ORIGINAL RESEARCH

Importance of Exercise Capacity in Predicting Outcomes and Determining Optimal Timing of Surgery in Significant Primary Mitral Regurgitation

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Background—In primary mitral regurgitation (MR), exercise echocardiography aids in symptom evaluation and timing of mitral valve (MV) surgery. In patients with grade ≥3 primary MR undergoing exercise echocardiography followed by MV surgery, we sought to assess predictors of outcomes and whether delaying MV surgery adversely affects outcomes.

Methods and Results—We studied 576 consecutive such patients (aged 57±13 years, 70% men, excluding prior valve surgery and functional MR). Clinical, echocardiographic (MR, LVEF, indexed LV dimensions, RV systolic pressure) and exercise data (metabolic equivalents) were recorded. Composite events of death, MI, stroke, and congestive heart failure were recorded. Mean LVEF was 58±5%, indexed LV end-systolic dimension was 1.7±0.5 mm/m^2, rest RV systolic pressure was 32±13 mm Hg, peak-stress RV systolic pressure was 47±17 mm Hg, and percentage of age- and gender-predicted metabolic equivalents was 113±27. Median time between exercise and MV surgery was 3 months (MV surgery delayed ≥1 year in 28%). At 6.6±4 years, there were 53 events (no deaths at 30 days). On stepwise multivariable survival analysis, increasing age (hazard ratio of 1.07 [95% confidence interval, 1.03 to 1.12], P<0.01), lower percentage of age- and gender-predicted metabolic equivalents (hazard ratio of 0.82 [95% confidence interval, 0.71 to 0.94], P=0.007), and lower LVEF (0.94 [0.89 to 0.99], P=0.04) independently predicted outcomes. In patients achieving >100% predicted metabolic equivalents (n=399), delaying surgery by ≥1 year (median of 28 months) did not adversely affect outcomes (P=0.8).

Conclusion—In patients with primary MR that underwent exercise echocardiography followed by MV surgery, lower achieved metabolic equivalents were associated with worse long-term outcomes. In those with preserved exercise capacity, delaying MV surgery by ≥1 year did not adversely affect outcomes. **(*J Am Heart Assoc.* 2014;3:e001010 doi: 10.1161/JAHA.114.001010)**

Key Words: exercise echocardiography • mitral regurgitation • surgery timing

Currently, myxomatous degeneration of mitral valve (MV) is the most common etiology of primary mitral regurgitation (MR).[1] MR progresses over time,[2] and the majority of patients with significant primary MR will eventually require surgery to prevent adverse outcomes.[3] However, the optimal timing of surgery in asymptomatic patients is not completely clear and has been debated in the literature.[4–9] Some have suggested that all patients should have surgery as soon as possible once severe MR is present to prevent deterioration of cardiac function. Others have recommended a conservative approach in which surgical intervention is recommended when patients reach specific end points such as symptomatic deterioration or reduction in LV systolic function. Valve guidelines endorse surgical intervention in patients with severe MR who have a >90% chance of surgical repair at a center where and when surgery is proposed.[10] Patients, however, often wish to defer surgery for a considerable time for personal or career reasons. Consequently, more evidence is required to better determine how long patients with asymptomatic, significant MR can safely defer surgery and whether any clinical factors can aid in that determination.

Exercise echocardiography is used in symptom evaluation and may help in timing of surgery for MR patients.[11,12] In addition to evaluation of exercise-induced changes in the severity of the regurgitation, pulmonary pressures and LV and RV systolic function,[13] exercise echocardiography is an objective measure of exercise capacity and symptoms.

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In patients with asymptomatic, significant MR, high exercise capacity is associated with better outcomes[14], whereas patients with reduced exercise capacity have more adverse events.[15] Given the current uncertainties and controversies about timing of surgery for MR patients, we sought to assess the predictors of poor long-term outcomes in asymptomatic patients with grade ≥3 primary myxomatous MR undergoing exercise echocardiography prior to MV surgery and whether delaying MV surgery adversely affects long-term outcomes in patients with preserved exercise capacity.

Methods

Study Design

This is an observational study of 576 consecutive patients with grade ≥3 myxomatous MR, all of whom underwent treadmill exercise echocardiography at our institution between January 2000 and December 2011, followed by MV surgery. We excluded patients with functional MR (including ischemic etiology), prior valvular surgery, hypertrophic cardiomyopathy, rheumatic valvular disease, and greater than mild mitral stenosis. After institutional review board approval, electronic medical records were analyzed for data collection. Baseline clinical and medication history was manually extracted from the electronic health records at a time closest to exercise echocardiography (within 1 month). Based on the available preoperative data, additive EuroSCORE was calculated to predict risk of postoperative mortality.[16] Presence of paroxysmal (lasting at least 30 seconds) or permanent atrial fibrillation or atrial flutter was recorded, according to guidelines.[17] Follow-up clinical data were collected. atrial fibrillation occurring within 30 days postoperatively was not included.

Resting and Exercise Echocardiography

All patients underwent comprehensive echocardiograms using commercial instruments (Philips Medical Systems, N.A.; Siemens Medical Solutions USA Inc). LVEF, indexed LV dimensions, and left atrial area were measured, according to guidelines.[18] Assessment of the severity of MR was made (at the time of initial clinical evaluation) using various parameters like color Doppler data (visual assessment and effective regurgitant orifice area in some cases), left atrial size, and pulmonary venous spectral Doppler data. At the point of inclusion in this study, all echo images were re-reviewed to document the severity of MR using vena contracta width. Doppler vena contracta width was measured in each patient on the resting study, and only patients with a width ≥0.5 cm were included.[19] Because of the confounding effect of severe MR, diastolic function was not reported. Presence of flail mitral leaflet was recorded. RV systolic pressure (RVSP) was measured in all patients at rest, according to guidelines.[19]

Subsequently, in conjunction with echocardiography, patients underwent a symptom-limited standard exercise treadmill test using the Bruce protocol under close observation. Patients held their medications on the day of the test. Blood pressure, heart rate, and electrocardiographic measurements were made at rest, at 1-minute intervals, and for at least 6 minutes in recovery. Maximal predicted heart rate (220−age), percentage of predicted maximal heart rate, and number of metabolic equivalents (METs) achieved were recorded. We also calculated expected METs based on age and gender. To calculate the expected METs for men, we used the US Department of Veterans Affairs cohort formula (predicted METs=18−[0.15×age]).[20] Similarly, for women, we used the St. James Take Heart Project formula (predicted METs=14.7−[0.13×age]).[21] These specific formulae for calculating expected METs have been previously demonstrated in the respective sexes to best predict outcomes.[22] We also calculated the following ratio: percentage of age-and gender-predicted METs=(METs achieved/age and gender expected METs)×100. Preserved exercise capacity was defined as percentage of predicted METs >100%, and patients with ≤100% predicted METs were considered to have suboptimal exercise capacity.

Immediately following exercise, peak-stress echocardiographic images were acquired, according to guidelines,[23] and regional wall motion abnormalities were assessed for evaluation of ischemia and peak-stress RVSP. We also visually evaluated for changes in LV cavity size (increase, decrease, or no change). Major events (sustained ventricular or atrial arrhythmias associated with severe symptoms, hemodynamic compromise, or need for cardioversion) and minor events (decrease in blood pressure, transient symptoms, or nonsustained arrhythmias) were recorded.

Follow-up and Outcomes

The date of the patient's first exercise echocardiography at our institution was defined as the beginning of the observational period for survival analysis. Follow-up data was ascertained by chart review, and we recorded the date at which cardiovascular events were addressed (whether locally or at our institution). Date and type (repair versus replacement) of MV surgery as well as concurrent procedures such as CABG, tricuspid valve repair, left atrial appendage exclusion, surgical MAZE procedure, and atrial fibrillation ablation were recorded. Time to MV surgery was recorded. Delayed surgery was defined as a gap of at least 1 year between exercise echocardiography and MV surgery for any reason. Decision for the type of MV surgery and the timing of surgery was made by the patient's cardiac surgeon and cardiologist at the time of initial cardiac evaluation, incorporating information obtained by history, physical examination, and echocardiography (both resting and exercise stress). The final decision regarding the surgical approach to MV surgery was made by the attending cardiac surgeon. Because this study involved patients over a long period of time, this decision was very much dependent on the individual patient's problems, the surgical era, and the preference of the surgeon. For a patient needing MV surgery plus CABG, the surgical approach was a median sternotomy. For those patients who required isolated MV repair, the process has evolved from full sternotomy to partial sternotomy to right thoracotomy and robotic surgery over the years. In the latter half of the study, the vast majority of the patients underwent isolated MV repair using either a robotic or a right thoracotomy approach. Adverse outcomes including MI, development of CHF, and stroke were recorded with their respective dates for each patient. CHF was defined as meeting the criteria for stage C or D of the American College of Cardiology/American Heart Association classification of CHF.[24] Stroke was defined as neurological impairment lasting >24 hours with radiographic evidence of ischemia or hemorrhage in the brain. All-cause mortality was obtained from medical records or from the US Social Security Death Index database (last inquiry in October 2012). A composite of all-cause mortality, MI, stroke, and progression to CHF was defined as the primary end point. We did not use surgical timing as an adverse clinical end point.

Statistical Analysis

Continuous variables are expressed as mean±SD and/or median and compared using the Student *t* test or analysis of variance (for normally distributed variables) or the Mann-Whitney test (for non-normally distributed variables). Categorical data is expressed as percentage and compared using χ^2. To assess outcomes, Cox proportional hazards analysis was performed. Initially, we performed univariable survival analysis using potential predictors known to be associated with outcomes in patients with MR undergoing MV surgery. Subsequently, we performed forward stepwise multivariable survival analysis including all of the variables studied on univariable analysis (using a *P* value cutoff of 0.1). Hazard ratios (HRs) with 95% confidence intervals were calculated. In addition, cumulative proportion of events as a function over time was obtained by the Kaplan-Meier method, and event curves were compared using a log-rank test in which proportional hazards were not violated and a generalized Wilcoxon (Breslow's) test in which the survival curves clearly cross and the proportional hazards were violated. Statistical analysis was performed using SPSS version 11.5 (IBM Corp) and Stata version 10.0 (StataCorp). A $P<0.05$ was considered significant.

Table 1. Baseline Characteristics of the Study Population

Variable	Total (N=576)	≤100% Predicted METs (N=177)	>100% Predicted METs (N=399)	*P* Value
Age, y	57±13	53±15	59±12	<0.001
Male sex	401 (70%)	133 (75%)	268 (67%)	0.03
Body mass index, kg/m^2	26±4	27±5	25±3	<0.01
Hypertension	268 (47%)	73 (43%)	195 (50%)	0.2
Diabetes mellitus	23 (4%)	11 (6%)	12 (3%)	0.06
CAD	57 (10%)	23 (14%)	34 (9%)	0.07
Prior stroke	11 (2%)	2 (1%)	9 (2%)	0.3
Atrial fibrillation				
Paroxysmal	8 (1.4%)	3 (2%)	5 (1%)	0.7
Persistent	113 (20%)	30 (17%)	82 (21%)	
Pacemaker/defibrillator	9 (2%)	4 (2%)	5 (1%)	0.3
Beta-blockers	165 (29%)	51 (30%)	114 (29%)	0.5
ACE-I or ARB	222 (39%)	71 (42%)	151 (39%)	0.3
Aspirin	211 (36%)	48 (28%)	163 (41%)	0.001
Additive EuroSCORE	4.6±2.2	4.4±2.4	4.7±2.2	0.1

ACE-I indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; METs, metabolic equivalents.

Results

Baseline characteristics of the study population, as a whole and divided based on whether they achieved >100% age- and gender-predicted METs, are shown in Table 1. By study design, all patients reported no or minimal symptoms and had MV surgery during follow-up. Results of treadmill exercise echocardiography are shown in Table 2. Patients terminated the stress test due to generalized fatigue. There were no significant arrhythmias, syncope, or deaths during the treadmill exercise test. Despite reporting NYHA class I and II symptoms, 30% of patients (n=177) did not achieve >100% of their age- and gender-predicted METs.

Follow-up Data

The distribution of MV surgeries was 520 repairs (90%) and 56 replacements (10%). There were no significant differ-

Table 2. Resting and Exercise Echocardiographic Parameters of the Study Population

Variable	Total (N=576)	≤100% Predicted METs (N=177)	>100% Predicted METs (N=399)	*P* Value
LVEF, %	58±5	57±6	59±5	0.004
Indexed LV end-diastolic dimension, cm/m^2	2.8±0.6	2.7±0.5	2.8±0.6	0.3
Indexed LV end-systolic dimension, cm/m^2	1.7±0.5	1.6±0.4	1.7±0.5	0.3
Left atrial area, cm^2	28±7	29±9	27±7	0.2
Flail mitral valve	210 (37%)	72 (41%)	138 (35%)	0.1
Mitral effective regurgitant orifice area, cm^2	0.49±0.23	0.49±0.24	0.49±0.23	0.9
Mitral regurgitation				
Grade 3	175 (30%)	56 (32%)	119 (30%)	0.6
Grade 4	401 (70%)	121 (68%)	280 (70%)	
Vena contracta width, cm	0.87±0.2	0.88±0.2	0.86±0.2	0.2
RV dysfunction				
None	565 (98%)	169 (97%)	397 (99%)	0.03
Mild	5 (1%)	3 (2%)	2 (1%)	
Moderate	3 (0.5%)	3 (2%)	0	
Resting RVSP, mm Hg	32±13	31±15	32±11	0.7
Tricuspid regurgitation				
None	42 (7%)	20 (11%)	22 (6%)	0.07
Trivial-mild	453 (79%)	135 (78%)	318 (80%)	
Moderate to moderate-severe	80 (14%)	21 (12%)	59 (15%)	
Severe	1 (0.2%)	1 (0.6%)	0	
MV prolapse				
Anterior	49 (9%)	15 (9%)	34 (9%)	0.9
Posterior	275 (48%)	87 (49%)	188 (47%)	
Bileaflet	252 (44%)	75 (42%)	177 (44%)	
Maximum predicted heart rate, %	95±11	92±10	97±11	<0.001
METs achieved	9.8±3	8.98±2	10.6±2	<0.001
Poststress RVSP, mm Hg	47±17	46±20	47±16	0.6
Stress-induced ischemia, %	25 (4)	14 (8)	11 (3)	0.006
Change in LV cavity size with stress				
Decrease	506 (88%)	151 (85%)	355 (89%)	0.14
Unchanged	51 (9%)	19 (11%)	32 (8%)	
Increased	19 (3%)	9 (5%)	10 (3%)	

BP indicates blood pressure; LV, left ventricle; LVEF, left ventricular ejection fraction; METs, metabolic equivalents; MV, mitral valve; RV, right ventricle; RVSP, right ventricular systolic pressure.

Table 3. Univariable Multivariable Cox Proportional Hazard Analysis for Outcomes in the Study Population

Variable	Univariable	
	Hazard Ratio	*P* Value
Age	1.07 (1.05 to 1.10)	<0.001
Gender	0.96 (0.60 to 1.57)	0.8
Body mass index	1.005 (0.94 to 1.07)	0.9
Hypertension	1.22 (0.73 to 2.03)	0.5
Diabetes mellitus	1.05 (0.26 to 4.32)	0.3
CAD	1.91 (0.93 to 3.91)	0.08
Baseline atrial fibrillation	2.40 (123 to 4.67)	0.01
Beta-blockers	1.46 (0.64 to 2.83)	0.4
ARB	1.23 (0.78 to 1.94)	0.3
Anticoagulation	1.28 (0.61 to 2.69)	0.4
Pacemaker	2.28 (0.56 to 9.40)	0.3
Resting LV ejection fraction	0.91 (0.88 to 0.95)	<0.001
Indexed LV end-systolic dimension	1.16 (0.66 to 2.04)	0.6
Bileaflet vs single leaflet prolapse	1.16 (0.77 to 1.72)	0.5
Flail mitral leaflet	0.80 (0.46 to 1.39)	0.4
Tricuspid regurgitation	1.84 (1.33 to 2.56)	<0.001
Resting RVSP	1.03 (1.01 to 1.05)	0.003
Postexercise RVSP	1.02 (1.00 to 1.03)	0.1
Left atrial area	1.03 (0.99 to 1.07)	0.1
METs achieved	0.68 (0.60 to 0.77)	<0.001
Percentage of age- and gender-predicted METs achieved	0.9830 (0.9718 to 0.9944)	0.004
Ischemia on stress echocardiography	1.24 (0.60 to 3.94)	0.8
Time to mitral valve surgery (1-month increment)	1.002 (0.99 to 1.01)	0.7
>30-Day postoperative atrial fibrillation	1.82 (0.98 to 3.32)	0.1

ARB indicates angiotensin receptor blocker; CAD, coronary artery disease; LV, left ventricle; METs, metabolic equivalents; RVSP, right ventricular systolic pressure.

Table 4. Forward Stepwise Multivariable Cox Proportional Hazard Analysis for Outcomes in the Study Population

Variable	Stepwise Multivariable Analysis	
	Hazard Ratio	*P* Value
Age	1.07 (1.03 to 1.12)	<0.01
Percentage of age- and gender-predicted METs achieved	0.82 (0.71 to 0.94)	0.005
LVEF	0.94 (0.89 to 0.99)	0.04

Because of collinearity, of the 2 variables, only percentage of age- and gender-predicted METs (and not absolute METs achieved) was entered into the model. The χ^2 for the model was 55, $P<0.001$. LVEF indicates left ventricular ejection fractionl; METs, metabolic equivalents.

ences in proportion of MV repair in those achieving ≤100% versus >100% age- and gender-predicted METs (88% versus 91%, 0.2). Additional procedures performed at the time of MV surgery were CABG (80, 14%), left atrial appendage excision (34, 6%), tricuspid valve repair (30, 5%), pulmonary vein isolation (144, 2%), and MAZE (48, 8%). The median time to MV surgery (from treadmill echocardiography) was 3 months (interquartile range: 1 to 14 months).

In the total group, 102 patients (18%) had new-onset atrial fibrillation during follow-up >30 days postoperatively. In addition, during follow-up, there were an additional 28 patients (5%) who required pacemaker implantation and 8 patients (1.4%) with ICD implantation. The breakdown of NYHA class at final follow-up was 534 (93%) in class I, 38 (6%) in class II, and 4 (0.6%) in class III.

Survival Data

During a mean follow-up of 6.6±4 years, a total of 53 patients (9%) met the composite end point (5 patients developed end points, between exercise echocardiography and MV surgery). The breakdown of individual end points was 20 deaths (4%), 11 strokes (2%), 13 transient ischemic attacks (2%), 4 MIs (0.7%), and 25 patients (4%) with progression to CHF. In patients who developed multiple end points, the time to first event was used as an event time cut-

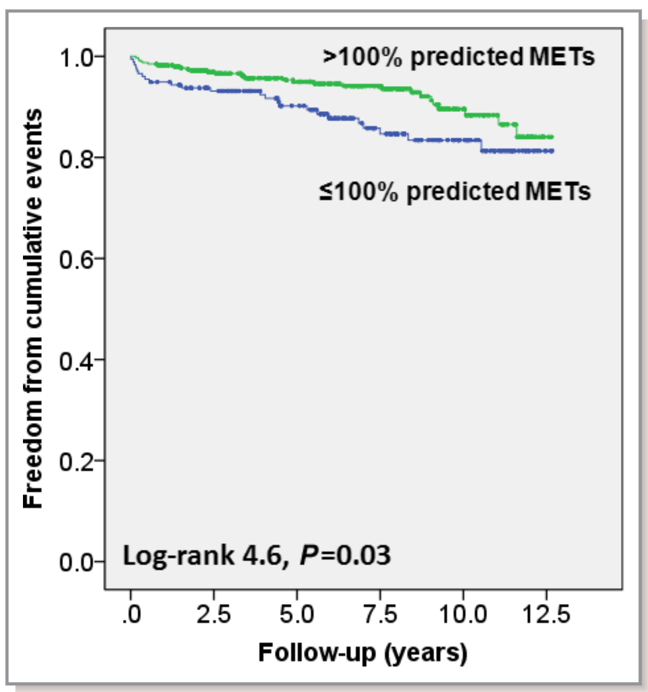

Figure 1. Kaplan-Meier survival curves of the entire study population separated on the basis of having achieved >100% of age- and gender-predicted metabolic equivalents (METs).

Table 5. Clinical Characteristics of Patients With >100% Achieved Exercise METs, Based on Delaying Mitral Valve Surgery by 1 Year

Variable	Surgical Delay ≥1 Year (N=127)	No Surgical Delay (N=272)	*P* Value
Age, y	58±12	59±12	0.6
Male sex	83 (65%)	185 (68%)	0.4
Body mass index, kg/m^2	25±4	25±4	0.4
Hypertension	59 (48%)	136 (51%)	0.6
Diabetes mellitus	1 (1%)	11 (4%)	0.07
CAD	8 (7%)	26 (10%)	0.2
Prior stroke	5 (4%)	4 (2%)	0.1
Atrial fibrillation			
Paroxysmal	2 (2%)	3 (1%)	0.4
Persistent	23 (18%)	59 (22%)	
Pacemaker/defibrillator	0	5 (2%)	0.2
Beta-blockers	37 (30%)	77 (29%)	0.5
ACE-I or ARB	35 (29%)	116 (44%)	0.002
Aspirin	43 (34%)	120 (44%)	0.03
Additive EuroSCORE	4.6±2.2	4.5±2.3	0.5
Median time to MV surgery, months	28 (17, 53)	2 (0 to 4)	<0.001

ACE-I indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; MV, mitral valve.

off. There were no deaths and 1 stroke at 30 days postoperatively. At the time of discharge, 98% patients had grade ≤1 residual MR. During follow-up, 7 patients required redo MV surgery, and all were MV replacements (none within 30 days postoperatively).

We performed univariable and forward stepwise multivariable Cox proportional survival analysis. The results are shown in Tables 3 and 4. On final stepwise multivariable survival analysis, the following parameters were independently predictive of adverse outcomes: increasing age (HR: 1.07 [95% confidence interval, 1.03 to 1.12], $P<0.01$), lower percentage of age- and gender-predicted METs (HR: 0.82 [95% confidence interval, 0.71 to 0.94], $P<0.007$), and lower LVEF or EF (HR: 0.94 [95% confidence interval, 0.89 to 0.99], $P=0.04$). Patients achieving >100% age- and gender-predicted METs had a significantly lower proportion of events during long-term follow-up compared with those achieving ≤100% (29 of 399 or 7% versus 24 of 177 or 14%; log-rank statistic, 4.6; $P=0.03$). The Kaplan-Meier curves showing the long-term outcomes in the study population, separated on the basis of achieving >100% age- and gender-predicted METs is shown in Figure 1. In a subgroup of patients who underwent MV surgery without CABG (n=496), lower percentage of age- and gender-predicted METs (HR: 0.86 [95% confidence interval, 0.76 to 0.96], $P<0.02$) remained significantly predictive of outcomes.

Impact of Delaying MV Surgery

Subsequently, we wanted to determine whether delaying surgery, especially in those patients with a high exercise capacity, would be associated with worse long-term outcomes. Consequently, we further divided the patients that achieved >100% age- and gender-predicted METs (n=399) into 2 further subgroups: those for whom MV surgery was delayed ≥1 year (n=127) and those for whom MV surgery was performed within <1 year (n=272). The clinical characteristics of these 2 subgroups are shown in Table 5. The median times for surgery in the 2 subgroups were 2 months (range: 0 to 4 months) versus 28 months (range: 17 to 53 months) ($P<0.001$). The treadmill and echocardiographic data of the 2 subgroups are shown in Table 6. As expected, patients for whom surgery was not delayed for 1 year had a higher proportion of flail MV, slight vena contracta width (and a higher degree of IV plus MR), and higher rest and stress RVSP. Of note is that even in the delayed surgery group, the recalculated vena contracta width fell in the severe category; however, the proportion of events was not significantly different between the delayed surgery versus no-delay subgroups (12 of 127 versus 17 of 272, modified Wilcoxon statistic of 0.02, $P=0.9$). The Kaplan-Meier curves showing the outcomes in the study population, separated on the basis of delaying MV surgery, are shown in Figure 2. The results were similar, even when the CABG subgroup was excluded.

Table 6. Echocardiographic Characteristics of Patients With >100% Achieved Exercise METs, Based on Delaying Mitral Valve Surgery by 1 Year

Variable	Surgical Delay >1 Year (N=127)	No Surgical Delay (N=272)	*P* Value
LVEF, %	59±4	58±5	0.4
Indexed LV end-diastolic dimension, cm/m^2	2.75±0.6	2.82±0.7	0.3
Indexed LV end-systolic dimension, cm/m^2	1.60±0.5	1.70±0.5	0.08
Left atrial area, cm^2	27±7	28±7	0.3
Flail mitral valve	28 (22%)	110 (40%)	<0.001
Mitral effective regurgitant orifice area, cm^2	0.44±0.24	0.48±0.19	0.03
Mitral regurgitation			
Grade 3	56 (44%)	63 (23%)	<0.001
Grade 4	71 (56%)	209 (77%)	
Mitral valve prolapse			
Anterior	13 (10%)	21 (8%)	0.04
Posterior	47 (37%)	141 (52%)	
Bileaflet	67 (54%)	110 (41%)	
Vena contracta width, cm	0.82±0.2	0.88±0.2	0.008
RV dysfunction			
None	127 (98%)	270 (98%)	0.5
Mild	0 (1%)	2 (1%)	
Resting RVSP, mm Hg	29±10	33±12	0.003
Tricuspid regurgitation			
None	10 (7%)	12 (4%)	0.8
Trivial-mild	100 (79%)	218 (80%)	
Moderate to moderate-severe	18 (14%)	41 (15%)	
Maximum predicted heart rate, %	98±10	96±12	0.02
METs achieved	10.8±2	10.4±2	0.1
Poststress RVSP, mm Hg	42±14	49±16	<0.001
Stress-induced ischemia, %	1 (1%)	11 (4%)	0.1
Change in LV cavity size with stress			
Decrease	118 (92%)	237 (87%)	0.3
Unchanged	10 (7%)	22 (8%)	
Increased	1 (1%)	9 (3%)	

LV indicates left ventricle; LVEF, left ventricular ejection fraction; METs, metabolic equivalents; RVSP, RV systolic pressure.

Discussion

We demonstrate that in patients with grade ≥3 primary MR undergoing exercise echocardiography followed by MV surgery, increased age, lower exercise capacity, and lower LVEF were independently predictive of poor long-term outcomes. Standard predictors like atrial fibrillation and RVSP predicted outcomes on univariable analysis but did not remain significant on multivariable analysis. Following MV surgery, patients who had achieved >100% of their age- and gender-predicted METs had better long-term outcomes than patients who had ≤100% of age- and gender-predicted METs. This is despite the fact that there was 0% 30-day mortality in the entire study group, regardless of their achieved exercise capacity. Furthermore, in patients who achieved >100% of their age- and gender-predicted METs, delaying MV surgery for ≥1 year did not adversely affect long-term outcomes.

This study is one of the largest studies that has investigated the predictors of poor long-term outcomes in surgically treated patients with significant primary MR and, to the best of our knowledge, is the first study to assess the clinical significance of using exercise capacity in timing of MV surgery. However,

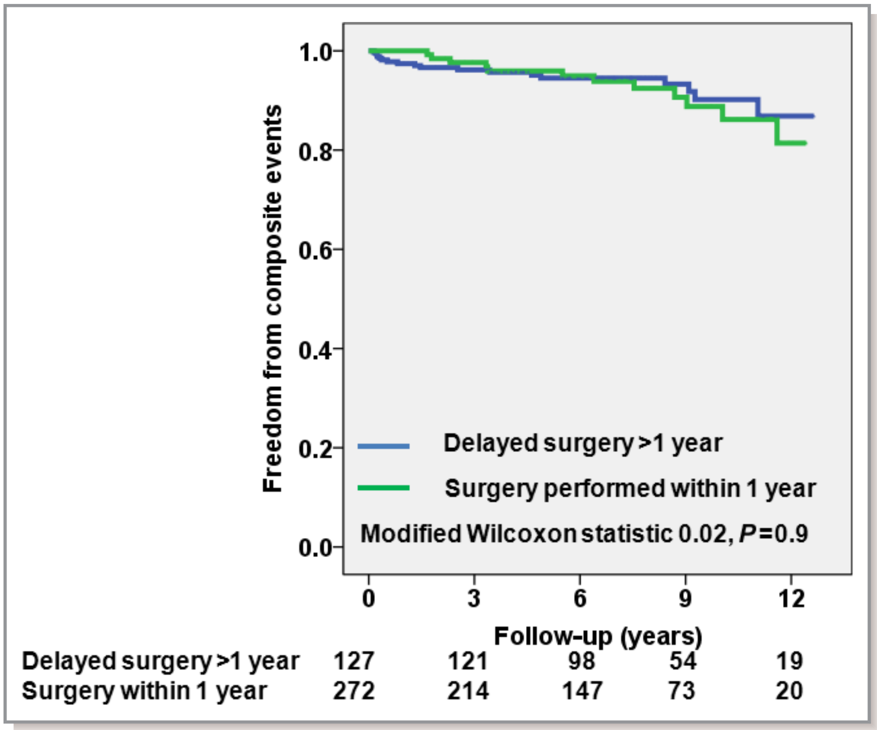

Figure 2. Kaplan-Meier survival curves of the subgroup that achieved >100% of age- and gender-predicted metabolic equivalents (METs), separated on the basis of whether or not surgery was delayed >1 year.

this still represents only a small proportion of patients who underwent MV surgery (total of ≈5000) at our institution during the time frame of the study. In addition, we recently reported outcomes of all patients with grade ≥3 primary MR that underwent exercise echocardiography.[25] Presence of symptoms is a well-known predictor of poor outcomes and a class I indication for surgery in MR patients.[10,26] However, many patients with severe MR remain asymptomatic or might misperceive their symptoms because of sedentary lifestyle or insidious progression of symptoms. Exercise testing can reveal objective results and has been used to evaluate and "unmask" the symptoms in MR patients.[11,12] In fact, 30% of the patients in our study, who were all considered to be asymptomatic or minimally symptomatic (NYHA class I or II), had ≤100% of age- and gender-predicted exercise capacity and subsequently had worse long-term outcomes. This further signifies the importance of exercise capacity in elucidating symptoms and identifying higher-risk patients who might appear to have stable disease.

Patients who had achieved >100% their age- and gender-predicted METs had better long-term outcomes, and their outcomes were not affected by performance of surgery ≥1 year later. Patients with good exercise capacity and early versus delayed surgery were similar in all clinical and echocardiographic characteristics except for higher severity of disease, prevalence of flail leaflet, and resting and poststress RVSP in the early surgery group. All of these factors are known to be associated with worse outcomes,[27,28] and thus surgery had been appropriately performed sooner in the early surgery group. However, earlier surgery did not translate into better outcomes in these patients. This finding raises the question of whether or not preserved exercise capacity outweighs some risk factors in MR patients. This outcome is further supported by the fact that, in our study, unlike exercise capacity, many of the conventional risk factors such as atrial fibrillation,[29] LV and LA dimensions,[30,31] and RVSP[27] did not remain independently predictive of poor long-term outcomes on multivariable analysis. Exercise capacity in MR patients is not directly affected by severity of regurgitation and seems to be more related to the complications of disease such as LV dysfunction.[15,32] Our results with regard to timing of surgery in patients with good exercise capacity might seem to be in contrast with a recent study that showed survival benefits of performing surgery within 3 months in patients with flail mitral leaflets.[8] However, relatively few patients in our delayed-surgery group had flail leaflet, and exercise capacity was not objectively evaluated in the other study, so the populations are not easily comparable.

Clinical Implications

In the absence of randomized trials, determination of optimal time of MV surgery remains challenging in the management of primary MR. Although MV surgery is safe and clearly improves outcomes in such patients, it is a major surgery and comes with the cost of postoperative morbidity. The durability of MV repair, and of bioprosthetic valve when MV repair is not feasible, along with the need for a potential reoperation can also influence the decision for surgery. Conservative management and early surgical approach have long been debated in the literature, but both try to find the optimal time for surgery in individual patients. The studies that have directly compared these 2 strategies[6–8] suggest that surgery should be done prior to or, at a minimum, immediately on appearance of NYHA class I indications. The case for earlier surgery in this condition is further supported by advancements in surgical techniques and reports of excellent long-term surgical outcomes.[33,34] However, this strategy still needs to allow for the needs of individual patients, some of whom may wish to defer surgery for a considerable time for personal or career reasons. We are able to identify a subset of patients with good exercise capacity whose outcome was not adversely affected by delaying surgery.

Limitations

Our study was done in a single referral center and thus is not free of selection bias. However, the patient characteristics were similar to multiple previous reports.[6,9,15,28] During the time frame of the study, ≈5000 patients with symptomatic significant primary MR underwent MV surgery. By design, patients who had not been able to undergo exercise echocardiography or patients who had advanced symptoms (and hence did not need further evaluation) were not included in our study, and the results cannot be generalized to them. In addition, the number of patients that underwent concomitant CABG was relatively small, hence recommendations (especially pertaining to delaying surgery) cannot be definitively extrapolated to that subgroup. It should be emphasized that exercise capacity can be influenced by several comorbidities, including higher body mass index, not just MR. Consequently, a global evaluation is required in patients with low exercise capacity, and other contributing mechanisms should be sought and considered in decision making. Moreover, we do not have systematic data on stress testing after MV surgery, especially in the patients that did not reach targeted METs. Furthermore, the event rate was low, and there is a potential for the study to be underpowered. However, the low event rate reflects a combination of factors including relatively asymptomatic patients and improved MV surgical techniques. We included patients over a broad time frame, and not all of the advanced echocardiographic measurements available today (eg, 3-dimensional echocardiogram, strain and effective regurgitant orifice area) were performed in all patients. Consequently, we were not able to study the role of effective regurgitant orifice area (a factor that has been shown to determine mortality[28]) or strain in the outcome of our patients. It can be argued that proximal isovelocity surface area measurements can be inaccurate in very eccentric MR jets. We ascertained that MR was grade ≥3 in the study population by repeat blinded evaluation of vena contracta width.

Conclusion

In patients with significant primary MR undergoing exercise echocardiography followed by MV surgery, increased age, lower exercise capacity, and lower LVEF independently predicted poorer long-term outcomes. Exercise capacity can potentially be used in timing of surgery in MR patients. Patients with preserved exercise capacity have better long-term outcomes, and delaying MV surgery in these patients was not associated with worse long-term outcomes. Future prospective studies are required to ascertain the results of our observation.

Disclosures

None of the authors have conflicts of interests or acknowledgements pertaining to this paper. Dr Gillinov is a consultant to Edwards Lifesciences, Abbott, and On-X and has received honoraria from St. Jude Medical and Intuitive Surgical. The other authors have no financial conflicts of interest.

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