CME

Exercise-Induced Changes in Degenerative Mitral Regurgitation

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JACC JOURNAL CME

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CME Objective for This Article: At the conclusion of this activity, the learner will be able to evaluate the relationship between exercise-induced changes in mitral regurgitation and systolic pulmonary artery pressure and identify the potential impact on symptom-free survival.

CME Editor Disclosure: *JACC* CME Editor Ajit Raisinghani, MD, FACC, reports that he has no financial relationships or interests to disclose.

Author Disclosures: Dr. Magne was supported by a grant from the Fonds de la Recherche en Santé du Québec, Québec, Canada.

Medium of Participation: Print (article only); online (article and quiz)

CME Term of Approval:

Issue date: July 20, 2010
Expiration date: July 19, 2011

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Objectives   We sought to quantify exercise-induced changes in patients with degenerative mitral regurgitation (MR), to examine the relationship between exercise-induced changes in MR and in systolic pulmonary artery pressure (PAP), and to identify their potential impact on symptom-free survival.

Background   MR severity can change during exercise in patients with functional MR. Quantified changes in MR severity during exercise remain undetermined in patients with degenerative MR.

Methods   Resting and bicycle exercise Doppler-echocardiography were performed in 61 asymptomatic patients (age 62 $\pm$ 14 years) with moderate to severe degenerative MR (i.e., mitral valve prolapse or flail). Mitral regurgitation was quantified at rest and exercise with effective regurgitant orifice (ERO) area and regurgitant volume calculated with the proximal isovelocity surface area (ERO_P) and the quantitative Doppler (ERO_D) methods.

Results   At rest, ERO_P and ERO_D were well-correlated ($r = 0.87$, $p < 0.0001$), but ERO_D was larger than ERO_P (54 ± 21 mm^2 vs. 42 ± 24 mm^2, $p < 0.0001$). During exercise, mean ERO and regurgitant volume markedly increased in 32% of patients by $\geq$10 mm^2 and $\geq$15 ml, respectively. There was good correlation between exercise ERO_P and ERO_D ($r = 0.84$, $p < 0.0001$). Changes in systolic PAP were correlated with changes in ERO and regurgitant volume ($r = 0.59$, $p = 0.02$ and $r = 0.60$, $p = 0.02$). Patients with a marked increase in regurgitant volume during exercise had lower symptom-free survival than those in whom MR decreased or remained unchanged ($p = 0.0015$).

Conclusions   Degenerative MR might be dynamic and increases during exercise in one-third of patients. Marked changes in MR severity are associated with exercise-induced changes in systolic PAP and reduced symptom-free survival.   (J Am Coll Cardiol 2010;56:300–9) © 2010 by the American College of Cardiology Foundation

Degenerative mitral regurgitation (MR) is the second most prevalent valvular disease (1) and, when severe, is associated with poor outcome (2,3). The management of patients with asymptomatic severe MR remains controversial (4–6). The current American College of Cardiology/American Heart Association guidelines (7) recommend mitral valve surgery when symptoms, left ventricular (LV) dysfunction, atrial fibrillation, or pulmonary hypertension occur or, in the absence of such criteria, when the likelihood of successful repair is >90%. In contrast, patients with moderate MR should not be operated (Class III, Level of Evidence: C). However, a recent study indicated that patients with moderate MR initially have a low complication rate that rises over time (3). Thus, some patients with moderate MR could have mid-term morbidity and mortality risk similar to patients with severe MR, possibly because of progression of regurgitation.

Functional MR is characteristically dynamic and sensitive to changes in ventricular size and loading conditions, regardless of the degree of resting MR. Exercise-induced changes in MR can be reliably quantified during exercise Doppler echocardiography and are unrelated to the degree of MR at rest (8,9). Large exercise-induced increases in functional MR identify patients at high risk of exertional dyspnea, acute pulmonary edema, and poor outcome (10–13). We hypothesized that similar dynamic changes can also occur in patients with degenerative MR. Indeed, the effect of exercise on quantified MR severity is still unexplored in such patients. Therefore the aims of this study were to determine: 1) whether degenerative MR can be dynamic; 2) whether eventual exercise-induced changes in MR are related to exercise-induced changes in systolic pulmonary arterial pressure (PAP); and 3) the potential influence of these changes on symptom-free survival.

Methods

Population. We prospectively examined 74 consecutive asymptomatic patients with degenerative MR due to mitral valve prolapse and with normal LV function (ejection fraction >60%, end-systolic diameter <45 mm) in our stress echocardiography laboratory. Of this population, 6 patients were excluded for $\geq$1 of the following criteria: <moderate MR (effective regurgitant orifice [ERO] area <20 mm^2 or regurgitant volume <30 ml), concomitant valvular stenosis or regurgitation, significant atrial arrhythmias, inability to exercise, and stress-induced myocardial ischemia. In addition, 7 other patients had nonoptimal acoustic window to accurately quantify MR and therefore were excluded from the final analysis. The remaining 61 patients (age 62 $\pm$ 14 years, 51% of males) were submitted to rest and exercise Doppler echocardiography.

Exercise echocardiography. A symptom-limited graded bicycle exercise test was performed in the semisupine position on a tilting exercise table. After an initial workload of 25 W maintained for 2 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 imaging was available throughout the test.

Abbreviations and Acronyms

ERO = effective regurgitant orifice

ERO$_D$ = effective regurgitant orifice by quantitative Doppler

ERO$_P$ = effective regurgitant orifice by proximal isovelocity surface area

LA = left atrial

LV = left ventricular

MR = mitral regurgitation

PAP = pulmonary artery pressure

PISA = proximal isovelocity surface area

TR = tricuspid regurgitation

Echocardiographic measurements. Echocardiographic examinations were performed with a Vivid 7 imaging device (GE Healthcare, Little Chalfont, United Kingdom). All echocardiographic and Doppler data were obtained in digital format, at rest and at peak exercise in the same semisupine position, and then stored on a workstation for offline analysis (EchoPAC, GE Vingmed Ultrasound AS, Horten, Norway). The quantification of MR was performed as previously described (9). Briefly, MR severity was measured with both Doppler volumetric method (i.e., by the difference between mitral and aortic stroke volumes) (14,15) and the proximal isovelocity surface area (PISA) method. The proximal isovelocity radius was measured from at least 3 frames with optimal flow convergence. The most appropriate negative aliasing velocity to obtain satisfactory hemispheric PISA was selected offline on the dedicated workstation. The PISA radius was measured in midsystole (16). The regurgitant volume and the ERO area were calculated with standard formulae. Marked exercise-induced increases or decreases in MR were defined as increase or decrease in ERO $\geq$10 mm^2 or in regurgitant volume $\geq$15 ml, as one-half of the differences between the thresholds of severity (20 mm^2 for ERO and 30 ml for regurgitant volume).

When the PISA and volumetric methods could be obtained, the results of the 2 methods were averaged, both at rest and during exercise. The reproducibility of the quantification of MR at rest and during exercise in our laboratory has previously been reported (9). The LV end-diastolic and end-systolic volumes and left atrial (LA) maximal volume were measured by biplane Simpson's rule method. The LV outflow tract stroke volume was calculated by multiplying the LV outflow tract area by the LV outflow tract velocity–time integral measured by pulsed-wave Doppler. Mitral annular diameter was measured in apical 4- and 2-chamber views, and mitral annular area was calculated with ellipsoidal formulae. Mitral annular velocity–time integral was measured in apical 4-chamber view with pulsed-wave Doppler. The LV outflow tract diameter was assumed as constant during exercise, whereas mitral annular dimension was measured both at rest and during exercise. Mitral E- and A-wave velocities were measured with pulsed-wave Doppler, and Ea-wave velocity was obtained with tissue Doppler imaging at the septal mitral annulus. These measurements were repeated at exercise, before or just after the eventual fusion of E and A or Ea and Aa (mean heart rate 94 $\pm$ 11 beats/min). Systolic PAP was derived from the regurgitant jet of tricuspid regurgitation (TR) with systolic transtricuspid pressure gradient calculated by the modified Bernoulli equation ($\Delta P = 4 \ v^2$, where v = maximal tricuspid regurgitant jet velocity in m/s and the addition of 10 mm Hg for right atrial pressure).

Sequence of exercise imaging. At peak exercise (i.e., within the minute before and the minute after the end of exercise) the stepwise sequence used was as follows: 1) pulsed-wave Doppler in LV outflow tract; 2) continuous wave Doppler of TR; 3) pulsed-wave Doppler of mitral inflow; 4) 4-chamber color view; 5) PISA; 6) continuous wave Doppler of MR; and 7) gray-scale images in 2- and 4-chamber apical and parasternal short- and long-axis views.

Symptom-free survival. Follow-up collection was complete in 61 (100%) patients. During follow-up, patients were re-evaluated every 12 months, including physical examination and echocardiography. Intervals were shortened to 6 or 3 months in patients with changes compared with previous measurements or if echocardiographic measurements were close to guidelines cutoff values used for surgical indication. At the end of this study, patients with a last follow-up >6 months were re-evaluated with telephone calls with physicians and (if necessary) with patients.

Physical examination was performed by experienced cardiologists and symptomatic status was carefully assessed. Patients were classified as symptomatic when shortness of breath, angina, dizziness, or syncope with exertion was identified.

Statistical analysis. Results are expressed as mean $\pm$ SD or percentages unless otherwise specified. Before analysis, normality distribution was tested with Kolmogorov-Smirnov test. The differences between exercise and resting data were compared for significance with a 2-tailed paired *t* test. Interobserver and intraobserver variability for the measurement of ERO and regurgitant volume both at rest and during exercise were determined from the analysis of the Doppler echocardiographic images of 14 randomly selected patients by 2 independent and blinded observers (J.M. and P.L.). The results were compared with a 1-way analysis of variance, Pearson correlation coefficient, and the Bland-Altman method.

The relationship between the PISA method and Doppler volumetric method to quantify resting and exercise MR severity was analyzed with linear regression and the Bland-Altman method (17), plotting and regressing the methods' difference against the methods' mean value. Correlations between echocardiographic data as well as between MR severity parameters and peak TR velocity were also evaluated with linear regression. Stepwise multiple regressions were used to assess whether exercise-induced changes in MR was significantly associated with changes in peak TR velocity after adjustment for age and sex. Probabilities of symptom-free survival were determined with Kaplan-Meier estimates for the group of patients with marked increase in MR compared with the group with no change or marked decrease in MR. Patients with marked exercise-induced

increase in regurgitant volume (i.e., ≥+15 ml) were compared with the remaining patients (i.e., those with either an exercise-induced decrease in regurgitant volume [≥−15 ml] or no marked changes in regurgitant volume [<+15 ml and >−15 ml], grouped together) for statistical significance with log-rank test.

A probability value of <0.05 was considered significant. All statistical analyses were performed with STATISTICA version 6 (StatSoft, Inc., Tulsa, Oklahoma).

Results

Clinical data of the whole cohort are summarized in Table 1. Mitral valve prolapse involved the anterior leaflet, the posterior leaflet, or both leaflets in 6 (10%), 23 (38%), and 31 (52%) patients, respectively. A flail mitral valve was present in 5 patients (8%). All patients had holosystolic MR at rest.

Exercise test. The mean exercise duration was 8.9 ± 2.3 min. Heart rate increased from 72 ± 11 beats/min at rest to 125 ± 13 beats/min during exercise (p < 0.0001). Systolic (from 136 ± 17 mm Hg to 178 ± 30 mm Hg) and diastolic blood pressures (from 76 ± 10 mm Hg to 83 ± 13 mm Hg) increased during exercise. During exercise, 1 patient developed atrial fibrillation, 6 had frequent premature beats, and 1 developed supraventricular tachycardia.

Of the 61 patients, 10 (16%) developed dyspnea at peak exercise with the need to stop exercise. The 51 remaining patients reached the predicted target heart rate (n = 14, 23%) or stopped the test because of fatigue or leg discomfort (n = 37, 61%).

Echocardiographic data. During exercise (Table 2), LV end-systolic and -diastolic volumes significantly decreased (−4.8 ± 1.5 ml, p = 0.0013 and −7.7 ± 2.3 ml, p = 0.0009), resulting in a mild increase in ejection fraction (+2.6 ± 1.2%, p = 0.04). As expected, LV stroke volume

Table 1	Demographic and Clinical Data
Variables	**Whole Cohort (n = 61)**
Age, yrs	62 ± 14
Male	31 (51)
Systemic hypertension	29 (48)
Hypercholesterolemia	12 (20)
Diabetes	5 (8)
Smoking	17 (28)
Medication	
ACE inhibitors	23 (38)
Beta-blockers	22 (36)
Diuretics	8 (13)
Mitral valve prolapsed	
Anterior	6 (10)
Posterior	23 (38)
Both	31 (52)
Flail leaflet	5 (8)

Values are mean ± SD or n (%).
ACE = angiotensin-converting enzyme.

Table 2	Resting and Exercise Echocardiographic Data		
Variables	**Rest**	**Exercise**	**p Value**
LV geometry and function			
LV end-diastolic volume, ml	111 ± 35	104 ± 38	0.0009
LV end-systolic volume, ml	34.5 ± 12	30 ± 15	0.0013
LV ejection fraction, %	69 ± 6	71 ± 10	0.04
Mitral E-wave velocity, cm/s	96 ± 32	134 ± 42	<0.0001
E/A ratio	1.5 ± 0.6	1.5 ± 0.4	0.5
E/Ea ratio	13.9 ± 5.7	14.6 ± 5.4	0.15
Heart rate, beats/min	71 ± 11	125 ± 13	<0.0001
LV stroke volume, ml	81 ± 23	85 ± 23	0.024
Mitral regurgitation severity			
Effective regurgitant orifice area, mm²	48 ± 14	53 ± 20	0.002
Regurgitant volume, ml	77 ± 22	81 ± 31	0.09
LA volume, ml	68 ± 24	78 ± 30	0.0015
Peak transtricuspid pressure gradient, mm Hg	30 ± 10	55 ± 18	<0.0001

Values are mean ± SD or n (%).
LA = left atrial; LV = left ventricular.

increased significantly from rest to peak exercise (+4 ± 2 ml, p = 0.024). Although mitral E-wave velocity significantly increased, E/A and E/Ea ratios remained statistically unchanged at exercise. LA volume increased significantly from 68 ± 24 ml to 78 ± 30 ml (p = 0.0015).

Reproducibility of MR severity quantification at rest and during exercise. There was an excellent correlation (r ≥0.90) between intraobserver measurements and between interobserver measurements for both resting and exercise data. Intraobserver and interobserver relative differences were <5% for ERO and regurgitant volume (range for intraobserver, 0.7% to 3.5% at rest, and 1.2% to 4.6% during exercise; interobserver, 0.7% to 3.3% at rest, and 1.1% to 3.9% during exercise).
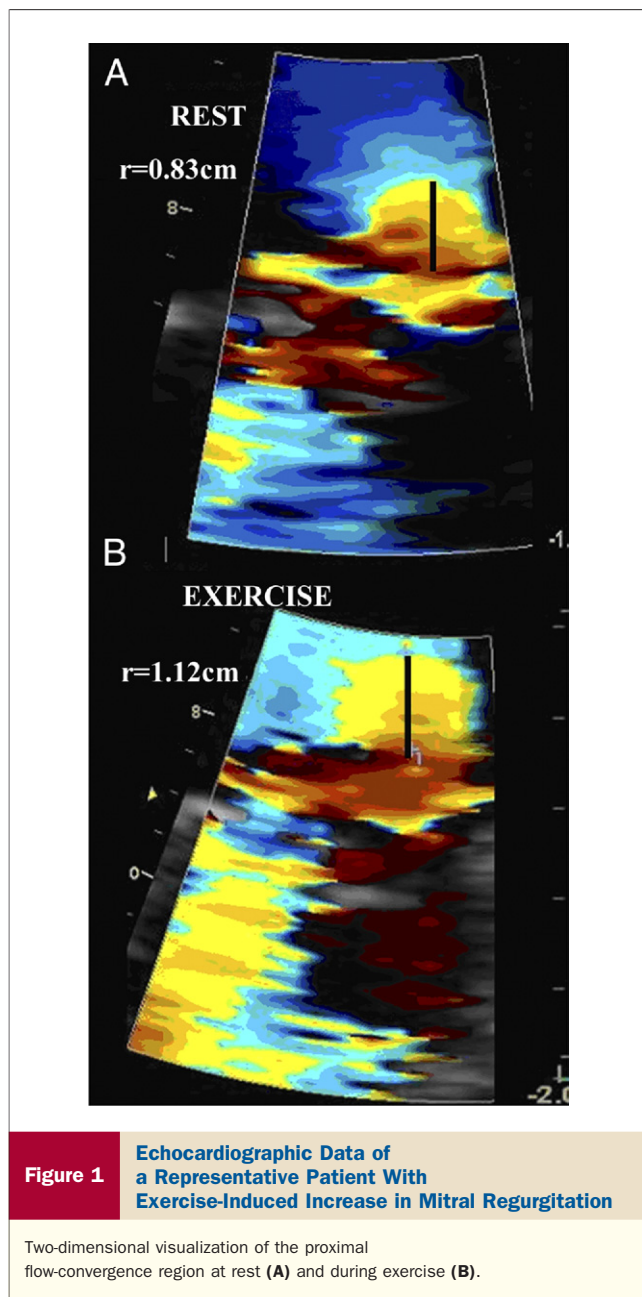
MR severity and exercise-induced changes in MR. Figure 1 shows a representative patient with exercise-induced changes in MR. Figure 2 shows the individual changes of each patient, which indicate that MR might be dynamic. Although ERO significantly increased during exercise with both methods (PISA: from 42 ± 24 mm² to 45 ± 27 mm², p = 0.01; Doppler: from 54 ± 21 mm² to 59 ± 26 mm², p = 0.006), there were no significant exercise-induced changes in regurgitant volume (Fig. 2).

According to mean resting ERO area, 33 patients (54%) had severe MR. There were good correlations between the Doppler and the PISA methods when comparing ERO (r = 0.87, p < 0.0001) and regurgitant volume (r = 0.83, p < 0.0001), and the Bland-Altman method showed good agreement between the 2 methods (Figs. 3A and 3B). However, both regurgitant volume and ERO calculated by the Doppler method were larger than those obtained with the PISA method (regurgitant volume: +19 ± 20 ml, ERO: +11 ± 12 mm²). During exercise, correlations between the 2 methods were similar to at rest (ERO: r = 0.84, p < 0.0001; regurgitant volume: r = 0.82, p < 0.0001), and the Bland-Altman method indicated good

Figure 1   Echocardiographic Data of
a Representative Patient With
Exercise-Induced Increase in Mitral Regurgitation

Two-dimensional visualization of the proximal
flow-convergence region at rest **(A)** and during exercise **(B)**.

agreement (Figs. 3C and 3D). The larger values by the Doppler method compared with the PISA method were slightly more important at exercise (regurgitant volume: $+22 \pm 24$ ml, ERO: $+14 \pm 17$ mm^2). There was no significant correlation between resting and exercise-induced changes in both ERO and regurgitant volume (Fig. 4). According to mean ERO (Fig. 4A), 18 patients (32%) had exercise-induced increase in MR ($\geq+10$ mm^2), and 6 patients (10%) had regression in MR (≥-10 mm^2), whereas the parameter did not change in the 33 remaining patients (60%). Mean regurgitant volume (Fig. 4B) markedly increased ($\geq+15$ ml) in 18 patients (32%), markedly decreased (≥-15 ml) in 15 patients (26%), and remained relatively unchanged in 24 patients (42%). Interestingly,

according to mean regurgitant volume, 25% of patients (n = 14) with moderate MR at rest exhibited severe MR during exercise (Fig. 5A), and 16% of the whole cohort (n = 9) had a decrease in MR severity resulting in a drop of at least 1 class (from moderate to mild or from severe to moderate or mild). According to mean ERO, 16% of patients (9 of 57) with moderate MR at rest had severe MR during exercise (Fig. 5B).
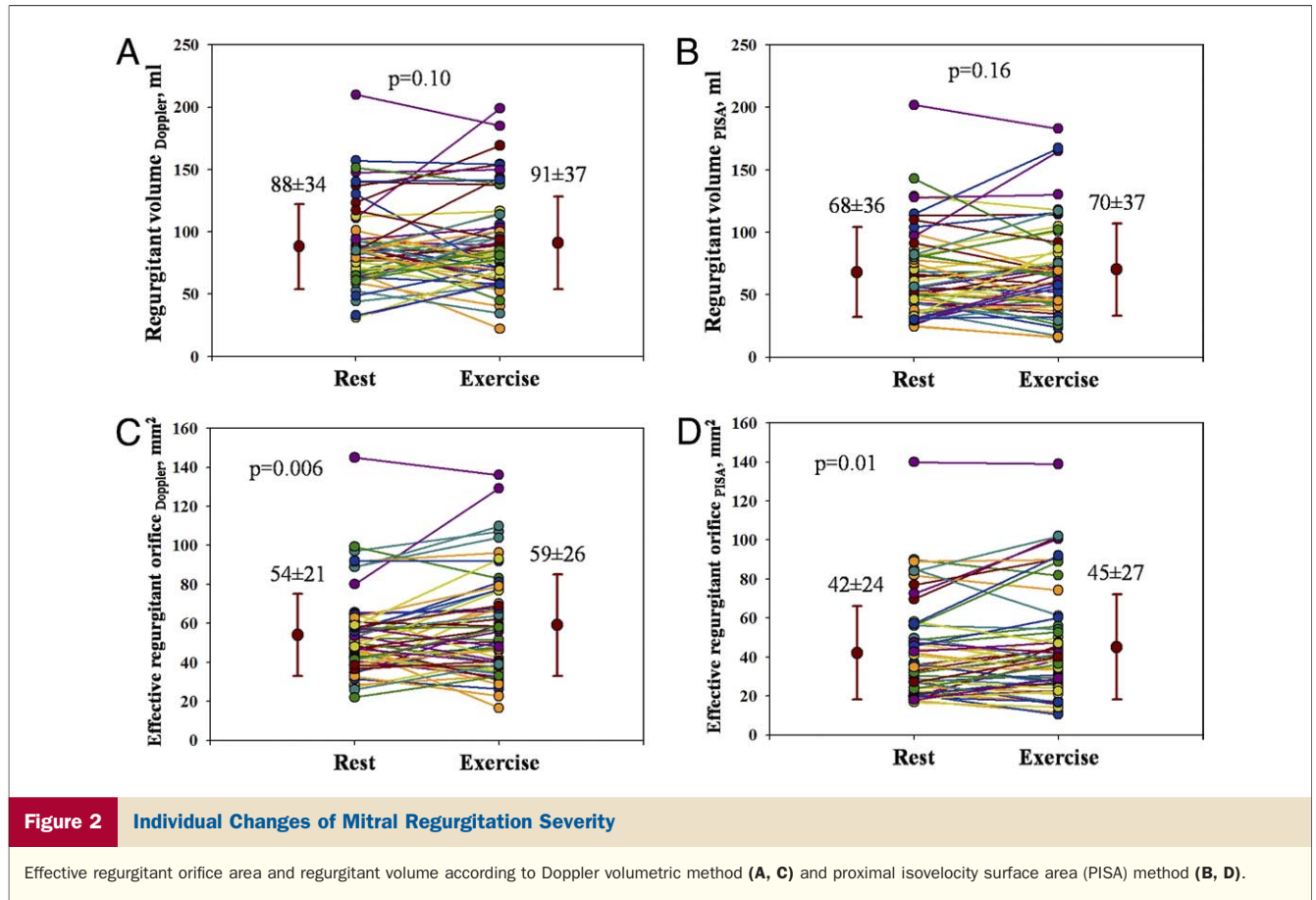
Exercise-induced changes in systolic pulmonary arterial pressure. Peak transtricuspid pressure gradient significantly increased during exercise from 30 ± 10 mm Hg to 55 ± 18 mm Hg (Table 2) (p < 0.0001). Whereas rest peak transtricuspid pressure gradient correlated with neither mean rest ERO (r = 0.10, p = 0.45) nor mean rest regurgitant volume (r = 0.07, p = 0.62), exercise peak transtricuspid pressure gradient correlated with both exercise ERO and regurgitant volume (r = 0.35, p = 0.01 and r = 0.28, p = 0.05, respectively). Furthermore, exercise-induced changes in peak transtricuspid pressure gradient correlated with changes in ERO (r = 0.59, p = 0.02) and with changes in regurgitant volume (r = 0.60, p = 0.02). After adjusting for age and sex, exercise-induced changes in MR severity remained associated with changes in peak transtricuspid pressure gradient (ERO: p = 0.007; regurgitant volume: p = 0.01).

Symptom-free survival. The mean follow-up time was 22 ± 13 months (range 2 to 50 months). During follow-up, 31 patients (51%) remained asymptomatic, whereas 30 (49%) developed symptoms. In the whole cohort, symptom-free survival was $72 \pm 6\%$, $54 \pm 7\%$, and $43 \pm 7\%$ at 12, 24, and 30 months, respectively. Patients with a marked exercise-induced increase in regurgitant volume ≥15 ml had significantly lower symptom-free survival than remaining patients (12-month: $53 \pm 12\%$ vs. $81 \pm 6\%$; 24-month: $26 \pm 11\%$ vs. $67 \pm 8\%$; 30-month: $13 \pm 9\%$ vs. $59 \pm 9\%$; p = 0.0015) (Fig. 6). Similar results were also found with the exercise-induced changes in ERO (p = 0.03).

Discussion

The results of the present study show that, as in functional MR, degenerative MR can be dynamic with marked exercise-induced changes. Quantitation of MR revealed that more than 30% of patients had marked exercise-induced increase in MR severity, whereas MR severity was unchanged or decreased during exercise in the remaining patients. Importantly, approximately one-fourth of patients with moderate resting MR develop severe MR during exercise. Exercise-induced changes in degenerative MR are correlated with changes in systolic PAP. In addition, marked exercise-induced increase in MR severity is associated with reduced symptom-free survival.

Feasibility and reproducibility. Previous studies reported good feasibility and reproducibility of MR quantification with regurgitant volume and ERO both at rest (16) and during exercise (9). Enriquez-Sarano et al. (16) found a

Figure 2   Individual Changes of Mitral Regurgitation Severity

Effective regurgitant orifice area and regurgitant volume according to Doppler volumetric method **(A, C)** and proximal isovelocity surface area (PISA) method **(B, D)**.

feasibility of 92% at rest in a large population of patients with MR including various etiologies. The present study shows good agreement between the 2 methods and, as previously described (16), confirms that the regurgitant volume and ERO obtained by the Doppler volumetric method are larger than measurements obtained by the PISA method. Agreement between the 2 methods was also good during exercise, suggesting that MR quantification remains accurate during exercise also in patients with mitral valve prolapse. In addition, we found excellent intra and interobserver reproducibility both at rest and during exercise. All patients included in this study had mitral prolapse or flail resulting, in the majority of cases, in eccentric MR jet. This might explain, at least in part, the lesser correlation between the 2 methods of quantitation than those previously reported by Lebrun et al. (9) and Enriquez-Sarano et al. (16). However, even in eccentric regurgitant jet, flow convergence might be hemispheric and remains optimal for radius measurement. In this regard, the use of offline analysis to quantify MR, allowing the selection of the optimal aliasing velocity, improves the accuracy of the measurements, especially during exercise.

Dynamic MR. In a series of 94 patients with mitral valve prolapse but without resting MR, Stoddard et al. (18) showed that MR as assessed qualitatively can substantially increase during exercise. Indeed, exercise-induced MR was

observed in 32% of their patients. Our quantitative results are in line with this study, showing a similar proportion of patients who experienced marked exercise-induced increase in the quantified degree of MR.

We found that the average of individual changes resulted in a significant increase in ERO and not statistically significant changes in regurgitant volume during exercise (Fig. 2). This could be because, although ERO and regurgitant volume are generally well-correlated, these 2 parameters are not identical. The ERO is a measure of the severity of the mitral leaflet lesion, and the regurgitant volume is a measure of the volume overload (19). Consequently, ERO is less dependent on hemodynamic condition than regurgitant volume.

In functional MR, exercise-induced decrease in MR is related to the decrease in LV volumes, which reduces tethering forces and improves mitral leaflet configuration and coaptation (8). Conversely, in degenerative MR due to mitral prolapse or flail, the decrease in LV cavity volume during exercise could possibly contribute to the raise in MR by increasing the extent of the leaflet prolapse.

Theoretically, changes in MR during exercise could be related to changes in systolic blood pressure. However, we only found correlations between exercise ERO and exercise heart rate ($r = 0.30$, $p = 0.04$) and exercise double product ($r = 0.32$, $p = 0.037$) but not with the changes in systolic
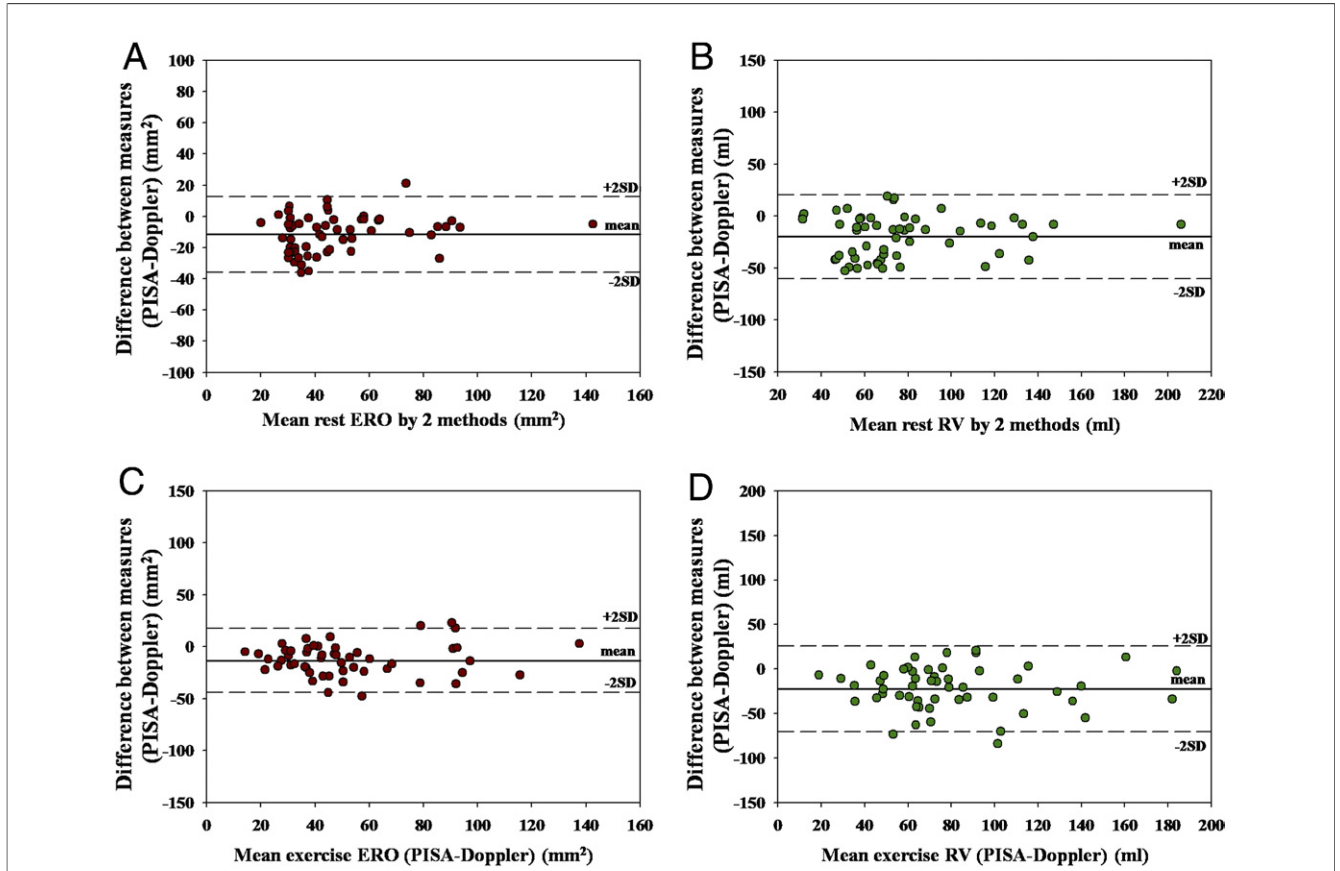
Figure 3   Agreement Between Doppler Volumetric and PISA Methods in Measurements of Resting and Exercise Mitral Regurgitation Severity

Bland-Altman analysis for effective regurgitant orifice (ERO) area **(A, C)** and regurgitant volume (RV) **(B, D)**. PISA = proximal isovelocity surface area.

blood pressure. Exercise regurgitant volume was only correlated with exercise double product (r = 0.30, p = 0.043). Surprisingly, we found no significant correlation between the changes in ERO or regurgitant volume and exercise or changes in heart rate, blood pressure, or double product. Nevertheless, patients with marked increase in MR during exercise had a trend for higher increase in heart rate during exercise (ERO: p = 0.06; regurgitant volume: p = 0.05).
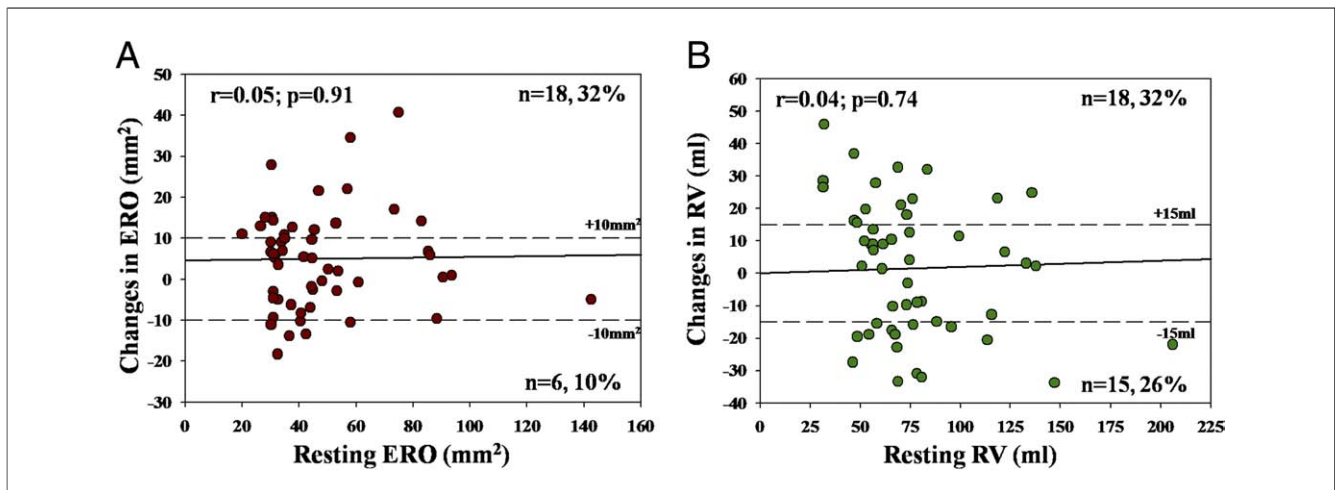

Figure 4   Relationship Between Exercise-Induced Changes in Mitral Regurgitation Severity and Resting Mitral Regurgitation Severity

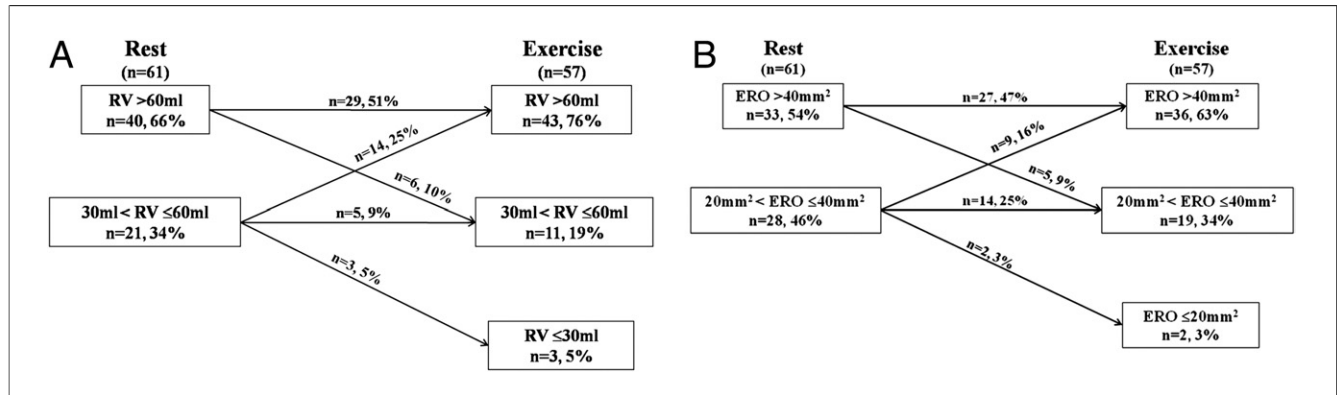Correlations with ERO area **(A)** and RV **(B)**. Abbreviations as in Figure 3.

Figure 5   Exercise-Induced Changes in Mitral Regurgitation Severity Class According to RV and ERO

The RV **(A)** and ERO **(B)** were stated as the average of PISA and volumetric methods. Four patients were not included in the exercise analysis due to incomplete stress data. Abbreviations as in Figure 3.

Stoddard et al. (18) found that patients with mitral valve prolapse and exercise-induced MR had a significant increase in mitral valve annulus area. They therefore hypothesized that the occurrence of MR during exercise might lead to mitral annulus dilation and, in turn, worsen MR, as in a vicious circle. In the present study, we found a good correlation between exercise-induced changes in mitral valve annulus area and the changes in regurgitant volume ($r = 0.57$, $p < 0.0001$) and ERO ($r = 0.56$, $p < 0.0001$) calculated with the PISA method, partially confirming the hypothesis of Stoddard et al. (18). The increase in mitral annulus area during exercise might result in a raise in the extent of mitral prolapse and in turn, increase the lack of coaptation and in MR severity. Conversely, patients with no

Figure 6   **Symptom-Free Survival**

Symptom-free survival of patients with marked exercise-induced increase in RV ($\geq +15$ ml) compared with those with marked decrease (≥ -15 ml) or no marked change ($< +15$ ml and > -15 ml). Abbreviations as in Figure 3.

change or a decrease in MR severity during exercise had no significant change in mitral annulus area.

The increase of systolic blood pressure and the reorganization of leaflet closing forces during exercise might also modify the leaflet prolapse configuration, improve coaptation, and lead to MR decrease. In addition, patients might develop nonholosystolic MR during exercise (i.e., late systolic MR). Because all patients included had resting holosystolic MR, this modification might also explain the decrease in MR severity during exercise. Nevertheless, our data provide no evidence to validate these hypothetical mechanisms, emphasizing the need for further studies.

Transient and recurrent increase of MR during daily life can accelerate progression of MR severity and induce LA and ventricular enlargements and possibly atrial fibrillation, LV dysfunction, or pulmonary hypertension. Indeed, degenerative MR tends to progress over time through increase in both ERO and regurgitant volume (20) but with wide individual variation. Although the mean annual rate of ERO progression was 5.9 mm^2/year, ERO has been shown to vary from -18 to $+75$ mm^2 (20). The independent predictors of MR progression were the development of a new flail leaflet and an increase in mitral annulus diameter. Another study from the same institution demonstrated that MR progression was associated with more severe ventricular and atrial remodeling and worse outcome (21).

Relation of exercise-induced changes in MR on pulmonary pressures. Systolic PAP increased in all patients during exercise. Changes in systolic PAP were associated with changes in MR severity during exercise, even after adjustment for age and sex. Few studies have assessed both rest and exercise pulmonary hypertension in patients with preserved LV function and degenerative MR. Recently, Ha et al. (22) found in 396 patients with normal LV function that the determinants of exercise pulmonary hypertension were E/Ea ratio, resting peak TR velocity, age, sex, and systolic blood pressure. However, they did not quantify MR severity. In the present study, patients with exercise pulmonary
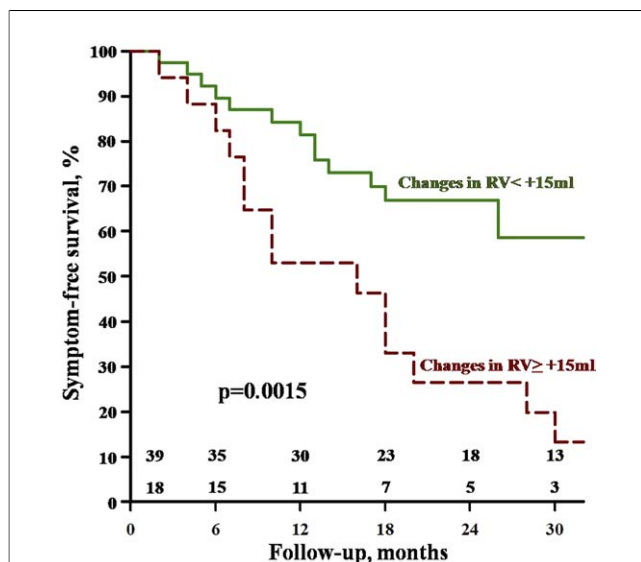
hypertension, defined as an exercise systolic blood pressure $\geq$60 mm Hg, had significantly higher exercise-induced changes in MR (regurgitant volume: p = 0.02, ERO: p = 0.03). These results highlight the impact of exercise-induced changes in MR on exercise pulmonary hypertension. Moreover, pulmonary hypertension is a Class IIa indication for surgery in asymptomatic patients with preserved LV function and is associated with worse clinical outcome (23). Consequently, the extent of increase in MR during exercise might be a predictor of cardiac event-free survival, and its measurement could be helpful in decision making.

Impact of exercise-induced changes in MR on symptoms. Stoddard et al. (18) reported that patients with mitral prolapse who developed MR during exercise had higher risk of adverse outcomes such as syncope, congestive heart failure, and need for mitral surgery than those with no exercise-induced MR. We found in our cohort that compared with patients with a decrease or only a mild increase in MR during exercise, those with marked exercise-induced increase in MR (ERO $\geq$+10 mm^2, regurgitant volume $\geq$+15 ml) had lower symptom-free survival (Fig. 6). The presence of symptoms is a class I indication for mitral surgery in current guidelines, underlying the potential clinical implication of these results. Indeed, exercise stress echocardiography can reveal the increase of MR severity during exercise and thus identify patients at risk to rapidly develop symptoms. Such patients should be followed-up more closely and could necessitate more aggressive strategy. Prompt surgery, to avoid LA and LV damage as well as morbid events, could be preferentially used in these patients. Conversely, a watchful waiting strategy seems more appropriate in patients with marked decrease in MR or no change in MR during exercise.

Study limitations. All patients included in this study presented with degenerative MR due to mitral valve prolapse. Therefore, these results cannot be automatically applied to patients with other organic etiologies, such as rheumatic valve disease or endocarditis. All patients were in normal sinus rhythm; thus, the results should not be extrapolated to patients with atrial fibrillation. Eccentric jet, frequently present in patients with mitral valve prolapse, might lead to suboptimal flow convergence, which might, in turn, convey less accurate measurements by the PISA method. However, patients with nonoptimal acoustic window to accurately quantify MR were excluded. Right atrial pressure could increase during exercise, but we did not record the diameter of the inferior vena cava and its changes during the respiratory cycle. The PISA radius was measured as usual in midsystole (16), but significant changes can occur during the cardiac cycle in patients with valve prolapse. This might have affected the measurement of MR severity at rest and during exercise, resulting in an underestimation with the PISA method as compared with the Doppler method. Real-time 3D echocardiography could provide more reliable geometry of the flow convergence region but has currently

low temporal resolution and is not practical during exercise. We found a relation between the occurrence of symptoms and exercise-induced increase in MR. The evaluation of the presence of symptoms remains subjective. However, Class I indications for mitral surgery in current European Society of Cardiology and American College of Cardiology/American Heart Association guidelines are based on the symptomatic status of patients. A significant impact of changes in blood pressure on increase in MR during exercise would be expected. Nevertheless, we found no correlation between these parameters. The mechanism explaining why MR increases during exercise in some patients and decreases in others remains unknown. Further studies are needed to clarify this phenomenon.

Conclusions

As in functional MR, degenerative MR due to mitral valve prolapse can be dynamic and markedly increases during exercise in >30% of patients. Changes in MR severity are associated with exercise-induced changes in systolic PAP and with reduced symptom-free survival. Further studies are needed to determine whether exercise-induced increase in MR is a determinant of MR progression.

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REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005–11.
2. Grigioni F, Tribouilloy C, Avierinos JF, et al. Outcomes in mitral regurgitation due to flail leaflets: a multicenter European study. J Am Coll Cardiol Img 2008;1:133–41.
3. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. N Engl J Med 2005;352:875–83.
4. Ling L, Enriquez-Sarano M, Seward J, et al. Early surgery in patients with mitral regurgitation due to partial flail leaflet: a long-term outcome study. Circulation 1997;96:1819–25.
5. Rosenhek R, Rader F, Klaar U, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. Circulation 2006;113:2238–44.
6. Tribouilloy C, Enriquez-Sarano M, Schaff H, et al. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. Circulation 1999;99:400–5.
7. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). J Am Coll Cardiol 2006;48:e1–148.
8. Lancellotti P, Lebrun F, Pierard LA. Determinants of exercise-induced changes in mitral regurgitation in patients with coronary artery disease and left ventricular dysfunction. J Am Coll Cardiol 2003;42:1921–8.
9. Lebrun F, Lancellotti P, Pierard LA. Quantitation of functional mitral regurgitation during bicycle exercise in patients with heart failure. J Am Coll Cardiol 2001;38:1685–92.

10. Pierard LA, Lancellotti P. The role of ischemic mitral regurgitation in the pathogenesis of acute pulmonary edema. N Engl J Med 2004;351: 1627–34.

11. Lancellotti P, Pierard LA. Chronic ischaemic mitral regurgitation: exercise testing reveals its dynamic component. Eur Heart J 2005;26: 1816–7.

12. Lancellotti P, Troisfontaines P, Toussaint AC, Pierard LA. Prognostic importance of exercise-induced changes in mitral regurgitation in patients with chronic ischemic left ventricular dysfunction. Circulation 2003;108:1713–7.

13. Pierard LA, Lancellotti P. Stress testing in valve disease. Heart 2007;93:766–72.

14. 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.

15. Enriquez-Sarano M, Tajik AJ, Bailey KR, Seward JB. Color flow imaging compared with quantitative Doppler assessment of severity of mitral regurgitation: influence of eccentricity of jet and mechanism of regurgitation. J Am Coll Cardiol 1993;21:1211–9.

16. Enriquez-Sarano M, Miller FA, Hayes SN, Bailey KR, Tajik J. Effective mitral regurgitation orifice area: clinical use and pitfalls of the proximal isovelocity surface area method. J Am Coll Cardiol 1995;25: 703–9.

17. Bland J, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–10.

18. Stoddard MF, Prince CR, Dillon S, Longaker RA, Morris GT, Liddell NE. Exercise-induced mitral regurgitation is a predictor of morbid events in subjects with mitral valve prolapse. J Am Coll Cardiol 1995;25:693–9.

19. Bursi F, Enriquez-Sarano M, Jacobsen SJ, Roger VL. Mitral regurgitation after myocardial infarction: a review. Am J Med 2006;119: 103–12.

20. Enriquez-Sarano M, Basmadjian A, Rossi A, Bailey K, Seward J, Tajik A. Progression of mitral regurgitation: a prospective Doppler echocardiographic study. J Am Coll Cardiol 1999;34:1137–44.

21. Avierinos JF, Detaint D, Messika-Zeitoun D, Mohty D, Enriquez-Sarano M. Risk, determinants, and outcome implications of progression of mitral regurgitation after diagnosis of mitral valve prolapse in a single community. Am J Cardiol 2008;101:662–7.

22. Ha JW, Choi D, Park S, et al. Determinants of exercise-induced pulmonary hypertension in patients with normal left ventricular ejection fraction. Heart 2009;95:490–4.

23. Abramson S, Burke J, Kelly JJ. Pulmonary hypertension predicts mortality and morbidity in patients with dilated cardiomyopathy. Ann Intern Med 1992;116:888–95.

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