Exercise-induced functional mitral regurgitation in heart failure and preserved ejection fraction: a new entity

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We report here the worsening of functional mitral regurgitation (MR) during dynamic exercise Doppler echocardiography in four female patients with heart failure and preserved ejection fraction. MR worsened concomitantly to an increase in systolic mitral tenting area and in E/Ea ratio, whereas local left ventricular (LV) remodelling was not substantially aggravated by exercise. We accordingly suggest that exercise-induced increase in LV filling or left atrial pressure that in turn leads to increase in mitral tenting area worsens functional MR during exercise.

Keywords
Functional mitral regurgitation • Left ventricular filling pressure • Exercise Doppler echocardiography • Heart failure with preserved ejection fraction

Case report
We here report four patients (40- to 84-year-old) with severe exertional dyspnoea who were referred for exercise echocardiography. A history of long-standing hypertension and heart failure with preserved left ventricular (LV) ejection fraction (HFrEF) (requiring mechanical ventilation in Case 3) in the past 6 months was found in all patients. Two patients (Cases 2 and 3) had diabetes mellitus. Coronary angiography was normal and renal artery stenosis was ruled out in all by Doppler ultrasound examination of the renal arteries and renal angiography in three patients. QRS width was normal. Symptom-limited exercise Doppler echocardiography was performed on a semi-recumbent bicycle ergometer starting at a 25 W workload with 20 W increments every 3 min. Beta-blockers were withdrawn 48 h before stress testing. Mitral valve apparatus and subapparatus were normal in all but in Case 4 who showed slightly calcified mitral annulus but without any valvular abnormality. Neither EKG nor wall motion abnormalities developed during exercise. Functional mitral regurgitation (MR) worsened during exercise in these patients (Case 2, loop 1; Case 3, loop 2; and Case 4, loop 3) (Table 1). The increase in MR during exercise was paralleled by an increase in mitral tenting area (Figure 1), in E/Ea ratio at low workload (Figure 2) and in left atrial (LA) size (Table 1). The rise in systolic pulmonary pressure was obvious in all patients (Figure 3). Importantly, the posterior papillary muscle (PPM)–fibrosa length, an important index of local LV remodelling, did not increase (Cases 1 and 4) during exercise. LV outflow tract velocity–time integral decreased or failed to increase in these four patients, thereby indicating that exercise-induced worsening of MR blunted the increase in forward stroke volume in these patients with pronounced exercise intolerance (Figure 3). In one patient (Case 2), non-invasive data were in agreement with those of right heart catheterization which showed a dramatic increase in mean pulmonary artery pressure (30–50 mmHg) and in mean pulmonary capillary wedge pressure (23–35 mmHg) during a minimal isometric exercise (Figure 4).

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Exercise-induced functional MR in HFpEF

Doppler echocardiographic data at rest and during exercise of five patients with heart failure and preserved ejection fraction and trivial mitral regurgitation at rest

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Workload (W)</th>
<th>Heart rate (bpm)</th>
<th>SBP (mmHg)</th>
<th>LVEF (%)</th>
<th>LVEDV (mL)</th>
<th>Index</th>
<th>E/A</th>
<th>PPM-fibrosa length (mm)</th>
<th>ERO (mm2)</th>
<th>TTG (mm)</th>
<th>ERO/Fibrosa</th>
<th>Tenting</th>
<th>RV (mL)</th>
<th>TTG</th>
<th>ERO</th>
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<td>25</td>
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<td>36.5</td>
<td>73</td>
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<tr>
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<td>25</td>
<td>93</td>
<td>122.6</td>
<td>50</td>
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<td>15</td>
<td>10</td>
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SBP, systolic blood pressure; LVEF, left ventricle ejection fraction; EDV, end-diastolic volume; ERO, effective regurgitant orifice; RV, regurgitant volume; TTG, transtricuspid gradient; Ex, exercise.

Large series of hypertensive and heart failure patients are needed.

Exercise because of comorbidities and frailty. Further studies in epidemiology of exercise-induced MR in HFpEF is nevertheless difficult to apprehend as many of those HFpEF patients are unable to exercise.

In spite of the absence of significant structural abnormalities of the mitral valve, QRS widening, and local and global LV remodelling, systolic mitral tenting area may increase during exercise in patients with HFpEF concomitantly to a significant rise in E/Ea ratio and hence worsening of MR. Marked increase in E/Ea ratio at low workload is a reliable harbinger of heightened LV filling or LA pressure during exercise and occurred in these patients. Dramatic rise in pulmonary capillary wedge pressure at low workload could be demonstrated invasively in one patient. Importantly, the PPM–fibrosa length did not aggravate during exercise while mitral valvular tenting increased, suggesting that alterations in local LV remodelling brought by exercise (tethering forces) do not seem primarily responsible for increased valvular tenting. Recently, Park et al. demonstrated that LA enlargement and diastolic dysfunction assessed by the mitral Doppler inflow pattern significantly contribute to functional MR at rest in patients with dilated cardiomyopathy. Similarly, elevated LA pressure at rest generates pushing forces that worsen mitral valve tenting and thereby facilitate functional MR in patients with either reduced or preserved EF. Exercise-induced worsening of MR was associated with the failure to increase in forward stroke volume in spite of increase in EF in these four patients, thereby suggesting that exercise MR contributes at least partially to exercise intolerance in patients with HFpEF as previously described in HF due to LV systolic dysfunction. Exercise-induced rise in LV filling and thereby in LA pressure is likely to be involved in functional MR exacerbation during exercise that in turn further contributes to exercise intolerance in patients with HFpEF free of coronary disease besides impaired chronotropic and cardiac reserve.

The epidemiology of exercise-induced MR in HFpEF is nevertheless difficult to apprehend as many of these HFpEF patients are unable to exercise because of co-morbidities and frailty. Further studies in large series of hypertensive and heart failure patients are needed.

Supplementary data

Supplementary data are available at *European Journal of Echocardiography* online.

References


**Figure 1** Exercise-induced increase in mitral regurgitation that is trivial at rest in a patient with heart failure and preserved left ventricular ejection fraction. The increase in mitral effective regurgitant orifice area is paralleled by an increase in mitral tenting area (Case 2).

**Figure 2** Exercise-induced increase in $E/E_a$ ratio in a patient with heart failure and preserved left ventricular ejection fraction and exercise-induced increase in severity of a trivial functional mitral regurgitation at rest (Case 2).
Figure 3 Failure to increase left ventricular forward stroke volume and rise in systolic transtricuspid pressure gradient are illustrated in this patient with heart failure and preserved left ventricular ejection fraction and exercise-induced worsening of mitral regurgitation (Case 2).

Figure 4 Right heart catheterism data showing an increase in pulmonary capillary wedge pressure (PCWP) and in pulmonary artery pressure (PAP) in Patient 2 during an isometric exercise.