

## Editorial



# Diastolic Stress Echocardiography to Quantify the Response of Diastolic Functional Indices to Dynamic Exercise in Abnormal Relaxation: Unmasking Diastolic Abnormalities is Getting Ready for Prime Time

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Left ventricular (LV) diastolic dysfunction is caused by impaired LV relaxation with or without reduced restoring forces (and early diastolic suction), and increased LV chamber stiffness. Abnormalities of LV diastolic function have a major role in producing signs and symptoms in patients presenting with heart failure (HF).<sup>1-4)</sup> Impaired myocardial relaxation, manifested echocardiographically showing reduced early (E) to late (A) diastolic filling ratio or prolonged deceleration time of E velocity, is the most common type of LV diastolic dysfunction, and it is recognized as an early manifestation in the spectrum of diastolic abnormalities. Myocardial relaxation is gradually reduced with aging but it also reduced in all forms of myocardial disease including myocardial ischemia, hypertensive heart disease, hypertrophic cardiomyopathy, and HF with preserved ejection fraction. However, because of its ubiquity, this abnormality is often recognized as an incidental finding. In fact, most people with impaired relaxation do not have symptoms or signs of HF at rest.<sup>5)</sup> This is because increased LV filling pressure is unusual in the absence of systolic dysfunction or comorbidities such as myocardial infarction or hypertensive heart disease.<sup>6)</sup> Instead, exertional dyspnea is quite common in these patients and therefore impaired relaxation is suggested as a precursor to overt HF.<sup>5)</sup> During exercise, there is less time for diastolic filling of LV because tachycardia decreases the duration of diastole. To maintain or augment the stroke volume, myocardial relaxation should be faster and LV suction should be exaggerated.<sup>7)8)</sup> However, in patients with diastolic dysfunction, the abnormal relaxation prevents augmentation of relaxation as heart rate increases during exercise. Therefore, exercise could unmask diastolic abnormalities not evident under rest conditions. However, the majority of measures to characterize LV diastolic function are obtained at rest. Moreover, it is not yet known whether impaired relaxation leads invariably to elevated LV filling pressure during exercise since, in patients with a similar grade of diastolic dysfunction at rest, there can be a spectrum of alterations in diastolic function during exercise. Although invasive hemodynamic monitoring during exercise would be accurate and is considered as gold standard, this method has an obvious limitation. Thus, a noninvasive demonstration of this phenomenon will be more practical and can be performed repeatedly and it would be clinically useful.

Diastolic stress echocardiography refers to the use of exercise Doppler echocardiography to detect impaired LV diastolic functional reserve and the resulting increase in LV filling pressure during exercise and it was introduced more than a decade ago and has been proven feasible.<sup>9-12)</sup> More recently, guidelines from American Society of Echocardiography (ASE)/ European Association of Cardiovascular Imaging (EACVI) regarding the evaluation of LV diastolic function by echocardiography<sup>13)14)</sup> and clinical use of stress echocardiography in non-ischemic heart disease<sup>15)16)</sup> included diastolic stress echocardiography as a valuable tool for the evaluation of patients with unexplained dyspnea and subclinical LV diastolic dysfunction.

In this issue of the Journal, Jang and colleagues<sup>17)</sup> present an interesting analysis emphasizing the importance of assessing LV diastolic function during exercise. The authors prospectively performed diastolic stress echocardiography in 120 patients with impaired relaxation and borderline E/e'. Markedly heterogeneous hemodynamic changes during exercise could be delineated and thus they suggested that diastolic stress echocardiography was useful to further characterize these patients. Their findings are consistent with a previous observation<sup>18)</sup> showing that subjects with impaired relaxation and normal ejection fraction at rest exhibit a wide spectrum of alterations in diastolic function during exercise. A previous study also showed that patients with impaired relation who had lower diastolic functional reserve during exercise had stiffer ventricle and higher LV filling pressure during exercise and showed lower exercise capacity.<sup>18)</sup> In the present study, despite normal LV filling pressure at rest, almost 40% of patients showed elevated filling pressure during exercise. These results further underscore the need for assessing hemodynamic performance during some forms of stress, especially exercise, since this could unmask further diastolic abnormalities in a significant proportion of patients with mild diastolic dysfunction at rest. Moreover, to better understand the pathophysiology of patients with impaired relaxation at rest, assessment of hemodynamic performance during exercise would be more revealing.

Another interesting observation from the study was that the proportion of patients who have significant dyspnea was almost double in patients who showed increased LV filling pressure during exercise when compared with that of patients without elevated filling pressure during exercise. These findings imply that increased in LV filling pressure during exercise may contribute to symptom of dyspnea and exercise intolerance. The cause of exercise intolerance in some patients with LV failure is diminished cardiac output, so that inadequate oxygen is delivered to working skeletal muscle to meet the demands of aerobic metabolism. However, in other patients, exercise intolerance is due to a rise in pulmonary capillary wedge pressure, resulting in marked dyspnea.<sup>19)</sup> The results of the present study further emphasized that an increase in LV filling pressure rather than abnormal stroke volume response may be a more important hemodynamic contributor during low level supine exercise in patients with impaired relaxation at rest.

In the current study, approximately 30% of patients developed exercise-induced pulmonary hypertension (PH). Exercise-induced PH is a less-well understood entity but it is common in subjects with reduced as well as preserved LV ejection fraction.<sup>20)</sup> It is considered as an important cause of exertional dyspnea and exercise intolerance.<sup>20)21)</sup> Although an increase in LV filling pressure is strongly related with exercise-induced PH, exercise-induced PH can occur in the absence of a significant increase in LV filling pressure. Exercise-induced PH in subjects with preserved LV ejection fraction has been shown to be associated with worse outcomes and an increase in LV filling pressure during exercise was the most important prognosticator.<sup>22)</sup> Diastolic stress echocardiography is quite helpful in this regard because a

reliable estimation of both LV filling pressure and pulmonary artery systolic pressure can be obtained non-invasively during exercise.

Including the current study, most of the previous studies regarding diastolic stress echocardiography excluded the patients with significant coronary artery disease (CAD) to avoid confounding effects from myocardial ischemia to diastolic dysfunction.<sup>9-12)</sup> However, in our clinical practice, patients with significant CAD with or without myocardial ischemia would be an important subset of patient population in whom the assessment of exercise-induced increase in LV filling pressure would be critically important. Future studies would be warranted to clarify this issue. In the present study, even after performing diastolic stress echocardiography, 47% of patients were classified as indeterminate. In recent guidelines, diastolic stress echocardiography is considered definitively abnormal when the septal E/e' ratio is >15, peak tricuspid regurgitant velocity is >2.8 m/sec with exercise and the septal e' velocity is <8 cm/sec at baseline.<sup>13-16)</sup> If the interpretation criteria from the recent guidelines were employed, the proportion of the patients who were classified as indeterminate would be much less.

Do we need a better diastolic stress echocardiography? The short answer is "yes." How can we improve the diagnostic accuracy and utility of diastolic stress echocardiography? Recently, it has been shown that the absence of a decrease in minimal LV pressure during exercise, a manifestation of impaired LV suction, was closely linked with impaired LV untwisting during exercise.<sup>23)</sup> In patients with normal LV ejection fraction, previously treated for CAD, we have shown a range of responses when measuring minimum LV diastolic pressure, *tau*, and untwisting velocity. Patients with decrease in minimum LV diastolic pressure had most marked increase in LV untwisting velocity with exercise. Furthermore, e' velocity during exercise was highest in patients with decrease in minimum LV diastolic pressure. Change in LV end-systolic volume was similar in patients with decrease and increase in LV minimum pressure, suggesting that restoring forces was not accounting for the difference in e' and untwisting velocity. These findings imply that dynamic changes in LV apical back rotation during exercise can be used as a non-invasive parameter of diastolic suction during exercise. More work would be needed to refine and standardize the methodology for measuring twisting deformation, but provided the technique is improved, untwisting velocity may become an important addition to the diastolic stress echocardiography.<sup>24)</sup>

The decades of investigation into the diastolic stress echocardiography have provided us with many wonderful insights into cardiovascular hemodynamics and have improved our delivery of care for patients with diastolic dysfunction and exertional dyspnea. The novel and important insights provided by Jang and colleagues<sup>17)</sup> in their elegant study have vertically advanced our understanding to diastolic dysfunction. With these efforts and the recommendations from the recent guidelines,<sup>13-16)</sup> it is quite evident that the integration of diastolic stress echocardiography into clinical practice will certainly enhance our understanding and better management to our patients.<sup>25)</sup>

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