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CMR Predictors of Mitral Regurgitation in Mitral Valve Prolapse

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OBJECTIVES We sought to assess the correlation between mitral valve characteristics and severity of mitral regurgitation (MR) in subjects with mitral valve prolapse (MVP) undergoing cardiac magnetic resonance (CMR) imaging.

BACKGROUND Compared with extensive echocardiographic studies, CMR predictors of MVP-related MR are unknown. The severity of MR at the time of diagnosis has prognostic implication for patients; therefore, the identification of determinants of MR and its progression may be important for risk stratification, follow-up recommendations, and surgical decision making.

METHODS Seventy-one MVP patients (age 54 ± 11 years, 58% males, left ventricular [LV] ejection fraction 65 ± 5%) underwent cine CMR to assess annular dimensions, maximum systolic anterior and posterior leaflet displacement, papillary muscle (PM) distance to coaptation point and prolapsed leaflets, as well as diastolic anterior and posterior leaflet thickness and length, and LV volumes and mass. Velocity-encoded CMR was used to obtain aortic outflow and to quantify MR volume.

RESULTS Using multiple linear regression analysis including all variables, LV mass ($p < 0.001$), anterior leaflet length ($p = 0.006$), and posterior displacement ($p = 0.01$) were the best determinants of MR volume with a model-adjusted $R^2 = 0.6$. When the analysis was restricted to valvular characteristics, MR volume correlated with anterior mitral leaflet length ($p < 0.001$), posterior mitral leaflet displacement ($p = 0.003$), posterior leaflet thickness ($p = 0.008$), and the presence of flail ($p = 0.005$) with a model-adjusted $R^2 = 0.5$. We also demonstrated acceptable intraobserver and interobserver variability in these measurements.

CONCLUSIONS Anterior leaflet length, posterior leaflet displacement, posterior leaflet thickness, and the presence of flail are the best CMR valvular determinants of MVP-related MR. The acceptable intraobserver and interobserver variability of our measurements confirms the role of CMR as an imaging modality for assessment of MVP patients with significant MR. (J Am Coll Cardiol Img 2010;3:1037–45)

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Mitral valve prolapse (MVP) is a common disorder afflicting 2% to 3% of the general population (1). Typical myxomatous changes in the mitral leaflet tissue cause superior displacement of the leaflets into the left atrium (1,2). MVP can be associated with significant mitral regurgitation (MR), arrhythmias, bacterial endocarditis, thrombotic events, congestive heart failure, and even sudden cardiac death (3–5).

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Controversy exists regarding the prognosis of MVP (1,6–8). These discrepancies may be due to selection bias in the referral of either tertiary care, symptomatic patients or, conversely, healthier asymptomatic volunteers (8). Changes in diagnostic criteria may have further exacerbated these controversies (9). More recently, a community-based study carried out in a primary care hospital has underscored the heterogeneity of MVP, and its wide prognostic spectrum (3). The common denominator of these and other prognostic studies is the role of MR at diagnosis in determining the risk for cardiovascular morbidity and mortality (6–8,10–13).

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

LV = left ventricle/ventricular

MR = mitral regurgitation

MVP = mitral valve prolapse

PM = papillary muscle

Given the prognostic implications of MR, identification of determinants of progression is important for risk stratification, follow-up recommendations and surgical decision making. Echocardiographic studies have analyzed determinants of MVP-related MR and its progression (12–14). Among these determinants, leaflet thickness, progression of the valvular lesion, particularly a new flail leaflet, and an increase in the mitral annular diameter were the most important predictors of MR (12).

Cardiac magnetic resonance (CMR) is an important noninvasive imaging modality that readily identifies MVP (15). In addition, CMR can quantify MR using phase-contrast velocity mapping (16,17). Because CMR can reliably provide quantitative determination of ventricular volumes and function (18,19), it is becoming an important clinical tool for follow-up of patients with MVP and moderate-to-severe MR in anticipation of future mitral valve repair (20).

Compared with echocardiography, CMR predictors of MVP-related MR are yet to be defined. We sought to investigate the correlation between mitral valve characteristics and MR in the MVP population, so as to further define the potential role of CMR in this common disease.

METHODS

Patient selection. Seventy-five subjects with echocardiographically identified MVP without greater than mild aortic regurgitation were prospectively enrolled based on an institutional review board–approved protocol. Similar to echocardiography (9,21), CMR evidence of MVP was defined as >2-mm displacement of the mitral leaflets into the left atrium as viewed in the left ventricular (LV) outflow tract orientation (15). Of the 75 subjects, 4 (5%) were excluded due to suboptimal CMR image quality, resulting in a final cohort of 71 participants (age 55 ± 11 years, 58% males). All subjects were in normal sinus rhythm without any history of coronary artery disease or intrinsic cardiomyopathies.

CMR. CMR imaging was performed using a Philips Achieva 1.5-T whole-body CMR scanner (Philips Medical Systems, Best, the Netherlands) equipped with a 5-element cardiac coil. Breath-hold, retrospectively electrocardiogram-gated cine, steady-state free-precession images were acquired in the 2- and 4-chamber long-axis views, and a short-axis stack covering the entire LV (8-mm slices with 2-mm gaps). The LV outflow track long-axis stack images (Fig. 1) were obtained by prescribing an image plane perpendicular to the mitral annular major axis centered at the aortic outflow track (15). Six to eight 7-mm slices with no gap were obtained to cover the entire mitral valve. Sequence parameters were repetition time 3 ms, echo time 1.5 ms, flip angle 60°, field-of-view 320 × 320 mm^2, matrix 160 × 160. Temporal resolution was 30 to 35 ms. A free-breathing, electrocardiogram-triggered, phase-contrast velocity-encoded CMR sequence of the aortic outflow was acquired in the axial plane at the level of the bifurcation of the pulmonary artery, as previously described (17).

Image analysis. The CMR images were analyzed using ViewForum (Release 4) software (Philips Medical Systems) as previously described (15). Briefly, in the LV outflow track view (Fig. 1A), anterior and posterior leaflet displacement were measured as the maximum excursion of the leaflets during systole (each phase repeatedly examined to find the maximum excursion) beyond the mitral annular diameter as defined by a line connecting the inferolateral mitral annulus to the aortomitral junction (Fig. 1A). Additional measurements on the same image included the distance between the

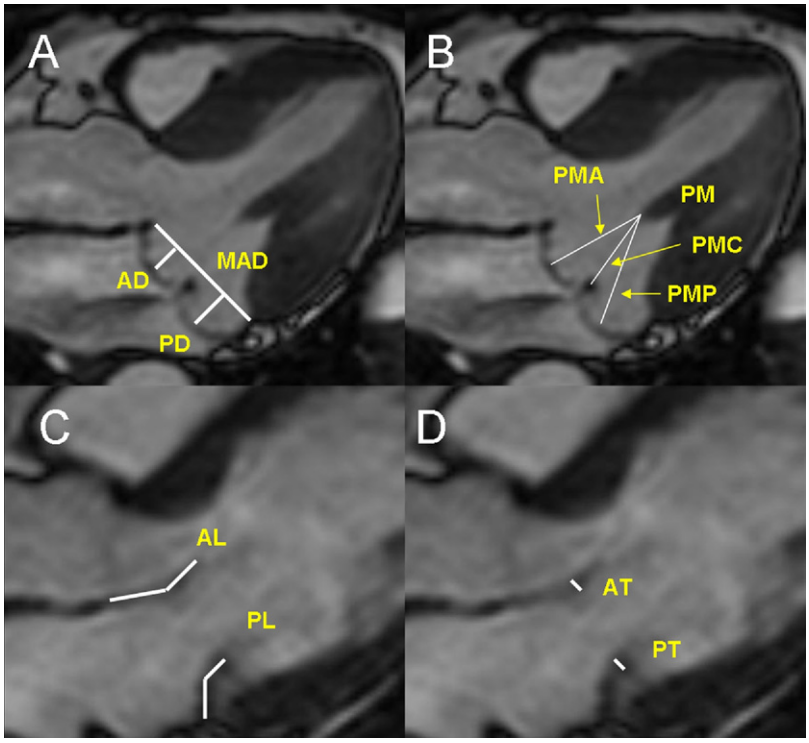

Figure 1. Cine CMR LV Outflow View

(Top panels) Systolic measurements of **(A)** anterior leaflet displacement (AD), posterior leaflet displacement (PD), and mitral annular diameter (MAD); and **(B)** papillary muscle (PM) distance to anterior leaflet (PMA), to posterior leaflet (PMP), and to coaptation point (PMC). (**Bottom panels** [zoomed in]): diastolic measurements of **(C)** anterior leaflet length (AL), posterior leaflet length (PL), and **(D)** anterior leaflet thickness (AT), posterior leaflet thickness (PT).

papillary muscle (PM) and the mitral leaflet coaptation point and the anterior and posterior prolapsed leaflets, respectively (Fig. 1B). In the same view, we measured anterior and posterior leaflet thickness and length in diastole (Figs. 1C and 1D) (each phase repeatedly examined for the most in-plane view). The annulus was measured at end-systole in the 2- and 4-chamber views. LV dimensions were measured in the short-axis view at the level of the chordae. LV volumes were measured by tracing the end-diastolic and -systolic LV endocardial contours in each slice and applying a summation of discs method. The LV ejection fraction was calculated as: (LV end-diastolic volume − LV end-systolic volume)/LV end-diastolic volume. LV mass was measured by tracing endocardial and epicardial contours including the PMs in the ventricular volumes. The MR volume was calculated as the difference between LV stroke volume and the forward aortic flow volume. The MR fraction was obtained by dividing MR volume by the LV stroke volume. MR categories were graded as: 0 (none to trace) (0% to 5%); 1+ (mild) (5% to 16%); 2+ (moderate) (6% to 25%); 3+ (moderate to severe) (26% to 48%); and 4+ (severe) (>48%) (17).

Statistical methods. Subject characteristics are presented as means with standard deviations for continuous traits and as frequency and percentage for categorical traits. The relationship between subject characteristics (age, gender, body surface area, LV mass, number of prolapsed leaflets, presence of flail leaflet) and mitral valve measurements (annular dimensions, leaflet displacement, thickness, and length, and PM distance to coaptation point and prolapsed leaflets) with the outcome (MR volume) was assessed using univariate linear regression with a significance level of 0.05.

Because MR volume calculations are derived from LV volumes, the LV volumes were not included in the models to investigate MR determinants. A multiple linear regression model was first performed with stepwise regression (forward and backward selection) and included all the aforementioned univariate variables, and interaction terms for variables with high correlation (correla-

Table 1. Patient Characteristics

	MVP (n = 71)
Age, yrs	55 ± 11
Male	41 (58%)
BSA, m^2	1.8 ± 0.2
LVEF, %	65 ± 5
MR	
0	2 (3%)
1+	5 (7%)
2+	13 (18%)
3+	39 (55%)
4+	12 (17%)
Presence of flail leaflet	15 (21%)
Number of prolapsed leaflets	
Bileaflet	37 (52%)
Posterior	34 (48%)
Anterior	0 (0%)

Values are mean ± SD or n (%).
BSA = body surface area; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; MVP = mitral valve prolapse.

tion coefficient >0.7). The resulting model included variables appearing in both forward and backward selection, as these variables had the most significant effects on MR volume. Recognizing the number of variables was large with respect to the sample size (overfitting), we further performed multiple linear regression, focusing only on valvular characteristics (the presence of flail, anterior and posterior length, thickness, and displacement). Residual plots were examined for a relationship between residual and predicted values. Shapiro-Wilk test was employed to test the normality of residuals for the overall and the valvular model. Receiver operating curve analysis was performed to determine the best cutoff for severe (3+ and 4+) MR for valvular determinants when appropriate.

Two independent observers performed measurements of annular dimension, leaflet displacement, PM distance to coaptation point and prolapsed leaflets in systole, and leaflet length and thickness in diastole in 30 randomly selected subjects separated by at least 5 days to assess intraobserver and interobserver variability. Intraobserver variability was calculated as the average of the percentage difference between the same observer's 2 measurements divided by the mean of the 2 measurements per subject. Interobserver variability was calculated by the average of percentage difference of the 2 observers' measurements over their mean measurements per subject. Bland-Altman graphs were plotted for the significant determinants for MR.

All statistical analyses were performed with STATA version 10 (StataCorp, College Station, Texas) and SAS version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Subject characteristics and CMR findings. The clinical characteristics and CMR parameters of the study subjects are summarized in Tables 1 and 2. The subjects were mostly middle aged with average body surface area and preserved LV ejection fraction. Fifty-one (72%) subjects had greater or equal to 3+ (moderate to severe) MR. Fifteen subjects (21%) had a flail leaflet on echocardiography, of which 12 (80%) were initially identified on CMR by 1 observer blinded to echocardiography results. The presence of flail in the remaining 3 patients was identified by consensus review of 2 observers.

Determinants of MR. By univariate regression analysis, MR volume correlated with annular dimen-

Table 2. CMR Parameters

	MVP (n = 71)
LVEDD, mm	59 ± 6
LVEDDI, mm/m^2	32 ± 4
LVESD, mm	37 ± 5
LVEDV, ml	193 ± 48
LVEDVI, ml/m^2	104 ± 21
LVESV, ml	68 ± 19
LV mass, g	118 ± 37
LVMI, g	63 ± 17
MAD, mm	
2-chamber	45 ± 6
3-chamber	40 ± 6
4-chamber	44 ± 6
AD, mm	2.8 ± 2.9
AL, mm	26 ± 5
AT, mm	2.7 ± 0.6
PD, mm	6.9 ± 3
PL, mm	17 ± 4
PT, mm	2.8 ± 0.5
PMC, mm	28 ± 7
PMA, mm	33 ± 7
PMP, mm	35 ± 8

Values are mean ± SD.
AD = anterior leaflet displacement; AL = anterior leaflet length; AT = anterior leaflet thickness; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEDDI = left ventricular end-diastolic diameter indexed to body surface area; LVEDV = left ventricular end-diastolic volume; LVEDVI = left ventricular end-diastolic volume indexed to body surface area; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; LVMI = left ventricular mass indexed to body surface area; MAD = mitral annular diameter; MVP = mitral valve prolapse; PD = posterior leaflet displacement; PL = posterior leaflet length; PMA = papillary muscle distance to anterior leaflet; PMC = papillary muscle distance to coaptation point; PMP = papillary muscle distance to posterior leaflet; PT = posterior leaflet thickness.

sions, posterior leaflet displacement, PM distance to coaptation point and prolapsed leaflets, the presence of flail, anterior and posterior leaflet thickness, LV diameters, LV mass, male sex, and body surface area (Table 3). The anterior leaflet displacement variable was positively skewed due to the "0" values assigned to the patients with posterior-only prolapse. In bileaflet subjects, anterior leaflet displacement was significantly correlated with MR volume ($p = 0.017$).

In the overall stepwise regression model, posterior leaflet displacement, anterior leaflet length, and LV mass remained significant in both forward and backward selections ($p = 0.01$, $p = 0.006$, and <0.001, respectively, model-adjusted $R^2 = 0.6$). When we performed stepwise regression on valvular characteristics only, forward and backward selections yielded the same significant predictors: anterior leaflet length, posterior displacement, posterior thickness, and the presence of flail ($p < 0.001$, $p = 0.003$, $p = 0.008$, and $p = 0.005$, respectively, with model-adjusted $R^2 = 0.5$) (Table 3). Residual plots showed a linear relationship between residual and predicted values. Shapiro-Wilk test showed normality of residuals for the overall model with a p value of 0.3857 and the valvular model with a p value of 0.4325.

Tertiles of anterior leaflet length in relationship to MR (Fig. 2) showed proportional increase with the amount of MR. Receiver operating curve analysis was performed on posterior leaflet thickness and displacement to determine the best cutoff for severe (3+ and 4+) MR. A thickness of 2.5 mm and a displacement of 6 mm had the most area under the curve (0.76 and 0.80, respectively). Significant differences in MR are shown using these cutoffs in Figure 2.

Reproducibility of measurements. The mean percentage intraobserver and interobserver variabilities are shown in Table 4 for each valvular parameter. Low intraobserver variability (≤10%) can be achieved with all parameters. Bland-Altman intraobserver and interobserver variability plots are shown in Figure 3 for posterior leaflet displacement, anterior leaflet length, and posterior leaflet thickness. The average intraobserver and interobserver biases are small. The variabilities are consistent across average values of the parameters.

Table 3. Correlation of Patient Characteristics and CMR Parameters With MR Volume

	Univariate Regression (p Value)	Overall Stepwise Regression (p Value)	Valvular Stepwise Regression (p Value)
Male sex	0.001		—
Body surface area	0.004		—
Age	0.90		—
LV mass	<0.001	<0.001	—
MAD			—
2-chamber	<0.001		—
3-chamber	<0.001		—
4-chamber	0.002		—
Flail	0.002		0.005
AD	0.30		
AL	<0.001	0.006	<0.001
AT	0.02		
PD	<0.001	0.01	0.003
PL	<0.001		
PT	<0.001		0.008
PMC	<0.001		—
PMA	<0.001		—
PMP	<0.001		—

CMR = cardiac magnetic resonance; MR = mitral regurgitation; other abbreviations as in Table 2.

DISCUSSION

In this CMR study of 71 subjects with MVP and MR, we found that anterior leaflet length, posterior leaflet displacement, posterior leaflet thickness, and the presence of flail are the best CMR valve determinants of MVP-related MR.

Surgical intervention for chronic mitral regurgitation in asymptomatic individuals is recommended on the basis of regurgitation severity and hemodynamic consequences on the LV (22). Echocardiography is commonly used to closely follow patients with chronic MR. Regurgitation volume and fraction can be determined both quantitatively and semiquantitatively (23). However, limitations exist with echocardiography due to poor image quality, significant variability in flow diameter measurements, and geometric assumptions of flow orifice (23).

CMR imaging is a flexible, noninvasive modality that provides the gold-standard measurement of LV volumes and function. In addition, phase-contrast CMR can easily quantify aortic and pulmonic flow velocities and volumes. These data can be combined with LV or right ventricular volumetric data to determine atrioventricular regurgitant volume and fraction (16,17,20). When properly acquired with correction of background eddy currents and concomitant gradients, phase-contrast velocity mapping can provide the most accurate indirect measurement of MR (24,25). Recently, CMR criteria for MVP diagnosis have been established based on a comparison with echocardiography (15). With properly prescribed imaging planes, cine CMR is able to visualize all parts of the mitral valve apparatus throughout the entire cardiac cycle

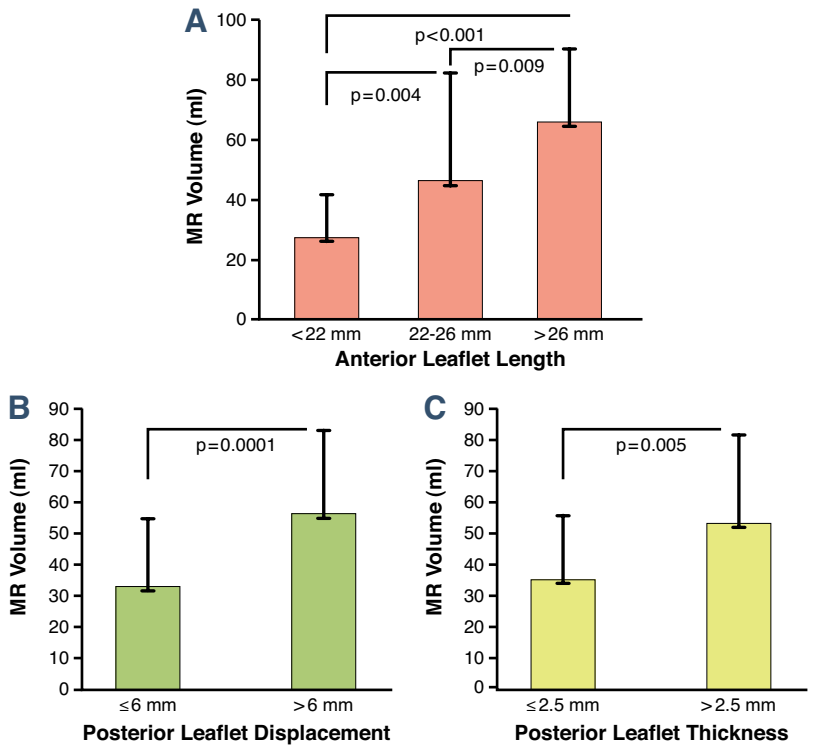

Figure 2. Relationship of MR With Mitral Valve Parameters

The **bar graphs** show mitral regurgitation (MR) volume according to **(A)** tertiles of anterior leaflet length, **(B)** posterior leaflet displacement using 6 mm as the cutoff, **(C)** posterior leaflet thickness using 2.5 mm as the cutoff. Student *t* test was used to assess significant differences between groups, and $p < 0.05$ was considered significant.

(15). In an era when interventions for mitral valve disease improve and are recommended earlier in the disease course (22), it becomes particularly important to assess MVP patients with a precise and accurate modality such as CMR.

Diffuse leaflet thickening, elongation, and redundancy are the classic echocardiographic features of myxomatous leaflets associated with significant MR requiring valvular surgery, ventricular arrhythmia, and sudden death (26–29). Compared with echocardiography, CMR predictors of MVP-related MR have not been reported. A prior echocardiographic study has shown that MVP patients have increased anterior and posterior leaflet lengths compared with controls, and both leaflet lengths were increased in MVP patients with MR, as compared with patients with no MR (30). We have found that MR correlates best with anterior leaflet length, not posterior length. This discrepancy may be explained by a different study population as the majority of our subjects had MR (97%) versus a minority of their patients (16%). Leaflet involvement may also be a factor as information regarding the percentages of bileaflet, anterior, or posterior MVP patients were not available in their study (30).

When considering only the bileaflet subjects, anterior leaflet displacement was a significant determinant of MR in univariate analysis. Among our study subjects, there were no cases of anterior leaflet–only prolapse. When all patients were considered, the involvement of the anterior leaflet did

Table 4. Intraobserver and Interobserver Variability

CMR Parameters	% Variability (Intraobserver 1)	% Variability (Intraobserver 2)	% Variability (Interobserver)
MAD (3-chamber)	3 ± 4	5 ± 5	6 ± 4
AD	8 ± 14	8 ± 10	15 ± 17
AL	8 ± 9	12 ± 10	13 ± 9
AT	10 ± 11	17 ± 13	12 ± 11
PD	8 ± 11	16 ± 15	24 ± 15
PL	7 ± 8	14 ± 12	24 ± 15
PT	9 ± 10	22 ± 14	14 ± 13
PMC	6 ± 6	13 ± 12	17 ± 15
PMA	7 ± 8	6 ± 7	13 ± 13
PMP	5 ± 5	11 ± 9	12 ± 11

Values are mean ± SD.
Abbreviations as in Table 2.

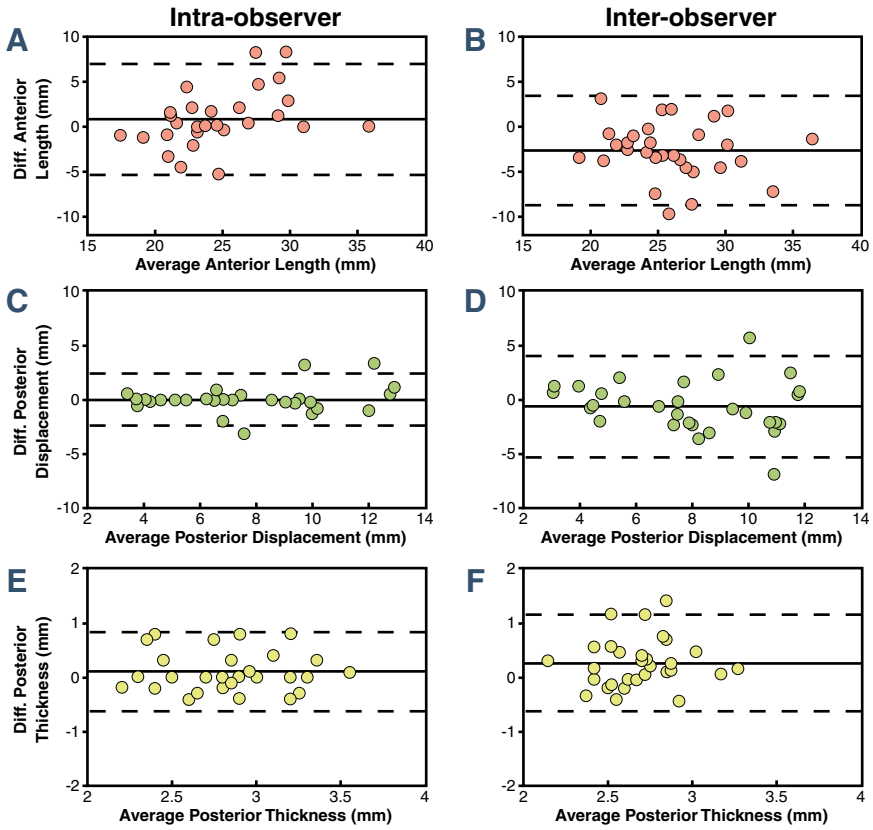

Figure 3. Bland-Altman Graphs of Intraobserver and Interobserver Variability Assessment of CMR Valvular Determinants of MR

(A and B) anterior leaflet length, **(C and D)** posterior displacement, and **(E and F)** posterior thickness. **Solid line** denotes the mean and **dotted lines** denote mean ± 2 SD. Diff. = difference; MR = mitral regurgitation.

not impact severity of MR, which is likely because the coaptation tends to be symmetric in bileaflet prolapse, as opposed to isolated posterior or anterior prolapse. The importance of posterior leaflet displacement in our analysis of determinants of MR supports the recognized role of leaflet coaptation asymmetry in the mechanism of MR (30–32).

Leaflet thickness, an echocardiographic valvular parameter associated with MR and MR-related prognosis in MVP patients (8,26), was relevant in the univariate, but not in the overall stepwise regression model. However, when the analysis was restricted to valvular characteristics only, posterior leaflet thickness was a determinant in the regression model. When compared with normal, healthy control subjects, anterior leaflet thickness in MVP patients was not significantly different, whereas posterior leaflet thickness was greater (15). On pathological findings in formalin-fixed tissue, mean normal mitral leaflet thickness was 1 mm and mean MVP leaflet thickness was 2 mm (33). Partial volume averaging affects thickness measurements because routine CMR steady-state free-precession imaging has an in-plane spatial resolution of 2 mm. CMR anterior and posterior leaflet thicknesses were previously found to be on average 3.2 mm in 25 patients (15) and 2.8 mm on the current study in 71 patients. Subtle changes in leaflet thickness with increased MR may have been undetectable due to partial volume averaging. The presence of flail was correlated with increased regurgitant volume in univariate analysis and in the valvular regression analysis, consistent with previous reports (12,34) of flail as a mechanism for severe MR. Annular dimension was significant in univariate regression and in 1 of the stepwise regression model analyses, but was not retained in the final overall model. LV mass was not evaluated in prior echocardiography studies, but had significant contribution in our overall model as a very strong predictor of MR ($p < 0.001$ and $R^2 = 0.5$), reflecting the effects of chronic regurgitation on development of compensatory hypertrophy.

It has been postulated that superior systolic displacement of the mitral valve may exert abnormal

tension on the PM tips, causing their superior traction, and that such traction may have adverse pathophysiologic effects (35). The distance between the PM tip and the mitral valve has been previously quantified in MVP patients in an echocardiographic study (36), but correlation with MR was not studied. In our study, we looked at the distance between the PM, the point of maximum leaflet displacement, and the mitral valve coaptation point in relation to MR. The distance between the PM and the mitral valve coaptation point was included in the analysis as it expresses the contribution of 1 leaflet length relative to the other. The PM distance to valve leaflets and coaptation point were significant MR determinants in the univariate but not the stepwise overall model.

Despite its many advantages over echocardiography, CMR is not as widely used, and clinical experience is relatively limited in assessing valvular heart disease with, in particular, a lack of correlation of CMR valvular parameters with clinical outcomes. Therefore, finding valvular determinants of MVP-related MR is crucial for development of prospective studies to define disease progression and the optimal timing of surgical intervention. Our study showed acceptable intraobserver and interobserver variability with low percentage variability achievable in a trained observer, further confirming the ideal role of CMR as an imaging modality for the assessment of MVP patients with significant MR. To our knowledge, this is the first study to fully investigate the reproducibility of CMR measurements for myxomatous valve disease.

Study limitations. Several limitations exist in our study. This is a cross-sectional study without longitudinal follow-up. To fully understand the prognostic role of CMR in patients with MVP, follow-up studies in valvular determinants for the progression of MR would be of particular interest. Our sample size is small when all the variables of the mitral apparatus are considered. To overcome the overfitting issue when performing regression analysis for significant predictors, we limited the valvular regression model input variables to valvular characteristics only and determined the final 4 predictors. Reassuringly, the strongest valvular predictors—anterior leaflet length and posterior leaflet displacement—were present in both the overall model and the valvular regression model. Our study has laid the foundation for conducting a longitudinal study by assessing comprehensive CMR parameters of valvular and ventricular characteristics of MVP patients. An additional limitation is the lack of anterior leaflet–only prolapse patients, which could be the result of excluding patients with more than mild aortic regurgitation in our study design.

CONCLUSIONS

In summary, anterior leaflet length, posterior leaflet displacement, posterior leaflet thickness, and the presence of flail leaflet are the best CMR valvular determinants of MVP-related MR. Our findings are reproducible and represent an important step towards the development of prospective CMR studies to define MR progression.

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