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Circulation 2010;122;33-41; originally published online Jun 21, 2010;
DOI: 10.1161/CIRCULATIONAHA.110.938241
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

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Background—Current guidelines recommend mitral valve surgery for asymptomatic patients with severe degenerative mitral regurgitation and preserved left ventricular systolic function when exercise pulmonary hypertension (PHT) is present. However, the determinants of exercise PHT have not been evaluated. The aim of this study was to identify the echocardiographic predictors of exercise PHT and the impact on symptoms.

Methods and Results—Comprehensive resting and exercise transthoracic echocardiography was performed in 78 consecutive patients (age, 61±13 years; 56% men) with at least moderate degenerative mitral regurgitation (effective regurgitant orifice area =43±20 mm^2; regurgitant volume =71±27 mL). Exercise PHT was defined as a systolic pulmonary arterial pressure (SPAP) >60 mm Hg. Exercise PHT was present in 46% patients. In multivariable analysis, exercise effective regurgitant orifice was an independent determinant of exercise SPAP ($P<0.0001$) and exercise PHT ($P=0.002$). Resting PHT and exercise PHT were associated with markedly reduced 2-year symptom-free survival (36±14% versus 59±7%, $P=0.04$; 35±8% versus 75±7%, $P<0.0001$). After adjustment, although the impact of resting PHT was no longer significant, exercise PHT was identified as an independent predictor of the occurrence of symptoms (hazard ratio=3.4; $P=0.002$). Receiver-operating characteristics curves revealed that exercise PHT (SPAP >56 mm Hg) was more accurate than resting PHT (SPAP >36 mm Hg) in predicting the occurrence of symptoms during follow-up ($P=0.032$).

Conclusions—Exercise PHT is frequent in patients with asymptomatic degenerative mitral regurgitation. Exercise mitral regurgitation severity is a strong independent predictor of both exercise SPAP and exercise PHT. Exercise PHT is associated with markedly low 2-year symptom-free survival, emphasizing the use of exercise echocardiography. An exercise SPAP >56 mm Hg accurately predicts the occurrence of symptoms. **(*Circulation*. 2010;122:33-41.)**

Key Words: echocardiography ■ exercise ■ hypertension, pulmonary ■ mitral regurgitation ■ mitral valve

Primary degenerative mitral regurgitation (MR) is a frequent and serious valvular heart disease[1] that may progressively and insidiously lead to pulmonary hypertension (PHT),[2] atrial fibrillation,[3] and left ventricular (LV) dilation and/or dysfunction[4] and symptoms.[5] These complications are involved in the occurrence of major cardiac events and indicate poor prognosis.[6,7] Although preoperative PHT was found to be associated with postoperative LV dysfunction,[8] its impact on outcome or symptoms in patients with degenerative MR is not well described. Nevertheless, current American College of Cardiology/American Heart Association (ACC/AHA)[9] and European Society of Cardiology (ESC)[10] guidelines recommend mitral surgery (Class IIa, Level of Evidence C) in asymptomatic patients with severe MR, preserved LV function, and PHT, defined as a systolic pulmonary arterial pressure (SPAP) >50 mm Hg. Likewise, ACC/AHA guidelines advise operating on such patients in the presence of exercise PHT (SPAP >60 mm Hg), but this recommendation, presented with a Level of Evidence C, is empirical.

Clinical Perspective on p 41

Exercise PHT may occur even if resting SPAP is in the normal range.[11] SPAP increases with exercise in healthy subjects[12] and in those with asymptomatic severe degenerative MR.[13] The extent of the exercise-induced increase in SPAP is related to age and is highly variable in relation to the respective contribution of recruitment of the pulmonary bed, increased pulmonary resistance, reduced compliance, and increased left atrial (LA) pressure. The mechanisms explaining the occurrence of exercise PHT have not been evaluated in asymptomatic patients with degenerative MR. The potential impact of exercise PHT on the occurrence of symptoms has not yet been characterized. Thus, the aim of this study was to identify the echocardiographic predictors of exercise SPAP and exercise PHT and the impact of exercise PHT on symptom-free survival in asymptomatic patients with degenerative MR.

Received January 12, 2010; accepted May 6, 2010.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.110.938241**

Methods

Population

From September 2005 to September 2009, consecutive asymptomatic patients with degenerative MR, preserved LV systolic function (LV end-systolic diameter <45 mm and LV ejection fraction >60%),[10] and at least moderate MR (effective regurgitant orifice [ERO] area >20 mm^2 or regurgitant volume [RV] >30 mL) referred for exercise stress echocardiography were prospectively included (n=88). Patients presenting with ≥1 of the following criteria were excluded from analysis: concomitant valvular stenosis or regurgitation (n=1), atrial arrhythmias (n=1), inability to exercise (n=1), stress-induced myocardial ischemia (n=3), and absence of measurable SPAP during exercise (n=4).

Exercise Echocardiography

After a comprehensive Doppler echocardiogram at rest, a symptom-limited graded bicycle exercise test was performed in the semisupine position on a dedicated tilting exercise table. Patients started with an initial workload of 25 W maintained for 2 minutes; the workload was increased every 2 minutes by 25 W. Blood pressure and a 12-lead ECG were recorded every 2 minutes. Two-dimensional and Doppler echocardiographic imaging was available throughout the test.

Echocardiographic Measurements

Echocardiographic examinations were performed with a Vivid 7 imaging device (GE Healthcare, Little Chalfont, UK). All echocardiographic and Doppler data were obtained at rest and at peak exercise in digital format and stored on a workstation for offline analysis (EchoPAC, GE Vingmed Ultrasound AS, Horten, Norway).

All measurements were averaged over 3 cardiac cycles. MR was quantified as previously described.[14] Briefly, MR severity was measured with both the Doppler volumetric method (ie, by the difference between mitral and aortic stroke volumes) and the proximal isovelocity surface area method. The results of the 2 methods were averaged, allowing calculation of RV and ERO. The proximal isovelocity radius was measured from at least 3 frames with optimal flow convergence. The most appropriate negative aliasing velocity to obtain hemispheric proximal isovelocity surface area was selected offline on the workstation. The proximal isovelocity surface area radius was measured in midsystole. RV and ERO area were calculated with standard formulas. The biapical Simpson disk method was used to measure LV end-diastolic and end-systolic volumes and LA maximal volume. The LV 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 E- and A-wave velocities were measured with pulsed-wave Doppler, and Ea-wave velocity was obtained by tissue Doppler imaging in the septal position of the mitral annulus. These measurements were repeated at exercise before or just after the eventual fusion of E and A or Ea and Aa. SPAP was derived from the regurgitant jet of tricuspid regurgitation using systolic transtricuspid pressure gradient calculated by the modified Bernoulli equation ($\Delta P=4v^2$, where v is maximal tricuspid regurgitant jet velocity in m/s) and the addition of 10 mm Hg for right atrial pressure as previously performed.[15] According to guidelines,[9] resting PHT and exercise PHT were defined as SPAP >50 and >60 mm Hg, respectively. Right atrial pressure was assumed to be constant from rest to exercise.

Symptom-Free Survival

Patient follow-up was performed according to current guidelines. Patients were classified as symptomatic when shortness of breath, angina, dizziness, or syncope with exertion was identified during follow-up. Physical examination and echocardiography were performed by experienced cardiologists, and symptomatic status was carefully assessed.

Patients were reevaluated every 12 months, including physical examination and echocardiography. Intervals of evaluations were shortened to 6 or 3 months in patients with changes compared with previous measurements or if echocardiographic measurements were close to guideline cutoff values used for surgical indication. At the end of this study, patients with a last follow-up at >6 months were reevaluated with telephone calls from physicians. To ensure blinding and to avoid influencing the physician's decision with stress echocardiographic results, data on exercise-induced changes in MR severity and SPAP and data on the occurrence of exercise PHT were not sent to the referral physician.

Statistical Analysis

Results are expressed as mean±SD or percentage unless otherwise specified. Before analysis, normality distribution was tested with the Kolmogorov-Smirnov test. Patients were studied in 2 groups according to the presence or absence of exercise PHT. Differences between groups were analyzed for statistical significance with the Student *t* test, Mann-Whitney *U* test, χ^2 test, or Fisher exact test as appropriate. The differences between resting and exercise SPAP were compared for significance through the use of a 2-tailed paired *t* test. Correlations between echocardiographic data were assessed with linear regression or Spearman coefficient when the normality test failed for the given variable. Independent predictors of both resting and exercise SPAP were obtained with the use of stepwise, forward, and backward multiple linear regressions. Because the results obtained were similar, the model with the lowest Akaike information criterion was considered the best model and is reported in the Results section. Predictors of resting and exercise PHT were determined with logistic regression. The goodness of fit of each model was estimated with the total r^2 for multiple linear regression and with the Hosmer-Lemeshow goodness-of-fit test for logistic regression. Probabilities of symptom-free survival were obtained by Kaplan-Meier estimates according to the presence of resting or exercise PHT and then compared by use of a 2-sided log-rank test. The effect of PHT on symptom-free survival was assessed with Cox proportional-hazards models in univariate and multivariable analyses. Variables with a univariate value of $P<0.10$ were incorporated into the multivariable models. Moreover, we generate the Harrell correspondence index (C index) for each multivariate model. Sensitivity, specificity, positive predictive value, and negative predictive value for the prediction of the occurrence of symptoms were determined for various cutoff values of SPAP with receiver-operating characteristic curves. Values of $P<0.05$ were considered significant. All statistical analyses were performed with STATISTICA version 6 (StatSoft Inc, Tulsa, Okla).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Characteristics of the Population

Among the 78 patients (age, 61±13 years; 56% men), the frequency of exercise PHT was higher than resting PHT (46% versus 15%; $P<0.0001$; Figure 1). Patients with exercise PHT were older, had higher systolic arterial pressure, and were more often male than patients without exercise PHT (Table 1). There was a trend for a higher prevalence of systemic hypertension in patients with exercise PHT. There was no other significant difference with regard to risk factors, medications, and mitral leaflet prolapse localization. Only 8 patients (10%) had a mitral flail leaflet.

Resting and Exercise Echocardiography

Patients with exercise PHT had higher resting LV end-diastolic volume, resting E/Ea ratio, and exercise E-wave velocity than patients with no exercise PHT (Table 2). There was no other significant difference between the 2 groups with regard to resting and exercise LV function and LA volume. SPAP significantly increased during exercise

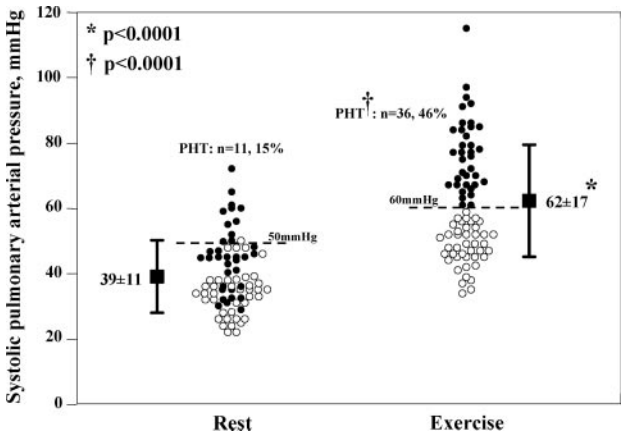

Figure 1. SPAP at rest and during exercise in the whole cohort. Solid circles identify patients with exercise PHT; squares and bars represent mean±SD. The number and percent indicate the number and percentage of patients with PHT at rest and during exercise. Dotted lines indicate threshold of PHT. *Significant difference between rest and exercise SPAP. †Significant difference between the frequency of resting and exercise PHT.

in the whole cohort (+22 mm Hg; $P<0.001$). As expected, the exercise-induced increase in SPAP was significantly higher in patients with exercise PHT (15±7 versus 30.5±13 mm Hg; $P<0.0001$). Although resting ERO and RV were similar in both groups, patients with exercise PHT had higher exercise ERO and RV than those with no exercise PHT (Table 2).

Echocardiographic Predictors of Resting SPAP and PHT

At rest, SPAP was correlated with age, LV end-systolic volume, and E/Ea ratio (Table 3). On multiple linear regression, after adjustment for age, LV end-systolic volume, and E/A ratio, only E/Ea ratio was independently associated with resting SPAP ($r^2=0.46$; $\beta=0.57\pm0.26$; $P=0.035$).

On univariate analysis, resting PHT was associated with age ($P=0.04$), male gender ($P=0.04$), LV end-systolic volume ($P=0.01$), and E/Ea ratio ($P=0.001$). In multivariable analysis, only E/Ea ratio (adjusted odds ratio, 1.2; 95% confidence interval [CI], 1.04 to 1.4; $P=0.01$) was an independent determinant of resting PHT (Hosmer-Lemeshow test: $\chi^2=7.55$, $P=0.48$). Resting MR severity was not associated with either resting SPAP (ERO: $r=0.19$, $P=0.14$; RV: $r=0.09$, $P=0.42$) or PHT (ERO: $P=0.38$; RV: $P=0.83$).

Echocardiographic Predictors of Exercise SPAP and PHT

During exercise, SPAP was correlated with age; resting LV end-diastolic volume, E/A ratio, E/Ea ratio, and SPAP; exercise ERO and RV; and exercise-induced changes in ERO and RV (Table 4). Multiple stepwise linear regression analysis revealed that age, resting SPAP, and exercise ERO were independent predictors of exercise SPAP ($r^2=0.72$; Table 5). The extent of exercise-induced changes in SPAP was unrelated to resting SPAP ($r=0.08$, $P=0.87$).

Patients with exercise PHT had a markedly higher exercise-induced increase in MR severity than those without

Table 1. Baseline Demographic and Clinical Data

Variables	All Patients (n=78)	No Exercise PHT (n=42, 54%)	Exercise PHT (n=36, 46%)	P
Demographic and clinical data				
Age, y	61±13	57±14	65±11	0.006
Male gender, n (%)	44 (56)	19 (45)	25 (69)	0.03
Body mass index, kg/m^2	26±4	27±4	26±4	0.27
Heart rate, bpm	73±11	73±11	72±11	0.69
Systolic arterial pressure, mm Hg	138±18	133±15	143±19	0.02
Diastolic arterial pressure, mm Hg	78±12	76±11	79±13	0.27
Risk factors, n (%)				
Hypertension	43 (55)	18 (43)	25 (69)	0.05
Hypercholesterolemia	16 (20)	7 (17)	9 (25)	0.53
Diabetes mellitus	8 (10)	3 (7)	5 (14)	0.72
Smoker	27 (35)	13 (30)	14 (39)	0.62
Medication, n (%)				
ACE inhibitor	34 (44)	17 (40)	17 (47)	0.71
β-blockers	34 (44)	17 (40)	17 (47)	0.71
Diuretic	2 (3)	1 (2)	1 (3)	1
Mitral valve prolapse, n (%)				
Anterior	5 (7)	2 (5)	5 (14)	0.24
Posterior	37 (47)	17 (40)	20 (56)	0.27
Both	36 (46)	23 (55)	13 (36)	0.16
Mitral flail	8 (10)	3 (7)	5 (14)	0.46

ACE indicates angiotensin-converting enzyme. Data are mean±SD when appropriate.

Table 2. Resting and Exercise Echocardiographic Data

Variables	All Patients (n=78)	No Exercise PHT (n=42, 54%)	Exercise PHT (n=36, 46%)	*P*
Resting LV function				
LVES volume, mL	36±11	35±12	38±12	0.27
LVED volume, mL	114±35	109±34	123±37	0.015
LV ejection fraction, %	69±6	68±5	69±6	0.42
E-wave velocity, $cm.s^{-1}$	100±33	95±28	107±37	0.11
A-wave velocity, $cm.s^{-1}$	75±25	74±20	77±29	0.59
E/A ratio	1.5±0.7	1.4±0.6	1.6±0.8	0.21
Ea-wave velocity, cm/s	7.4±1.9	7.6±2	7.3±1.7	0.48
E/Ea ratio	14±5	13±4	16±5	0.01
Exercise LV function				
LVES volume, mL	31±16	33±20	31±11	0.59
LVED volume, mL	106±39	103±39	111±39	0.37
LV ejection fraction, %	72±9	70±9	71±10	0.64
E-wave velocity, cm/s	138±42	132±43	146±44	0.046
A-wave velocity, cm/s	94±43	92±56	90±31	0.85
E/A ratio	1.5±0.4	1.5±0.3	1.6±0.4	0.21
Ea-wave velocity, cm/s	9.9±2.3	9.6±2.4	9.4±2.2	0.70
E/Ea ratio	14.5±5	14±5	15±5	0.38
Resting LA volume, mL	71±24	74±27	73±21	0.86
Exercise LA volume, mL	81±29	83±35	87±26	0.56
MR				
Severe MR, n (%)	47 (60)	26 (62)	21 (58)	0.93
Resting ERO, mm^2	43±20	43±23	42±16	0.83
Exercise ERO, mm^2	48±26	42±27	55±23	0.03
Resting RV, mL	71±27	73±35	69±20	0.55
Exercise RV, mL	73±36	65±39	83±28	0.03
Resting SPAP, mm Hg	39±11	33±6	46±10	<0.0001
Exercise SPAP, mm Hg	62±17	46±10	77±12	<0.0001

LVES indicates LV end-systolic; LVED, LV end-diastolic. Data are mean±SD when appropriate.

exercise PHT (ERO: 12.4±2.2 versus −1.2±1.6 mm^2, $P<0.0001$; RV: 13.8±3.2 versus −7.6±2.6 mL, $P<0.0001$). The exercise was stopped for dyspnea in 30 patients (38%). These patients had significantly higher exercise-induced changes in ERO (14.5±2 versus −1±1.6 mm^2; $P<0.0001$), in RV (14.5±3 versus −6.6±3 mL; $P<0.0001$), and in SPAP (32±1.8 versus 16±1.5 mm Hg; $P<0.0001$).

In multiple logistic regression, age, resting SPAP, and exercise ERO were independently associated with exercise PHT (Table 6, Hosmer-Lemeshow test: $\chi^2=5.29$, $P=0.73$). Similar results were found with exercise RV (odds ratio, 1.11; 95% CI, 1.02 to 1.14; $P=0.002$).

Symptom-Free Survival

Follow-up collection was complete in 78 patients (100%) with a mean follow-up of 19±14 months (range, 2 to 56 months). During follow-up, 40 patients (51%) remained asymptomatic and 38 (49%) developed symptoms. There was no significant difference between symptomatic and asymptomatic patients relative to clinical data and medications. Patients who developed symptoms during follow-up had higher resting and exercise LV end-diastolic volume and mitral E-wave velocity and resting E/A ratio (Table 7). Despite similar resting MR severity, patients with symptoms had higher MR severity during exercise (Table 7) and higher exercise-induced changes in ERO and in RV (12±13 versus −2±10 mm^2, $P<0.0001$, and 13±19 versus −8±17 mL, $P<0.0001$, respectively). Resting SPAP and exercise SPAP were also significantly higher in patients with symptoms.

In the whole cohort, symptom-free survival was 71±5% and 54±6% at 1 and 2 years, respectively. Patients with resting PHT had lower symptom-free survival than patients without resting PHT ($P=0.04$; Figure 2A). After adjustment for age and sex, the impact of resting PHT on symptom-free survival was no longer significant (hazard ratio [HR], 2.1; 95% CI, 0.9 to 4.9; $P=0.08$; Table 8). Exercise PHT was associated with markedly reduced 2-year symptom-free survival (35±8% versus 75±7%; $P<0.0001$; Figure 2B), resulting in an unadjusted HR of 2.8 (95% CI, 1.4 to 5.4; $P=0.002$).

Receiver-operating characteristic curve analysis revealed that exercise PHT was significantly more accurate in predict-

Table 3. Correlations With Resting SPAP

	Correlation With Resting SPAP	
Variables	*r*	*P*
Age	0.25	0.04
Resting heart rate*	0.04	0.74
Resting systolic arterial pressure*	0.12	0.56
Resting diastolic arterial pressure*	0.04	0.77
Resting LV function		
LVES volume	0.29	0.04
LVED volume	0.21	0.13
LV ejection fraction*	0.11	0.44
E/A ratio	0.28	0.06
Ea-wave velocity	0.11	0.42
E/Ea ratio	0.32	0.02
Resting LA volume*	0.21	0.15
MR		
Resting ERO	0.19	0.14
Resting RV	0.09	0.42

LVES indicates LV end-systolic; LVED, LV end-diastolic.
*Spearman coefficient was used because of normality test failure.

ing the occurrence of symptoms during follow-up than resting PHT. At rest, the best cutoff value to predict the occurrence of symptoms was SPAP >36 mm Hg (specificity=56%, sensitivity=72%, positive predictive value=60%, negative predictive value=69%). Resting SPAP >50 mm Hg was associated with higher specificity and positive predictive value but markedly lower sensitivity and negative predictive value (95%, 83%, 25%, and 58%, respectively). During exercise, SPAP >56 mm Hg was associated with the best specificity (73%), sensitivity (82%), positive predictive value (72%), and negative predictive value (80%). The cutoff value used in ACC/AHA guidelines (exercise SPAP >60 mm Hg) had slightly higher specificity (78%) and positive predictive value (75%) but lower sensitivity (71%) and negative predictive value (74%).

In the Cox proportional-hazards model, after adjustment for age and sex, exercise PHT remained independently associated with symptom-free survival (HR, 3.4; 95% CI, 1.6 to 7.4; $P=0.002$; Table 8). Further adjustment for resting E-wave velocity and exercise LV end-diastolic volume conveyed a 2.1-fold increase in risk of symptom occurrence during follow-up (95% CI, 1.4 to 3.1; $P=0.0004$). In the same model, when exercise SPAP was introduced instead of exercise PHT, a similar significant association was found (HR, 1.03; 95% CI, 1.01 to 1.05; $P=0.02$; Table 8).

Outcome

During follow-up, 5 patients were hospitalized for congestive heart failure, 1 for syncope, and 1 for acute pulmonary edema. Four patients developed atrial fibrillation. Mitral valve surgery was performed in 25 patients (mean follow-up, 19±10 months): 5 patients underwent mitral valve replacement and 20 patients had mitral valve repair. All patients were operated on because of symptoms. There was no operative mortality. However, 5 patients died during postoperative period (median follow-up, 24 months; range, 5 to 55 months). No other cardiac events have been noted in the 20 remaining operated patients.

Table 4. Correlations With Exercise SPAP

	Correlation With Exercise SPAP	
Variables	*r*	*P*
Age	0.25	0.03
Resting heart rate*	0.01	0.99
Exercise heart rate*	0.08	0.58
Resting systolic arterial pressure*	0.14	0.39
Exercise systolic arterial pressure*	0.05	0.70
Resting diastolic arterial pressure*	−0.03	0.84
Exercise diastolic arterial pressure*	0.11	0.43
Resting LV function		
LVES volume	0.22	0.10
LVED volume	0.31	0.02
LV ejection fraction*	0.04	0.75
E/A ratio	0.31	0.03
Ea-wave velocity	0.06	0.64
E/Ea ratio	0.29	0.03
Exercise LV function		
LVES volume	0.10	0.24
LVED volume	0.26	0.09
LV ejection fraction*	0.12	0.39
E/A ratio	0.10	0.37
Ea-wave velocity	0.12	0.33
E/Ea ratio	0.04	0.27
Resting LA volume*	0.01	0.96
Exercise LA volume*	0.15	0.32
MR		
Resting ERO	0.16	0.16
Exercise ERO	0.46	<0.0001
Changes in ERO	0.62	<0.0001
Resting RV	0.06	0.56
Exercise RV	0.42	0.0001
Changes in RV	0.62	<0.0001
Resting SPAP	0.69	<0.0001

LVES indicates LV end-systolic; LVED, LV end-diastolic.
*Spearman coefficient was used because of normality test failure.

Table 5. Multiple Regression Analysis to Determine Exercise SPAP

Variables	β	SE	*P*
Age	0.23	0.11	0.028
Sex	5.28	2.72	0.15
Exercise LVED volume	0.14	0.04	0.17
Resting SPAP	0.64	0.14	<0.0001
Exercise ERO	0.37	0.08	<0.0001

LVED indicates LV end-diastolic.

Table 6. Multivariable Logistic Regression: Prediction of Exercise Arterial PHT

Variables	Odds Ratio	95% CI	*P*
Age	1.15	1.06–1.41	0.004
Sex	3.74	0.24–6.97	0.41
Exercise LVED volume	1.01	0.98–1.05	0.31
Resting SPAP	1.33	1.14–1.52	0.006
Exercise ERO	1.12	1.04–1.25	0.002

LVED indicates left ventricular end-diastolic.

Discussion

The results of this study show that (1) exercise PHT (ie, SPAP >60 mm Hg) is frequent in asymptomatic patients with moderate or severe degenerative MR; (2) resting LV filling pressure, as assessed by E/Ea ratio, is the only echocardiographic predictor of SPAP at rest; (3) exercise MR severity is an independent echocardiographic predictor of exercise SPAP and exercise PHT; (4) exercise PHT is associated with reduced symptom-free survival; and (5) exercise PHT is more accurate than resting PHT for predicting the occurrence of symptoms.

Table 7. Resting and Exercise Echocardiographic Data According to the Occurrence of Symptoms During Follow-Up

Variables	No Symptoms (n=40, 51%)	Symptoms (n=38, 49%)	*P*
Resting LV function			
LVES volume, mL	33±14	38±10	0.075
LVED volume, mL	106±34	124±34	0.02
LV ejection fraction, %	69±6	69±6	0.98
E-wave velocity, cm/s	91±25	109±37	0.014
A-wave velocity, cm/s	74±23	76±26	0.72
E/A ratio	1.3±0.6	1.7±0.7	0.024
Ea-wave velocity, cm/s	7±1.4	7.6±2.2	0.15
E/Ea ratio	13.5±5	15±6	0.23
Exercise LV function			
LVES volume, mL	28±16	34±16	0.09
LVED volume, mL	94.5±33	119±41	0.005
LV ejection fraction, %	72±10	71±9	0.68
E-wave velocity, $cm.s^{-1}$	125±33	149±49	0.013
A-wave velocity, cm/s	84±34	102±48	0.05
E/A ratio	1.4±0.4	1.6±0.3	0.14
Ea-wave velocity, cm/s	9.3±2.2	10.4±2.3	0.08
E/Ea ratio	14.3±5.5	15.1±5.2	0.51
Resting LA volume, mL	63±21	73±27	0.09
Exercise LA volume, mL	75±30	85.5±30	0.12
MR			
Severe MR, n (%)	18 (45)	21 (55)	0.15
Resting ERO, mm^2	40±22	45±17	0.27
Exercise ERO, mm^2	38±25	58±23	<0.0001
Resting RV, mL	69±32	73±24	0.58
Exercise RV, mL	61±37	86±30	0.0013
Resting SPAP, mm Hg	36±8	43±12	0.0045
Exercise SPAP, mm Hg	54±14	69±16	<0.0001

LVES indicates LV end-systolic; LVED, LV end-diastolic. Data are mean±SD when appropriate.

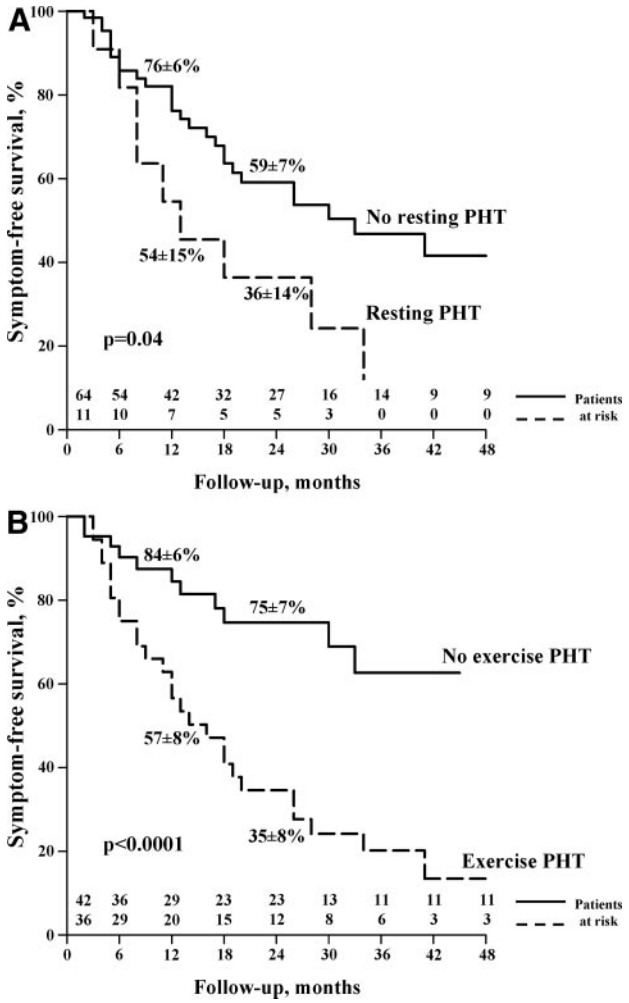

Figure 2. Symptom-free survival according to resting (A) and exercise (B) PHT.

Resting PHT

In this cohort of asymptomatic degenerative MR with preserved LV systolic function, resting PHT was found in only 15% of cases. The only independent echocardiographic predictor of PHT and SPAP at rest was the E/Ea ratio reflecting LV diastolic filling pressure. The severity of MR was not correlated with SPAP and was not significantly different between patients with or without resting PHT. This suggests that LA volume overload may be balanced by LA compliance and/or pulmonary resistance even when chronic MR is severe. Recently, a retrospective study reported that MR severity, LA emptying fraction, E/Ea ratio, and lateral Aa velocity were independently associated with SPAP.[16] The association of MR severity with SPAP in that study contrasts with our results. The patients in that study had a higher frequency of flail leaflet (52% versus 10%) and elevated SPAP and probably had more severe MR than those in the present study. Indeed, 40% of our patients had moderate MR, and all were asymptomatic, explaining, at least in part, why only E/Ea ratio was an independent predictor of resting SPAP.

Table 8. Cox Proportional-Hazards Regression Analysis for the Prediction of Symptom-Free Survival

	Univariable			Adjustment for Age and Sex		
Variables	HR (95% CI)	C Index	*P*	HR (95% CI)	C Index	*P*
Rest SPAP	1.04 (1.01–1.07)	0.63	0.005	1.04 (1.01–1.08)	0.64	0.01
Exercise SPAP	1.02 (1.01–1.04)	0.66	0.002	1.02 (1.01–1.04)	0.67	0.009
Rest PHT	2.18 (1.02–4.66)	0.55	0.044	2.13 (0.91–4.93)	0.56	0.08
Exercise PHT	2.83 (1.44–5.40)	0.64	0.002	3.44 (1.59–7.43)	0.69	0.002

A passive increase in pulmonary venous pressure caused by LA volume overload is not the only mechanism leading to PHT. In addition to this passive elevation of SPAP, there is often superimposed active vasoconstriction of the pulmonary arterioles and a vascular remodeling that may cause an increase in pulmonary vascular resistance and thus contribute to the elevation of SPAP. At an early stage of the disease (ie, moderate MR), SPAP is driven mainly by elevated filling pressure. Progressively, chronic severe MR may damage LA geometry and function and lead to LV diastolic dysfunction, which in turn increases SPAP. The independent association of E/Ea with SPAP suggests that this parameter may be useful for identifying an early stage of LV diastolic dysfunction and resting PHT. Interestingly, E/Ea ratio has been found to be well correlated with LV end-diastolic pressure in patients with MR (predominantly degenerative) independently of LV systolic function.[17]

Exercise PHT

Limited data are available on the impact of exercise on SPAP and the frequency of PHT in asymptomatic degenerative MR. However, exercise PHT is a Class IIa indication for surgical intervention in asymptomatic severe degenerative MR with preserved LV systolic function in the 2006 ACC/AHA guidelines[9] but not in the 2007 ESC guidelines.[10]

Exercise-induced changes in MR are unrelated to resting MR severity and may occur in patients with moderate or severe MR. The present study demonstrates that changes in MR during exercise are strong independent echocardiographic predictors of exercise SPAP and exercise PHT. Furthermore, patients with the highest increase in SPAP during exercise develop the most severe increase in MR. Consistently, these patients frequently stop exercise because of dyspnea.

We found that 46% of asymptomatic patients with moderate or severe degenerative MR developed exercise PHT. Moreover, among patients with moderate MR, 43% had exercise PHT. Surprisingly, this frequency is rather similar to that reported by Mahjoub et al[12] in healthy subjects. However, our patients reached a lower peak exercise workload (106±32 versus 142±51 W).

Impact of Exercise PHT on the Occurrence of Symptoms

In contrast to exercise PHT, resting PHT did not differentiate the reason to stop exercise ($P=0.69$). Although resting PHT was associated with reduced symptom-free survival, this association was no longer significant after minimal multivariable adjustment. In contrast, exercise PHT was identified as an important independent predictor of the occurrence of symptoms during follow-up. Because the management of patients with degenerative MR remains controversial[5,6] and the presence of symptoms is a Class I indication for mitral surgery in current guidelines, our results may have clinical implications.

Exercise stress echocardiography is useful for unmasking latent LV contractile dysfunction and predicting postoperative LV ejection fraction[18] in degenerative MR. In addition, exercise echocardiography can reveal the increase in MR severity and the development of PHT during exercise and identify patients at risk of rapidly developing symptoms. Such patients should be followed up more closely. Prompt surgery to prevent adverse LA remodeling, irreversible LV damage, and morbid events could potentially be indicated in these patients. On the other hand, a strategy of watchful waiting seems more appropriate in patients without exercise PHT.

Although the quantification of MR severity during exercise is reproducible, accurate, and clinically relevant in both functional[14] and organic MR,[13] the simple measurement of peak systolic velocity of tricuspid regurgitation may be less demanding and may provide helpful information. Nonetheless, tricuspid regurgitation is not always available or may be too severe during exercise, limiting the evaluation of SPAP. In such cases, quantified exercise ERO and RV are preferred.

We found that exercise SPAP >56 mm Hg was the best cutoff value to predict the occurrence of symptoms during follow-up. The cutoff of SPAP >60 mm Hg used in the current ACC/AHA guidelines for surgical decision making had slightly higher specificity but lower sensitivity. However, this empirical cutoff was not yet validated in asymptomatic degenerative MR. Given that the cutoff value found in our study is almost similar to the recommendation, an exercise SPAP >60 mm Hg seems appropriate.

On the other hand, SPAP >36 mm Hg was the best cutoff value at rest. SPAP >50 mm Hg, advised by the guidelines, had high specificity but markedly low sensitivity. Furthermore, patients with resting PHT also had lower symptom-free survival.

A recent study reported that enlarged LV end-systolic diameter is associated with reduced long-term survival in patients with flail leaflet.[19] Surprisingly, our results show no significant relationship between LV systolic function parameters and the occurrence of symptoms. However, patients included in the present study had preserved LV systolic function, inhibiting the identification of such association.

Limitations

The multivariable analysis used to identify the echocardiographic predictors of resting PHT is based on small number of patients (n=11). In this regard, the results of the logistic regression should be interpreted cautiously. However, multiple regression and logistic regression found similar results, ie, that E/Ea ratio was the only independent predictor of both resting SPAP and PHT.

Our patients had degenerative MR caused by mitral valve prolapse. These results cannot be automatically applied to patients with other organic causes. Furthermore, only 10% of the cohort presented with flail leaflet, which is associated with a more severe MR. In the setting of mitral flail leaflet, the acute increase in MR resulting from chordal rupture is associated with acute pulmonary vascular vasoconstriction, arteriolar stiffening, and remodeling. The increase in MR severity during exercise could not have an impact on SPAP similar to that in patients with only mitral prolapse.

The right atrial pressure was estimated at 10 mm Hg both at rest and during exercise. Resting right atrial pressure is extensively variable between subjects. In addition, this estimation may also miss the potential influence of exercise-induced changes in right atrial pressure. Nevertheless, the noninvasive evaluation of right atrial pressure during exercise (ie, when venous compliance is known to decrease) with noninvasive methods such as Doppler echocardiography remains difficult, is probably subject to low accuracy, and is not validated. Moreover, right atrial pressure is frequently assumed to be 5 mm Hg in normal subjects[12] and 10 mm Hg in patients with heart disease.[15] We found a relation between the occurrence of symptoms and exercise PHT.

The evaluation of the presence of symptoms remains subjective. However, the Class I indication for mitral surgery in current ACC/AHA and ESC guidelines is based on the symptomatic status of patients.

Conclusions

Exercise PHT is frequent in asymptomatic patients with degenerative MR. Exercise MR severity is a strong independent predictor of exercise SPAP and exercise PHT. Exercise PHT is associated with markedly reduced 2-year symptom-free survival and is more accurate than resting PHT for predicting the occurrence of symptoms. The results of the present study emphasize the usefulness of exercise stress echocardiography in asymptomatic patients with moderate to severe degenerative MR. Larger studies are needed to evaluate the prognostic importance of exercise PHT.

Source of Funding

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

Disclosures

None.

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CLINICAL PERSPECTIVE

Current American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend mitral valve surgery for asymptomatic patients with severe degenerative mitral regurgitation and preserved left ventricular systolic function when atrial fibrillation or pulmonary hypertension (PHT) is present. The American College of Cardiology/American Heart Association guidelines state that mitral valve surgery is reasonable in such patients in the presence of exercise PHT (defined as a systolic pulmonary arterial pressure >60 mm Hg, Class IIa, Level of Evidence C). In this study, 78 consecutive asymptomatic patients with preserved left ventricular systolic function and moderate or severe mitral regurgitation were submitted to resting and exercise echocardiography. The results show that exercise PHT is frequent, is related to exercise mitral regurgitation severity, and is associated with 3.4-fold increase in the risk of development of symptoms. The best cutoff value of exercise systolic pulmonary arterial pressure was 56 mm Hg, which is close to the empiric threshold of 60 mm Hg used in the American College of Cardiology/American Heart Association guidelines. We found that exercise PHT is more accurate than resting PHT for predicting symptoms. Hence, exercise echocardiography appears to be useful in patients with asymptomatic degenerative mitral regurgitation for revealing the increase in mitral regurgitation severity and the presence of PHT during exercise and thus identifying patients at risk of developing symptoms rapidly. Close follow-up (3 to 6 months) is advised in asymptomatic patients developing exercise PHT. Prompt surgery to prevent adverse left atrial remodeling, irreversible left ventricular damage, and morbid events could potentially be indicated in these patients. On the other hand, a strategy of watchful waiting seems to be more appropriate in patients without exercise PHT.