Quantitation of the diastolic stress test: filling pressure vs. diastolic reserve

Conrad Gibby¹,²†, Dominik M. Wiktor¹,³†, Malcolm Burgess⁴, Kenya Kusunose¹, and Thomas H. Marwick¹*

¹Cardiovascular Imaging J-5, Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA; ²Case Western Reserve University School of Medicine, Cleveland, OH, USA; ³Department of Medicine, University Hospitals, Cleveland, OH, USA; and ⁴Aintree University Hospital, Liverpool, UK

Received 13 January 2012; accepted after revision 20 March 2012; online publish-ahead-of-print 22 June 2012

Aims
The diastolic stress test (DST) may facilitate the attribution of exertional dyspnoea to cardiac and non-cardiac diseases. However, there is currently no consensus as to the optimal marker of exertional diastolic dysfunction (DD)—the main alternatives being estimated left ventricular (LV) filling pressure (exercise E'/e') and diastolic functional reserve (DFRI). We sought to compare the correlates of these parameters.

Methods and results
DST was performed by adding the measurement of the transmural (E) and annular (e') velocities to standard exercise echo in 559 consecutive patients without significant rest or exercise mitral regurgitation. Exertional DD was separately defined by post-stress E'/e' >13 or DFRI <13.5. Logistic regression was used to identify the correlates of abnormal responses and linear regression was used to identify the contribution of both to exercise capacity. Abnormal exercise E'/e' (n = 112, 20%) and DFRI (n = 317, 57%) were modestly associated (κ 0.35, P < 0.0001). In a linear regression, abnormal exercise E'/e' (β = −0.19, P < 0.001) and DFRI (β = −0.15, P = 0.001) were associated with exercise capacity, independent of age, body mass index, wall thickness, haemodynamics or abnormal stress results. Logistic regression revealed abnormal exercise E'/e' (R² = 0.34) to be independently associated with female gender (β = 0.26, 95% CI: 0.11–0.60, P = 0.002), age (β = 1.04, 95% CI: 1.01–1.07, P = 0.01), hypertension (β = 0.35, 95% CI: 0.15–0.80, P = 0.01) and wall thickness (β = 4.3, 95% CI: 1.3–14.1, P = 0.02). The closest association of abnormal DFRI was exercise capacity (β = 0.89, 95% CI: 0.79–1.02, P = 0.09); no other clinical or stress variable was independently associated.

Conclusion
Exercise E'/e' and DFRI are both associated with exercise capacity, but E'/e' is more closely associated with the expected parameters of DD.

Keywords
Diastole  •  Exercise test  •  LV filling

Introduction
Exertional dyspnoea is a common symptom, with a wide range of aetiologies, and difficulties are frequently encountered in distinguishing cardiac from non-cardiac causes.¹ Diastolic dysfunction (DD), most commonly assessed on the relationship between the transmural flow velocity (E velocity) and the myocardial (e') velocity, is a common finding. However, exertional dyspnoea in this setting does not necessarily imply DD as the cause of this symptom.² The two most frequent problems are the attribution of a cardiac aetiology when another explanation is present and the absence of resting DD in a patient with exertional symptoms [in whom abnormal left ventricular (LV) filling may only occur during stress].

The cause of exercise intolerance in some patients with LV failure is fatigue, which may be due to diminished cardiac output. However, in other patients, exercise intolerance is due to a rise in the pulmonary capillary wedge pressure, resulting in dyspnoea. Abnormalities in LV diastolic function may occur with exercise in patients with clinical evidence of heart failure and a normal resting systolic function.³ Exercise has been demonstrated to unmask diastolic abnormalities not evident under resting

¹ These authors contributed equally to this work.
* Corresponding author. Tel: +1 216 445 7275; Fax: +1 216 445 7306; Email: marwict@ccf.org
Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2012. For permissions please email: journals.permissions@oup.com
conditions. Objective evidence of DD or raised filling pressure at the time of exertional dyspnoea is more persuasive that DD is causative. The diastolic stress test (DST), which examines LV filling on exertion, may be useful to separate cardiac from non-cardiac causes of dyspnoea, and has been shown previously to provide prognostic as well as diagnostic information. Unfortunately, there is currently no consensus as to the optimal marker of exertional DD, the main methods being the estimation of LV filling pressure (exercise $E/e'$) and diastolic functional reserve (DFRI). DFRI is calculated as the product of $\Delta e'$ and baseline $e'$ (an early diastolic mitral annular velocity at rest). We sought to provide haemodynamic validation and compare the correlates of these parameters. Our hypotheses were that (i) exercise $E/e'$ is a better marker of filling pressure than the diastolic reserve index and (ii) exercise $E/e'$ is more closely associated with other diastolic markers and exercise capacity than is the diastolic reserve index.

**Methods**

**Study design**

Two groups of patients were included in this study. The first (validation group), consisting of 37 patients undergoing haemodynamic assessment during exercise and previously used to validate exercise $E/e'$, were used for the validation of each parameter against a filling pressure as a reference standard. The second association group comprised 559 consecutive patients undergoing standard exercise echocardiography, where the physiological correlates of each diastolic measurement strategy were assessed. Drugs with anti-isaemic effects (beta-adrenoceptor and calcium blockers, and nitrates) were withheld on the day of the test. We excluded patients who were unable to exercise and those with mitral regurgitation.

**Resting echocardiography**

Standard two-dimensional measurements (LV diastolic and systolic dimensions, wall thickness, and left atrial volume) were obtained from patients in the left lateral position. The LVEF and left atrial volume were calculated in accordance with the guidelines and indexed to body surface area. Stroke volume (SV) was measured from the LV outflow tract diameter and the pulse-wave Doppler signal, as previously described, assuming the absence of significant aortic regurgitation. The $E/e'$ ratio was used as an estimate of the mean left atrial pressure. Operant ventricular elastance ($E_d$) was estimated as $E/e'$ divided by SV.

**Diastolic stress echocardiography**

In the haemodynamic validation group, patients undergoing diagnostic coronary angiography agreed to undertake a stress test during the procedure. After obtaining rest images from standard parasternal and apical views, a multistage supine bicycle exercise test was performed with a variable load bicycle ergometer in the validation group and treadmill exercise in the association group. Supine ergometer stress was performed on the angiography table; patients pedalled at a constant speed, starting with a workload of 25 W and increasing by an increment of 25 W every 3 min.

For the treadmill group, we undertook exercise $E/e'$ measurement in consecutive patients undergoing test for diagnostic and prognostic evaluation. Most patients undertook a standard Bruce protocol, but those with a reduced functional capacity were studied with a Naughton or Cornell protocol.

Echocardiography was performed using a standard ultrasound system (GE Vingmed Vivid 7, GE Medical, Milwaukee, Wisconsin, USA) with a 2.5-MHz transducer during rest, each stage of cycle exercise and recovery. From the apical window, a 1–2 mm pulsed Doppler sample volume was placed at the mitral valve tip. Mitral flow velocities from 5 to 10 cardiac cycles were traced to provide peak passive ($E$) and active ($A$) filling and the deceleration time (DT) of passive filling. The tricuspid regurgitant jet velocity was also obtained whenever possible to estimate the pulmonary artery systolic pressure using continuous-wave Doppler imaging. The mitral annular velocity was measured by Doppler tissue imaging using the pulsed-wave Doppler mode. The filter was set to exclude high-frequency signals and the Nyquist limit was adjusted to a range of 15–20 cm/s. The gain and sample volume were minimized to allow for a clear tissue signal with minimal background noise. The early diastolic ($e'$) velocity of the septal mitral annulus was measured from the apical four-chamber view, with a 2–5 mm sample volume. These measurements were performed at baseline, at each stage of exercise and recovery. We compared two markers of exertional DD: a post-stress $E/e'$ of $>13$ and a DFRI of $<13.5$.

Wall motion scoring was performed at each level of stress by a minimum of two readers; new or worsening wall motion abnormalities were identified as being due to ischaemia.

**Invasive haemodynamic assessment**

As previously described, haemodynamic measurements were obtained using a fluid-filled 6 French pigtail catheter in the mid-LV cavity, before the performance of LV angiography. The measurement of the mean LV diastolic pressure (LVDP) was made offline from digital recordings of high-frequency LV pressure tracings of at least five cardiac cycles. Significant elevation of the mean LVDP was defined by a value of $>15$ mmHg.

**Statistical analysis**

Results are expressed as mean ± standard deviation. Continuous variables were compared using the t-test or Mann–Whitney test, depending on whether the parameter was normally distributed. Categorical measures were compared with the $\chi^2$ or Fisher’s exact test, depending on the numbers compared. We used logistic regression to identify the correlates of abnormal responses. We used linear regression to identify the contribution of both to exercise capacity.

**Results**

**Validation study**

The clinical characteristics of the validation and association groups are summarized in Table 1. These patients were divided into normal ($n = 22$) and elevated exercise filling pressure groups ($n = 15$, $>15$ mmHg). Using the predefined cutoffs of post-stress $E/e'$ $>13$ and DFRI of $<13.5$, the sensitivities for identification of raised exercise filling pressure were 67% with $E/e'$ and 100% with DFRI ($P = 0.04$). However, the specificities were, respectively, 95 vs. 9% ($P < 0.0001$).

**Association study**

The clinical picture of patients in the association study was similar to that of patients in the validation study (Table 1). Patients were divided into two sets of comparison groups. The first group consisted of those with normal $E/e'$ during exercise ($E/e' \leq 13$)
compared with those with increased E/e' with exercise (E/e' > 13); the second group included those with normal DFRI during exercise (DFRI \geq 13.5) compared with those with decreased DFRI during exercise (DFRI <13.5). Abnormal exercise E/e' (n = 112, 20%) and DFRI (n = 317, 57%) were modestly associated (κ = 0.35, P < 0.0001). Of those with abnormal E/e' on exercise, 53 (47%) had increased E/e' at rest. Of those with normal E/e' on exercise, 18 (4%) had increased E/e' at rest [the numbers of abnormal E/e' for patients with normal and abnormal DFRI were 23 (7%) and 48 (20%) patients, respectively]. An example of a patient with discrepant DST results is shown in Figure 1.

Table 2 compares groups with and without increasing E/e' and with and without increasing DFRI. Diabetes and inducible ischaemia were more frequent in both those with abnormal E/e' with exercise and those with abnormal DFRI with exercise. The mean resting heart rate and the ejection fraction were the same across all groups, and 19 patients (3.5%) had echocardiographic evidence of ischaemia during exercise.

Exercise capacity was associated with abnormal exercise E/e' (β = −0.19, P < 0.001) and DFRI (β = −0.15, P = 0.001) by linear regression (independent of age, body mass index, wall thickness, haemodynamics, or abnormal stress echo). Correlates of abnormal exercise E/e' by logistic regression (R^2 = 0.34) were female gender, age, hypertension, and wall thickness. The only association of abnormal DFRI was exercise capacity; no other clinical or stress variable was associated (Table 3) with abnormal DFRI. Table 3 also

![Figure 1](https://example.com/figure1.png)

**Figure 1** Discordant results of diastolic exercise echocardiography in a patient with normal diastolic function at baseline and evidence of elevated filling pressures as reflected by increased E/e' with stress, but normal diastolic functional reserve.
shows other factors that were not correlated with E/e’ and DFRI. These included coronary artery disease (CAD), resting systolic blood pressure, and exercise systolic blood pressure.

Discussion

There are two principal findings in this study. The first is that although exercise E/e’ and DFRI are both associated with exercise capacity, E/e’ has a much greater specificity for raised filling pressure in response to exercise. In other words, this equates to an increased accuracy of the DST to discern whether the cause is DD when used to evaluate exertional dyspnea. The second principal finding is that E/e’ is more closely associated with the parameters expected to be associated with DD.

LV filling at rest and exercise

Most measures that use E/e’ to characterize LV function are obtained at rest. While overt LV diastolic and systolic dysfunction can be readily identified by conventional diagnostic techniques including echocardiography, the initial stages of myocardial dysfunction may be hidden by compensatory mechanisms, especially at rest.8–11,20 In patients with a similar grade of DD at rest, there can be a spectrum of alterations in diastolic function during exercise.8–11,20–22

Table 2  Clinical characteristics of groups with and without raised filling pressure and with and without abnormal diastolic functional reserve

<table>
<thead>
<tr>
<th></th>
<th>Normal (n = 436)</th>
<th>Increased (n = 112)</th>
<th>P-value</th>
<th>Normal (n = 312)</th>
<th>Decreased (n = 236)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54 ± 14</td>
<td>65 ± 12</td>
<td>0.003</td>
<td>55 ± 14</td>
<td>58 ± 15</td>
<td>0.99</td>
</tr>
<tr>
<td>Male (%)</td>
<td>283 (65)</td>
<td>66 (59)</td>
<td>0.29</td>
<td>209 (67)</td>
<td>146 (62)</td>
<td>0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>31.9</td>
<td>28.0</td>
<td>0.03</td>
<td>32.5</td>
<td>29.8</td>
<td>0.26</td>
</tr>
<tr>
<td>EF (%)</td>
<td>56 ± 5</td>
<td>52 ± 5.5</td>
<td>0.01</td>
<td>56 ± 5.1</td>
<td>56 ± 4.9</td>
<td>0.89</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>52 (12)</td>
<td>26 (23)</td>
<td>0.004</td>
<td>28 (9)</td>
<td>47 (20)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>235 (54)</td>
<td>93 (83)</td>
<td>&lt;0.0001</td>
<td>178 (57)</td>
<td>149 (63)</td>
<td>0.18</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>100 (23)</td>
<td>50 (45)</td>
<td>&lt;0.0001</td>
<td>78 (25)</td>
<td>71 (30)</td>
<td>0.22</td>
</tr>
<tr>
<td>DFRI</td>
<td>24.1 ± 28</td>
<td>1.99 ± 27.6</td>
<td>&lt;0.0001</td>
<td>35.6 ± 27</td>
<td>-1.54</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>E/e’ rest</td>
<td>8.6 ± 2.5</td>
<td>13.8 ± 3.8</td>
<td>&lt;0.0001</td>
<td>9 ± 2.8</td>
<td>10.4 ± 4.7</td>
<td>0.10</td>
</tr>
<tr>
<td>E/e’ exercise</td>
<td>8.7 ± 2.1</td>
<td>18.3 ± 5.4</td>
<td>&lt;0.0001</td>
<td>8.6 ± 2.5</td>
<td>13.4 ± 6.8</td>
<td>0.99</td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>68 ± 12</td>
<td>66 ± 12</td>
<td>0.06</td>
<td>68 ± 12</td>
<td>68 ± 13</td>
<td>0.22</td>
</tr>
<tr>
<td>Resting SBP (mmHg)</td>
<td>126 ± 18</td>
<td>133 ± 18</td>
<td>0.80</td>
<td>127 ± 18</td>
<td>129 ± 18</td>
<td>0.63</td>
</tr>
<tr>
<td>Peak HR (bpm)</td>
<td>155 ± 22</td>
<td>134 ± 24</td>
<td>&lt;0.0001</td>
<td>153 ± 22</td>
<td>147 ± 23</td>
<td>0.12</td>
</tr>
<tr>
<td>Peak SBP (mmHg)</td>
<td>176 ± 27</td>
<td>174 ± 27</td>
<td>&lt;0.0001</td>
<td>174 ± 28</td>
<td>176 ± 26</td>
<td>0.33</td>
</tr>
<tr>
<td>Exercise capacity (METs)</td>
<td>9.5 ± 2.4</td>
<td>7.7 ± 2.5</td>
<td>&lt;0.0001</td>
<td>9.5 ± 2.3</td>
<td>8.6 ± 2.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Ischaemia (%)</td>
<td>9 (2)</td>
<td>10 (9)</td>
<td>0.002</td>
<td>8 (3)</td>
<td>11 (5)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Table 3  Associations between parameters of diastolic dysfunction and clinical/echocardiographic variables

<table>
<thead>
<tr>
<th></th>
<th>Abnormal exercise E/e’</th>
<th>Abnormal exercise DFRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R² (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Female</td>
<td>0.26 (0.11–0.6)</td>
<td>P = 0.002</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.04 (1.01–1.07)</td>
<td>P = 0.007</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.35 (0.15–0.80)</td>
<td>P = 0.012</td>
</tr>
<tr>
<td>Septal thickness (per 1 cm)</td>
<td>4.3 (1.32–14.06)</td>
<td>P = 0.016</td>
</tr>
<tr>
<td>Exercise capacity (per metabolic equivalent)</td>
<td>0.83 (0.67–1.02)</td>
<td>P = 0.76</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.35 (0.66–2.74)</td>
<td>P = 0.41</td>
</tr>
<tr>
<td>Resting systolic BP (mmHg)</td>
<td>1.01 (0.99–1.04)</td>
<td>P = 0.21</td>
</tr>
<tr>
<td>Exercise systolic BP (mmHg)</td>
<td>0.99 (0.98–1.01)</td>
<td>P = 0.24</td>
</tr>
<tr>
<td>Ejection fraction (per 1%)</td>
<td>1.04 (0.98–1.11)</td>
<td>P = 0.21</td>
</tr>
</tbody>
</table>
A reduced early (E) to late (A) diastolic filling ratio or prolonged DT of E velocity is the most common type of LVDD in the elderly and is believed to indicate disturbances of myocardial relaxation. However, many elderly subjects and patients with hypertension or LV hypertrophy have Doppler echocardiographic evidence of abnormal LV relaxation with no symptoms of heart failure at rest. An increase in the myocardial tissue diastolic velocity (e') has been shown to parallel increased transmural gradient in subjects with normal myocardial relaxation, whereas it remains unchanged in subjects with DD in experimental and human studies. Thus, in patients with DD, already impaired myocardial relaxation does not augment as much as in normal individuals during exercise. However, the transmural flow is driven not only by LV relaxation and suction but also by the pressure gradient across the valve.

Most patients with chronic heart failure do not have symptoms at rest but, rather, develop symptoms of dyspnoea with exertion. Exertion can unmask not only dyspnoea from cardiac causes, but also can help identify patients in whom filling pressure increases with workload. The DST can help in risk stratification of patients with abnormal diastolic function. DFRI can often be normal in those patients with abnormal diastolic function as demonstrated by comparison to data gathered from exercise haemodynamics.

Conclusions

Although exercise E/e' and DFRI are both associated with exercise capacity, E/e' has greater specificity for raised filling pressure and is more closely associated with the expected parameters of DD. The high sensitivity of DFRI makes it a better test for screening for exercise-induced DD. E/e' is the superior test when attempting to rule out cardiac reasons as a cause for dyspnoea on exertion.

Conflict of interest: none declared.

References