Clinical perspectives and evidence of diastolic stress test in heart failure with preserved ejection fraction

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Diastolic stress test; Heart failure with preserved ejection fraction; Echocardiography; Exercise test

Abstract The diagnosis of heart failure with preserved ejection fraction (HFPEF) remains on the basis of echocardiographic analyses at rest. However, some patients with HFPEF have symptoms such as dyspnea only during exercise. Accordingly, echocardiographic analyses at rest could be insufficiently sensitive to identify these patients. In line, recent studies demonstrated that in some patients with HFPEF left ventricular diastolic abnormalities occur only during exercise. This review discusses and analyzes the clinical relevance and evidence of using diastolic stress test echocardiography in patients with HFPEF.

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1. Introduction

The diagnosis of heart failure with preserved ejection fraction (HFPEF) remains on the basis of echocardiographic analyses at rest. However, some patients with HFPEF have symptoms such as dyspnea only during exercise. Accordingly, non-invasive echocardiographic analyses at rest could be insufficiently sensitive to identify these patients. In line, recent studies demonstrated that in some patients with HFPEF left ventricular diastolic abnormalities occur only during exercise. This review discusses and analyzes the clinical relevance and evidence of using diastolic stress test echocardiography in patients with HFPEF.

2. Pathophysiological diastolic processes in HFPEF

Left ventricle (LV) diastolic dysfunction plays a key role in the pathophysiology of HFPEF, which is principally characterized by delayed myocardial relaxation and increased ventricular stiffness. However, it remains poorly understood why some patients with diastolic dysfunction have symptoms of HF such as dyspnea, while others remain asymptomatic. Recent studies using invasive cardiac catheterization suggested that, unlike asymptomatic subjects, HFPEF patients have a significant increase of LV filling during exercise which leads to a rise of pulmonary capillary pressures and thereby, to the development of dyspnea. Moreover, invasive exercise testing substantially improves prediction of long-term mortality in such patients. Hence, one could expect that if in patients with HFPEF these important pathophysiological hemodynamic measurements could be reproducible during exercise using non-invasive techniques such as diastolic echocardiographic analyses (diastolic stress test), and it would be of great clinical and diagnostic relevance in the management of these patients.

3. Echocardiography at rest in HFPEF

Echocardiography at rest remains an important method to characterize the underlying functional and structural changes in HFPEF. Tissue-Doppler derived \( E'/e' \) ratio stays as one of the cornerstones in the non-invasive evaluation of diastolic function at rest in these patients. The \( E'/e' \) ratio \( \geq 15 \) if using \( e' \) of septal site of the mitral annulus or \( \geq 13 \) if using average values of septal and lateral site indicates accurately increased left ventricle end-diastolic pressure (LVEDP), whereas an \( E'/e' \) value \( < 8 \) indicates normal filling pressures. It has been shown that \( E'/e' > 15 \) may be able to provide stand-alone evidence of diastolic LV dysfunction without further need of serial noninvasive tests in HFPEF patients. However, many patients with signs and symptoms of HFPEF fall into the “grey zone” of key echocardiographic diagnostic parameters, such as \( E'/e' = 8-15 \), and thus, other echocardiographic indices should be used. Hence, a technique that may accurately categorize these border-line patients with \( E'/e' = 8-15 \) as truth HFPEF could be of great importance in the clinical practice.

4. Echocardiography during exercise – diastolic stress test in HFPEF

At the moment the diagnosis of HFPEF remains on the basis of echocardiographic analyses at rest. However, some patients with HFPEF have symptoms such as dyspnea only during exercise. Accordingly, non-invasive echocardiographic analyses at rest could be insufficiently sensitive to identify these patients. In line, several studies demonstrated that in some patients with HFPEF LV diastolic abnormalities occur only during exercise. In addition, Kitzman et al. showed that symptoms of primary diastolic dysfunction occur only during exertion because diastolic filling pressure is normal at rest and increases only with exertion. Furthermore, Ha et al. in 45 patients with normal LVEF referred for evaluation of exertional dyspnea highlighted the importance of the diastolic stress test. In this regard, the authors confirmed that diastolic stress echocardiography using supine bicycle exercise is technically feasible for demonstrating changes of \( E'/e' \) ratio during exercise as a result of changes in exercise-induced diastolic filling pressures. In agreement, Burgess et al. demonstrated that \( E'/e' \) ratio correlates with invasively measured left ventricle diastolic pressure (LVPD) during exercise and approximately one-quarter of the patients manifested an elevated LV filling pressure only during exercise. Moreover, it was found that even despite normal echocardiographic analyses at rest, patients with early-stage HFPEF may display hemodynamic abnormalities (elevated filling pressures) exclusively during exercise stress-test. In such patients diastolic stress test can provide additional useful information (using the non-invasive estimation of LVEDP by the \( E'/e' \) ratio) that might clarify the diagnosis of early-stage HFPEF. (Table 1 shows invasive diastolic stress-test studies in HFPEF). Measurement of \( E'/e' \) during exercise is feasible and had been invasively validated for the estimation of raised LVEDP, with \( E'/e' > 13 \) accurately identifying raised LVEDP (\( > 15 \) mmHg). (Table 2 shows non-invasive diastolic stress-test studies in HFPEF.) It means that exercise echocardiography focusing on the evaluation of diastolic function may be the basic step for the diagnosis of HFPEF manifested only during exercise.

Several studies showed that the pathophysiology of HFPEF is a complex process involving not only worsening of relaxation and an increase in myocardial stiffness but also abnormalities in longitudinal systolic function. Therefore in last years there is growing evidence that the diastolic stress test with myocardial deformation analysis can provide important diagnostic findings that can be helpful in the management of patients presenting with dyspnea of an unclear etiology or suspected HFPEF. In this regard, Tan et al. demonstrated that HFPEF patients have a combination of systolic and...
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<tr>
<th>Author</th>
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<th>Changes of exercise hemodynamics</th>
<th>Max workload</th>
<th>Conclusion/results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Tschöpe 2005</td>
<td>15 HFPEF Pts</td>
<td>Invasive</td>
<td>15 Pts with excluded CAD</td>
<td>15 HFPEF Pts</td>
<td>87 ± 27 W</td>
<td>“Basal NT-proBNP correlated strongly with filling pressures during maximal exercise”</td>
</tr>
<tr>
<td></td>
<td>IC: preserved LVEF, HF symptoms</td>
<td>PCWP:</td>
<td>PCWP:</td>
<td></td>
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<tr>
<td></td>
<td>EC: AF, COPD or VHD</td>
<td>6 ± 2 → 14 ± 5 mmHg</td>
<td>7 ± 2 → 24 ± 8 mmHg</td>
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<td>134 ± 26 W</td>
<td></td>
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<tr>
<td>Burgess, 2006</td>
<td>37 Pts</td>
<td>Invasive Echo</td>
<td>No</td>
<td>Mean LVDP:</td>
<td>88 ± 10 W</td>
<td>“E/e ratio correlates with invasively measured LVDP during exercise”</td>
</tr>
<tr>
<td></td>
<td>(1) LVDP normal (n = 20)</td>
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<td>(2) LVDP high only with exercise (n = 9)</td>
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<td>(3) LVDP high at rest (n = 8)</td>
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<tr>
<td>Talreja, 2007</td>
<td>12 Pts</td>
<td>Invasive Echo</td>
<td>No</td>
<td>12 HFPEF Pts,</td>
<td>n.d, symptom-limited</td>
<td>“E/e’ ratio of greater than 15 during exercise is associated with a significantly elevated PAWP of greater than 20 mmHg”</td>
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<tr>
<td></td>
<td>IC: LVEF &gt; 50%, NYHA II-III</td>
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<td>PAWP significantly increased:</td>
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<tr>
<td></td>
<td>EC: more than moderate VHD, COPD, known or suggested primary Pulmonary hypertension or pulmonary embolism CAD: n.d.</td>
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<td>14 ± 4 → 22 ± 10 mmHg</td>
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<td>Plehn, 2009</td>
<td>28 HFPEF Pts</td>
<td>Invasive</td>
<td>10 healthy</td>
<td>28 HFPEF Pts</td>
<td>88 ± 28 W</td>
<td>“Important number of HFNEF patients cannot be identified by their baseline pattern of ventricular filling or direct measurement of the left ventricular pressure at rest. Diastolic stress-test should be performed with accurate non-invasive methods as a primary approach”</td>
</tr>
<tr>
<td></td>
<td>IC: HTN (&gt;3 years), exertional dyspnea, LVEF ≥ 50%, PAP &lt; 15 mmHg, PCWP &gt; 12 mmHg during peak exercise</td>
<td>PCWP: increased</td>
<td>PCWP: significantly increased</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>EC: LBBB, VHD, LVH (&gt;14 mm), COPD, diabetes CAD: no</td>
<td>7.5 ± 2 → 10 ± 2 mmHg</td>
<td>7.4 ± 2 → 19 ± 9 mmHg</td>
<td></td>
<td>98 ± 27 W</td>
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<tr>
<th>Author</th>
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<th>Conclusion/results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maeder, 20105</td>
<td>14 HFPEF Pts</td>
<td>Invasive Echo</td>
<td>8 controls</td>
<td>14 HFPEF Pts</td>
<td>n.d., symptom-limited</td>
<td>“Invasive hemodynamic studies with exercise are required to formally establish the pathophysiologic profile in patients with suspected HFNEF and to evaluate the effects of novel therapies”</td>
</tr>
<tr>
<td>Borlaug, 20106</td>
<td>32 HFPEF Pts</td>
<td>Invasive Echo</td>
<td>23 non-cardiac dyspnea (NCD) Pts</td>
<td>32 HFPEF Pts</td>
<td>n.d., symptom-limited</td>
<td>“Euvolemic patients with exertional dyspnea, normal brain natriuretic peptide, and normal cardiac filling pressures at rest may have markedly abnormal hemodynamic responses during exercise, suggesting that chronic symptoms are related to heart failure. Invasive exercise hemodynamic testing may enhance diagnosis of HFPEF in this expanding population of patients with exertional dyspnea of unknown etiology”</td>
</tr>
<tr>
<td>Penicka, 201016</td>
<td>20 HFPEF Pts</td>
<td>Invasive Echo</td>
<td>10 controls with LVEDP &lt; 16 mmHg or/ and no increase during exercise</td>
<td>20 HFPEF Pts</td>
<td>54 ± 19 W HFPEF 91 ± 24 W controls</td>
<td>“A significant proportion of stable outpatients with unexplained chronic dyspnea may have HFPEF. Because the majority of these outpatients do not fulfill the diagnostic criteria for heart failure and noninvasive tests do not show overt pathology, a correct diagnosis of HFPEF represents a challenge”</td>
</tr>
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</table>

IC: HF symptoms, LVEF > 50%, (NYHA II-II) + impaired exercise capacity, SR ECL:BBB, CMP, more than mild valvular heart disease, COPD CAD: all have negative stress-echo, myocardial perfusion scan or exercise ECG

PCWP: PCWP:

* = 0.31 between exercise PCWP in controls and HFPEF

LVEDP: no changes:

12 ± 3 → 14 ± 4 mmHg

LVEDP: significantly increased:

13 ± 2 → 34 ± 6 mmHg

9 ± 1.5 → 13 ± 1.6 mmHg

5 ± 0.31 between exercise PCWP in controls and HFPEF

10 ± 4 → 20 ± 7* mmHg

10 ± 4 → 23 ± 6* mmHg

11 ± 1.5 → 13 ± 1.6 mmHg

21 ± 6.3 → 28 ± 5.4 mmHg

“IC: EF > 50%, exertional dyspnea, normal brain natriuretic peptide assay, normal resting hemodynamics CAD: no Pts with peak exercise PCWP > 25 mmHg were classified as having HFPEF (n = 32), and those with values < 25 mmHg were classified as having noncardiac dyspnea (NCD) (n = 23)”
(2) Leg lifting
(2) LVEDP: significantly increased 11 ± 1.5 → 14 ± 1.0 mmHg
(3) Nitroprusside infusion
(3) LVEDP: significantly decreased 21 ± 6.3 → 8 ± 2.6 mmHg
(4) Dobutamine infusion
(4) LVEDP: significantly decreased 21 ± 6.3 → 8 ± 2.6 mmHg

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</table>

8 Borlaug, 2011
20 HFPEF Pts
IC: preserved EF, exertional dyspnea
CAD: no
Mean LVDP: significantly increased: n.d, symptom-limited
Patients with early HFPEF develop increased LV diastolic filling pressures during supine exercise

9 Dorfs, 2013
355 HFPEF Pts
IC: unexplained dyspnea (suspected HFPEF)
EC: LVEF ≤ 50%, significant CAD, VHD, prior cardiac surgery, PM, cardiac shunt, constrictive pericarditis, CMP, pulmonary artery hypertension
PCWP: significantly increased
74.1 ± 32.6 W
“Hemodynamic stress testing should be considered in particular if measurements at rest are normal, because it provides not only the unique opportunity to rule out a cardiac cause of dyspnea in uncertain cases, but also to identify patients at risk. An excessive rise of PCWP during exercise despite normal PCWP at rest is associated with increased mortality and may be considered as early HFPEF”

Differences were considered statistically significant when P < 0.05.

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<tr>
<th>Author</th>
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<th>Max workload</th>
<th>Conclusion/results</th>
</tr>
</thead>
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<tr>
<td>Mottram, 2004</td>
<td>26 HFPEF Pts:</td>
<td>Echo</td>
<td>No</td>
<td>$E/e'$ lateral significantly increased: 7.7 ± 2.0 → 10.0 ± 4.8 $E/e'$ septal significantly increased: 9.1 ± 2.2 → 11.6 ± 3.6</td>
<td>n.d., symptom-limited</td>
<td>“In patients with limited capacity due to suspected DHF, BNP increases during exercise and is higher in those patients who likely have elevated filling pressures at maximal exercise. This increase in BNP with exercise is associated with enhanced myocardial function.”</td>
</tr>
<tr>
<td>Ha, 2005</td>
<td>45 HFPEF Pts:</td>
<td>Echo</td>
<td>No</td>
<td></td>
<td>75 W</td>
<td>“Diastolic stress echocardiography using supine bicycle exercise is technically feasible for demonstrating changes of $E/e'$ ratio and tricuspid regurgitant velocity during exercise as a result of changes in exercise-induced diastolic filling pressures”</td>
</tr>
<tr>
<td>Burgess, 2006</td>
<td>166 Pts</td>
<td>Echo</td>
<td>No</td>
<td>$E/e'$ at rest &lt; 10 without increase $E/e'$ during exercise ($n = 17$) $E/e'$ at rest &lt; 10 with increase $E/e'$ during exercise ($n = 9$) $E/e'$ at rest &gt; 10 ($n = 19$)</td>
<td>n.d., symptom-limited</td>
<td>“The findings of this study validate exercise $E/e'$ as a marker of ventricular filling pressure, and suggest that its measurement may explain functional impairment in patients with normal or mildly abnormal diastolic parameters at rest”</td>
</tr>
<tr>
<td>Talroja, 2007</td>
<td>12 HFPEF Pts</td>
<td>Echo</td>
<td>No</td>
<td>$E/e'$ at rest &lt; 10 without increase $E/e'$ during exercise ($n = 17$) $E/e'$ at rest &lt; 10 with increase $E/e'$ during exercise ($n = 9$) $E/e'$ at rest &gt; 10 ($n = 19$)</td>
<td>n.d., symptom-limited</td>
<td>“Noninvasively obtained Doppler of mitral and mitral annulus velocities provides a reliable estimation of PAWP not only at baseline, but also with exercise. Specifically, an $E/e'$ ratio of greater than 15 during exercise is associated with a significantly elevated PAWP of greater than 20 mmHg.”</td>
</tr>
<tr>
<td>Ennezat, 2008</td>
<td>25 HFPEF Pts</td>
<td>Echo</td>
<td>25 hypertensive as controls: significantly increased $8 \pm 3 \rightarrow 10 \pm 2^#$</td>
<td>25 HFPEF Pts: significantly increased $13 \pm 4 \rightarrow 15 \pm 2$</td>
<td>45 W Pts, 65 W controls</td>
<td>“When compared with patients with similar comorbidities but without history or evidence of heart failure, patients with HFPEF experience greater arterial stiffening and thereby a deterioration of global LV systolic performance during dynamic exercise”</td>
</tr>
<tr>
<td>Ha, 2009</td>
<td>141 Pts</td>
<td>Echo</td>
<td>No</td>
<td>141 Pts</td>
<td>50 W</td>
<td>“Patients with preserved LV systolic function and impaired myocardial relaxation at rest exhibit a wide spectrum of alterations in diastolic function during exercise”</td>
</tr>
<tr>
<td>Tan, 2009</td>
<td>56 HFPEF Pts</td>
<td>Echo</td>
<td>27 healthy as controls: No changes: $8.2 \pm 2.0 \rightarrow 8.8 \pm 1.8$</td>
<td>56 HFPEF Pts</td>
<td>n.d, symptom-limited (to max HR = 100/min)</td>
<td>“HFNEF patients have a combination of systolic and diastolic abnormalities of ventricular function that is more obvious on exercise than at rest”</td>
</tr>
<tr>
<td>Maeder, 2010</td>
<td>14 HFPEF Pts</td>
<td>Echo, invasive</td>
<td>8 controls, increased $9.5 \pm 3.4^* \rightarrow 11.1 \pm 3.4$</td>
<td>14 HFPEF Pts</td>
<td>n.d, symptom-limited</td>
<td>“E/e’ septal doesn’t reflect hemodynamic changes during exercise in HFPEF patients”</td>
</tr>
<tr>
<td>Tan, 2010</td>
<td>30 Pts</td>
<td>Echo</td>
<td>22 healthy as controls: No changes: $8.4 \pm 2.1 \rightarrow 9.3 \pm 2.2$</td>
<td>30 Pts</td>
<td>n.d, symptom-limited</td>
<td>“Patients with treated hypertension with normal resting echocardiography can have exercise limitation associated with widespread systolic and diastolic left ventricular dysfunction on exercise”</td>
</tr>
</tbody>
</table>
| Holland, 2011 | 15 HFPEF Pts | Echo | 15 healthy as controls Submax exercise: $E/e’$ significantly decreased: $10.7 \pm 3.5 \rightarrow 11.9 \pm 3.0$ | 15 HFPEF Pts: Submax exercise: $E/e’$ significantly increased: $13.8 \pm 3.5 \rightarrow 17.6 \pm 6.8^*$ | n.d, submaximal (steady state for $\geq 1$ min at 60% of maximal HR) | “Patients with HFPEF have increased E/e’ with exercise compared with age-matched and sex-matched controls. This response to exercise is clearly evident at low workloads similar to those experienced during activities of daily living, when symptoms are present, and is associated with indices of abnormal central, but not peripheral BP” | (continued on next page)
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<th>Max workload</th>
<th>Conclusion/results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meluzin 2011</td>
<td>84 Pts:</td>
<td>Echo</td>
<td>14 healthy as controls</td>
<td>10.7 ± 3.5 → 8.6 ± 2.5* ( *p &gt; 0.05 ) between ( E'/e' ) at submax and max level in controls</td>
<td>84 Pts:</td>
<td>n.d., symptom-limited</td>
</tr>
<tr>
<td></td>
<td>IC: LVEF &gt; 50%, exertional dyspnea, diastolic dysfunction (( E'/e' &gt; 15 ))</td>
<td></td>
<td></td>
<td>13.8 ± 3.5 → 16.3 ± 4.3* ( *p = 0.433 ) between ( E'/e' ) at submax and max level in HFPEF</td>
<td></td>
<td>“A significant proportion of patients require exercise to diagnose HFNEF. The prevalence of isolated, only exercise-induced HFNEF must be viewed cautiously due to a relatively small number of patients included.”</td>
</tr>
<tr>
<td></td>
<td>(steno &gt; 40%), history of MI, VHD, CMP, liver, renal, lung disease, anemia</td>
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<td>(1) HFPEF Pts (n = 30), were selected according to current HFPEF recommendations (+11 patients had the exercise-induced ( E'/e' &gt; 15 ) or ( E'/e' ) septal &gt; 13)</td>
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<td>(2) Pts with NCD (n = 54)</td>
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<td>Donal 2012</td>
<td>21 HFPEF Pts</td>
<td>Echo</td>
<td>15 hypertensive as controls: significantly increased</td>
<td>54 PTs with NCD 8.5 ± 0.3 → 8.0 ± 0.2</td>
<td>45–60 W</td>
<td>“In patients recently hospitalized for treatment of HF with HFPEF (EF &gt; 45%) subtle abnormalities of systolic and diastolic functions were present at rest and increased by a submaximal exercise stress echocardiography”</td>
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<tr>
<td></td>
<td>IC: LVEF &gt; 45%, acute HF hospitalization.</td>
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<td>CAD: 23%</td>
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<tr>
<td>Tartiere-Kesri 2012</td>
<td>23 HFPEF Pts</td>
<td>Echo</td>
<td>15 hypertensive as controls: no changes:</td>
<td>23 HFPEF Pts: no changes: 76 ± 27 W HFPEF 143 ± 55 W controls</td>
<td>143 ± 55 W</td>
<td>“In HFPEF patients, moderate exercise leads to a steep increase in proximal afterload that is underestimated at rest and is associated with unfavorable ventriculo arterial coupling and exercise intolerance”</td>
</tr>
<tr>
<td></td>
<td>IC: LVEF &gt; 45%, SR, stable hemodynamic conditions, CAD: 10%</td>
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Differences were considered statistically significant when \( P < 0.05 \).

diastolic abnormalities of ventricular function that is more obvious on exercise than at rest and that includes reduced myocardial systolic strain, rotation, LV suction, longitudinal (anular) function, and delayed untwisting.

5. Future considerations concerning to diastolic stress test in HFPEF

At the moment there is no defined protocol how the stress-test should be performed. The methodological approach during diastolic stress test is less standardized and issues remain on feasibility, accuracy and prognostic value. Recently, Erdei et al. have shown a lack of consensus concerning the specific diagnostic objectives of diastolic stress test, the optimal diagnostic targets, and the methods that should be employed. In addition, the authors evidenced that there is no agreement concerning diagnostic criteria that could correlate with responses to targeted treatment. Therefore, we consider that in order to establish the usefulness of diastolic stress test in HFPEF, new expert consensus or guidelines should standardize the protocol of diastolic stress test in these patients.

6. Clinical perspectives and conclusion

The diagnostic of HFPEF remains considered on echocardiographic resting examinations. However, some patients with HFPEF have symptoms such as dyspnea only during exercise. Accordingly, LV echocardiographic analyses at rest could be insufficiently sensitive to identify these patients. In line, recent studies demonstrated that LV diastolic abnormalities and elevation of LV filling pressures with consequent dyspnea occur only during exercise in some patients with HFPEF. Noninvasive diastolic stress test showing LV diastolic changes only during exercise has demonstrated to be of great importance in diagnosis and management of these patients. Nonetheless, large studies are needed to validate the role of diastolic stress test in HFPEF.

Conflict of interest

All authors have no conflicts of interest to declare.

References