Predictive Factors for Progression of Mitral Regurgitation in Asymptomatic Patients With Mitral Valve Prolapse

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Risk factors predicting progression from low grade to severe mitral regurgitation (MR), which is a guideline criterion for surgical intervention, remain unknown. We hypothesized that abnormalities of cardiac structure and function may predict progression in MR severity. We followed 82 asymptomatic mitral valve prolapse (MVP) patients (65 ± 12 years, 51% men) with mild or moderate MR (36 mild, 46 moderate, mean LVEF: 62%), without significant co-morbidities. We examined clinical findings and 13 echo measurements. The primary end point was progression to severe MR. In a mean follow-up period of 4.5 ± 2.7 years, mortality and heart failure development were similar for mild and moderate MR. No mild MR patient progressed to severe, but 23 moderate MR patients (50.0%) progressed to severe with 9 patients (39.1%) who underwent surgery. No clinical variables were predictive for progression. Only mean mitral annulus diameter (apical 4 and 2 chamber) was predictive for progression to severe MR (hazards ratio 1.14, 95% confidence interval 1.03 to 1.26, p = 0.01). A cut-off annulus diameter of 39.6 mm had a good accuracy (area under the curve 0.78, sensitivity 100%, and specificity 63.8%) for progression to severe. In conclusion, over a 4.5-year period, 50% of asymptomatic MVP patients with moderate MR, but none with mild, progressed to severe MR. Only mitral annular dimension predicted progression of moderate to severe MR, and values >39.6 mm predicted progression accurately. Mitral annulus diameter may be of value in identifying asymptomatic MVP patients at risk of developing severe MR. **(Am J Cardiol 2019;123:1309−1313)**

Mitral valve prolapse (MVP) affects 2% to 3% of the general population and is a frequent etiology of degenerative mitral regurgitation (MR) requiring valve surgery.[1] The decision to pursue surgical intervention is straightforward if patients are symptomatic or have left ventricular dysfunction.[2] Monitoring patients with asymptomatic MVP who do not yet meet criteria for surgical intervention continues to be a challenge. Moreover, the natural history of low-grade MR progressing to severe MR has yet to be fully defined in the literature. We hypothesized that certain abnormalities of cardiac structure and function on echocardiogram may predict the progression in MR severity.

Methods

This was a retrospective study of patients with MVP at the University of California, San Diego Medical Center from January 2010 to December 2015. A total of 254 consecutive patients without co-morbidities were diagnosed with MVP by echocardiography. We excluded patients with ejection fraction <60% and a history of previous adverse events (n = 20), baseline symptoms (n = 54), and baseline severe mitral regurgitation (n = 33). We also excluded patients without a follow-up echocardiogram (n = 65). Our final patient population was intentionally very selective and specific in order to reflect asymptomatic patients commonly encountered in the clinical setting.

We therefore studied 82 asymptomatic patients (mean age: 65 ± 12 years, mild MR: n = 36 and moderate MR: n = 46). Patient co-morbidities, medications, and outcomes were collected from a review of the electronic medical record (Epic Systems Corporation, Verona, WI). The primary end point was defined as the progression to severe MR. We also analyzed the need for mitral valve surgery, development of heart failure, and all-cause mortality. Our study complies with the Declaration of Helsinki, and is approved by the ethics committee of the University of California San Diego (UCSD) Human Research Protection Program. Written informed consent was waived given the retrospective nature of the study.

All patients underwent comprehensive transthoracic 2-dimensional echocardiography using Philips iE33 (Philips Medical Systems, Bothell, WA), Siemens SC2000 (Siemens Medical Solutions, Malvern, PA), and General Electric Vivid E9 (GE Medical Systems, Milwaukee, WI) ultrasound units with harmonic imaging. Echocardiograms were performed with patients in the left lateral decubitus position to obtain the standard parasternal and apical views. All echocardiographic data were stored on a work station (Siemens Medical USA, Malvern, PA) for subsequent measurement

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and analysis. MVP was diagnosed according to the American Heart Association/American College of Cardiology guidelines, as abnormal systolic displacement of one or both leaflets >2 mm into the left atrium below the annulus as visualized in the parasternal long-axis view.[3] Grading of MR was determined according to the American Society of Echocardiography guidelines, using the quantitative parameters of regurgitant volume, regurgitation fraction, and effective regurgitant orifice area obtained from 2-dimensional echocardiography.[4] Severe MR was defined by the quantitative parameters of regurgitant volume ≥60 ml, regurgitation fraction ≥50%, and effective regurgitant orifice area ≥0.4 cm^2.[2,4] Measurements were performed with off-line or on-line analysis, and LVEF was calculated using the biplane Simpson's method. We measured mitral valve thickness as the largest dimension of the middle of the anterior leaflet from the parasternal long-axis view in open position in mid-diastole, or as the thickest segment of the posterior leaflet. Mean mitral annulus diameter was defined as the distance from the aortic hinge point of the anterior mitral leaflet to the attachment of the posterior leaflet at the annulus, taking the average of the apical 4- and 2-chamber views in mid-systole. Left atrial volume (LAV) was measured both as maximum (LAV max: left ventricular end-systolic period) and minimum volume (LAV min: left ventricular end-diastolic period) using the biplane area-length method. Left atrial ejection fraction (LAEF) was calculated as follows: LAEF = 100 × (LAV max − LAV min) / LAV max. Left ventricular and LAV were indexed by dividing the body surface area.[5]

Continuous data were presented as mean ± standard deviation (SD) or medians with the interquartile range. The Shapiro-Wilk test was performed to evaluate the assumption of normality. The Kaplan-Meier log-rank test was used to compare the difference in clinical outcomes between patients with mild MR to those with moderate MR. Receiver operating characteristic (ROC) curves were performed to identify cut-off values for MR progression. The optimal cut-off values were defined using the maximum of Youden's index (sensitivity + specificity − 1). Cox proportional hazards regression analysis was used to relate the association between MR progression and echocardiographic factors. Values of $p < 0.05$ were considered to indicate statistical significance. All statistical analyses were performed using the SPSS system (IBM, Chicago, IL).

Results

A total of 82 asymptomatic MVP patients (mean age: 65 ± 12 years, 51% men) with either mild MR (n = 36, 44%) or moderate MR (n = 46, 56%) fulfilled criteria for enrollment in the study (Tables 1 and 2). Valves for mean valve thickness, mitral annulus diameter, max LA volume index (max LAVI), min LA volume index (min LAVI), left ventricular end-diastolic volume index (LVEDVI) and left ventricular end-systolic volume index are shown in Table 2. During follow-up, 2 patients (2.4%) died for noncardiac reasons, 1 each from the mild and moderate MR groups. Eleven patients (13.4%) developed heart failure (3 mild MR, 8 moderate MR, p = 0.19). Event rates of death and heart failure were not significantly different between the mild MR and moderate MR groups (death: mild MR vs moderate MR, p = 0.71, heart failure: mild MR vs moderate MR, p = 0.35). The rate of mitral valve surgery in patients with moderate MR was greater than those of mild MR (p = 0.02).

Of 82 patients, 30 patients (83%) with mild MR and 23 patients (50%) with moderate MR did not show progression in severity. However, 6 of 36 patients (17%) with mild MR progressed to moderate MR, and 23 of 46 patients (50%) with moderate MR progressed to severe MR during the follow-up period. Among the patients with progression to

Table 1
Patient characteristics (n = 82)

Parameters	Values
Age (years)	65 ± 12
Men	42 (51%)
Body surface area (m^2)	1.8 ± 0.2
Diabetes mellitus	4 (5%)
Stroke	3 (4%)
Hypertension	34 (42%)
Dyslipidemia*	23 (28%)
Atrial fibrillation	17 (21%)
Medications	
Beta blockers	29 (35%)
Calcium channel blockers	14 (17%)
Angiotensin-converting-enzyme inhibitors or angiotensin II receptor blocker	29 (35%)
Digoxin	1 (1%)
Diuretics	14 (17%)
Anticoagulants	19 (23%)
Acetylsalicylic acid	29 (35%)
Statin	26 (32%)

n = number.
Values are number (%), mean ± 1SD.
* Dyslipidemia: an abnormal of lipid metabolisms.

Table 2
Echocardiographic parameters in patients with mild and moderate mitral regurgitation

Parameters	Values
Mild mitral regurgitation	36 (43.9%)
Moderate mitral regurgitation	46 (56.1%)
Mitral valve thickness* (mm)	2.7 (2.3−3.2)
Mitral E wave* (cm/s)	84.0 (67.9−106.5)
EA ratio*	1.3 (0.9−1.6)
Mitral deceleration time* (msec)	223.0 (192.5−252.5)
Mean E/e' ratio*	11.0 (8.8−13.2)
Tricuspid regurgitation peak gradient (mm Hg)	18.4 ± 9.3
Mean mitral annulus (mm)	39.3 ± 5.6
Max left atrial volume index* (ml/m^2)	35.2 (25.6−52.3)
Min left atrial volume index* (ml/m^2)	20.0 (13.6−32.6)
Left atrial ejection fraction (%)	40.1 ± 13.0
Left ventricular end diastolic volume index* (ml/m^2)	55.6 (44.2−67.2)
Left ventricular end systolic volume index* (ml/m^2)	19.9 (15.9−26.3)
Left ventricular ejection fraction (%)	61.9 ± 7.7

Values are number (%), mean ± 1SD.
* Median (interquartile range).

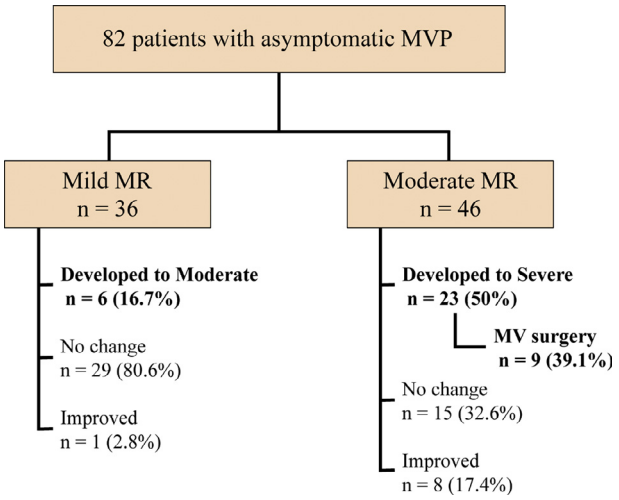

Figure 1. The change of MR degree after follow-up.

severe MR, 9 patients (39%) underwent mitral valve surgery (Figure 1). We performed ROC analysis to determine the cut-off value for predicting the development of severe MR in moderate MR patients. Mitral E wave velocity, mean mitral annulus diameter, and LVEDVI yielded an area under the curve value of at least 0.7 ($p < 0.01$ for all). Cut-off values of mitral E wave (84.8 cm/s), and the mean mitral annulus diameter (39.6 mm) were highly sensitive in predicting the development of severe MR (Figure 2). In the Cox proportional hazard regression analysis adjusted for age and gender, only mean mitral valve annulus diameter significantly predicted MR progression to severe (hazards ratio 1.14, 95% confidence interval 1.03 to 1.26, $p = 0.01$, Table 3). All patients who progressed from moderate to severe MR had a mean mitral annulus of >39.6 mm.

Assuming an alpha error of 0.05 and a power of 0.8, a minimum sample size of 30 would be required. The statistical power is 0.99 when we compared the mitral annulus dimension between group 1 (no progression to severe MR) and group 2 (progression to severe MR).

Table 3
Predictive factor associated with MR progression to severe by Cox proportional hazards regression analysis adjusted by the age and gender

Parameters	Hazard ratio	95% Confidence interval	p Value
Mitral E wave*	2.67	0.62−11.61	0.19
Mean mitral annulus	1.14	1.03−1.26	0.01

* Log-transformed value was used.

Discussion

Severe MR is an important criterion for intervention in MVP patients and may be sufficient to justify intervention under certain circumstances. We conducted a retrospective study of the predictive factors for the progression of mild-moderate to severe MR in asymptomatic patients with MVP. The most significant findings were that 50% of moderate MR patients progressed to severe MR over a nearly 5-year follow-up period, and that mean mitral annulus diameter was a powerful predictor of progression of moderate to severe MR. A cutoff of 39.6 mm for mitral annulus had high diagnostic accuracy in predicting which patients would develop severe mitral regurgitation. Conversely, only 17% of mild MR patients progressed to moderate, and none to severe. These data identified those MVP patients with MR who are most likely to develop severe regurgitation and need close follow-up.

The mitral annulus is the base for leaflet coaptation, unloads mitral valve closing forces, and promotes LA/LV filling and emptying.[6,7] Annular contraction anticipates increasing LV systolic pressure, draws the mitral leaflets together, and forms an overlapping seal.[7,8] Its role in the pathogenesis of MR in MVP is not unexpected. Ormiston et al found that asymptomatic MVP patients with mild MR had either normal or dilated annular diameters, whereas all patients with moderate MR had dilated annulus.[9] Other studies found that mitral annulus remodeling predicted MR severity due to a variety of causes[10] and was associated with LV dilatation and reduced function.[11] Since some

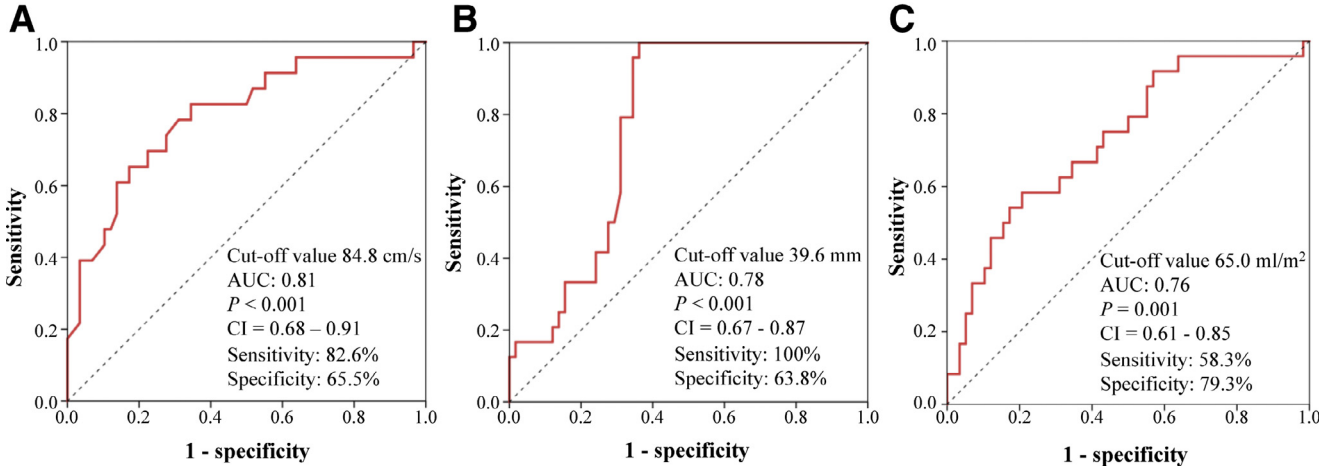

Figure 2. ROC analysis for MR progression to severe. (*A*) Mitral E wave, (*B*) mean mitral annulus, (*C*) LVEDVI. AUC = area under the curve; LVEDVI = left ventricular end diastolic volume index; ROC = receiver operating characteristic.

patients with moderate MR may develop left ventricular dysfunction despite optimal medical management, utilizing mitral annulus diameter measurements may guide physicians to advocate for earlier intervention to improve outcomes.[12]

Previous reports in the literature have described an association of mitral valve thickness with higher risk of regurgitation and subsequent cardiovascular complications.[13–15] Conversely, Sénéchal et al also found that mitral valve thickening was not associated with significant MR among MVP patients.[16] These latter findings are more consistent with the results of our study, which did not find a significant association between mitral leaflet thickness and progression of MR severity. Likewise, certain demographic and clinical variables have been demonstrated in previous literature to confer elevated risk for MR progression in MVP patients.[17] We did not find any significant association of progression in MR severity with clinical variables, including age, weight, BMI, or gender.

MVP patients can manifest complications, including atrial fibrillation and congestive heart failure. Kim et al indicated that the development of these complications was associated with the degree of MR, as well as the magnitude of enlarged LA and LV end-diastolic dimension.[18] The ability to predict the appearance of these abnormalities plays an important role in the management of asymptomatic MVP patients. No echo factors predicting the progression to severe MR due to MVP have been reported, especially for patients with mild/moderate MR, normal LV volume and EF, and normal pulmonary pressure. Our data provide direction in how to evaluate MVP patients for the potential for MR progression and risk of complications.

Current AHA/ACC guidelines recommend serial transthoracic echocardiography every 3 to 5 years for asymptomatic patients with mild MR, every 1 to 2 years with moderate MR, and every 6 to 12 months with severe MR.[2] Incorporating the mitral annulus diameter as a marker for risk stratification may aid in earlier identification and closer monitoring of patients at risk for deterioration and need for mitral valve surgery. Moreover, our data provide strong support for the lack of necessity for frequent echo recordings in patients with mild MR.

There are a number of limitations to this study. First of all, we studied a specific population from a single center, which limits multiple regression analysis with adjustment for all potential confounding variables. We did not control the interval of which echoes were repeated and patients with moderate MR that did not progress may not have been referred for a second exam. Our aim was to study patients with a definite diagnosis of MVP who were free of symptoms, LV dysfunction, and significant co-morbidities. Second, it is unclear if the potential predictive value for severe MR found for the mitral annulus diameter translates into a significant difference in clinical outcomes. We also did not consider physical examination findings such as auscultation. Further, quantitation of MR by echo is often challenging for MVP patients with an eccentric regurgitant jet.

Since severe MR is an important criterion for intervention, we analyzed the risk of progression to severe MR for asymptomatic patients with mild or moderate MR. We found that mild MR never progressed to severe MR over 4.5 years, but that progression was found in half of the moderate MR patients. Of a large number of clinical and echocardiographic factors examined, only mean mitral annular diameter was predictive of progression to severe MR in these MVP patients. A mitral annulus diameter of >39.6 mm had good sensitivity and specificity in the prediction of progression to severe MR. These findings should be of value in the management of asymptomatic MVP patients.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.01.026.

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