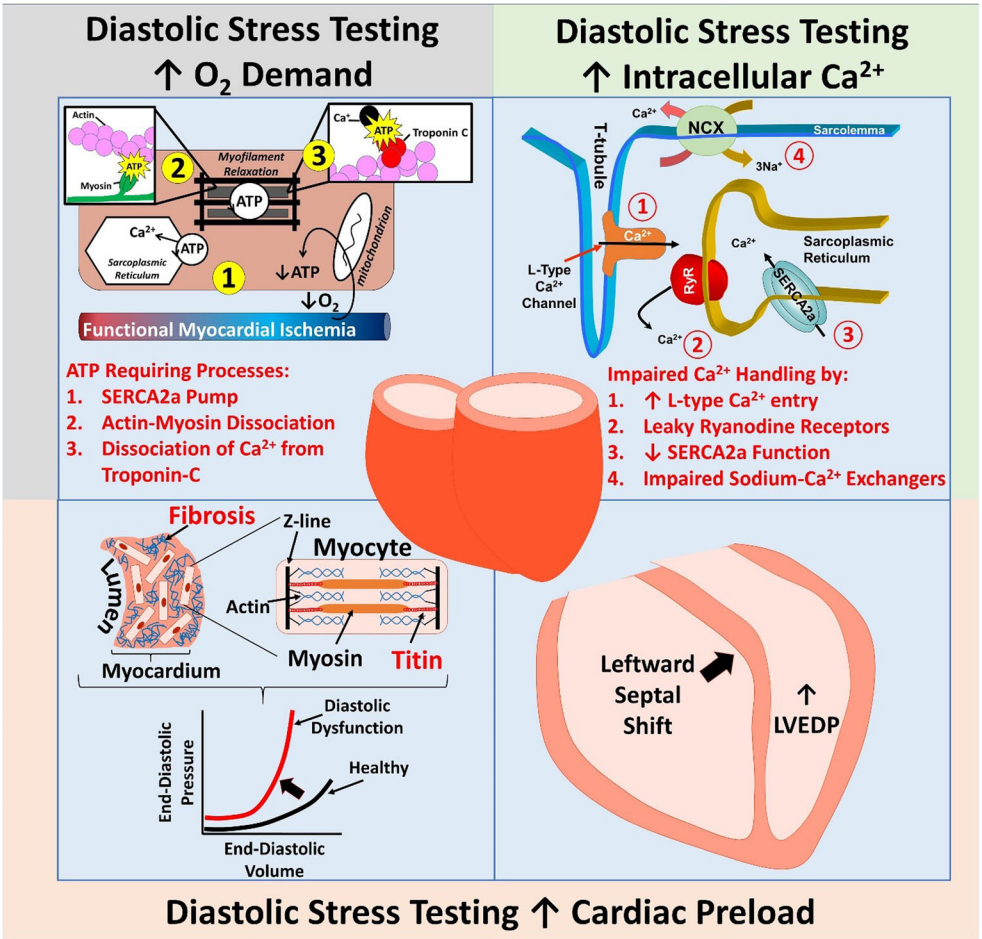

Fig. 1 Key pathological mechanisms involved in the development of diastolic dysfunction and the role of diastolic stress testing in exacerbating each mechanistic pathway. Clockwise from top-left: functional myocardial ischemia caused by an increased myocardial oxygen (O_2) demand can lead to insufficient production of myocardial adenosine triphosphate (ATP); impaired calcium (Ca^{2+}) handling due to elevated intracellular Ca^{2+} concentrations can lead to prolonged and delayed myocardial relaxation; pericardial constraint can be exacerbated by increases in preload and lead to an increased right ventricular pressure, causing a leftward shift of the interventricular septum, and ultimately leading to increased left ventricular end-diastolic pressures (LVEDP); increased diffuse fibrosis and impaired titin function can be exacerbated by increases in preload and lead to a shift in the end-diastolic pressure volume relationship upwards and to the left. SERCA2a sarco/endoplasmic reticulum Ca^{2+} ATP-ase; RyR ryanodine receptor; NCX sodium-Ca^{2+} exchanger

(increased myocardial fibrosis), left ventricular hypertrophy, and dysregulation of structural proteins like titin can each reduce passive ventricular compliance both independently and in concert [16–20]. Moreover, factors external to the myocardium can also negatively affect passive LV stiffness. For example, pericardial fat deposition, in combination with pericardial constraint, has recently been implicated as a major source of diastolic dysfunction [21–23]. Under this paradigm, with the LV constrained by the pericardium, right ventricular filling causes a leftward septal shift and an elevation in LV end-diastolic pressure [23].

While in extreme cases, each of the above mechanisms can independently contribute to overt diastolic dysfunction, less extreme cases often fail to present under resting conditions. Diastolic stress testing is therefore necessary to exacerbate these underlying mechanisms and unmask diastolic dysfunction (Fig. 1). For example, increasing myocardial oxygen demand can disrupt myocardial energetics and the processes governing calcium handling [24–26, 27••, 28•]. Increasing cardiac afterload floods the myocardium with calcium to support increased force production, but places greater stress on the processes governing intracellular calcium homeostasis. Finally, increasing cardiac preload (e.g., saline infusion, leg lifts, dynamic exercise) can exacerbate LV passive stiffness, augment LV/RV interaction, and adversely increase cardiac filling pressures [23].

Diastolic Stress Testing Along the Heart Failure Continuum

The term "diastolic stress testing" was first coined by Ha and colleagues [29], describing an abnormal rise in left ventricular filling pressures during exercise. However, in practice, "diastolic stress testing" has been utilized for several decades [30, 31]. For example, more than 60 years ago, Lewis and colleagues demonstrated an abnormal rise in pulmonary capillary wedge pressure (PCWP) in response to recumbent cycle exercise in some, but not all, patients with cardiovascular disease despite normal PCWP at rest [30]. More recently, Levine and coworkers have used acute volume loading/unloading to characterize LV compliance in health and disease [24, 31–38]. Today, diastolic stress testing is recognized as the most robust method for discriminating between cardiac and non-cardiac involvement in exercise-induced dyspnea [39–42]. Some of the most compelling and influential examples of this have recently come from Borlaug and colleagues at the Mayo Clinic in Rochester, MN, using invasive assessment of left ventricular filling pressures during submaximal cycle exercise to differentiate patients with HFpEF from those without cardiac involvement [5, 10, 25, 39–41, 43–62, 63••]. Importantly, while the majority of these studies have focused on direct, gold-standard, invasive measures of LV filling pressure, Borlaug and colleagues have also shown strong agreement between PCWP and its non-invasive, Doppler-derived surrogate (early mitral inflow velocity to early annual tissue velocity ratio, E/e') [63••]. Indeed, this helps further validate the non-invasive work of Ha and colleagues, who have consistently used E/e' during cycle exercise to differentiate cardiac from non-cardiac pathology [29, 64]. Specifically, in 2005, this group was able to identify individuals who had seemingly normal resting diastolic function (i.e., normal E/e'), but upon exercise, shared an exaggerated E/e' response (i.e., abnormal rise in cardiac filling pressure) [29]. Across each of these studies, the common threshold defining an abnormal rise in cardiac filling pressure was a change in E/e' > 1.5.

Cycle echocardiography is susceptible to several limitations, however, including respiratory and movement artifacts that are exaggerated in clinical populations at risk for diastolic dysfunction (obese, elderly, etc.). Moreover, while Borlaug and colleagues have convincingly demonstrated that only a mild-level of exercise is needed to elicit an abnormal diastolic response (~20–40 W), this approach hinges upon the ability of patients to perform dynamic leg exercise. In an effort to overcome these limitations, our group has advocated replacing cycle exercise with isometric handgrip [27••, 28•]. Indeed, isometric handgrip causes a robust, and highly reproducible pressor-mediated increase in heart rate and blood pressure [65], without causing dramatic increases in respiration or chest wall movement. Importantly, isometric handgrip also elicits marked increases in invasively measured LV filling pressures [42, 66, 67, 68•]. In our hands, isometric handgrip echocardiography is capable of differentiating normal from abnormal diastolic function (defined as a rise in E/e' > 1.5) [28•], with comparable hemodynamic changes to conventional cycle exercise [27••].

While isometric handgrip produces a similar hemodynamic challenge compared to low-level cycle exercise [27••], these two stressors likely exacerbate diastolic dysfunction through somewhat different mechanisms. Independent of increased myocardial oxygen demand, the primary mechanism driving diastolic dysfunction during cycle exercise is likely related to the demand for increased cardiac output and reduced LV relaxation time. In this scenario, a stiff ventricle combined with increased venous return leads to an increase in LV filling pressure. In contrast, isometric handgrip uniquely increases LV afterload secondary to a neurally mediated exercise pressor reflex [69–73]. To support the ejection of blood during systole, this increase in afterload is met by a concomitant increase in intracellular calcium, which must either be sequestrated back in to the sarcoplasmic reticulum or extruded from the myocyte during ventricular relaxation [74–76]. Dysregulation of this processes will lead to prolonged actin-myosin cross-bridge formation and impaired active relaxation [77, 78] and thus increased LV stiffness and elevated LV filling pressure [24]. The potential for varying mechanistic pathways ought to be

Table 1 Diastolic stress testing along the heart failure continuum, data from seminal investigations and those from the last 5 years

First author and date	Population	Measurement modality	Stress modality	Main outcomes
ACC/AHA stage A				
Gibby, 2013 [80]	559 hypertensives with diabetes and no structural remodeling	Echo	Cycle	20% of participants showed post-exercise E/e' > 13 (max exercise ~ 7.7 METs).
Shim, 2013 [79]	Hypertensives with no increase in LV mass—72 with abnormal ventricular-vascular interaction and 72 normal ventricular-vascular interaction	Echo	Cycle	Patients with abnormal ventricular-vascular interaction during exercise—ΔE/e' 2.1 during 50 W cycle exercise. Patients with normal ventricular-vascular interaction—ΔE/e' 1.3 (below established diastolic cutoff).
van Empel, 2014 [10]	7 hypertensives with no increase in LV mass and 12 healthy controls	Invasive	Cycle	Hypertensives—ΔPCWP of 8 mmHg at max exercise (~ 87 W). Healthy controls—ΔPCWP of 8 mmHg at max exercise (~ 114 W).
Samuel, 2017 [28•]	17 asymptomatic elderly and 19 young healthy controls	Echo	IHG	65% of the elderly individuals showed ΔE/e' > 1.5. 0% of healthy controls showed ΔE/e' > 1.5.
Samuel, 2018 [27••]	12 asymptomatic elderly individuals	Echo	IHG, cycle	75% of individuals had a ΔE/e' > 1.5 during IHG. 67% of individuals had a ΔE/e' > 1.5 during cycle.
ACC/AHA stage B				
Sonaglioni, 2015 [81]	90 asymptomatic patients with aortic stenosis	Echo	Cycle	ΔE/e' of 6.5 at peak exercise (only 16.7% of patients reached > 75 W).
Christensen, 2016 [82]	25 asymptomatic patients with aortic stenosis and LA volume index > 35 mL/m^2 and 14 asymptomatic patients with aortic stenosis and LA volume index < 35 mL/m^2	Invasive	Cycle	Group with LA volume index < 35 mL/m^2—ΔPCWP of 15 mmHg at 75 W. Group with LA volume index > 35 mL/m^2—ΔPCWP of 16 mmHg at 75 W.
ACC/AHA stage C				
Borlaug, 2015 [49]	28 HFpEF patients	Invasive	Cycle	ΔPCWP of 13 mmHg at 20 W.
Borlaug, 2016 [50]	26 HFpEF patients	Invasive	Cycle	ΔPCWP of 13 mmHg at 20 W.
Obokata, 2016 [63••]	50 HFpEF patients and 24 patients with non-cardiac dyspnea	Invasive, echo	Cycle	HFpEF—ΔPCWP of 14 mmHg and ΔE/e' of 3 at 20 W. Non-cardiac dyspnea—ΔPCWP of 7 mmHg and ΔE/e' of 1 at 20 W.
Obokata, 2017 [83]	37 HFpEF patients and 43 HFrEF patients	Echo	Cycle	HFpEF—ΔE/e' 1.7 at 10 W. HFrEF—ΔE/e' 1.6 at 10 W.
Gorter, 2018 [85]	21 HFpEF patients with no pulmonary hypertension, 95 HFpEF patients with post-capillary pulmonary hypertension, and 45 HFpEF patients with pre- and post-capillary pulmonary hypertension	Invasive	Cycle	No pulmonary hypertension—ΔPCWP 12 mmHg at max exercise (~ 42 W). Post-capillary pulmonary hypertension—ΔPCWP 13 mmHg at max exercise (~ 32 W). Pre- and post-capillary pulmonary hypertension—ΔPCWP 12 mmHg at peak exercise (~ 31 W).
Hieda, 2018 [88]	10 HFpEF patients and 12 healthy controls.	Invasive	LBNP and saline	Up- and leftward shift of the end-diastolic pressure volume relationship (i.e., increased LV stiffness).
Kosmala, 2018 [84]	171 patients with unexplained dyspnea and suspected HFpEF	Echo	Treadmill	60% abnormal exercise response (post-exercise E/e' > 14).
Obokata, 2018 [86]	38 HFpEF patients and 20 patients with non-cardiac dyspnea	Invasive	Cycle	HFpEF—ΔPCWP of 14 mmHg at 20 W. Non-cardiac dyspnea—ΔPCWP of 7 mmHg at 20 W.
Obokata, 2018 [87]	50 HFpEF patients and 24 patients with non-cardiac dyspnea	Invasive	Cycle	HFpEF—ΔPCWP 14 mmHg at 20 W. Non-cardiac dyspnea—ΔPCWP 7 mmHg at 20 W.
Rommel, 2018 [68•]	24 HFpEF patients and 9 patients with non-cardiac dyspnea	Invasive	IHG	HFpEF—ΔPCWP of 11.1 mmHg. Non-cardiac dyspnea—ΔPCWP of 6.2 mmHg.

ACC/AHA American College of Cardiology/American Heart Association, *LV* left ventricular, *Echo* echocardiography, *E/e'* ratio between Doppler-derived early diastolic mitral inflow velocity and early diastolic tissue velocity, *W* watts, *PCWP* pulmonary capillary wedge pressure, *IHG* isometric handgrip exercise, *METs* metabolic equivalents, *LA* left atrial, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *LBNP* lower body negative pressure

considered when designing diastolic stress tests and warrants future investigation.

Regardless of the mechanism driving diastolic dysfunction during physiological stress, or the method by which diastolic dysfunction is measured, there is increasing body of literature supporting the use of diastolic stress testing across the heart failure continuum (Table 1). Indeed, diastolic stress testing can successfully unmask diastolic dysfunction in asymptomatic patients with hypertension with no structural remodeling (i.e., stage A, [10, 79, 80]), asymptomatic patients with mild aortic stenosis (i.e., stage B, [81, 82]), and compensated HFpEF patients (i.e., stage C, [10, 39, 42, 49, 50, 63••, 68•, 83–88]. While cycle exercise has been the predominant method of diastolic stress testing [10, 39, 86], isometric handgrip echocardiography has been shown to be a robust alternative [27••, 28•, 42, 68•], with comparable end-results [27••].

The Future of Diastolic Stress Testing

The demonstration of clinical benefit for early diagnosis and management of diastolic dysfunction advocates for the widespread clinical adoption of diastolic stress testing. Indeed, cardiac stress testing (particularly recumbent cycle exercise) is already integrated and practiced in echocardiography laboratories worldwide. Inclusion of simple Doppler-derived estimates of LV filling pressures can be easily added to standard of care measures, providing relevant diagnostic and prognostic information [2–4, 63••]. That non-invasive diastolic stress testing can also be done by simply performing handgrip exercise [27••, 28•] holds even greater promise for widespread clinical adoption. In an ideal world, every echocardiography machine would come equipped with a stress ball or handgrip dynamometer so that diastolic stress testing may be included as part of every routine cardiac scan. While diastolic stress testing has strong prognostic and diagnostic utility in patients with unexplained dyspnea and/or heart failure symptoms, it remains unclear what the predictive capacity is for asymptomatic patients (e.g., ACC/AHA stage A). Longitudinal studies are therefore needed to define the predictive value of diastolic stress testing across the heart failure continuum.

Conclusions

Diastolic stress testing provides diagnostic and prognostic value in those at risk for heart failure and those with symptoms of unexplained dyspnea. The ability of non-invasive diastolic stress testing to successfully discriminate between cardiac and non-cardiac limitation to exercise and unmask diastolic dysfunction in both clinical and sub-clinical patients highlights its potential application in the cardiology clinic. That non-invasive diastolic stress testing, either with cycle echocardiography or isometric handgrip echocardiography, is both simple and relatively low cost, holds great promise. Future work is needed using this approach to better understand specific pathophysiological mechanisms and the predictive capacity of these novel diastolic stress tests.

Compliance with Ethical Standards

Conflict of Interest The authors 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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- •• Of major importance

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