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Determinants of Exercise-Induced Changes in Mitral Regurgitation in Patients With Coronary Artery Disease and Left Ventricular Dysfunction

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OBJECTIVES We sought to examine the determinants of exercise-induced changes in ischemic mitral regurgitation (MR) in patients with left ventricular (LV) dysfunction.

BACKGROUND In the post-myocardial infarction (MI) phase, ischemic MR contributes to worsening of symptoms and of LV dysfunction.

METHODS In this study, 70 patients in the chronic, post-MI phase, with LV ejection fraction <45% and at least mild MR, underwent semi-supine exercise Doppler echocardiography. The effective regurgitant orifice (ERO) of MR was quantified at rest and during exercise. Exercise-induced changes in ERO were compared with changes in mitral deformation and in local and global LV remodeling.

RESULTS The wide range of exercise-induced ERO changes that were observed was unrelated to the degree of MR at rest ($r = 0.20$). Effective regurgitant orifice changes correlated best with changes in mitral deformation (i.e., differences in systolic mitral tenting area, systolic annular area, and coaptation height) ($p < 0.0001$). Posterior displacement of the papillary muscles was associated with larger changes in the ERO in both infarct groups. In patients with inferior MI, a decrease in the ERO was related to improvement in wall motion ($r = 0.68$). The independent predictors of ERO changes during exercise were changes in systolic annular area for all infarct categories, in tenting area and wall motion score in the global population and those with inferior infarction, and in apical displacement of mitral leaflets for patients with anterior MI.

CONCLUSIONS The degree of MR at rest is unrelated to exercise-induced changes in EROs, which are related to those in local LV remodeling and in mitral deformation but not those in global LV function. (J Am Coll Cardiol 2003;42:1921–8) © 2003 by the American College of Cardiology Foundation

In the context of ischemic heart disease, the incidence of mitral regurgitation (MR) is frequent and carries a dismal prognosis (1). The increased mortality is independent of the severity of left ventricular (LV) dysfunction but is related to the severity of the MR (2). Incomplete closure of normal mitral leaflets—the cause of MR—is due to a complex distortion of ventricular geometry and of the mitral apparatus (3–6). Annular enlargement (7), persistent leaflet

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tethering (8), LV dilation, sphericalization (9), and dysfunction (10) have all been proposed as determinants of ischemic MR. Recent clinical studies have showed that the degree of functional MR is related to mitral valvular deformation that is dependent on local rather than global LV remodeling (11,12). Ischemic MR is a dynamic condition (13). Many patients probably have episodes of increased regurgitant volume and effective regurgitant orifice (ERO) during various conditions, resulting in worsening of dyspnea and orthopnea. We have recently reported the feasibility and reliability of quantifying MR during exercise by Doppler echocardiography (14). A wide range of exercise-induced changes in regurgitant volume was observed and correlated well with changes in pulmonary pressures. The determinants of exercise-induced changes in MR have never been investigated. The purposes of this study were to analyze: 1) the mechanisms of functional MR in patients in the chronic, post-infarction phase of anterior myocardial infarction (MI) versus the mechanisms of those with inferior MI; 2) exercise-induced changes in MR; and 3) the determinants responsible for increases or decreases in the ERO during exercise.

METHODS

Patient population. This prospective study involved 81 consecutive patients with ischemic LV dysfunction (ejection fraction <45%) and at least mild MR who were able to perform a semi-supine exercise echocardiographic test. None of these patients had the following exclusion criteria: technically inadequate echocardiogram, structurally abnormal mitral valve, more than trivial aortic regurgitation, intraventricular conduction abnormality, functional class IV, history of MI <6 months, and atrial fibrillation or flutter.

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Abbreviations and Acronyms

EDV = end-diastolic volume
ERO = effective regurgitant orifice
LV = left ventricular
MI = myocardial infarction
MR = mitral regurgitation
PISA = proximal isovelocity surface area

Eleven of these patients were excluded for technical problems (n = 4), evidence of exercise-induced ischemia (n = 4), and significant arrhythmias (n = 3). The final study population consisted of the 70 remaining patients. The protocol was approved by the Human Ethical Committee of our University Hospital, and all patients gave informed consent.

Exercise echocardiography. Beta-blockers were discontinued 48 h before the test. A symptom-limited graded bicycle exercise test was performed in the semi-supine position on a tilting exercise table. After an initial workload of 25 W maintained for 6 min, the workload was increased every 2 min by 25 W. Blood pressure and a 12-lead electrocardiogram were recorded every 2 min. Two-dimensional and Doppler echocardiographic recordings were made throughout the test.

Echocardiographic measurements. Echocardiographic examinations were performed using a phased-array Acuson Sequoia imaging device. All echocardiographic and Doppler data were obtained in digital format and stored on optical disks for off-line analysis. For each measurement, at least three cardiac cycles were averaged. Quantitation of MR was performed by both the quantitative Doppler method using mitral and aortic stroke volumes and the proximal isovelocity surface area (PISA) method as previously described (11). The results of these two methods were averaged, allowing the regurgitant volume and ERO to be calculated. For the quantitative Doppler method, mitral and aortic stroke volumes were calculated, and regurgitant volume was the difference between these two stroke volumes. The ERO was the ratio of regurgitant volume to the regurgitant time-velocity integral. For the PISA method, the radius of the PISA was measured from at least three frames with optimal flow convergence. The largest radius, usually in mid-systole, was selected for analysis. The ERO was the ratio of regurgitant flow to peak regurgitant velocity. Left ventricular end-diastolic and end-systolic volumes and ejection fraction were measured by the biapical Simpson disk method. Mitral annulus diameter was measured at end-systole and end-diastole in two- and four-chamber views. Annular area was calculated using an ellipse formula. Annular contraction was also calculated. The valvular tenting area was obtained from the parasternal long-axis view at mid-systole (11) and was measured as the area enclosed between the annular plane and mitral leaflets (Fig. 1, left). Displacement of mitral coaptation (coaptation height) toward the LV apex was measured by the distance between leaflet coaptation and the mitral annulus plane in the apical four-chamber view. The distance between the posterior papillary muscle head and the intervalvular fibrosa (PPM-fibrosa) in the long-axis view measured the apical displacement of the posterior papillary muscle (Fig. 1, right) (12). Lateral and posterior displacements of both papillary muscles were evaluated from the short-axis view as previously described by Yiu et al. (11). Separation between papillary muscles was also measured from the short-axis view. Wall motion and thickening at the mitral and the papillary muscle levels were evaluated at rest and at peak exercise with a four-grade scale, eight-segment (4 basal and 4 mid-ventricular) model, allowing calculation of a wall motion score index. Myocardial contractile reserve was defined as improvement in wall thickening of ≥1 grade.

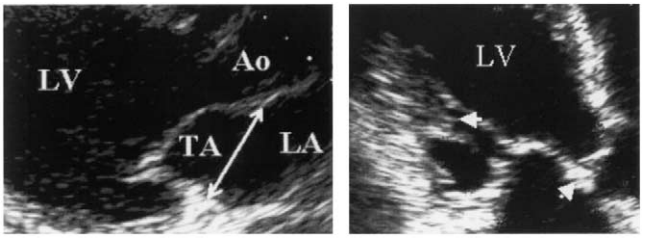

Figure 1. (Left) Parasternal long-axis view of aorta (Ao), left ventricle (LV), and left atrium (LA) showing tenting area (TA). **(Right)** Apical long-axis view demonstrating measurement of the distance between the posterior papillary muscle and the intervalvular fibrosa **(arrowheads)**.

Statistical analysis. Data are expressed as mean ± 1 SD. Continuous variables were tested by the Student *t* test, and nominal findings by a chi-square test. Group comparisons used analysis of variance. A value of $p < 0.05$ was considered statistically significant. Linear regression analysis was applied to study the correlation between the ERO at rest and exercise and different parameters. To determine independent predictors of the degree of MR at rest and of exercise-induced changes in the ERO (with the ERO as dependent variables and variables measuring mitral deformation, global and local LV remodeling as independent variables), stepwise multiple linear regression was performed. All variables with a p value <0.10 were included in the multivariate model. A similar univariate and multivariate analysis was also performed according to the site, inferior and anterior, of previous MI.

RESULTS

Characteristics: baseline and exercise. The site of MI was anterior in 28 patients, inferior in 31, and both anterior and inferior in 11. No patient had chest pain, significant ST-segment depression, or echocardiographic evidence of ischemia during exercise. Heart rate and systolic blood pressure increased significantly from rest to peak stress (76 ± 13 vs. 113 ± 14 beats/min and 130 ± 16 vs. 156 ± 19 mm Hg, respectively, $p < 0.0001$). Left ventricular end-diastolic volume (EDV) remained unchanged during exercise (144 ± 29 vs. 143 ± 21 ml/m^2), whereas end-systolic

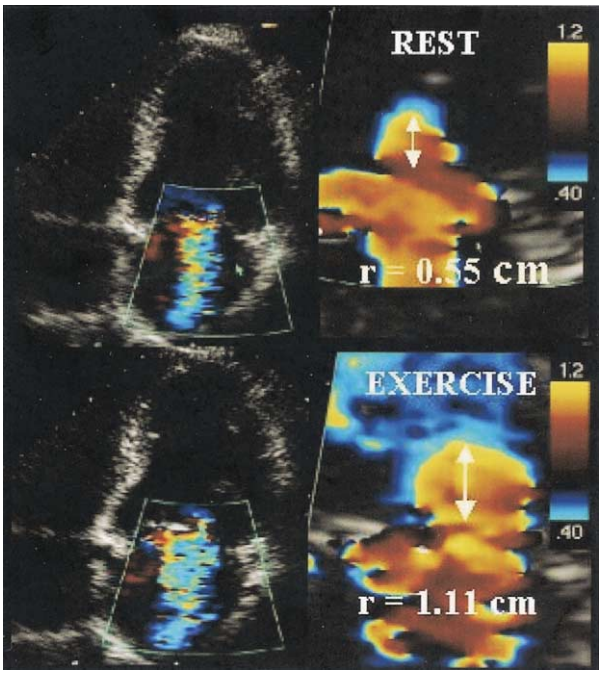

Figure 2. Apical four-chamber view showing color-flow Doppler and proximal flow-convergence region at rest and during exercise in a patient with a large exercise-induced increase in mitral regurgitation. r = proximal isovelocity surface area (PISA) radius.

volume decreased (91 ± 22 vs. 80 ± 26 ml/m^2, $p < 0.0001$), and EF increased (36 ± 7% vs. 44 ± 9%, $p < 0.0001$). Mitral regurgitation was measured by quantitative Doppler in all patients and by the PISA method in 59 (84%) patients at rest and in 64 (91%) during exercise. Regurgitant volume and the ERO increased from 21 ± 12 ml (range 5 to 65 ml) to 33 ± 21 ml (range 4 to 94 ml) and from 17 ± 9 mm^2 (range 3.5 to 50 mm^2) to 24 ± 14 mm^2 (range 0.5 to 54 mm^2), respectively (all $p < 0.0001$) (Fig. 2).

Determinants of the degree of MR at rest. Global and local LV remodeling as well as mitral valvular deformation in patients as a function of resting ERO are shown in Table 1. Patients were divided into three groups according to the ERO at rest (i.e., ERO <10 mm^2 [n = 13], ERO 10 to 20 mm^2 [n = 37], and ERO >20 mm^2 [n = 20]). Higher LV volumes were associated with higher EROs, but the correlations were weak. A better correlation was observed between EDV and ERO in patients with anterior MI ($r = 0.64$, $p = 0.00013$), whereas no correlation was found in patients with inferior MI. Mitral deformation increased significantly with higher degrees of MR, irrespective of the site of previous MI. The strongest correlation was observed with the systolic mitral tenting area ($r = 0.76$, $p < 0.000001$). Larger mitral annular areas, decreased annular contraction, and greater left atrial area were also associated with an increasing ERO. As concerns local LV remodeling, apical displacement of papillary muscles was associated with larger EROs independently of MI location ($r = 0.6$). Posterior displacement of both papillary muscles was also associated with greater ERO ($r = 0.46$ and 0.41, respectively). No significant correlation was found with lateral displacement. The correlation between wall motion score index and ERO was better in patients with inferior MI ($r = 0.56$, $p = 0.0047$). Multivariate analysis of ERO determinants (Table 2) showed the systolic tenting area to be the most important predictor in the overall population and in patients with anterior or inferior MI. Apical displacement of the papillary muscles was also found to be predictive in the total population and in patients with inferior MI. End-diastolic volume was a factor only for patients with anterior MI.

Determinants of exercise-induced changes in the ERO. During exercise, the ERO decreased in 13 patients (−9.2 ± 6 mm^2, −3.3 to −23.1 mm^2) and increased in the 57 remaining patients. A small increase (<13 mm^2) was observed in 38 patients (4.7 ± 3.1 mm^2), and a larger increase (>13 mm^2) was noted in 19 patients (22.2 ± 7.8 mm^2). Comparison between patients grouped according to changes in the ERO for mitral deformation and global and local LV remodeling are shown in Table 3. The degree of MR at rest did not correlate with exercise-induced changes in the ERO ($r = -0.2$) (Fig. 3). Heart rate and systolic arterial pressure increased similarly in each group; changes in LV volumes and in EF were also similar. Exercise-induced changes in mitral deformation corresponded to changes in the ERO, independent of MI location. The strongest correlations with changes in the ERO were observed with the differences in systolic mitral tenting area (Fig. 4), in coaptation height, and in systolic annular area in all MI categories ($r = 0.85$, 0.81, and 0.78 respectively, $p < 0.0001$). In terms of local LV remodeling, changes in posterior displacement of both papillary muscles were associated with larger changes in the ERO, whereas changes in lateral displacement showed weaker association. Improvement in wall motion score index was associated with exercise-induced decreases in EROs of patients with previous inferior MI ($r = 0.68$, $p < 0.0001$) (Fig. 5). Under multivariate analysis, an increase in systolic mitral annular area emerged as an independent predictor of ERO changes in the global population and in patients with both anterior and inferior MI (Table 4). The absence of contractile reserve and an increase in systolic mitral tenting area were also associated with greater changes in EROs in the overall population and in patients with inferior MI but not in the subgroup of patients with anterior MI. On the other hand, greater apical mitral leaflet displacement, measured as coaptation height distance, was selected as significant in patients with anterior MI only.

Reproducibility of measurements. Reproducibility between the quantitative Doppler method and the PISA method at rest and during exercise has previously been published (14). In the 13 patients with improved EROs at exercise, the correlation between the two methods was excellent ($r = 0.91$, $p < 0.0001$; 3.5 ± 3.9 mm^2 for absolute differences between exercise and rest). Interobserver variability for LV and mitral remodeling was assessed in 10

Table 1. Characteristics of Patients at Rest

Resting Data	ERO <10 mm² (n = 13)	ERO 10–20 mm² (n = 37)	ERO >20 mm² (n = 20)	p for Trend	Correlation With ERO r	Correlation With ERO p
Left atrial area (cm^2)	16 ± 4	18 ± 3	24 ± 4	< 0.000001*†	0.52 (0.54, 0.48)	0.000003*†
Clinical data						
Height (cm)	173 ± 8	172 ± 6	171 ± 7	—	0.02 (0.01, 0.004)	0.83
Body surface area (m^2)	1.86 ± 0.14	1.83 ± 0.21	1.85 ± 0.17	—	0.07 (0.05, 0.10)	0.72
Heart rate (beats/min)	76 ± 13	75 ± 14	78 ± 12	—	0.11 (0.19, 0.26)	0.36
Systolic arterial pressure (mm Hg)	128 ± 20	131 ± 13	129 ± 17	—	0.05 (0.002, 0.18)	0.68
Global LV remodeling						
EDV (ml/m^2)	122 ± 34	145 ± 27	154 ± 23	0.006*	0.31 (0.64, 0.18)	0.0086*
ESV (ml/m^2)	78 ± 21	93 ± 24	99 ± 17	0.028*	0.24 (0.36, 0.18)	0.042
EF (%)	36 ± 7	37 ± 7	36 ± 6	—	0.02 (0.21, 0.11)	0.86
Mitral valvular deformation						
Tenting area (cm^2)	4.3 ± 0.5	5.9 ± 1.1	7.6 ± 0.9	< 0.000001*†	0.76 (0.82, 0.74)	0.000001*†
Coaptation height (cm)	1.7 ± 0.2	1.8 ± 0.1	2.0 ± 0.2	0.00002†	0.59 (0.30, 0.71)	0.000001†
Diastolic MA area (cm^2)	6.1 ± 1.1	6.1 ± 0.8	6.8 ± 1.3	0.023†	0.36 (0.28, 0.48)	0.0019†
Systolic MA area (cm^2)	4.6 ± 1.1	4.6 ± 0.8	5.6 ± 1.5	0.029†	0.46 (0.45, 0.53)	0.00006*†
MA contraction (%)	24 ± 9	24 ± 8	19 ± 7	0.04	0.36 (0.48, 0.30)	0.0024*
Local LV remodeling						
PMs separation (cm)				0.00011*†	0.57 (0.73, 0.52)	0.00003*†
PPM fibrosa (cm)	3.1 ± 3.0	3.4 ± 2.1	3.6 ± 2.4	0.000001*†	0.60 (0.70, 0.61)	0.00001*†
PPM posterior (cm)	5.4 ± 1.8	5.9 ± 3.3	6.2 ± 4.2	0.000003*†	0.46 (0.41, 0.55)	0.001†
APM posterior (cm)	2.0 ± 1.0	2.3 ± 1.5	2.4 ± 1.9	0.018*	0.41 (0.49, 0.32)	0.0039*
PPM lateral (cm)	2.3 ± 1.1	2.4 ± 1.6	2.6 ± 3.8	0.014†	0.18 (0.32, 0.19)	0.22
APM lateral (cm)	2.1 ± 1.2	2.3 ± 1.7	2.3 ± 1.3	—†	0.005 (0.01, 0.08)	0.97
WMI	1.1 ± 0.9	1.2 ± 0.9	1.1 ± 1.4	—	0.29 (0.23, 0.56)	0.016†
	1.64 ± 0.23	1.61 ± 0.19	1.72 ± 0.28			

p = p value for the entire population; p ≤ 0.05: *anterior infarct patients, †inferior infarct patients; r for total population; in parentheses, r for anterior and inferior infarcts.
APM = anterior papillary muscle; EDV = end-diastolic volume; EF = ejection fraction; ERO = effective regurgitant orifice; ESV = end-systolic volume; MA = mitral annular; PMs = papillary muscles; PPM = posterior papillary muscle; WMI = wall motion score index.

patients. The correlation coefficients between the variables obtained by the two observers at rest and at exercise were as follows: r = 0.88, p = 0.0008 (0.77 ± 0.45 cm^2) and r = 0.81, p = 0.0038 (0.64 ± 0.38 cm^2) for systolic mitral tenting; r = 0.88, p = 0.0007 (0.39 ± 0.19 cm) and r = 0.78, p = 0.0072 (0.35 ± 0.21 cm) for papillary-fibrosa distance; and r = 0.87, p = 0.0011 (0.78 ± 0.44 cm^2) and r = 0.82, p = 0.0034 (0.77 ± 0.45 cm^2) for systolic mitral annulus area.

DISCUSSION

Under basal conditions, regurgitant volume is determined by the ERO, the systolic pressure gradient across the orifice, and the duration of systole (15). During exercise, the systolic pressure gradient increases, the duration of systole decreases, and regurgitant volume depends mainly on the size of the ERO. The mechanisms of ischemic MR are complex and relate to the site of previous MI. Systolic mitral valvular tenting is the strongest determinant of MR at rest. Apical displacement of the papillary muscles has an additional independent association with the degree of MR in patients with previous inferior MI, whereas in patients with anterior MI, the independent determinant is increased EDV. Exercise-induced changes in MR relate to changes in local LV remodeling and in mitral valvular deformation but to neither the degree of MR at rest nor to changes in global LV function. Systolic mitral annular area is an independent determinant in patients with previous anterior or inferior MI. Tenting area is the major determinant in patients with inferior infarction, whereas apical displacement of the mitral coaptation is the most powerful predictor in those with anterior MI. A decrease in the ERO during exercise occurs mainly in patients with inferior MI and recruitable viable myocardium.

Table 2. Determinants of ERO at Rest

Data	ERO at rest Total	ERO at rest Anterior	ERO at rest Inferior
Tenting area	0.000001	0.000007	0.00013
PPM-fibrosa	0.0034	—	0.025
EDV	—	0.014	—
R^2	0.71	0.74	0.72

Abbreviations as in Table 1.

Determinants of chronic ischemic MR. Most experimental and clinical studies investigating the mechanisms of ischemic MR have been performed during acute ischemia, a condition in which the role of LV remodeling is modest (16–19). In patients with chronic systolic LV dysfunction, the presence and degree of functional MR are predominantly related to mitral valvular deformation (11). In the present study, we also found that the degree of systolic mitral valvular tenting was correlated with the severity of

Table 3. Changes in the ERO With Exercise and Patient Characteristics

Exercise-Resting Data	ERO			p for Trend	Correlation With ERO	
	Decreased (n = 13)	Increased <13 mm² (n = 38)	Increased ≥13 mm² (n = 19)		r	p
Left atrial area (cm²)	−1.0 ± 2.9	1.5 ± 3.6	1.8 ± 3.3	†	0.23 (0.23, 0.49)	0.06†
Hemodynamic data						
Heart rate (beats/min)	37 ± 16	39 ± 16	38 ± 14	—	0.07 (0.16, 0.12)	0.54
Systolic arterial pressure (mm Hg)	29 ± 16	28 ± 19	20 ± 11	—	0.12 (0.13, 0.18)	0.34
Global LV remodeling						
EDV (ml)	−4.9 ± 13	0.5 ± 21	0.9 ± 21	—	0.10 (0.09, 0.01)	0.40
ESV (ml)	−11 ± 13	−13 ± 19	−7 ± 14	—	0.15 (0.14, 0.08)	0.24
EF (%)	6.8 ± 7.7	10 ± 7.4	5.5 ± 3.1	†	0.18 (0.16, 0.19)	0.14
Mitral valvular deformation						
Tenting area (cm²)	−1.1 ± 0.9	0.44 ± 0.65	1.6 ± 0.75	< 0.000001*†	0.85 (0.86, 0.84)	< 0.000001*†
Coaptation height (cm)	−0.2 ± 0.2	0.03 ± 0.15	0.28 ± 0.20	0.000001*†	0.81 (0.89, 0.78)	0.000001*†
Diastolic MA area (cm²)	−0.4 ± 0.7	0.3 ± 0.4	0.7 ± 0.8	0.00002*†	0.54 (0.66, 0.31)	0.00002*
Systolic MA area (cm²)	−0.5 ± 0.8	0.3 ± 0.4	1.0 ± 0.7	< 0.000001*†	0.78 (0.83, 0.79)	0.000001*†
MA contraction (%)	2.0 ± 12	−1.1 ± 4.6	7.5 ± 14	0.013†	0.44 (0.54, 0.57)	0.00016*†
Local LV remodeling						
PMs separation (mm)	0.38 ± 2.3	−0.5 ± 2.2	−0.4 ± 2.6	—	0.15 (0.31, 0.15)	0.31
PPM-fibrosa (cm)	−1.9 ± 2.7	−3.8 ± 3.4	−0.3 ± 5.4	0.0445	0.06 (0.32, 0.30)	0.69
PPM posterior (mm)	−2.3 ± 1.6	−0.5 ± 1.6	1.4 ± 1.9	0.00006†	0.68 (0.43, 0.63)	0.000001†
APM posterior (mm)	−2.1 ± 1.4	−0.7 ± 1.6	1.4 ± 2.3	0.00015	0.66 (0.48, 0.81)	0.000001*†
PPM lateral (mm)	−1.8 ± 1.5	−0.9 ± 1.5	0.4 ± 1.4	0.005	0.43 (0.31, 0.46)	0.002†
APM lateral (mm)	−1.0 ± 1.1	−0.2 ± 1.5	0.1 ± 1.7	—	0.06 (0.51, 0.26)	0.64*
WMI	−0.6 ± 0.19	−0.29 ± 0.15	−0.25 ± 0.19	0.000001†	0.50 (0.21, 0.68)	0.00002†

p = p value for the entire population; p ≤ 0.05; *anterior infarct patients, †inferior infarct patients; r for total population; in parentheses, r for anterior and inferior infarcts. Abbreviations as in Table 1.

MR at rest. The greater the tenting, the larger the ERO. In patients in the chronic, post-infarction phase of inferior MI, incomplete closure of the mitral leaflets was also generated by apical displacement of the papillary muscles. As demonstrated experimentally, displacement of the papillary muscles away from the annulus tethers the leaflets within the LV and restricts their ability to close effectively (19). In patients with anterior MI, LV dilation has a major adjunctive role in the genesis of MR. Geometric changes associated with LV remodeling induce a stretching of the leaflets more widely over the annulus, resulting in apical tenting and MR (8).

Determinants of exercise-induced changes in MR. Of note, changes in the ERO during exercise were unrelated to the degree of MR under basal conditions. Thirteen patients had a decrease in the ERO, and 19 had a major (>13 mm²) increase in the ERO. A slight increase in the ERO was found in the 38 remaining patients. Similar exercise-induced changes in heart rate, systolic arterial pressure, LV

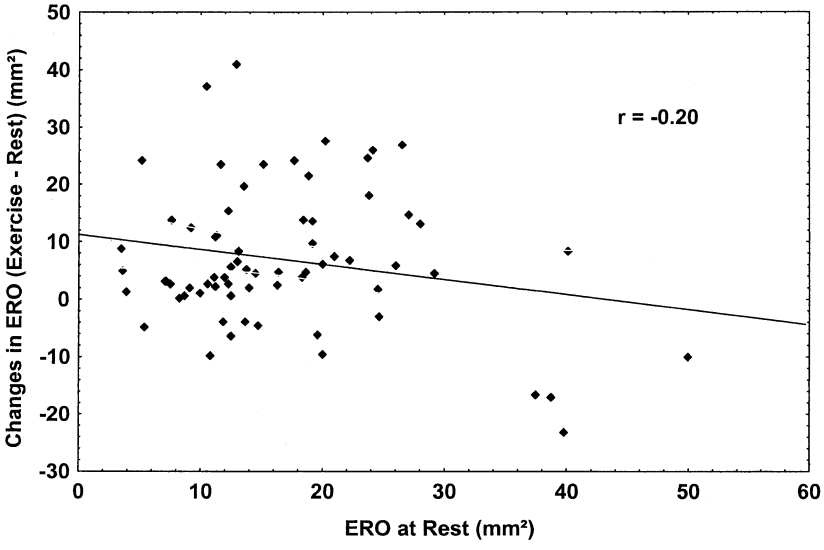

Figure 3. Correlation between changes in effective regurgitant orifice (ERO) during exercise and the degree of mitral regurgitation at rest.

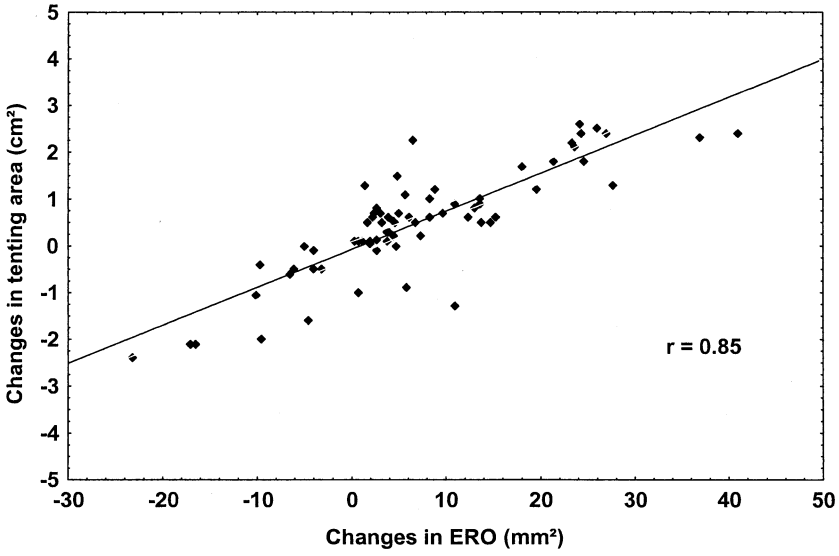

Figure 4. Correlation between changes in effective regurgitant orifice (ERO) and changes in tenting area during exercise.

volumes, and ejection fraction were observed in these subgroups. Progressive dilation of the mitral valve annulus during exercise was associated with exercise-induced worsening of MR. Systolic expansion of the annulus indeed might affect leaflet coaptation and contribute to exercise-induced increases in MR by increasing systolic mitral valvular tenting. Restriction of the mitral leaflet closure might also be accentuated by the posterior displacement of papillary muscles during exercise. However, significant bulging of the tenting area was an independent determinant only in patients with either two different MI sites or inferior MI. In contrast, apical displacement of the mitral leaflets was the major determinant of exercise-induced increases in MR in patients in the chronic, post-infarction phase of anterior MI. Less systolic expansion of the annulus with preserved annular contraction characterized patients with a decrease in the ERO, which was most frequently observed in patients with inferior MI and recruitable contractile reserve during exercise (9 of the 13 patients). Improvement of wall thickening in basal segments may indeed reduce the degree of MR during exercise by decreasing mitral annulus distortion and tethering forces.

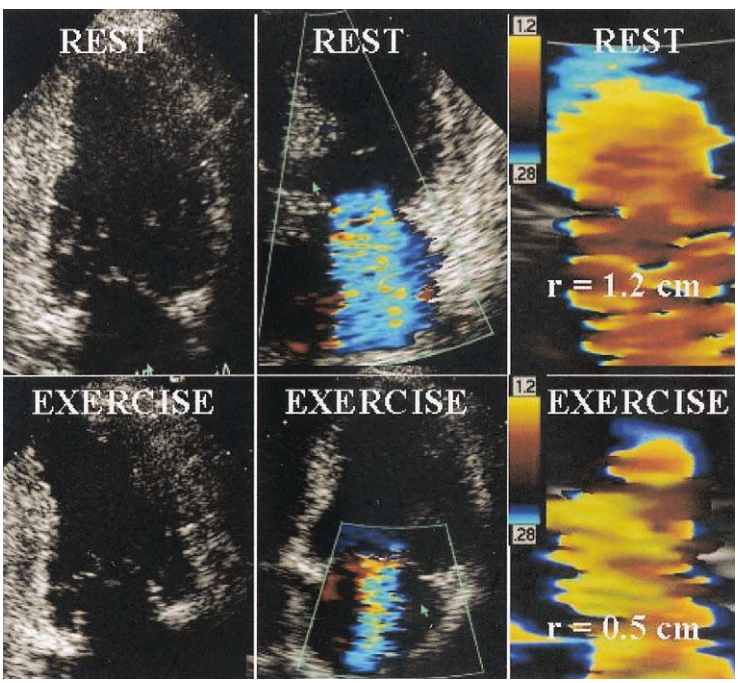

Figure 5. End-systolic stop frame images and proximal flow-convergence region at rest and during exercise in a patient with chronic inferior myocardial infarction and mitral regurgitation. Contractile reserve of the basal inferior wall is recruited during exercise and is associated with a reduction of the proximal isovelocity surface area radius and a decrease in effective regurgitant orifice.

Table 4. Determinants of the ERO Changes During Exercise

Data	ERO at Exercise		
	Total	Anterior	Inferior
Tenting area	0.000001	—	0.000004
Coaptation height	—	0.00002	—
Systolic MA area	0.0009	0.006	0.034
WMI	0.019	—	0.009
R^2	0.79	0.85	0.86

Abbreviations as in Table 1.

Clinical implications. Medical treatment aimed at LV unloading reduces dynamic MR (20) but is often insufficient. A surgical approach may therefore be warranted (21,22). The traditional surgical procedure consists of a ring annuloplasty. Such an approach is likely to be more efficacious in patients with exercise-induced increases in MR. Keeping in mind our results, new surgical techniques could focus on reducing tenting in addition to applying a specific approach to an individual patient's anatomy. In patients with anterior MI, our results argue for LV reshaping by infarct exclusion or resection combined with annuloplasty. These reconstructions may relieve ischemic MR (23) and result in symptomatic improvement (24,25). In patients with inferior MI, the surgical strategy should be guided by the presence or absence of viable myocardium; papillary muscle repositioning might be an appropriate complementary treatment (26). Precise cutting of the critically positioned chordae responsible for restriction of leaflet closure has also been proposed as a possible new therapeutic approach (27).

Study limitations. Several limitations should be acknowledged. No patient included in the present study had evidence of exercise-induced myocardial ischemia, obviously one of the potential mechanisms of dynamic MR. For technical reasons, images were not recorded side by side to evaluate ischemia. However, no patient developed exercise-induced electrocardiographic ischemic changes. Doppler methods used to quantify MR have some pitfalls (28). In the present study, a limitation of the PISA method is the measurement of the PISA radius at only one velocity and time point. Nevertheless, the two methods used have been validated at rest and during exercise in our institution (14). Measurements of tenting area and local LV remodeling have been obtained only at mid-systole from high-resolution images. The physiologic variation during systole was not assessed. The effects of upright position on MR, hemodynamics, and volumes have not been studied. The results might be different in this position.

Conclusions. Ischemic heart failure is frequently accompanied by dynamic and sometimes severe MR. The ERO at rest does not predict changes in the ERO during exercise. Thus, resting evaluation of ischemic MR may underestimate the full severity of the lesion and its impact. The degree of exercise-induced increase or decrease in MR appears to relate to local LV remodeling and mitral valvular deformation but not to changes in global LV function. Because new therapeutic approaches to ischemic MR could be proposed based on these observations, their prognostic importance needs to be assessed.

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REFERENCES

1. Lamas GA, Mitchell GF, Flaker GC, et al. Clinical significance of mitral regurgitation after acute myocardial infarction. Survival and ventricular enlargement investigators. Circulation 1997;96:827–33.
2. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001; 103:1759–64.
3. Kono T, Sabbah HN, Rosman H, et al. Mechanism of functional mitral regurgitation during acute myocardial ischemia. J Am Coll Cardiol 1992;19:1101–5.
4. Sabbah HN, Rosman H, Kono T, Alam M, Khaja F, Golstein S. On the mechanism of functional mitral regurgitation. Am J Cardiol 1993;72:1074–6.
5. Gorman RC, McCaughan JS, Ratcliffe MB, et al. Pathogenesis of acute ischemic mitral regurgitation in three dimensions. J Thorac Cardiovasc Surg 1995;109:684–93.
6. Sharma SK, Seckler J, Israel DH, Borrico S, Ambrose JA. Clinical, angiographic and anatomic findings in acute severe ischemic mitral regurgitation. Am J Cardiol 1992;70:277–80.
7. Izumi S, Miyatake K, Beppu S, et al. Mechanism of mitral regurgitation in patients with myocardial infarction: a study using real-time two-dimensional Doppler flow imaging and echocardiography. Circulation 1987;76:777–85.
8. He S, Fontaine AA, Schwammenthal E, Yoganathan AP, Levine RA. Integrated mechanism for functional mitral regurgitation: leaflet restriction versus coapting force: in vitro studies. Circulation 1997;96: 1826–34.
9. Kono T, Sabbah HN, Rosman H, Alam M, Jafri S, Golstein S. Left ventricular shape is the primary determinant of functional mitral regurgitation in heart failure. J Am Coll Cardiol 1992;20:1594–8.
10. Kaul S, Pearlman JD, Touchstone DA, Esquival L. Prevalence and mechanisms of mitral regurgitation in the absence of intrinsic abnormalities of the mitral leaflets. Am Heart J 1989;118:963–72.
11. Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. Circulation 2000;102:1400–6.
12. Otsuji Y, Kumanohoso T, Yoshifuku S, et al. Isolated annular dilation does not usually cause important functional mitral regurgitation: comparison between patients with lone atrial fibrillation and those with idiopathic or ischemic cardiomyopathy. J Am Coll Cardiol 2002;39:1651–6.
13. Kizilbash AM, Willett DL, Brickner E, Heinle SK, Grayburn PA. Effects of afterload reduction on vena contracta width in mitral regurgitation. J Am Coll Cardiol 1998;32:427–31.
14. Lebrun F, Lancellotti P, Piérard LA. Quantitation of functional mitral regurgitation during bicycle exercise in patients with heart failure. J Am Coll Cardiol 2001;38:1685–92.
15. Yoran C, Yellin EL, Becker RM, Gabbay S, Frater RW, Sonnenblick EH. Dynamic aspects of acute regurgitation: effects of ventricular volume, pressure and contractility on the effective regurgitant orific area. Circulation 1979;60:170–6.
16. Gorman JH, 3rd, Jackson BM, Gorman RC, Kelley ST, Gikakis N, Edmunds LH, Jr. Papillary muscle discoordination rather than increased annular area facilitates mitral regurgitation after acute posterior myocardial infarction. Circulation 1997;96:II124–7.
17. Komeda M, Glasson JR, Bolger AF, et al. Geometric determinants of ischemic mitral regurgitation. Circulation 1997;96:II128–33.
18. Kaul S, Spotnitz WD, Glasheen WP, Touchstone DA. Mechanism of ischemic mitral regurgitation. An experimental evaluation. Circulation 1991;84:2167–80.

19. Dagum P, Timek TA, Green GR, et al. Coordinate-free analysis of mitral valve dynamics in normal and ischemic hearts. Circulation 2000;102:III62–9.
20. Rosario LB, Stevenson LW, Solomon SD, Lee RT, Reimold SC. The mechanism of decrease in dynamic mitral regurgitation during heart failure treatment: importance of reduction in the regurgitant orifice size. J Am Coll Cardiol 1998;32:1819–24.
21. Bach DS, Bolling SF. Early improvement in congestive heart failure after correction of secondary mitral regurgitation in end-stage cardiomyopathy. Am Heart J 1995;129:1165–70.
22. Bolling SF, Pagani FD, Deeb GM, Bach DS. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. J Thorac Cardiovasc Surg 1998;115:381–6.
23. Liel-Cohen N, Guerrero JL, Otsuji Y, et al. Design of a new surgical approach for ventricular remodeling to relieve ischemic mitral regurgitation: insights from 3-dimensional echocardiography. Circulation 2000;101:2756–63.
24. Qin JX, Shiota T, McCarthy PM, et al. Real-time three-dimensional echocardiographic study of left ventricular function after infarct exclusion surgery for ischemic cardiomyopathy. Circulation 2000;102: III101–6.
25. Kaza AK, Patel MR, Fiser SM, et al. Ventricular reconstruction results in improved left ventricular function and amelioration of mitral insufficiency. Ann Surg 2002;235:828–32.
26. Hung J, Guerrero JL, Handshumacher MD, Supple G, Sullivan S, Levine RA. Reverse ventricular remodeling reduces ischemic mitral regurgitation: echo-guided device application in the beating heart. Circulation 2002;106:2594–600.
27. Messas E, Guerrero JL, Handschumacher MD, et al. Chordal cutting: a new therapeutic approach for ischemic mitral regurgitation. Circulation 2001;104:1958–63.
28. Enriquez-Sarano M, Seward JB, Bailey KR, Tajik AJ. Effective regurgitant orifice area: a noninvasive Doppler development of an old hemodynamic concept. J Am Coll Cardiol 1994;23:443–51.