Prognostic Significance of Exercise-induced Right Ventricular Dysfunction in Asymptomatic Degenerative Mitral Regurgitation
Kenya Kusunose, Zoran B. Popovic, Hirohiko Motoki and Thomas H. Marwick
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The management of patients with asymptomatic degenerative mitral regurgitation (MR) remains controversial. 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. 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). Exercise echocardiography has been proposed as an additional test because the occurrence of PHT during exercise has been linked to prognosis, 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). 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. 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 area >20 mm² or regurgitant volume >30 mL) were referred for exercise stress echocardiography. 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 (\(\chi^2, 15.9\)) was improved by RV strain and RV chamber size (\(\chi^2, 28.8; P=0.003\)) and exercise systolic pulmonary arterial pressure (\(\chi^2, 40.1; P=0.002\)) and further increased by exercise tricuspid annular plane systolic excursion (\(\chi^2, 52.2; P=0.002\)).

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

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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 mm²) 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 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 (\(\chi^2, 15.9\)) was improved by RV strain and RV chamber size (\(\chi^2, 28.8; P=0.003\)) and exercise systolic pulmonary arterial pressure (\(\chi^2, 40.1; P=0.002\)) and further increased by exercise tricuspid annular plane systolic excursion (\(\chi^2, 52.2; P=0.002\)).

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. 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. 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). Exercise echocardiography has been proposed as an additional test because the occurrence of PHT during exercise has been linked to prognosis, 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). 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. 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.
in accordance with current guidelines. RV fractional area change

Standard echocardiographic measurements of the RV were made

Echocardiographic images were digitally recorded and downloaded to an imaging server for offline analysis. MR was quantified as previ-

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. The ERO area was calculated to an imaging server for offline analysis. MR was quantified as previ-

Right Ventricular Function

Standard echocardiographic measurements of the RV were made in accordance with current guidelines. 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. SPAP was estimated from the maximal continuous-wave Doppler velocity of the tricuspid regurgitation (TR) jet using systolic transtri-

Clinical Outcome

Patients were followed in accordance with current guidelines, 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
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 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 fitting the scaled Schoenfeld residuals for each independent variable against time—where 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 $\chi^2$ of the model defined incremental prognostic value. Based on a surgery rate of $\approx 50\%$, we anticipated being able to develop a stable model with $8$ variables from a population of about $180$ patients. 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.

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 ($56\pm13$ years, $64\%$ men). Patients had preserved exercise capacity (%predicted metabolic equivalents [PMTs], $115\pm27\%$) and LV function (LV ejection fraction, $65\pm3\%$), but MR was moderate or severe (average ERO area, $38\pm17$ mm$^2$; regurgitant volume, $61\pm27$ mL).

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**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56±13</td>
<td>68±17</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>126 (64)</td>
<td>78 (40)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>56±13</td>
<td>68±17</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>26±4</td>
<td>30±4</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70±11</td>
<td>156±24</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>129±17</td>
<td>176±26</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>80±15</td>
<td>83±11</td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td>196 (40)</td>
<td>115±27</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td>196 (40)</td>
<td>115±27</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>48 (25)</td>
<td>86 (44)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>78 (40)</td>
<td>80 (41)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>13 (6)</td>
<td>68 (35)</td>
</tr>
<tr>
<td>Resting LAVi, mL/m$^2$</td>
<td>43 (33–56)</td>
<td>43 (33–56)</td>
</tr>
<tr>
<td>Resting LV strain, %</td>
<td>−18.8±3.0</td>
<td>−18.8±3.0</td>
</tr>
<tr>
<td>Mitral valve prolapse, n (%)</td>
<td>36 (18)</td>
<td>31 (16)</td>
</tr>
<tr>
<td>Anterior</td>
<td>36 (18)</td>
<td>31 (16)</td>
</tr>
<tr>
<td>Posterior</td>
<td>85 (44)</td>
<td>75 (38)</td>
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<tr>
<td>Both</td>
<td>75 (38)</td>
<td>13 (6)</td>
</tr>
<tr>
<td>Mitral flail</td>
<td>31 (16)</td>
<td>85 (43)</td>
</tr>
<tr>
<td>Severe MR</td>
<td>85 (43)</td>
<td>196 (40)</td>
</tr>
<tr>
<td>MR</td>
<td>43 (33–56)</td>
<td>43 (33–56)</td>
</tr>
<tr>
<td>ERO, mm$^2$</td>
<td>38±17</td>
<td>38±17</td>
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<tr>
<td>Regurgitant volume, mL</td>
<td>61±27</td>
<td>61±27</td>
</tr>
<tr>
<td>RV end-diastolic area, cm$^2$</td>
<td>22±7</td>
<td>22±7</td>
</tr>
<tr>
<td>RV end-systolic area, cm$^2$</td>
<td>13±4</td>
<td>13±4</td>
</tr>
<tr>
<td>RVFAC, %</td>
<td>41±5</td>
<td>41±5</td>
</tr>
<tr>
<td>RV strain, %</td>
<td>−19.8±3.4</td>
<td>−19.8±3.4</td>
</tr>
<tr>
<td>PVR, Wood Units</td>
<td>2.0 (1.7–2.4)</td>
<td>2.0 (1.7–2.4)</td>
</tr>
<tr>
<td>SPAP, mm Hg</td>
<td>39±8</td>
<td>56±13</td>
</tr>
<tr>
<td>TAPSE, cm</td>
<td>1.8±0.3</td>
<td>1.9±0.4</td>
</tr>
</tbody>
</table>

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, transmirtal atrial filling wave; BP, blood pressure; DT, deceleration time; E/A, transmirtal 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, transmirtal 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.
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...
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.
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, χ²=15.9; model 2: plus RV end-diastolic area and RV strain, χ²=28.8, P=0.003; model 3: plus exercise SPAP, χ²=40.1, P=0.002; model 4: plus exercise TAPSE, χ²=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, χ²=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 19.4% 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 12.0% 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.
than other echocardiographic variables. On the contrary, it helps to detect more subtle abnormalities of RV contractility and provides a direct measure of regional deformation and may have additional value for RV failure, and it is simple and easy to measure 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, and it is simple and easy to measure this value during exercise. 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. Our results are consistent with this previous work that links exercise SPAP with poor prognosis in asymptomatic degenerative MR.

### 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. 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. Longitudinal strain provides a direct measure of regional deformation and may help to detect more subtle abnormalities of RV contractility than other echocardiographic variables. 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, and it is simple and easy to measure this value during exercise.

### Determinants of RV Function

MR leads to increased pulmonary venous and arterial pressure, in turn increasing RV afterload, which is the major source of RV dysfunction. In our study, resting and exercise SPAP (RV afterload) were correlated with resting RV strain and exercise TAPSE, but this relationship was weak.
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. 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 $\beta=0.18; P=0.02$), 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 and postoperative LV dysfunction in MR patients. The results of this study are consistent with the previous work linking LV strain with outcome in asymptomatic degenerative MR, suggesting that earlier identification of LV dysfunction could be helpful for decision making. LV strain has a good reproducibility and

<table>
<thead>
<tr>
<th>Clinical+LV function</th>
<th>+ Resting RV function</th>
<th>+ Ex SPAP</th>
<th>+ Ex TAPSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-square=15.9</td>
<td>Chi-square=28.8</td>
<td>Chi-square=40.1</td>
<td>Chi-square=52.2</td>
</tr>
</tbody>
</table>

**Figure 3.** Incremental value of rest and exercise echocardiographic data to clinical data. This figure illustrates the global $\chi^2$ 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).

<table>
<thead>
<tr>
<th>LV Strain at Rest, %</th>
<th>RV Strain at Rest, %</th>
<th>TAPSE at Rest, cm</th>
<th>TAPSE at Exercise, cm</th>
<th>TAPSE at Exercise Using M-mode, cm</th>
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</thead>
<tbody>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>19.2±2.4</td>
<td>21.2±3.4</td>
<td>2.1±0.4</td>
<td>2.1±0.5</td>
<td>2.1±0.6</td>
</tr>
</tbody>
</table>

**Table 6. Intraobserver and Interobserver Variability of Echocardiographic Parameters**

**LV indicates left ventricular; RV, right ventricular; and TAPSE, tricuspid annular plane systolic excursion.**
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.4 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.

References


**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 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.