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Original Article

Prognostic Significance of Exercise-induced Right Ventricular Dysfunction in Asymptomatic Degenerative Mitral Regurgitation

Kenya Kusunose, MD, PhD; Zoran B. Popović, MD, PhD; Hirohiko Motoki, MD, PhD; Thomas H. Marwick, MBBS, PhD, MPH

Background—The role of exercise-induced pulmonary hypertension in decision making regarding surgical timing for asymptomatic chronic mitral regurgitation is controversial. We reasoned that the exercise-induced pulmonary hypertension response could not be interpreted without knowledge of right ventricular (RV) function. The aim of this study was to assess the role of RV measures at rest and during exercise as predictors of prognosis in asymptomatic mitral regurgitation.

Methods and Results—Comprehensive resting and exercise echocardiography was performed in 196 consecutive patients (56±13 years; 64% male) with isolated moderate to severe mitral regurgitation (effective regurgitant orifice area, 38±18 mm^2) and preserved left ventricular function in whom initial management was expectant. Left ventricular and RV longitudinal strain were analyzed at rest using velocity vector imaging. Tricuspid annular plane systolic excursion and systolic pulmonary arterial pressure were measured at rest and during exercise. Valve surgery was performed in 88 patients (45%) over 27±15 months. After adjustment for age and sex in a Cox proportional-hazards model, exercise tricuspid annular plane systolic excursion (hazard ratio, 0.26; $P<0.001$), was associated with valve surgery-free survival, independent of resting left ventricular strain (hazard ratio, 1.09; $P=0.027$), exercise systolic pulmonary arterial pressure (hazard ratio, 1.03; $P<0.001$), and resting RV strain (hazard ratio, 1.10; $P=0.004$). In sequential Cox models, a model based on clinical data and left ventricular strain (χ^2, 15.9) was improved by RV strain and RV chamber size (χ^2, 28.8; $P=0.003$) and exercise systolic pulmonary arterial pressure (χ^2, 40.1; $P=0.002$) and further increased by exercise tricuspid annular plane systolic excursion (χ^2, 52.2; $P=0.002$).

Conclusions—Exercise-induced RV dysfunction provides important incremental prognostic value in the management of asymptomatic mitral regurgitation. **(*Circ Cardiovasc Imaging*. 2013;6:167-176.)**

Key Words: echocardiography ■ exercise ■ mitral regurgitation ■ mitral valve ■ right ventricular

The management of patients with asymptomatic degenerative mitral regurgitation (MR) remains controversial.[1] Degenerative MR may cause elevated systolic pulmonary arterial pressure (SPAP) and lead to pulmonary hypertension (PHT) before the development of symptoms or left ventricular (LV) dysfunction.[2] The current American College of Cardiology/American Heart Association guidelines describe severe MR as a class I or class IIa indication for mitral valve surgery in the presence of symptoms, LV dysfunction, atrial fibrillation, or resting PHT (resting SPAP >50 mm Hg).[3] Exercise echocardiography has been proposed as an additional test because the occurrence of PHT during exercise has been linked to prognosis,[4,5] and American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for asymptomatic degenerative MR recommend mitral valve surgery in the presence of exercise PHT (exercise SPAP >60 mm Hg).[6] Nonetheless, the evidence to support this is limited (level of evidence C), and evaluation of PHT in the absence of knowledge of right ventricular (RV) function may be problematic.[7] The potential impact of both SPAP and RV function during exercise has not been characterized. Therefore, we sought to identify the independent and incremental value of exercise SPAP and exercise RV function as an adjunct to standard clinical and echocardiographic evaluation in the prediction of event-free survival in asymptomatic degenerative MR.

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Methods

Study Population

Between January 2007 and January 2011, a total of 403 consecutive asymptomatic patients with degenerative MR, preserved LV systolic function (LV end-systolic diameter <45 mm and LV ejection fraction >60%), and at least moderate MR (effective regurgitant orifice [ERO] area >20 mm^2 or regurgitant volume >30 mL) were referred for exercise stress echocardiography.[6] Clinical variables (eg, symptom status, diabetes mellitus, hypertension, dyslipidemia, and smoking and body mass

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index) were prospectively gathered from the patient and their medical record at the time of the exercise echocardiogram. The protocol was approved by the Cleveland Clinic Institutional Review Board, and verbal consent was obtained at the time of the exercise stress echocardiogram.

Echocardiography

Transthoracic echocardiography was performed in the left-lateral decubitus position by experienced sonographers before and after symptom-limited exercise using a commercially available ultrasound machine (Vivid 7 or Vivid 9, GE Vingmed, Horten, Norway; Sonos 5500 or iE33, Philips, Andover, MA). Most exercise tests were performed using a Bruce or modified Bruce protocol. Standard imaging windows were used, including parasternal long and short axes, as well as apical 4-chamber, 2-chamber, and long-axis views. Echocardiographic images were digitally recorded and downloaded to an imaging server for offline analysis. MR was quantified as previously described and recommended.[8] The ERO area was calculated from the proximal isovelocity surface area. End-diastolic and end-systolic LV dimension were measured from the M-mode echocardiogram. LV and left atrial volumes were calculated by the Simpson method using 2-dimensional images and indexed to body surface area. The transmitral early diastolic velocity (E) and peak atrial filling velocity (A) were acquired in the apical 4-chamber view using pulsed-wave Doppler at the level of the mitral valve tips during diastole. The early mitral annular tissue velocity (e′) was also measured in the apical 4-chamber view with the sample volume positioned at both the septal and lateral mitral annulus and e′ being the average of these 2 values. LV peak longitudinal strain measurements were obtained from gray scale–recorded images in the apical 4-chamber, 2-chamber, and long-axis views. Strain was analyzed offline using velocity vector imaging (Syngo VVI, Siemens Medical Solutions, Mountain View, CA). After manual definition of the LV endocardial border, this was automatically tracked throughout the cardiac cycle. Strain was defined as instantaneous lengthening or shortening. LV strain was obtained by averaging all segment strain values from the apical 4-chamber, 2-chamber, and long-axis views.

Right Ventricular Function

Standard echocardiographic measurements of the RV were made in accordance with current guidelines.[9] RV fractional area change (RVFAC) was defined using the formula: (end-diastolic area−end-systolic area)/end-diastolic area×100. Tricuspid annular plane systolic excursion (TAPSE) was measured as the distance of systolic movement of the junction between the tricuspid valve and the RV free wall using 2-dimensional images and anatomic M-mode.[10,11] SPAP was estimated from the maximal continuous-wave Doppler velocity of the tricuspid regurgitation (TR) jet using systolic transtricuspid pressure gradient calculated by the modified Bernoulli equation and the addition of estimated right atrial pressure as previously described.[12] An index of pulmonary vascular resistance was derived by dividing the maximal velocity of the TR jet by the RV outflow tract velocity–time integral. RV strain was measured offline (Syngo VVI, Siemens Medical Solutions) as previously described.[13] The endocardial border of the RV was traced from an apical 4-chamber view, and segmental strain curves were generated automatically. Peak strain for the 3 RV free wall segments was averaged to produce global RV longitudinal strain. All measurements were made offline by an investigator blinded to all clinical and demographic information. All patients underwent symptom-limited exercise treadmill testing using standard treadmill protocols with 12-lead ECG monitoring. After acquisition of the wall motion study postexercise, at a usual interval of 1 to 2 minutes after exercise, Doppler echocardiographic imaging data were obtained again.[14] The duration of the exercise was measured and the maximal exercise tolerance was expressed as estimated metabolic equivalents (METs). Predicted exercise capacity was calculated in accordance with described nomograms (predicted METs; in men=18−[0.15×age], in women=14.7−[0.13×age]), and percent predicted METs was described as the difference between actual and predicted METs divided by predicted METs.[15] All measurements were performed and averaged over 3 cardiac cycles.

Clinical Outcome

Patients were followed in accordance with current guidelines,[3,16] and the end point was mitral valve surgery. The decision to refer the subject for valve surgery was made by the patient's physician, based on symptoms and LV status, or concomitant coronary artery bypass surgery, or new onset of resting PHT, or new onset of atrial fibrillation. Neither LV strain nor quantitative RV function data were available to the treating physician or surgeon. Therefore, the patients' personal physician determined the clinical management of the patients independent of the measurements of interest.

Statistical Analysis

Data are presented as mean±SD after testing for normal distribution (Kolmogorov–Smirnov test). In non-normally distributed data, the median and interquartile range are indicated. Linear regression was used to evaluate the association between resting RV strain and exercise TAPSE and other variables. Median values of TAPSE (cutoff value, 19 mm) and exercise SPAP (cutoff value, 54 mm Hg) were used to divide groups using Kaplan-Meier analysis, and survivals were compared using a 2-sided log-rank test. Potential determinants of resting RV strain and exercise TAPSE were identified by univariate

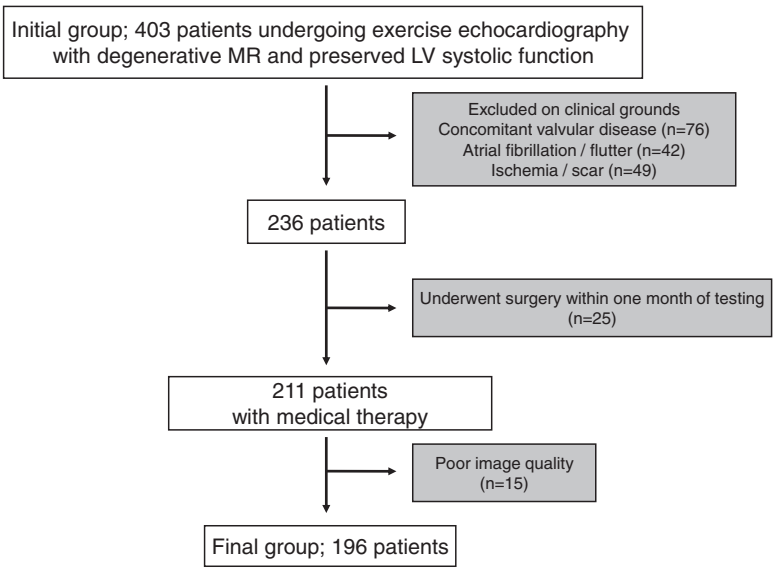

Figure 1. Flow chart of the recruitment of patients. LV indicates left ventricular; and MR, mitral regurgitation.

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Table 1. Baseline Characteristics

Variables	Rest	Exercise
Clinical data		
Age, y	56±13	
Male sex, n (%)	126 (64)	
Body mass index, kg/m^2	26±4	
Heart rate, bpm	70±11	156±24
Systolic BP, mm Hg	129±17	176±26
Diastolic BP, mm Hg	80±15	83±11
Risk factors, n (%)		
Hypertension	86 (44)	
Dyslipidemia	80 (41)	
Diabetes mellitus	14 (7)	
Smoker	68 (35)	
Medication, n (%)		
ACE inhibitor or ARB	48 (25)	
β-Blockers	78 (40)	
Diuretic	13 (6)	
Exercise capacity, METs		8.6 (7.2–10.5)
% Predicted METs, %		115±27
LV function		
LV end-diastolic volume, mL	127±43	105±36
LV end-systolic volume, mL	43±16	34±12
LVEF, %	65±3	68±4
E-wave velocity, cm/s	100±24	118±23
A-wave velocity, cm/s	70±22	85±22
E/A ratio	1.4 (1.2–1.8)	1.4 (1.2–1.7)
E wave-DT, ms	184±44	165±34
e′ velocity, cm/s	8±2	8±2
Resting LAVi, mL/m^2	43 (33–56)	
Resting LV strain, %	−18.8±3.0	
Mitral valve prolapse, n (%)		
Anterior	36 (18)	
Posterior	85 (44)	
Both	75 (38)	
Mitral flail	31 (16)	
Severe MR	85 (43)	
MR		
ERO, mm^2	38±17	
Regurgitant volume, mL	61±27	
RV function		
RV end-diastolic area, cm^2	22±7	
RV end-systolic area, cm^2	13±4	
RVFAC, %	41±5	
RV strain, %	−19.8±3.4	
PVR, Wood Units	2.0 (1.7–2.4)	
SPAP, mm Hg	39±8	56±13
TAPSE, cm	1.8±0.3	1.9±0.4

Demographic, clinical, and echocardiographic data in asymptomatic degenerative MR.

Data are presented as mean±SD or median (interquartile range).

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; A-wave, transmitral atrial filling wave; BP, blood pressure; DT, deceleration time; E/A, transmitral early diastolic velocity/atrial filling velocity; e′ velocity, early mitral annular tissue velocity; EF, ejection fraction; ERO, effective regurgitant orifice; RV, right ventricular; E-wave, transmitral early diastolic wave; FAC, fractional area change; LAVi, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; METs, estimated metabolic equivalents; MR, mitral regurgitation; PVR, pulmonary vascular resistance; SPAP, systolic pulmonary arterial pressure; and TAPSE, tricuspid annular plane systolic excursion.

regression analysis, and variables with a univariate value of $P<0.20$ in resting or exercise RV function were entered into the multivariate models without the other RV functional parameters because of colinearity, but resting and exercise LV functions (LV end-systolic volume and LV ejection fraction), and MR status (ERO area) were forced into the multivariate models regardless of their association on univariable analysis because we suspected to influence RV functions. The association of RV function with outcome was identified by Cox proportional-hazards models in univariable and multivariable analyses. Variables with a univariate value of $P<0.10$ after adjustment for age and sex were incorporated into the multivariate models, but clinical and LV variables which were suspected to influence prognosis in previous studies[3,9,14] were forced into the multivariable models regardless of their association on univariable analysis. To avoid collinearity in situations where >1 variable measured a physiological parameter (eg, RVFAC and RV strain as markers of resting RV function) separate models were created for each categorical variable. A hazard ratio with a 95% confidence interval was calculated for each variable. The assumption of proportional hazards was assessed by plotting the scaled Schoenfeld residuals for each independent variable against time—these correlations were found to be nonsignificant. Sequential Cox models were performed to determine the incremental prognostic benefit of echocardiographic parameters over clinical data. A statistically significant increase in the global log-likelihood χ^2 of the model defined incremental prognostic value. Based on a surgery rate of ≈50%, we anticipated being able to develop a stable model with 8 variables from a population of about 180 patients.[17] Receiver operating characteristic curves were generated and compared using MedCalc 12.3.0 (MedCalc Software, Mariakerke, Belgium). A net reclassification index was calculated for comparison of each risk parameters.[18]

Inter- and intraobserver variability were examined for LV strain, RV strain, resting TAPSE, exercise TAPSE, and exercise TAPSE by anatomic M-mode. Measurements were performed in a group of 15 randomly selected subjects by 1 observer then repeated on 2 separate days by 2 observers who were unaware of the other's measurements and of the study time point.

Data are presented as means of the absolute and relative differences between measurements and by the correlation coefficient (r). Statistical analysis was performed using a standard statistical software package (SPSS software 20.0, SPSS Inc., Chicago, IL), and statistical significance was defined by $P<0.05$.

Results

Study Population

From a potential group of 403 patients undergoing exercise stress echocardiography with degenerative MR and preserved LV systolic function, we excluded patients with more than mild concomitant valvular disease (n=76), atrial fibrillation or flutter (n=42), stress-induced myocardial ischemia or scar (n=49), leaving 236 eligible patients. No patients had known pulmonary disease. We excluded 25 patients (11%) who underwent surgery within 1 month of testing, as we sought to evaluate responses among patients during medical follow-up. We also excluded 15 patients (7%) because of poor echocardiographic image quality. Therefore, 196 patients with medical follow-up were included for the final analysis, 85 of whom (43%) had severe MR with regurgitant volume >60 mL (Figure 1).

Clinical and Echocardiographic Features

The clinical features of the study group (Table 1) were typical of a degenerative MR population (56±13 years, 64% men). Patients had preserved exercise capacity (%predicted metabolic equivalents [PMTs], 115±27%) and LV function (LV ejection fraction, 65±3%), but MR was moderate or severe (average ERO area, 38±17 mm^2; regurgitant volume, 61±27 mL).

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Table 2. Associations of Resting RV Function

Variables	Univariable		Multivariable		
	r	*P* Value	β (95% CI)	Standardized β	*P* Value
Clinical data					
Age	0.07	0.31	0.02 (−0.02 to 0.06)	0.06	0.40
Sex	−0.02	0.78	0.07 (−1.04 to 1.19)	0.01	0.90
Diabetes mellitus	0.12	0.09	1.85 (−0.06 to 3.75)	0.14	0.06
Hypertension	0.11	0.11	0.79 (−0.25 to 1.82)	0.11	0.14
Smoker	0.03	0.67			
Resting heart rate	0.09	0.22	0.04 (−0.01 to 0.08)	0.11	0.12
Exercise heart rate	0.01	0.95			
Resting systolic BP	−0.08	0.30			
Resting diastolic BP	−0.03	0.67			
Exercise systolic BP	−0.07	0.31	−0.02 (−0.04 to 0.01)	−0.12	0.13
Exercise diastolic BP	−0.02	0.75			
Resting LV function					
LVEDV	−0.02	0.84			
LVESV	0.04	0.55	−0.01 (−0.03 to 0.03)	−0.01	0.96
LVEF	−0.13	0.08			
E/A	−0.04	0.60			
LV strain	0.17	0.02	0.20 (0.04 to 0.37)	0.18	0.02
Exercise LV function					
LVEDV	−0.06	0.40			
LVESV	−0.09	0.20			
LVEF	0.07	0.34	0.07 (−0.05 to 0.19)	0.09	0.24
E/A	0.03	0.69			
Resting LAVi	0.04	0.60			
MR					
Resting ERO	0.02	0.76	0.63 (−2.16 to 3.42)	0.03	0.66
Resting regurgitant volume	0.04	0.63			
Resting RV function					
RV end-diastolic area	−0.11	0.13			
RV end-systolic area	0.01	0.84			
RVFAC	−0.39	<0.001			
RV strain	—				
PVR	0.14	0.05			
Resting TAPSE	−0.19	0.007			
Resting SPAP	0.22	0.002			
Exercise RV function					
Exercise SPAP	0.26	<0.001			
Exercise TAPSE	−0.24	0.001			

Univariable and multivariable associations with resting RV strain (multiple r=0.29).

BP indicates blood pressure; CI, confidence interval; E/A, transmitral early diastolic velocity/atrial filling velocity; ERO, effective regurgitant orifice; FAC, fractional area change; LAVi, left atrial volume index; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; PVR, pulmonary vascular resistance; RV, right ventricular; SPAP, systolic pulmonary arterial pressure; and TAPSE, tricuspid annular plane systolic excursion.

There was a small but significant increase in TAPSE during exercise (1.8±0.3 versus 1.9±0.4 cm; P<0.001).

Associations of RV Function

Resting RV function (measured as RV strain, Table 2) was associated with LV strain (but not standard LV function variables), other indices of RV function (RVFAC, rest and exercise TAPSE) and PA pressure (pulmonary vascular resistance, resting and exercise SPAP). The only independent predictor of RV strain was resting LV strain (P=0.02).

The associations of exercise RV function (measured as exercise TAPSE, Table 3) were age, RV size (end-systolic

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Table 3. Associations of Exercise RV Function

	Univariable		Multivariable		
Variables	*r*	*P* Value	β (95% CI)	Standardized β	*P* Value
Clinical data					
Age	−0.19	0.008	−0.01 (−0.02 to −0.01)	−0.20	0.008
Sex	0.05	0.49	0.02 (−0.11 to 0.14)	0.02	0.82
Diabetes mellitus	−0.07	0.31	−0.16 (−0.38 to 0.05)	−0.11	0.14
Hypertension	−0.08	0.28	−0.03 (−0.15 to 0.09)	−0.04	0.60
Smoker	0.07	0.37			
Resting heart rate	−0.11	0.14	−0.01 (−0.01 to 0.00)	−0.14	0.05
Exercise heart rate	0.12	0.10			
Resting systolic BP	0.01	0.85			
Resting diastolic BP	0.01	0.90			
Exercise systolic BP	0.11	0.13	0.01 (0.00 to 0.01)	0.13	0.09
Exercise diastolic BP	−0.02	0.80			
Resting LV function					
LVEDV	−0.06	0.36			
LVESV	−0.06	0.40	−0.01 (−0.01 to 0.01)	−0.01	0.91
LVEF	0.03	0.64			
E/A	−0.05	0.52			
LV strain	0.02	0.81	−0.01 (−0.03 to 0.01)	−0.09	0.19
Exercise LV function					
LVEDV	0.06	0.44			
LVESV	0.06	0.39			
LVEF	0.01	0.94	0.01 (−0.01 to 0.01)	0.01	0.98
E/A	−0.05	0.49			
Resting LAVi	−0.04	0.62			
MR					
Resting ERO	−0.04	0.56	−0.17 (−0.49 to 0.16)	−0.07	0.31
Resting regurgitant volume	−0.03	0.67			
Resting RV function					
RV end-diastolic area	−0.13	0.07			
RV end-systolic area	−0.17	0.01			
RVFAC	0.25	<0.001			
RV strain	−0.23	0.001			
PVR	−0.06	0.43			
Resting TAPSE	0.55	<0.001			
Resting SPAP	−0.16	0.02			
Exercise RV function					
Exercise SPAP	−0.15	0.03			
Exercise TAPSE	—				

Univariable and multivariable associations with exercise TAPSE (multiple r=0.30).

BP indicates blood pressure; CI, confidence interval; E/A, transmitral early diastolic velocity/atrial filling velocity; ERO, effective regurgitant orifice; FAC, fractional area change; LAVi, left atrial volume index; LV, left ventricular; LVEDV, end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; PVR, pulmonary vascular resistance; RV, right ventricular; SPAP, systolic pulmonary arterial pressure; and TAPSE, tricuspid annular plane systolic excursion.

area), other indices of RV function (RVFAC, RV strain, resting TAPSE) and PA pressure (resting and exercise SPAP). Exercise TAPSE was independent of LV echocardiographic parameters in our population; the independent predictors of exercise TAPSE were age (P=0.008) and resting heart rate (P=0.05).

Event-free Survival

All 196 patients were followed up; over a period of 27±15 months (range, 3–66 months), 88 patients (45%) underwent mitral valve repair or replacement, and no patients died. Mitral valve surgery was indicated by symptomatic severe MR in 61 patients, the presence of LV dysfunction or dilation

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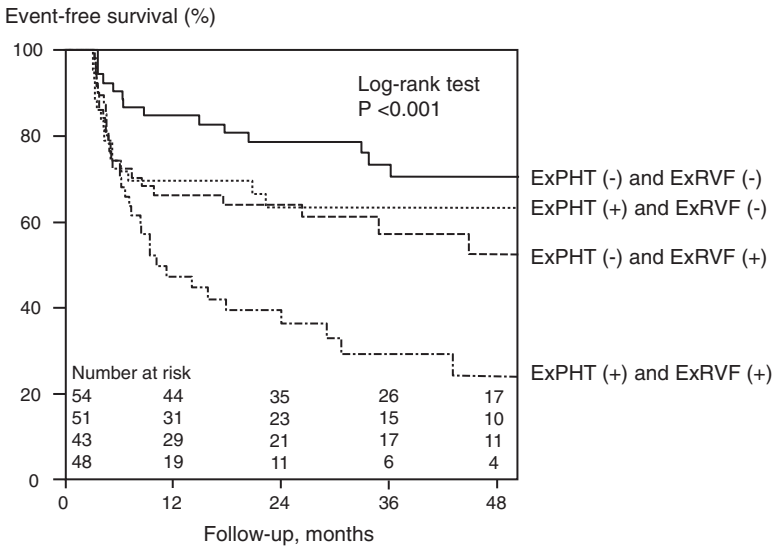

Figure 2. Kaplan-Meier analysis of event-free survival. Exercise-induced right ventricular dysfunction (exRVF) was defined as tricuspid annular plane systolic excursion during exercise <19 mm (median) and exercise-induced pulmonary hypertension (exPHT) was defined as systolic pulmonary arterial pressure during exercise >54 mm Hg (median).

in 20 patients, the occurrence of coronary artery bypass surgery in 4 patients, and the new onset of resting pulmonary hypertension (PAH) in 3 patients. No patients had the new onset of atrial fibrillation. Event-free survival was 68±8% and 60±4% at 1 and 2 years, respectively. Figure 2 illustrates the event rate of patients with asymptomatic degenerative MR stratified according to median values of exercise RV dysfunction (exercise TAPSE <19 mm) and exercise-induced PHT (SPAP >54 mm Hg). Patients with exercise RV dysfunction and exercise PHT had significantly shorter event-free survival than without exercise RV dysfunction or exercise PHT; the 4-year event-free survivals in patients without RV dysfunction and exercise PHT and with RV dysfunction and exercise PHT were 71% and 25%, respectively (P=0.001). Regurgitant volume, LV strain, RV end-diastolic area, RV end-systolic area, RVFAC, RV strain, resting and exercise SPAP, resting TAPSE, and exercise TAPSE were associated with event-free survival, independent of age and sex (Table 4). In multivariable Cox proportional-hazards models, exercise TAPSE (hazard ratio, 0.32; 95% confidence interval, 0.18–0.56; P<0.001, model 1) and exercise SPAP (hazard ratio, 1.03; 95% confidence interval, 1.02–1.05; P<0.001, model 2) were independently associated with event-free survival (Table 5). The incremental benefit of echocardiographic parameters in the prediction of events is shown in Figure 3. The addition of echocardiographic parameters significantly improved the prognostic power of a model containing clinical variables (model 1: age, sex, regurgitant volume, and LV strain, χ^2=15.9; model 2: plus RV end-systolic area and RV strain, χ^2=28.8, P=0.003; model 3: plus exercise SPAP, χ^2=40.1, P=0.002; model 4: plus exercise TAPSE, χ^2=52.2, P=0.002). Even in patients without the inclusion of the coronary artery bypass graft patients, the results were the same (Cox proportional-hazards model: age, sex, regurgitant volume, LV strain, RV end-systolic area, RV strain, exercise SPAP, and exercise TAPSE, χ^2=50.1, P<0.001).

Areas under the receiver operating characteristic curves (AUC) were used to designate the best cutoff values to predict the occurrence of events, namely, regurgitant volume >52 mL, exercise SPAP >60 mm Hg, and exercise TAPSE <17.6 mm. The standard risk model was based on sex and regurgitant volume >52 mL (AUC, 0.62; P<0.001). The prediction of events was enhanced by combination of the clinical model with exercise SPAP >60 mm Hg (exPAH: AUC, 0.68; P<0.001) or exercise TAPSE <17.6 mm (exRVF: AUC, 0.69; P<0.001), although there was no difference between the 2 (P=0.82). There was a significant difference between the AUCs for the combined model with both exPAH and exRVF (AUC, 0.68 versus 0.74; P=0.012). Using exPAH and exRVF, we reclassified cases based on the standard risk model. Combining exPAH with clinical risk lead 14.8% with events to be correctly reclassified and 12.0% without events to be incorrectly reclassified, leading to a net reclassification index of +2.8%. Combining both exPAH and exRVF with the clinical score would lead 33.0% with events to be correctly reclassified and 19.4% without events to be incorrectly reclassified, leading to a net reclassification index of +13.6% (P=0.004).

Reproducibility

Inter- and intraobserver variabilities are reported in Table 6. Close intra- and interobserver agreements were found for both resting TAPSE and exercise TAPSE. TAPSE has been shown to be highly reproducible because of the lack of reliance on RV endocardial definition or geometric assumptions. In addition, there is a strong correlation between the 2D and anatomic M-mode of TAPSE (r=0.96; P<0.001).

Discussion

The results of this study of a large, consecutive population undergoing exercise echocardiography with asymptomatic degenerative MR showed that resting LV and RV strain, exercise TAPSE, and exercise SPAP were independent predictors of the time to surgery. TAPSE is a readily available and feasible marker during exercise, and exercise TAPSE provided information that was incremental to resting TAPSE. Exercise-induced RV dysfunction provided important incremental prognostic value.

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Table 4. Univariable Associations of Mitral Surgery During Follow-up

	Adjustment for Age and Sex	
Variables	HR (95% CI)	*P* Value
Mitral		
Flail	1.58 (0.94–2.67)	0.084
ERO	2.51 (0.95–6.64)	0.064
Regurgitant volume	1.01 (1.00–1.01)	0.050
Resting LV function		
LVEDV	1.00 (0.99–1.01)	0.215
LVESV	1.01 (0.99–1.03)	0.075
LVEF	0.94 (0.86–1.00)	0.085
E/A	1.18 (0.88–1.58)	0.273
LAVi	1.01 (0.99–1.02)	0.270
LV strain	1.09 (1.01–1.17)	0.027
Resting RV function		
RV end-diastolic area	1.04 (1.01–1.08)	0.015
RV end-systolic area	1.09 (1.03–1.15)	0.003
RVFAC	0.95 (0.92–0.99)	0.019
RV strain	1.10 (1.03–1.17)	0.004
PVR	1.45 (0.97–2.16)	0.069
Resting SPAP	1.03 (1.00–1.06)	0.029
Resting TAPSE	0.37 (0.18–0.78)	0.008
Exercise data		
LVEDV	1.00 (0.99–1.01)	0.501
LVESV	1.01 (0.99–1.02)	0.385
LVEF	0.97 (0.92–1.02)	0.219
E/A	1.15 (0.74–1.81)	0.534
Exercise SPAP	1.03 (1.02–1.05)	<0.001
Exercise TAPSE	0.26 (0.15–0.46)	<0.001

Cox proportional-hazards regression analysis showing associations of the time until mitral surgery after adjustment for age and sex.

BP indicates blood pressure; CI, confidence interval; E/A, transmitral early diastolic velocity/atrial filling velocity; ERO, effective regurgitant orifice; FAC, fractional area change; HR, hazard ratio; LAVi, left atrial volume index; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; PVR, pulmonary vascular resistance; RV, right ventricular; SPAP, systolic pulmonary arterial pressure; and TAPSE, tricuspid annular plane systolic excursion.

Table 5. Cox Proportional-Hazards Regression Analysis for the Prediction of Mitral Surgery in Multivariate Model

Variables	HR (95% CI)	*P* Value
Model 1 with exercise TAPSE	χ^2=41.4	
Clinical		
Age	0.99 (0.98–1.01)	0.313
Sex	1.33 (0.83–2.14)	0.236
Regurgitant volume	1.01 (1.00–1.01)	0.105
Resting LV and RV function		
Resting LV strain	1.11 (1.02–1.20)	0.015
Resting RV end-systolic area	1.06 (1.00–1.12)	0.046
Exercise LV and RV function		
Exercise LVEF	0.98 (0.93–1.04)	0.509
Exercise TAPSE	0.32 (0.18–0.56)	<0.001
Model 2 with exercise SPAP	χ^2=38.8	
Clinical		
Age	0.99 (0.98–1.01)	0.427
Sex	1.55 (0.96–2.51)	0.072
Regurgitant volume	1.01 (1.00–1.01)	0.295
Resting LV and RV function		
Resting LV strain	1.12 (1.03–1.21)	0.006
Resting RV end-systolic area	1.07 (1.02–1.13)	0.011
Exercise LV and RV function		
Exercise LVEF	0.99 (0.94–1.04)	0.611
Exercise SPAP	1.03 (1.02–1.05)	<0.001

CI indicates confidence interval; HR, hazard ratio; LV, left ventricular; LVEF, left ventricular ejection fraction; RV, right ventricular; SPAP, systolic pulmonary arterial pressure; and TAPSE, tricuspid annular plane systolic excursion.

RV Dysfunction as a Predictor of Outcome

There is an increasing recognition of the prognostic information provided by RV function in cardiovascular disorders such as heart failure and PHT. Moreover, quantitative measurement of RV size and function is important in the prediction of clinical outcomes.[19] However, assessment of RV function is often challenging and the assessment of the RV by conventional echocardiography remains difficult because of the complex shape of the chamber.[7] Longitudinal strain provides a direct measure of regional deformation and may help to detect more subtle abnormalities of RV contractility than other echocardiographic variables.[20] On the contrary, it is extremely difficult to measure RV strain during exercise because of requirements for high frame rate, image quality, and complete visualization of the structure. Tricuspid excursion has been previously reported to have good predictive value for RV failure,[21] and it is simple and easy to measure this value during exercise.[11,22] In the present study, several parameters of resting RV function proved to be predictors of events including RV chamber size (RV end-diastolic and end-systolic area) and RV systolic function (RVFAC, RV strain, and TAPSE). More importantly, exercise RV dysfunction had additional value in the prediction of time until surgery in asymptomatic MR. A recent study reported that exercise SPAP was more accurate than resting SPAP for predicting the occurrence of symptoms in patients with asymptomatic MR.[5] Our results are consistent with this previous work that links exercise SPAP with poor prognosis in asymptomatic degenerative MR, but in our study, we also evaluated the contribution of exercise RV systolic function and exercise PAH. Receiver operating characteristic analysis revealed that the best cutoff value of exercise SPAP was 60 mm Hg which is similar to the cutoff value in guidelines and the best cutoff value of exercise TAPSE was 17.6 mm. On the contrary, the median cutoff value of exercise SPAP and TAPSE may be used for indication of MR operation in mainly moderate MR patients.

Determinants of RV Function

MR leads to increased pulmonary venous and arterial pressure, in turn increasing RV afterload,[23] which is the major source of RV dysfunction.[24] In our study, resting and exercise SPAP (RV afterload) were correlated with resting RV strain and exercise TAPSE, but this relationship was weak,

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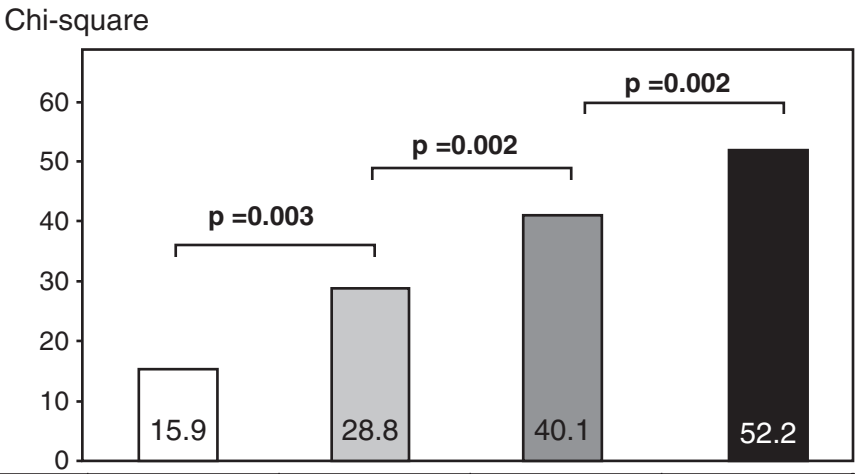

	Clinical+LV function Chi-square=15.9	+ Resting RV function Chi-square=28.8	+ Ex SPAP Chi-square=40.1	+ Ex TAPSE Chi-square=52.2
Age	0.99 (0.98-1.02), p=0.87	0.99 (0.98-1.01) , p=0.79	0.99 (0.98-1.01) , p=0.43	0.99 (0.98-1.01) , p=0.23
Gender	1.38 (0.86-2.21) , p=0.18	1.39 (0.87-2.22) , p=0.16	1.57 (0.97-2.54) , p=0.07	1.48 (0.91-2.40) , p=0.11
Regurgitant volume	1.01 (1.00-1.01) , p=0.06	1.01 (0.99-1.01) , p=0.18	1.00 (0.99-1.01) , p=0.28	1.01 (0.99-1.01) , p=0.24
LV strain	1.14 (1.05-1.23) , p=0.003	1.11 (1.02-1.20) , p=0.02	1.11 (1.02-1.20) , p=0.01	1.10 (1.02-1.19) , p=0.02
RV end-systolic area		1.07 (1.02-1.13) , p=0.008	1.07 (1.02-1.13) , p=0.01	1.06 (1.00-1.12) , p=0.04
RV strain		1.08 (1.01-1.15) , p=0.03	1.05 (0.98-1.13) , p=0.16	1.03 (0.96-1.11) , p=0.38
Exercise SPAP			1.03 (1.01-1.05) , p=0.001	1.02 (1.01-1.04) , p=0.007
Exercise TAPSE				0.39 (0.22-0.71), p=0.002

Figure 3. Incremental value of rest and exercise echocardiographic data to clinical data. This figure illustrates the global χ^2 of sequential Cox models incorporating clinical (age, sex, and mitral regurgitant volume), resting left ventricular (LV) function (LV strain), resting right ventricular (RV) function (RV end-systolic area and RV strain), exercise systolic pulmonary arterial pressure (exSPAP), and exercise tricuspid annular plane systolic excursion (exTAPSE).

suggesting that increased PA pressure may not fully explain RV dysfunction. Recent animal studies have suggested that complex heart–lung interactions at cellular and molecular levels result in angioproliferative pulmonary vascular disease, as well as myocardial fibrosis, underlie RV dysfunction.[25] Interestingly, the severity of MR (regurgitant volume) was not correlated with exercise SPAP (r=0.05; P=0.47). These results suggest that effects of MR on RV afterload (SPAP) may be buffered by left atrial functional capacity and the pulmonary circulation. On the contrary, RV strain was related with LV strain (standardized β=0.18; P=0.02), possibly reflecting not only the hemodynamic influence of LV on RV function but also the potential role of ventricular interaction.

LV Dysfunction as a Predictor of Outcome

LV ejection fraction and dimensions at rest and exercise are associated with outcome in asymptomatic MR, but in this study, neither was associated with outcome, probably reflecting preserved LV systolic function and exclusion of patients who underwent surgery within a month of testing. In some previous studies, LV longitudinal function has been identified as a predictor of recovery of exercise capacity[26] and postoperative LV dysfunction[27] in MR patients. The results of this study are consistent with the previous work linking LV strain with outcome in asymptomatic degenerative MR,[28] suggesting that earlier identification of LV dysfunction could be helpful for decision making. LV strain has a good reproducibility and

Table 6. Intraobserver and Interobserver Variability of Echocardiographic Parameters

	LV Strain at Rest, %	RV Strain at Rest, %	TAPSE at Rest, cm	TAPSE at Exercise, cm	TAPSE at Exercise Using M-mode, cm
Mean	19.2±2.4	21.2±3.4	2.1±0.4	2.1±0.5	2.1±0.6
Intraobserver variability					
Mean absolute difference	1.1±0.7	1.7±1.1	0.1±0.1	0.2±0.2	0.2±0.1
Mean relative difference, %	5.8±3.3	8.3±5.4	4.9±3.9	7.7±7.0	7.9±5.4
Correlation	0.86	0.86	0.92	0.94	0.94
Interobserver variability					
Mean absolute difference	1.4±0.9	2.4±1.9	0.2±0.1	0.2±0.2	0.2±0.2
Mean relative difference, %	7.7±5.1	11.6±9.5	8.8±5.5	9.5±8.9	9.9±7.3
Correlation	0.83	0.79	0.94	0.93	0.94

LV indicates left ventricular; RV, right ventricular; and TAPSE, tricuspid annular plane systolic excursion.

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it may be more useful than ejection fraction, which remains normal in the presence of moderate to severe MR.[29]

Limitations

This is a single-center study that included a relatively selected population of patients with preserved LV ejection fraction and sinus rhythm without concomitant valvular disease and stress-induced myocardial ischemia or scar—these findings cannot be extrapolated to all patients with MR. Although previous work has shown exercise ERO to be a good predictor of events with MR patients,[4] we considered that the limited time for gathering postexercise data should be directed toward LV global, regional, RV, and TR data. Recent guidelines for MR patients deem LV dysfunction to be present when LV end-systolic diameter is >40 mm in the setting of flail.[6] Therefore, our data may not be applicable to this particular subgroup (which accounted for 13% of our patients) in the current era.

Conclusions

The management and timing of surgery of patients with asymptomatic degenerative MR remains controversial. In asymptomatic MR, resting LV and RV strain, exercise TAPSE, and exercise SPAP were independently associated with the need for earlier mitral surgery. It is likely that the combination of progressive RV dysfunction and PHT contribute to the worse prognosis in asymptomatic MR patients.

Disclosures

None.

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CLINICAL PERSPECTIVE

Exercise echocardiography has a role in the management of asymptomatic mitral regurgitation (MR), where it may be useful in the unmasking of occult symptoms, left ventricular contractile reserve, worsening MR with stress, and identification exercise-induced pulmonary hypertension (exPHT). The role of exPHT in decision making regarding surgical timing for asymptomatic chronic MR is controversial, partly because of variability in responses. We reasoned that the exPHT response could not be interpreted without knowledge of right ventricular (RV) function. We aimed to explore the role of RV measures at rest and during exercise to predict prognosis (survival free of mitral surgery) in 196 asymptomatic patients with moderate to severe MR and preserved left ventricular function. Exercise-induced RV dysfunction, measured by exercise TAPSE, as well as exPHT and left ventricular and RV strain at rest were independent predictors of survival free of mitral surgery. Moreover, we showed the incremental predictive value of exercise RV dysfunction for prognosis over a model based on clinical data and exPHT. Early selection for surgery may improve prognosis in selected patients with asymptomatic MR, and the results of this study suggest that exercise RV dysfunction should be considered as an additional risk marker in these patients.

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