Exercise-induced changes in mitral regurgitation in patients with prior myocardial infarction and left ventricular dysfunction: relation to mitral deformation and left ventricular function and shape

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Aims The aim of this study was to assess the relationship between exercise-induced changes in mitral regurgitation (MR) and echocardiographic characteristics of mitral deformation, global left ventricular (LV) function and shape at rest and after exercise.

Methods and results Forty consecutive patients with ischaemic MR due to prior myocardial infarction (MI), ejection fraction ≤45% in sinus rhythm underwent exercise-echocardiographic testing. Exercise-induced changes in effective regurgitant orifice (ERO) were compared with baseline and exercise-induced changes in mitral deformation and global LV function and shape. There was significant correlation between exercise-induced changes in ERO and changes in coaptation distance ($r = 0.80$, $P = 0.0001$), tenting area ($r = 0.79$, $P = 0.0001$) and mitral annular diameter ($r = 0.65$, $P = 0.0001$), as well as in end-systolic sphericity index ($r = -0.50$, $P = 0.001$, respectively), and wall motion score index ($r = 0.44$, $P = 0.004$). In contrast, exercise-induced changes in ERO were not related to the echocardiographic features at rest. By stepwise multiple regression model, the exercise-induced changes in mitral deformation were found to independently correlate with exercise-induced changes in ERO (generalized $r^2 = 0.80$, $P = 0.0001$).

Conclusion Exercise-induced changes in severity of ischaemic MR in patients with LV dysfunction due to prior MI were independently related to changes in mitral deformation.

KEYWORDS
Mitral regurgitation; Exercise; Left ventricular dysfunction

Introduction

Functional mitral regurgitation (MR) is frequently present in the acute phase of myocardial infarction (MI), as well as in the patients with left ventricular (LV) dysfunction in whom LV remodelling precedes LV dysfunction and functional MR. It has been recently established that the degree of functional MR at rest in patients with systolic LV dysfunction is determined by local (apical and posterior displacement of papillary muscles) and not global LV remodelling. It has been shown that quantitation of functional MR changes during exercise is not only feasible and reliable but also carries an additional prognostic value in patients with ischaemic LV dysfunction. Specifically, increase in functional MR during exercise carries adverse and unfavourable prognosis. However, the determinants of the exercise-induced changes in functional MR are not yet fully understood.

The objective of this study was to assess the relationship between exercise-induced changes in functional MR and the severity of MR and LV function at rest on one hand and to evaluate exercise-induced changes in functional MR with those of mitral deformation and global LV function and shape during exercise in patients with previous MI and LV dysfunction on the other.

Methods

Study population

From June 2003 to November 2004, 72 consecutive patients with previous MI and MR caused by LV dysfunction and previous successful percutaneous coronary intervention (PCI), who underwent exercise echocardiography study, were assessed for eligibility. Twenty-seven patients were excluded from further evaluation mainly because of the presence of exercise-induced ischaemia. Remaining 45 patients participated in the study. However, proximal isovelocity surface area (PISA) quality was not satisfactory in five patients. The final study population consisted of 40 patients (14 women, 26 men; mean age 54 ± 8) with previous MI (14 ± 4 months old), MR solely

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due to LV dysfunction, and previous successful PCI (5 ± 2 months before exercise study).

All the patients were in sinus rhythm with ejection fraction < 45%. Exclusion criteria for the study were presence of atrial fibrillation, papillary muscle dysfunction, mitral valve prolapse or other valvular diseases, presence of greater than trivial aortic regurgitation, intraventricular conduction abnormality, New York Heart Association (NYHA) functional class IV, or other non-cardiac conditions that limit exercise capacity. In addition, patients with clinical, electrocardiographic (ECG), or echocardiographic evidence of exercise-induced myocardial ischaemia were not included in this study.

Twenty-six patients had previous anterior and 14 patients had previous inferior or inferolateral MI. Thrombolysis was performed in 28/40 patients. All patients had successful elective PCI with stent implantation, for a single-vessel disease in 13 patients and for a two-vessel disease in 27 patients, which resulted in complete revascularization.

Patients were in NYHA functional class II (n = 26) or class III (n = 14). Pharmacological therapy included ACE-inhibitor and aspirin in all patients, a beta-blocker in 26, a diuretic in 20, nitrates in 19, spironolactone in eight, and amiodarone in eight patients. Diabetes mellitus was present in 17 patients.

Exercise echocardiography

Patients performed symptom limited upright exercise test according to submaximal Bruce treadmill protocol. Continuous 12-lead ECG monitoring was performed during the test and recorded at the end of each stage of study protocol. Blood pressure was measured before exercise and at the end of each stage of Bruce protocol. All cardiovascular drugs, including beta-blockers, were maintained during exercise stress echocardiography test.

Echocardiographic imaging and analysis

The diagnosis of functional MR was based on echocardiographic findings of restricted leaflet motion and systolic tenting, moving of coaptation zone from the mitral annulus toward the apex of left ventricle, of structurally normal valve. All echocardiographic pictures (Agilent Image Point HX) were obtained at rest and within 1 min after the peak exercise in recumbent (left lateral decubitus) position and stored on videotape for further off-line analysis. For each measurement, minimum of three cardiac cycles were averaged. Two-dimensional echocardiography was performed in the apical four- and two-chamber views, as well as in parasternal long-axis view, using harmonic imaging to optimize endocardial definition. The biplane Simpson method was used to calculate end-diastolic and end-systolic LV volumes and ejection fraction, both at rest and after the peak exercise. The mean value of ejection fraction obtained in apical four- and two-chamber views was considered to represent ejection fraction. Mitral annular diameter and the distance between mitral annulus plane and the coaptation of mitral leaflets, representing coaptation distance were measured from apical four-chamber view at rest and after the peak exercise. Valvular tenting area was measured by the area enclosed between the annular plane and the mitral leaflets from the parasternal long-axis view. All parameters of mitral deformation were measured in late systole within 1 min after peak exercise stress echocardiography test.

Regional wall motion was assessed according to the recommendations of the American Society of Echocardiography, by a 16-segment model. In all patients, segmental wall motion was semi-quantitatively graded: normal—1, hypokinetic, marked reduction in endocardial motion—2, akinetic, virtual absence of inward motion and thickening—3, and dyskinetic—4, paradoxical wall motion away from the center of left ventricle in systole. Wall motion score index was calculated from the rest and the peak exercise echocardiograms dividing the sum of the individual segments scores by the number of interpreted segments. Inadequately visualized segments were not scored. Exercise-induced changes in echocardiographic variables were expressed as an absolute difference between values after the peak exercise and values at rest (Δvalue). Left atrial dimension was measured from the parasternal long-axis view at rest.

Quantification of functional MR was performed using PISA method, whereas effective regurgitant orifice (ERO), representing severity of functional MR, was calculated at rest and after the peak exercise. ERO of > 20 mm² in patients with functional MR due to ischaemic heart disease was considered as severe MR. Mitral annular diameter, tenting area, and coaptation distance were considered as the key features of mitral deformation, whereas LV ejection fraction, end-diastolic and end-systolic LV volumes, and global wall motion score index were considered as the markers of LV function. LV end-diastolic and end-systolic sphericity indices were markers of LV shape.

Statistical analysis

All data management and statistical analyses were performed using SPSS statistical software for Windows version 10.0. Measurements were expressed as the mean ± SD. Sample size was quantified according to the assumed mean increase in coaptation distance of 0.2 cm after the exercise, with an alpha error 0.05 (Z₁₋₂ = 1.96), power of the study 1 − β = 80% (Z₁₋₂ = −0.84), and for estimated SD in population of 0.325. The calculated sample size was 40. Difference between variables at rest and after the peak exercise were tested for significance using two-sided Student’s t-test for paired data. Two-sided Student’s t-test for independent samples was used to test the difference in echocardiographic features between patients with inferior and anterior MI as well as the difference in echocardiographic features in patients who exhibited decrease and increase in MR with exercise. To estimate the possible correlations between exercise-induced changes in ERO (ΔERO) and other echocardiographic variables at rest and after the exercise, Pearson’s linear correlation analysis was used. To identify predictors of exercise-induced changes in MR, we applied an epidemiological approach using only few factors known to be important predictors of the outcome in our analysis. Because we performed 36 consecutive statistical analyses, we chose a level of significance of 0.05/36 = 0.001 (α-adjustment according to the modified Bonferroni procedure).

Results

Echocardiography features and exercise echocardiography stress test

The patients exercised for an average of 7.6 ± 2.3 min. Heart rate increased from 78 ± 11 b.p.m. at rest to 118 ± 9 b.p.m. with peak exercise (P < 0.0001), whereas systolic blood pressure increased from 126 ± 9 mmHg to 158 ± 13 mmHg (P < 0.0001). The reasons for exercise termination were dyspnea in 24 (60%) patients, fatigue in 14 (35%) patients, and severe rhythm disturbances (short-run ventricular tachycardia) in two (5%) patients. None of the patients had chest pain, ECG, or echocardiographic signs of myocardial ischaemia during the test.

Echocardiographic variables at rest and after exercise

Ejection fraction in this group of patients with functional MR was 31 ± 5%. All the patients had left atrial enlargement with mean left atrial dimension of 5.0 ± 0.4 cm. Patients...
with anterior and inferior MI had comparable severity of MR at rest (ERO rest 16 ± 4 mm² for anterior vs. 15 ± 6 mm² for inferior infarction, \( P = 0.201 \)). However, patients with anterior MI had a more pronounced impairment of LV ejection fraction (end-diastolic sphericity index 29 ± 4 vs. 34 ± 4%, \( P = 0.001 \)), more spherically shaped left ventricle both in diastole (end-diastolic sphericity index 1.38 ± 0.04 vs. 1.43 ± 0.04, \( P = 0.009 \)) and in systole (end-systolic sphericity index 1.41 ± 0.03 vs. 1.44 ± 0.04, \( P = 0.031 \)) as well as more pronounced impairment of contractility (wall motion score index 1.80, \( r = 0.65, P < 0.0001 \)) when compared with patients with inferior MI.

Severe MR according to ERO was present in 13 patients (32%), whereas in 27 patients (68%) mild to moderate MR was present.

Changes in echocardiographic variables corresponding to LV function and shape, as well as mitral deformation during exercise, are presented in Table 1. In fact, during exercise determinants of mitral deformation including coaptation distance, tenting area, and mitral annular diameter have shown significant increase. In contrast, improvement in ejection fraction as a result of significant decrease in LV end-systolic volume characterized changes in LV function.

**Exercise-induced changes in ERO**

Mean ERO at rest was 16 ± 5 mm² (range from 9 to 29 mm²). Thirty-one patients (78%) exhibited increase in functional MR during exercise (increase in ERO), whereas functional MR decreased in nine patients (22%).

Changes in ERO during exercise were not related to any echocardiographic features at rest (Table 2). Similarly, exercise-induced changes in mitral deformation (coaptation distance, mitral annulus, and tenting area) were not related to any resting echocardiographic features.

In contrast, exercise-induced changes in ERO were related to exercise-induced changes in coaptation distance \((r = 0.80, P < 0.0001)\), tenting area \((r = 0.79, P < 0.0001)\), and mitral annular diameter \((r = 0.65, P < 0.0001)\). In addition, exercise-induced changes in ERO were also related to exercise-induced changes of end-systolic sphericity index \((r = -0.50, P = 0.001)\) as well as changes in global wall motion score index \((r = 0.44, P = 0.004)\). Exercise-induced changes in MR were not related to the haemodynamic parameters during exercise. Results are summarized in Table 3. However, increase in exercise-induced ERO was related to the presence of previous anterior MI, whereas in patients with previous inferior MI heterogeneous changes in ERO during exercise was observed. Patients who exhibited decrease in MR had more pronounced recruitable contractile reserve with exercise when compared with patients who exhibited increase in MR (Δwall motion score index \(-0.14 ± 0.04\) vs. \(-0.06 ± 0.05\), respectively, \( P = 0.001 \)), as well as less spherical shape of left ventricle in systole (Δ-end-systolic sphericity index 0.06 ± 0.03 vs. \(-0.12 ± 0.04\), respectively, \( P = 0.0001 \)). Patients with previous inferior MI who demonstrated a decrease in MR (nine patients) had improvement in contractility with exercise, whereas no improvement in contractility was observed in patients with inferior MI and increase in MR (five patients).

By stepwise multiple regression model, exercise-induced changes in coaptation distance \((P < 0.0001)\) and tenting area \((P < 0.0001)\) were the strongest predictors of exercise-induced changes in ERO (generalized \( r^2 = 0.80, P < 0.0001 \)), as presented in Table 4. Correlation between exercise-induced changes in ERO and mitral deformation is presented in Figure 1A–C.

**Table 1** Echocardiographic variables at rest and after exercise.

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic volume (mL)</td>
<td>191 ± 14</td>
<td>196 ± 14</td>
<td>0.047</td>
</tr>
<tr>
<td>LV end-systolic volume (mL)</td>
<td>147 ± 13</td>
<td>134 ± 15</td>
<td>0.0001</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>31 ± 5</td>
<td>41 ± 5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Global WMSI</td>
<td>1.76 ± 0.17</td>
<td>1.68 ± 0.16</td>
<td>0.0001</td>
</tr>
<tr>
<td>End-diastolic sphericity index</td>
<td>1.40 ± 0.15</td>
<td>1.38 ± 0.20</td>
<td>0.503</td>
</tr>
<tr>
<td>End-systolic sphericity index</td>
<td>1.42 ± 0.14</td>
<td>1.39 ± 0.18</td>
<td>0.044</td>
</tr>
<tr>
<td>Mitral annulus (cm)</td>
<td>3.7 ± 0.2</td>
<td>3.8 ± 0.3</td>
<td>0.014</td>
</tr>
<tr>
<td>Coaptation distance (cm)</td>
<td>1.5 ± 0.1</td>
<td>1.9 ± 0.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Tenting area (cm²)</td>
<td>3.5 ± 0.3</td>
<td>4.4 ± 0.9</td>
<td>0.0001</td>
</tr>
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</table>

WMSI, wall motion score index.

**Table 2** Correlation of echocardiographic parameters at rest to exercise-induced changes in ERO.

<table>
<thead>
<tr>
<th></th>
<th>( r )</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERO</td>
<td>0.284</td>
<td>0.076</td>
</tr>
<tr>
<td>LV end-diastolic volume (mL)</td>
<td>0.079</td>
<td>0.628</td>
</tr>
<tr>
<td>LV end-systolic volume (mL)</td>
<td>0.139</td>
<td>0.394</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>-0.025</td>
<td>0.878</td>
</tr>
<tr>
<td>Global WMSI</td>
<td>0.116</td>
<td>0.477</td>
</tr>
<tr>
<td>End-diastolic sphericity index</td>
<td>-0.202</td>
<td>0.210</td>
</tr>
<tr>
<td>End-systolic sphericity index</td>
<td>-0.006</td>
<td>0.972</td>
</tr>
<tr>
<td>Mitral annulus (cm)</td>
<td>0.275</td>
<td>0.086</td>
</tr>
<tr>
<td>Coaptation distance (cm)</td>
<td>0.037</td>
<td>0.823</td>
</tr>
<tr>
<td>Tenting area (cm²)</td>
<td>0.168</td>
<td>0.300</td>
</tr>
</tbody>
</table>

**Table 3** Exercise-induced changes in ERO: relation to changes in haemodynamic parameters, mitral deformation, and global LV function and shape.

<table>
<thead>
<tr>
<th></th>
<th>( \Delta ) Value</th>
<th>( r )</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>30 ± 9</td>
<td>-0.179</td>
<td>0.268</td>
</tr>
<tr>
<td>Heart rate (1/min)</td>
<td>32 ± 6</td>
<td>0.085</td>
<td>0.603</td>
</tr>
<tr>
<td>LV end-diastolic volume (mL)</td>
<td>3 ± 12</td>
<td>0.165</td>
<td>0.308</td>
</tr>
<tr>
<td>LV end-systolic volume (mL)</td>
<td>13 ± 12</td>
<td>0.163</td>
<td>0.316</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>11 ± 4</td>
<td>-0.178</td>
<td>0.271</td>
</tr>
<tr>
<td>Global WMSI</td>
<td>-0.08 ± 0.87</td>
<td>0.441</td>
<td>0.004</td>
</tr>
<tr>
<td>End-diastolic sphericity index</td>
<td>-0.02 ± 0.18</td>
<td>0.339</td>
<td>0.032</td>
</tr>
<tr>
<td>End-systolic sphericity index</td>
<td>-0.05 ± 0.14</td>
<td>0.400</td>
<td>0.011</td>
</tr>
<tr>
<td>Mitral annulus (cm)</td>
<td>0.13 ± 0.32</td>
<td>0.646</td>
<td>0.0001</td>
</tr>
<tr>
<td>Coaptation distance (cm)</td>
<td>0.41 ± 0.55</td>
<td>0.802</td>
<td>0.0001</td>
</tr>
<tr>
<td>Tenting area (cm²)</td>
<td>0.87 ± 1.34</td>
<td>0.791</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

BP, blood pressure.
Discussion

Our study has shown that functional MR increases with exercise in the majority of patients with previous MI and LV dysfunction. Changes in ERO were unrelated to the severity of functional MR at rest, as well as to the severity of LV dysfunction. Exercise-induced changes in MR were related to changes in wall motion score index, as well as to changes in end-systolic sphericity index in univariate analysis. However, exercise-induced changes in mitral deformation were, by multivariate analysis, the strongest predictors of exercise-induced changes in functional MR in patients with LV dysfunction due to prior MI.

Importance of functional MR: relation to previous studies

Ischaemic MR often accompanies acute MI and carries an adverse prognosis. The mortality in patients with chronic ischaemic LV dysfunction depends on the quantified degree of MR, but it has been shown that even moderate ischaemic MR also has negative prognostic value after MI. Functional MR also causes pulmonary hypertension and LV volume overload, further facilitating LV remodelling and deterioration in function. In addition, it has been recently shown that significant exercise-induced increase in MR in patients with chronic ischaemic LV dysfunction also carries a poor prognosis.

Previous studies have also shown that ERO is not related to the severity of LV dysfunction at rest. Correspondent to the findings of our study, Lancellotti et al. evaluating determinants of exercise-induced changes in MR have also shown no relationship between resting ERO and exercise-induced changes in functional MR. However, exercise-induced changes in MR were related to mitral deformation during exercise. Our results, including echocardiographic parameters of LV function and shape as well as mitral deformation, further extends previous observation that only mitral deformation parameters (changes in coaptation distance, tenting area, and mitral annular dimension) are independent predictors of exercise-induced changes in functional MR.

Mechanisms of exercise-induced changes in functional MR

Movement of coaptation zone from the mitral annulus toward apex of the left ventricle is the main characteristic of MR due to ischaemic LV systolic dysfunction, resulting in so-called tenting phenomenon. Tenting area has been implicated as the major determinant of functional MR at rest, and during exercise, whereas changes in coaptation distance have been associated with an increase in MR in patients with previous anterior MI and LV dysfunction.

This apical displacement of mitral leaflets further reduces the contact between the leaflets and compromises valve competence. In addition, mitral annular dilatation is considered to be one of the main causes of MR at rest.

Table 4 Predictors of exercise-induced changes in MR

<table>
<thead>
<tr>
<th>Predictor</th>
<th>β</th>
<th>95% CI for β</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔCoaptation distance</td>
<td>11.349</td>
<td>7599 to 15 099</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔTenting area</td>
<td>3462</td>
<td>2140 to 4785</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔMitral annular dimension</td>
<td>7218</td>
<td>13 490 to 13 490</td>
<td>0.063</td>
</tr>
</tbody>
</table>

Figure 1 (A) Correlation between exercise-induced changes in ERO and changes in coaptation distance. (B) Correlation between exercise-induced changes in ERO and changes in mitral annular diameter. (C) Correlation between exercise-induced changes in ERO and changes in tenting area.
Proposed mechanisms include loss of systolic annular function and/or mechanical dilatation of mitral annulus. Septal-lateral mitral annular diameter is implicated in leaflet malcoaptation, whereas the importance of commissure-to-commissure annular dilatation has been debated. Our study showed that mitral annular dilatation is related to the severity of exercise-induced changes in ERO, suggesting possible importance of mitral annuloplasty in surgical treatment of patients with ischaemic MR.

Previous studies have demonstrated that MR may be related to more spherical shape of left ventricle at rest as well as with exercise. However, it has been shown that functional MR is not dependent on more spherical shape of left ventricle at rest. In contrast, global spherical shape is common in any LV enlargement including those without MR. Our study demonstrated that a more spherical shape of left ventricle in systole may contribute to the increase in MR with exercise.

Unlike previous study, our study failed to demonstrate that global wall motion score index is independently related to the exercise-induced changes in ERO. The majority of patients with anterior MI in our study group could explain this finding. It has been shown that changes in wall motion score index in this group of patients were not related to the changes in ischaemic MR with exercise. In contrast, presence of viable myocardium with recruitable contractile reserve in basal segments is responsible for the decrease in MR in patients with inferior MI. Similar finding was also observed in our study.

It has been shown that improvement in contractility with dobutamine infusion results in the decrease in coaptation distance and mitral annular dimension and that decreased inotropy leads to increase in earlier mentioned indices. Our study demonstrated that not only the presence but also the extent of recruitable contractile reserve is responsible for the decrease in MR with exercise. In contrast, the presence of viable myocardium in patients with anterior MI is probably not sufficient to provide the decrease in MR.

Study limitations

We have not included in the analysis the delicate parameters of local LV ventricular remodelling, as the objective of our study was to compare the effects of mitral deformation and global LV function and shape on the severity of functional MR with exercise. The method we used for quantification of MR has its own limitations that might be even more pronounced with exercise. Measurements of ischaemic MR at end-systole lead to an overestimation of its severity. Ischaemic MR is a dynamic condition which has peak in early and late systole with a decrease in mid-systole.

The reported heart rate and blood pressure corresponded to peak exercise. The influence of the decrease in blood pressure after the test, which may contribute to larger ERO through decreased coaptation pressure, was not specifically assessed in our study. Although patients with clinical, ECG, and echocardiographic evidence of exercise-induced myocardial ischaemia were excluded from the study, the use of beta-blockers might affect the identification of myocardial ischaemia, which could obviously be a trigger to exercise-induced dynamic MR. Our findings cannot be applied to the patients with exercise-induced ischaemia because those patients were excluded from the study.

Clinical implications

Exercise-induced changes in functional MR cannot be predicted by resting echocardiographic parameters either of severity of MR or of global LV function and shape. As the presence of functional MR in patients with ischaemic LV dysfunction has an adverse prognosis, increase in severity of MR during exercise can further unmask those at high risk of poor outcome. Our study demonstrated that in patients with previous inferior MI and viable myocardium revascularization procedures alone can provide the decrease in MR with exercise. In contrast, in patients with previous anterior MI revascularization procedures alone seemed to be insufficient to reduce MR. However, further studies addressing this issue should be conducted.

References


