Mitral Annular Disjunction of Degenerative Mitral Regurgitation: Three-Dimensional Evaluation and Implications for Mitral Repair

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Background: The dynamic consequences of mitral annular disjunction (MAD) on the mitral apparatus and the left ventricle remain unclear and are crucial in the context of mitral surgery. Thus, the aim of this study was to assess mitral valvular, annular, and ventricular dynamics in mitral valve prolapse (MVP) stratified by presence of MAD.

Methods: In 61 patients (mean age, 62 ± 11 years; 25% women) with MVP and severe mitral regurgitation undergoing mitral surgery between 2009 and 2016, valvular and annular dimensions and dynamics by two-dimensional transthoracic and three-dimensional transesophageal echocardiography and left ventricular dimensions and dynamics were analyzed stratified by presence of MAD before and after surgery.

Results: MAD (mean, 8 ± 3 mm) was diagnosed in 27 patients (44%; with a mean effective regurgitant orifice area of 0.55 ± 0.20 cm^2 and similar to patients without MAD), more frequently in bileaflet prolapse (52% vs 18% in patients without MAD, $P = .004$), consistently involving P2 ($P = .005$). Patients with MAD displayed larger diastolic annular areas (mean, 1,646 ± 410 vs 1,380 ± 348 mm^2), circumferences (mean, 150 ± 19 vs 137 ± 16 mm), and intercommissural diameters (mean, 48 ± 7 vs 43 ± 6 mm) compared with those without MAD ($P \leq .008$ for all). Dynamically, mid- and late systolic excess intercommissural diameter, annular area, and circumference enlargement were associated with MAD ($P \leq .01$ for all). MAD was also associated with dynamically annular slippage, larger prolapse volume and height ($P \leq .007$), and larger leaflet area (mean, 2,053 ± 620 vs 1,692 ± 488 mm^2, $P = .01$). Although patients with MAD compared with those without MAD showed similar ejection fractions (mean, 65 ± 5% vs 62 ± 8%, respectively, $P = .10$), systolic basal posterior thickness was increased in patients with MAD (mean, 19 ± 2 vs 15 ± 2 mm, $P < .001$), with higher systolic thickening of the basal posterior wall (mean, 74 ± 27% vs 50 ± 28%) and higher ratio of basal wall thickness to diameter ($P \leq .01$ for both). However, after mitral repair, MAD disappeared, and LV diameter, wall thickness, and wall thickening showed no difference between patients with MAD and those without MAD ($P \geq .10$ for all).

Conclusions: MAD in patients with MVP involves a predominant phenotype of bileaflet MVP and causes profound annular dynamic alterations with considerable expansion and excess annular enlargement in systole, potentially affecting leaflet coaptation. MAD myocardial and annular slippage simulates vigorous left ventricular function without true benefit after surgical annular suture. Thus, although MAD does not hinder the feasibility and quality of valve repair, it requires careful suture of ring to ventricular myocardium, lest it persist postoperatively. (J Am Soc Echocardiogr 2021;■:■-■.)

Keywords: Mitral annular disjunction, Degenerative mitral valve disease, 3D transesophageal echocardiography, Mitral valve prolapse, Mitral valve repair

Mitral valve prolapse (MVP) is a frequent valvular disease in Western countries[1] and the leading indication for mitral valve (MV) repair.[2] Although morphologic and physiologic understanding of MVP has evolved, particularly thanks to recognition of the mitral annular saddle shape,[3] it has remained rudimentary with regard to the complexity and heterogeneity of various components of MVP.

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Abbreviations

2D = Two-dimensional
3D = Three-dimensional
IVS = Interventricular septal
LV = Left ventricular
MAD = Mitral annular disjunction
MR = Mitral regurgitation
MV = Mitral valve
MVP = Mitral valve prolapse
PW = Posterior wall
TEE = Transesophageal echocardiography

Most focus in MVP disease has been on outcome and its determinants, principally mitral regurgitation (MR) severity and its left ventricular (LV) consequences.[4] However, morphologic and physiologic aspects, such as excess or deficient tissue,[5] or cleftlike indentations,[6] have recently attracted attention through three-dimensional (3D) transesophageal echocardiographic analysis. Indeed, any potential impact on valve repair feasibility and success is critical to clinical outcomes.[7]

In this context, mitral annular disjunction (MAD), defined as a detachment of the annular roots from the ventricular myocardium in systole, has been described as a component of MVP morphologic and functional heterogeneity.[8] However, current literature remains quite confusing, as MAD is alternatively considered as insignificant,[9] as independent of MVP,[10] as a constant by-product of MVP,[11] or as the cause of MVP.[8] Most important, MAD annular[11-13] and LV[14,15] consequences remain uncertain. However, those are crucial to resolve, as they may interfere with mitral repair feasibility and success,[12] which in the hands of expert surgeons restores life expectancy.[16]

Indeed, although the main function of the normal mitral annulus occurs in early systole with anteroposterior contraction and accentuation of its saddle shape,[17] previous studies of MAD focused only on late systolic assessment.[12] Thus, it is uncertain whether the mitral annulus with MAD performs its function appropriately throughout the entire cardiac cycle. Moreover, reported consequences of MAD on LV remodeling have been discordant,[12,14,18] often not accounting for the severity and impact of MR.[15] Thus, MVP remains generally described on the basis of limited characteristics (leaflet prolapse type and MR severity), and the impact of MAD on mitral physiology and function, on LV characteristics, and on the feasibility and success of mitral repair remains unsubstantiated.

To fill these gaps in knowledge, comprehensive morphologic and dynamic characterization using quantitative 3D transesophageal echocardiography (TEE) throughout the cardiac cycle is required. For the first time, we gathered a cohort of patients with MVP undergoing MV repair to evaluate the presence and severity of MAD and its comprehensive morphology (including leaflets, prolapse, and LV remodeling), static and dynamic. We hypothesized that for similar MR severity, presence of MAD affects annular and valvular dynamics and LV geometry but does not hinder the feasibility or success of valve repair.

METHODS

All consecutive patients available to our research team, with isolated MVP and severe regurgitation, referred to our institution for elective surgical MV repair between 2009 and 2016 with (1) comprehensive two-dimensional (2D) transthoracic Doppler echocardiography performed at the Mayo Clinic before surgery, (2) additional 3D intraoperative transesophageal Doppler echocardiography, (3) postoperative comprehensive 2D transthoracic Doppler echocardiography, and (4) available electronic echocardiographic images for detailed morphologic assessment were enrolled. Patients were excluded if they denied research authorization (per Minnesota law) or presented with any of the following: (1) moderate or greater aortic regurgitation or stenosis; (2) moderate or greater mitral stenosis; (3) previous valvular surgery; (4) congenital heart disease (patent foramen ovale not excluded); (5) hypertrophic, infiltrative, restrictive, pericardial, or infectious cardiac disease; and (6) uncontrolled atrial fibrillation. As a low-risk study, the requirement to obtain written informed consent was waived by the Mayo institutional review board, which approved this study.

Echocardiographic Standard Evaluation

Comprehensive transthoracic[19] and transesophageal[20] Doppler echocardiographic examinations were performed by trained sonographers or Mayo consultants, following standard imaging protocol and guidelines.[19,20] Three-dimensional TEE was performed intraoperatively, after initial anesthesia induction and endotracheal intubation, before cardiopulmonary bypass or thoracic incisions, and 3D TEE was performed as recommended.[20,21] Full-volume 3D data set acquisition and measurement details are available in the online supplemental material. Integrative grading of degenerative MR used specific, supportive, and quantitative measures to classify degenerative MR as severe according to American Society of Echocardiography recommendations.[22] A diffuse myxomatous MV was defined by the presence of excess leaflet tissue and leaflet thickening >5 mm, resulting in prolapse >2 mm into the left atrium on the parasternal long-axis view and confirmed by direct surgical valve inspection. Fibroelastic deficiency was defined according to the current description.[5] All standard measurements were performed at diagnosis and downloaded from the digital echocardiographic repository without alteration.

Echocardiographic MAD and LV Examination

Nonstandard measurements of mitral leaflet length and thickness, of leaflet redundancy presence and severity (graded semiquantitatively), of the presence and maximum length of MAD, and of LV measurements were performed by an experienced echocardiographer on digitally stored images without knowledge of preoperative and intraoperative Doppler echocardiographic and surgical finding (preoperative 2D assessment of MAD was performed after intraoperative 3D data set collection). MAD was defined as a separation between the annulus located at the base of MV–left atrial junction and the endocardial LV free wall in the parasternal long-axis view,[8,23] with MAD length measured in the same view from annulus to LV wall bulge in end-systole. LV internal diameters were measured at the LV midlevel, close to the mitral leaflet tips at end-diastole and end-systole. Interventricular septal (IVS) and posterior wall (PW) thicknesses were measured at the basal level and at the middle level of the left ventricle in end-diastole and end-systole.

Statistical Analysis

Results are expressed as mean ± SD or as percentages. Qualitative variable were compared using χ^2 tests and quantitative data using analysis of variance or the Wilcoxon test accordingly. Patients with MAD were compared with those without MAD. Intra- and interobserver variability for 3D measurements was calculated.

HIGHLIGHTS

- 3D TEE provides insights into the impact of MAD on MV, annulus, and LV function.
- MAD compounds annular alteration with excess late systolic annular enlargement.
- No early systolic annular function impairment is observed with MAD.
- Mid- and late systolic consequences of MAD should be accounted for during MV repair.
- MAD LV annular slippage simulates stronger LV-EF without benefit post-surgery.

Variability of measurement was determined by repeating measurements on stored 3D data sets at least 1 week after initial measurement by the same observer (intraobserver) and a different observer (interobserver). Variability of measurements was assessed using the Bland-Altman method and the within-subject coefficient of variation. Using the Bland-Altman method, we calculated 95% CIs of the variability range for absolute dimensions. The within-subject coefficient of variation (calculated as ratio of the SD of the measurement difference to the mean value of all measurements) provides a scale-free and unitless metric of variation expressed as a percentage, which is particularly useful when the association between the variability magnitude and the value of the parameter measured is uncertain at the outset. The effect of group (MAD vs no MAD) was adjusted for effect of cardiac cycle timing, and interactions between group and cardiac cycle timing were assessed. All pairwise multiple-comparison procedures were done using the Holm-Sidak method. P values $< .05$ were considered to indicate statistical significance.

RESULTS

Clinical Characteristics

All consecutive patients diagnosed at the Mayo Clinic (Rochester, MN) between 2009 and 2016 with isolated severe MVP available to our research team for 3D mitral data set collection, with detailed Doppler echocardiographic 2D characterization of the presence and extent of MAD before (2 ± 3 months) and after (16 ± 56 days) surgery were included in the cohort, which encompassed 61 patients (15 women; mean age, 62 ± 11 years). Baseline clinical, echocardiographic, and surgical characteristics are presented in Table 1. Overall, bileaflet MVP was found in 20 patients (33%), P2 scallop prolapse in 50 (with 18 of 20 [90%] of patients with bileaflet MVP presenting with P2 scallop prolapse), flail leaflet in 39 (64%), diffuse myxomatous disease in 21 (37%), and cleftlike indentation in 24 (39%). Clinically, 10% had histories of coronary heart disease, 49% had hypertension, 16% had atrial fibrillation, and 26% were in New York Heart Association functional class III or IV. Morphologically, MR was graded as severe, with effective regurgitant orifice area of 0.53 ± 0.28 cm^2, regurgitant volume of 87 ± 47 mL, and systolic pulmonary artery pressure was 35 ± 11 mm Hg. LV diameter was normal on average (mean LV ejection fraction, 63 ± 7%; mean left atrial volume index, 31 ± 11 mL/m^2). End-systolic MAD diagnosed on the 2D transthoracic echocardiographic parasternal view (Figure 1A) and seen on corresponding 3D transesophageal echocardiographic views (Figure 1B) was present in 27 patients (44%), with a length of 8 ± 3 mm (median, 7 mm), and persisted in diastole in four patients. The posterior detachment of the mitral annulus with MAD in systole characterized the mitral annular "slippage" from its normal anchoring (Figure 1A, Video 1 available at www.onlinejase.com).

Table 1 (middle and right columns) shows patients' clinical echocardiographic and surgical characteristics stratified by the presence of MAD. Older age in patients without MAD was associated a trend toward more frequent comorbidities and atrial fibrillation, without clinical or surgical consequences except for more frequent use of diuretics preoperatively. On echocardiography, P2 scallop prolapse was significantly associated with MAD (96% vs 71%, $P = .005$), because of the high frequency of P2 involvement in MVP, with more frequent bileaflet MVP with MAD (often concomitant but independent; see supplemental material). Although bileaflet MVP was associated with presence of MAD, most patients with nonbileaflet MVP with MAD had isolated P2 scallop prolapse. No differences were noted regarding flail leaflet or cleftlike indentation prevalence between groups. Interestingly, the fibroelastic deficiency phenotype was less frequent with MAD. Also, there was no difference between groups with regard to LV diastolic diameters, LV ejection fraction, and MR severity, so that morphologic and dynamic differences between patients with and those without MAD could not be explained by MR severity. Of note, systolic pulmonary artery pressure was lower in patients with MAD compared with those without MAD, although within the normal range (30 ± 5 vs 38 ± 13 mm Hg, $P = .006$).

Mitral Annular Static and Dynamic Analysis

Static 3D measurements were performed as indicated in Figure 2 and are presented in Table 2 for mitral annular, leaflet area, and prolapse characteristics measured in end-systole. These measures showed multiple differences according to presence of MAD, with larger mitral annulus with MAD, including larger intercommissural and anteroposterior diameters (48 ± 7 vs 43 ± 6 mm and 41 ± 6 vs 38 ± 6 mm, respectively, $P \leq .04$ for both; Figure 3), annular area (1,646 ± 410 vs 1,380 ± 348 mm^2, $P = .008$), and circumference (159 ± 19 vs 137 ± 16 mm, $P = .005$), while annular height and saddle shape were similar between groups (7 ± 2 vs 6 ± 2 mm and 15 ± 4% vs 15 ± 4%, respectively, $P \geq .10$ for both). Tissue redundancy described as leaflet area was larger for the total of both leaflets in the group with MAD compared with group without MAD (2,053 ± 620 vs 1,692 ± 488 mm^2, $P = .01$; Figure 3), because of a larger posterior mitral leaflet (1,086 ± 364 vs 852 ± 327 mm^2, $P = .01$), while the difference in anterior leaflet area did not reach statistical significance (967 ± 334 vs 840 ± 219 mm^2, $P = .08$). MVP was larger with MAD, for height and volume (9 ± 3 vs 6 ± 4 mm and 4 ± 4 vs 2 ± 2 mL, respectively; Figure 3), as well as volume-to-height ratio (0.4 ± 0.3 vs 0.2 ± 0.2; $P \leq .007$ for all). No quantitative link between MAD depth and degree of valvular thickening was observed ($P = .40$). In terms of valvular and annular associations with MAD depth, only intercommissural diameter ($r = 0.59$, $P < .0001$), posterior leaflet area ($r = 0.63$, $P = .0004$), and prolapse volume ($r = 0.62$, $P = .0005$) reached statistical significance.

Dynamic changes in mitral annular dimensions over the cardiac cycle, analyzed for the first time, are displayed in Figure 4. Interestingly, mitral annular dynamic assessment between MAD (*red line*) and no MAD (*blue line*) showed comparable physiologic early systolic annular contraction and accentuation of saddle shape in both groups, with similar changes in mitral annular anteroposterior

Table 1 Clinical, echocardiographic, and surgical characteristics

	MVP (n = 61)	No MAD (n = 34)	MAD (n = 27)	P
Clinical characteristics				
Age, y	62 ± 11	64 ± 10	59 ± 11	.08
Female gender	15 (25)	9 (27)	6 (22)	.70
Hypertension	30 (49)	17 (50)	13 (48)	.90
History of CAD	6 (10)	3 (9)	3 (11)	.80
Atrial fibrillation	10 (16)	8 (24)	2 (7)	.08
NYHA functional class III or IV	16 (26)	13 (38)	3 (11)	.03
Medications				
ACE inhibitors/ARBs	26 (43)	16 (47)	10 (37)	.40
β-blockers	22 (36)	14 (41)	8 (30)	.30
Diuretics	18 (30)	15 (44)	3 (11)	.004
Echocardiographic variables				
LV end-diastolic diameter, mm	54 ± 5	53 ± 5	55 ± 4	.20
LV end-systolic diameter, mm	34 ± 6	33 ± 6	34 ± 5	.90
LV ejection fraction, %	63 ± 7	62 ± 8	65 ± 5	.10
LAVI, mL/m^2	31 ± 11	31 ± 11	31 ± 9	1.00
Regurgitant volume, mL/beat	87 ± 47	90 ± 57	83 ± 31	.60
Effective regurgitant orifice, cm^2	0.53 ± 0.28	0.51 ± 0.33	0.55 ± 0.20	.60
sPAP, mm Hg	35 ± 11	38 ± 13	30 ± 5	.006
Posterior leaflet prolapse	57 (93)	30 (88)	27 (100)	.03
P2 scallop prolapse	50 (82)	24 (71)	26 (96)	.005
Bileaflet prolapse	20 (33)	6 (18)	14 (52)	.004
Flail leaflet	39 (64)	22 (65)	17 (63)	.90
Cleftlike indentation	24 (39)	13 (38)	11 (41)	.80
Diffuse myxomatous disease	21 (37)	6 (19)	15 (60)	.001
Fibroelastic deficiency	36 (63)	26 (81)	10 (40)	.001
Surgical characteristics				
Bypass time, min	71 ± 30	74 ± 33	68 ± 25	.50
Clamp time, min	51 ± 21	53 ± 23	49 ± 17	.40
Concomitant CABG	7 (11)	5 (15)	2 (7)	.40
Mitral repair surgery	60 (98)	33 (97)	27 (100)	.30

Data are expressed as mean ± SD or as number (percentage).
ACE, Angiotensin-converting enzyme; *ARB*, angiotensin II receptor blocker; *CAD*, coronary artery disease; *CABG*, coronary artery bypass grafting; *LAVI*, left atrial volume index; *NYHA*, New York Heart Association, *sPAP*, systolic pulmonary artery pressure.

and intercommissural diameters (Figure 4A), mitral annular area, and mitral annular circumference (Figure 4B). However, in mid- and late systole, patients with MAD displayed marked increases in anteroposterior mitral annular diameter (vs those without MAD, $P < .0001$), with slight increases in late systolic annular area ($P \leq .003$; Figures 4A and 4B, *left*). Mitral annular intercommissural diameter and circumference, which are overall larger in patients with MAD, behaved similarly throughout systole in the groups with and without MAD (Figures 4A and 4B, *right*). Additional dynamic analysis of mitral leaflet area, which is larger in patients with MAD than those without MAD, showed greater increases in leaflet area throughout systole in patients with MAD, with different temporal patterns between the two groups (Figure 4C).

Intra- and interobserver variability for 3D measurements was assessed and shown to be small (anteroposterior diameter, 3.3 ± 1.1% and 5.1 ± 3.7%; annular height, 4.6 ± 0.3% and 1.4 ± 0.6%; annular circumference, 2.2 ± 2.8% and 2.3 ± 6.4%; valvular area, 3.3 ± 0.3% and 7.4 ± 0.8%), similar to values previously reported.[17]

Consequences of MAD on LV Geometry and Function

LV diameters and IVS and PW thicknesses in diastole and systole, before and after MV surgery, are presented in Table 3. Overall, measurements of LV geometry and function were within normal ranges, indicating early referral to surgery. Preoperatively, diastolic basal and mid-LV diameters and IVS and PW thicknesses (Table 3, top left) were all similar between patients with and those without MAD ($P \geq .07$ for all), with a trend toward higher basal PW thickness with MAD. Conversely, in systole (Table 3, middle left), basal PW became markedly thicker in patients with MAD (19 ± 2 vs 15 ± 2 mm, $P < .001$), with a lesser difference in basal septal thickness (16 ± 3 vs 14 ± 2 mm, $P = .04$), while no differences

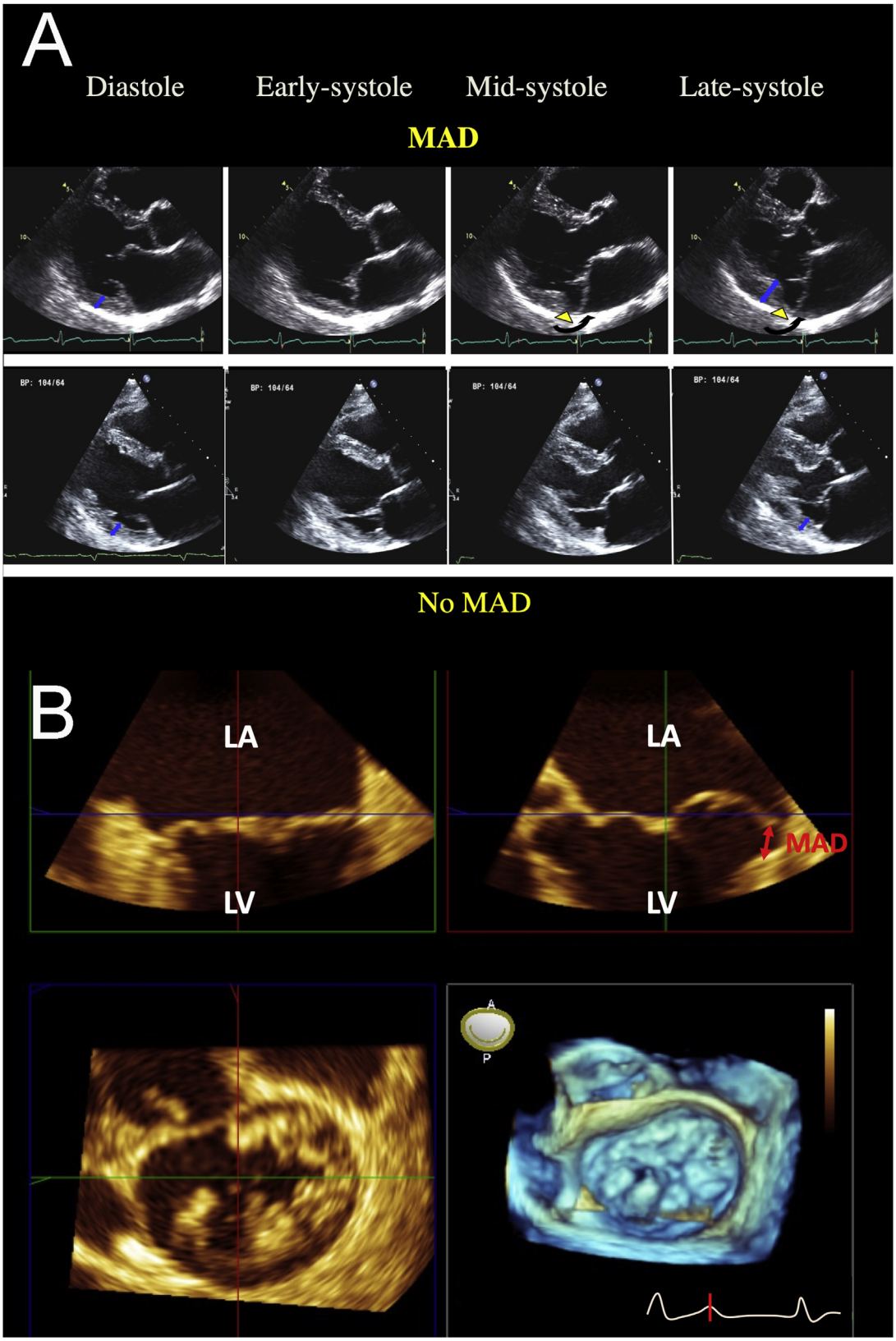

Figure 1 MAD of degenerative MV disease. Two-dimensional transthoracic echocardiographic long-axis dynamic view through the cardiac cycle **(A)** displaying degenerative MV disease with prolapse and MAD *(yellow triangle)* in systole *(top)* versus no MAD *(bottom)*. Note the excess left ventricular PW thickening *(top right, blue arrow)*, along with the annular slippage *(top right, black arrow)* with MAD. **(B)** Three-dimensional intraoperative transesophageal echocardiographic view of degenerative myxomatous valve disease with MAD. *LA*, Left atrium; *LV*, left ventricle.

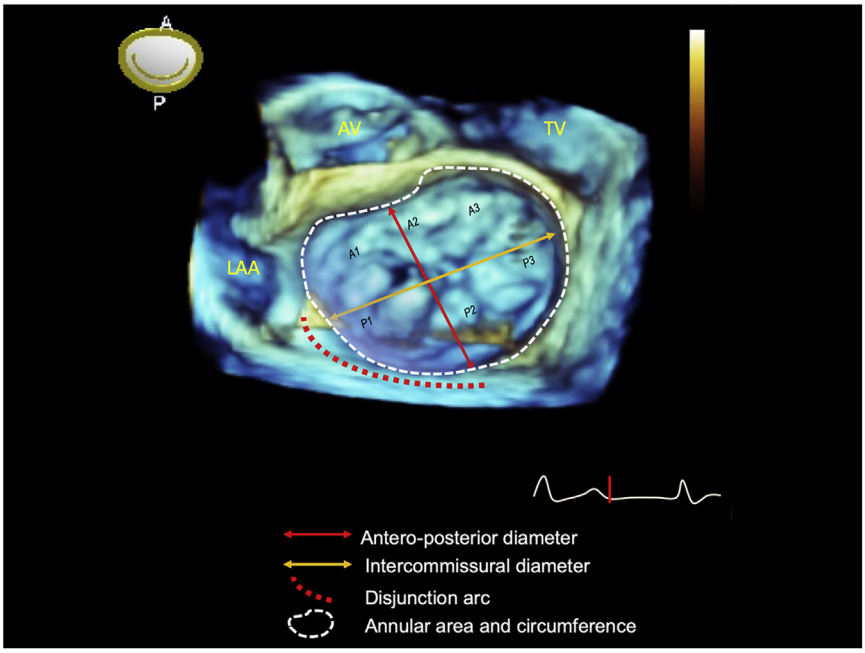

Figure 2 Three-dimensional evaluation of degenerative MV disease before mitral repair. Intraoperative 3D transesophageal echocardiographic reconstruction of myxomatous MVP for comprehensive dynamic analysis of the mitral annulus and MV leaflets. Note the posterior disjunction arc associated with enlarged annular diameters (vs no disjunction). *AV*, Aortic valve; *LAA*, left atrial appendage; *TV*, tricuspid valve.

Table 2 Three-dimensional echocardiographic characteristics measured in end-systole

	MVP (n = 61)	No MAD (n = 34)	MAD (n = 27)	P
Mitral annular measurements				
Intercommissural diameter, mm	45 ± 7	43 ± 6	48 ± 7	.003
Anteroposterior diameter, mm	40 ± 6	38 ± 6	41 ± 6	.04
Annular area, mm^2	1,498 ± 396	1,380 ± 348	1,646 ± 410	.008
Circumference, mm	143 ± 18	137 ± 16	150 ± 19	.005
Annular height, mm	7 ± 2	6 ± 2	7 ± 2	.10
Saddle shape, %	15 ± 4	15 ± 4	15 ± 4	.80
Mitral leaflet measurements				
Anterior leaflet area, mm^2	896 ± 281	840 ± 219	967 ± 334	.08
Posterior leaflet area, mm^2	955 ± 361	852 ± 327	1,086 ± 364	.01
Total leaflet area, mm^2	1,851 ± 575	1,692 ± 488	2,053 ± 620	.01
Mitral prolapse measurements				
Height of prolapse, mm	7 ± 4	6 ± 4	9 ± 3	.007
Volume of prolapse, mL	3 ± 3	2 ± 2	4 ± 4	.003
Prolapse volume/height ratio	0.3 ± 0.2	0.2 ± 0.2	0.4 ± 0.3	.001

Data are expressed as mean ± SD.

were seen in systolic LV diameter and mid-LV IVS and PW thicknesses ($P \geq .30$ for all). Hence, systolic wall thickening was higher in MAD for basal PW (74 ± 27% vs 50 ± 28%, $P = .001$) and ratio of basal (PW + IVS) wall thickness to diameter was higher in patients with MAD (1.2 ± 0.2 vs 0.9 ± 0.2, $P = .01$; Table 3, bottom left) with cavity deformation (mid/basal diameter ratio) larger in patients with MAD ($P = .004$). No differences in diastolic basal and middle wall thickness/diameter ratio were observed between groups ($P \geq .40$ for both).

Surgical Outcomes

The surgical intervention involved MV repair in 60 patients overall (98%) using a flexible 63-mm band, with one patient intended for valve repair requiring valve replacement because of a severely calcified mitral annulus. Mean bypass time was 71 ± 30 min, with concomitant coronary artery bypass graft required in 11% (Table 1, bottom). Leaflet resection was frequent, more common in patients with MAD, with no difference in chord implantation or Alfieri procedure ($P \geq .30$; see supplemental material). Importantly,

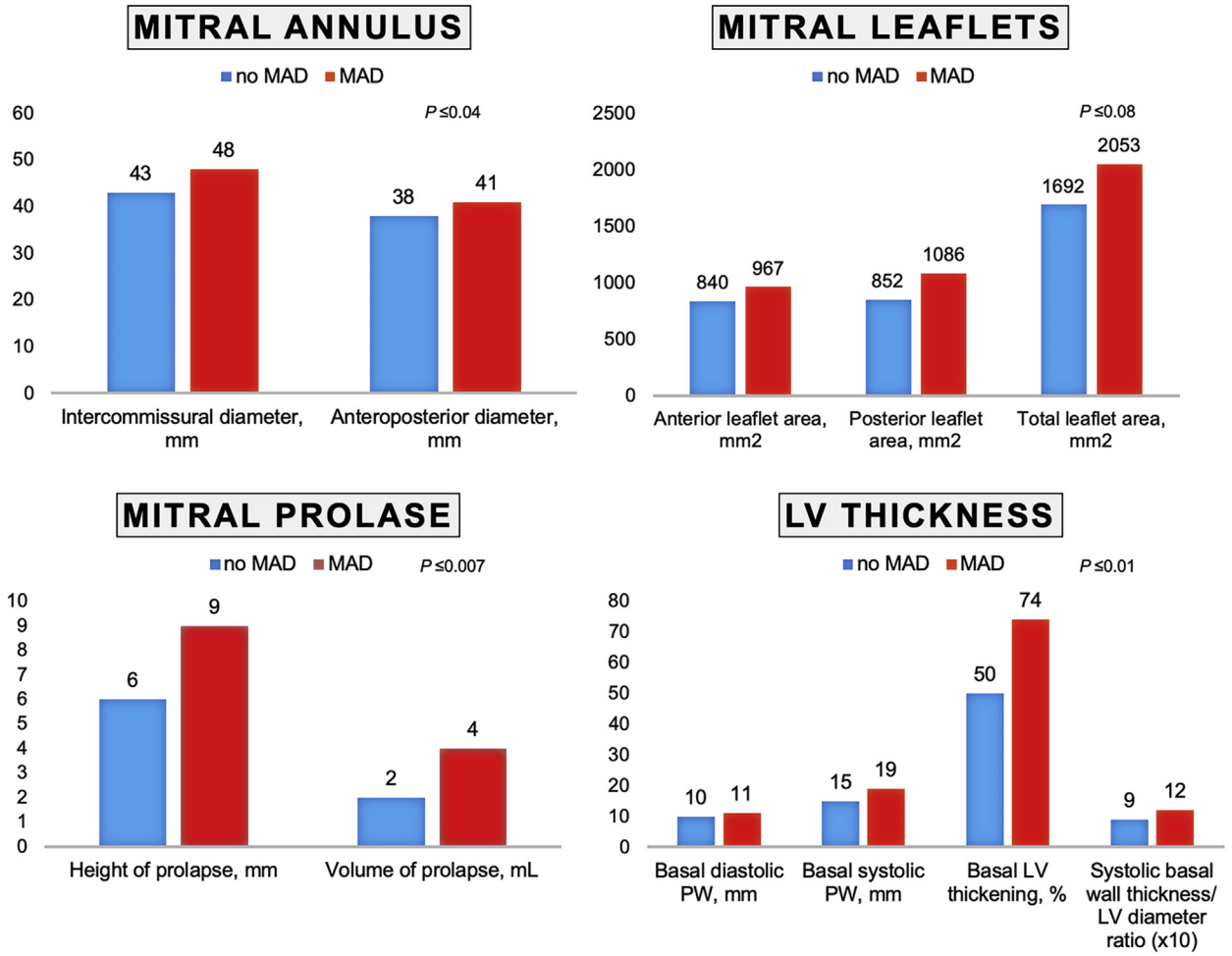

Figure 3 Mitral annulus and leaflets and left ventricular static analysis stratified by MAD. Bar graphs representing mitral annulus, leaflets, prolapse characteristics, and LV PW thickness stratified according to presence or absence of MAD. Note the significant annular diameter enlargement, leaflet area, and prolapse volume, with left ventricular basal PW thickening in the presence of MAD. *LV*, Left ventricle.

no difference between groups was observed in terms of repair performance (mild or less postoperative MR in 100% vs 97%, respectively, $P = .30$), and bypass time and aortic clamping time were similar, suggesting no added difficulty in performing the valve repair in patients with MAD. Postoperatively, MAD was no longer detectable in 22 patients (81%) with mitral annulus/ring firmly sutured to the LV myocardium in the area of the preoperative MAD. Postoperative echocardiography demonstrated in five patients that MAD was still visible postoperatively, with a mean length of 8 ± 3 mm in end-systole due to a ring mostly sutured to the annulus and adjoining the atrial wall. In these patients there was persistent excess systolic LV PW thickness (17 vs 14 mm in those without MAD, $P = .04$) associated with the annular detachment. No or trivial postoperative MR was noted in all patients, regardless of MAD presence. After MV repair, LV dimensions in both diastole and systole showed no differences between groups ($P \geq .07$ for all; Table 3, right panel). Interestingly, LV wall thickening in patients with MAD declined in all segments postoperatively and became similar to that in patients without MAD ($P \geq .30$).

DISCUSSION

The present study comprehensively characterizes using quantitative 3D TEE the morphology and dynamic changes of the MV complex in patients with isolated MVP and severe MR. It provides unique insights into MAD phenotype, allowing the identification of the potential impact of MAD on mitral and LV function and its association with surgical outcomes. It shows that MAD in such MVP is detectable in almost half of these patients (44%) and, although predominantly associated with bileaflet MVP, may be present with any type of MVP. MAD is almost universally associated with a markedly enlarged annulus and profoundly redundant mitral leaflets. Dynamically, despite its annular enlargement, the annular detachment or "slippage" of MAD in systole (Figure 1A, Video 1) does not impair early systolic normal annular function. However, in mid- and late systole, MAD is associated with abnormal and considerable annular enlargement that potentially contributes to abnormal coaptation. Moreover, the present study demonstrates that MAD is associated with profound LV alterations despite similar MR severity and left atrial size. Indeed,

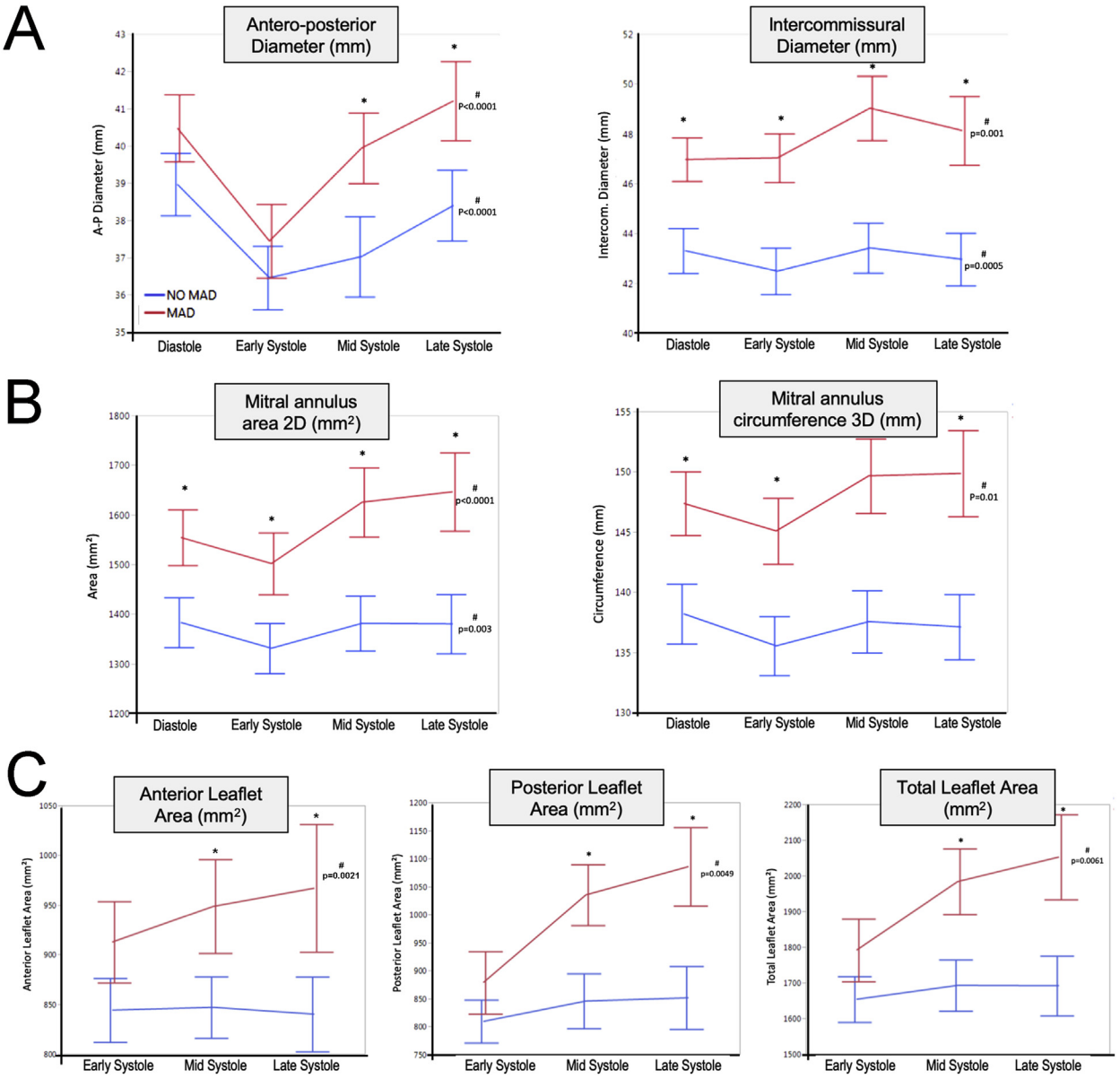

Figure 4 Mitral annulus and mitral leaflet dynamic analysis through the entire cardiac cycle, including early systole. Note the dynamic changes in mitral annular anteroposterior diameter, 2D area, and leaflet area in mid- and late systole (vs early systole) in the presence of MAD. **P* value for MAD versus no MAD; *#P* value for change.

MAD is associated with late systolic excessive PW thickening, belying "vigorous" LV function, as demonstrated by the return to normal thickening following MAD correction on postoperative assessment (Graphical Abstract). In terms of surgical outcome, MAD does not impair the feasibility and success of valve repair that allows collapsing the annular detachment, but great care should be paid to careful suturing of the annulus to the ventricular myocardium, lest MAD persist postoperatively and portend LV consequences. Hence, MAD is highly consequential in patients with MVP and should be carefully detected and quantified.

MAD as a Component of MVP

Since its first description,[8] the significance of MAD in MVP has remained uncertain, variably considered as causing myxomatous degeneration and MVP[8] or as simple anatomic mitral annular variation present in the general population.[9] In view of contrasting reports regarding the prevalence of MAD in MVP,[11,23] our observation of MAD in 44% of patients with MVP with severe MR underscores the importance of defining its associated characteristics and physiologic implications. The present study demonstrated that presence of MAD was strongly associated with a predominant phenotype involving bileaflet MVP, almost invariably with P2 scallop prolapse, and with extensive leaflet redundancy, particularly in systole. Original pathologic studies[8,9] showed that MAD may affect a wide area or a limited portion of the annulus circumference, but the profound separation of the annulus from its myocardial attachment occurred only under the posterior leaflet in our study. Indeed, the mitral annulus at the anterior and medial leaflet level is an extremely dense fibrotic tissue in which we did not observe

Table 3 Pre- and postoperative LV internal dimension and thicknesses in diastole and systole

	Preoperative measurements				Postoperative measurements			
	MVP (n = 61)	No MAD (n = 34)	MAD (n = 27)	P	MVP (n = 61)	No MAD (n = 34)	MAD (n = 27)	P
LV diastolic dimensions								
Basal IVS, mm	11 ± 2	11 ± 2	12 ± 3	.30	12 ± 2	11 ± 2	12 ± 3	.10
Basal PW, mm	11 ± 2	10 ± 2	11 ± 3	**.07**	11 ± 2	11 ± 2	11 ± 2	.50
Middle IVS, mm	9 ± 2	9 ± 2	9 ± 2	.90	10 ± 2	10 ± 1	10 ± 3	.80
Middle PW, mm	9 ± 1	9 ± 1	9 ± 2	.90	9 ± 1	9 ± 1	10 ± 1	.50
LV diameter, mm	54 ± 5	53 ± 5	55 ± 4	.20	50 ± 6	51 ± 5	49 ± 7	.30
LV systolic dimensions								
Basal IVS, mm	15 ± 3	14 ± 2	16 ± 3	.06	15 ± 3	14 ± 3	15 ± 3	.30
Basal PW, mm	17 ± 3	15 ± 2	19 ± 2	**<.001**	14 ± 3	14 ± 3	15 ± 3	.30
Middle IVS, mm	13 ± 2	13 ± 2	13 ± 2	.40	12 ± 2	12 ± 2	12 ± 2	.20
Middle PW, mm	13 ± 2	13 ± 2	13 ± 2	.30	12 ± 2	12 ± 2	12 ± 2	.50
LV diameter, mm	34 ± 6	33 ± 6	34 ± 5	.90	34 ± 5	34 ± 6	34 ± 4	.90
LV wall thickening								
Basal IVS, %	36 ± 19	32 ± 15	39 ± 23	.20	29 ± 18	30 ± 17	28 ± 18	.70
Basal PW, %	61 ± 28	50 ± 28	74 ± 27	**.001**	31 ± 24	29 ± 26	33 ± 22	.50
Middle IVS, %	42 ± 25	41 ± 27	43 ± 22	.70	21 ± 25	20 ± 25	22 ± 25	.50
Middle PW, %	42 ± 21	39 ± 18	46 ± 24	.20	30 ± 28	31 ± 33	30 ± 22	.90
Wall thickness/LV diameter systolic ratio								
Systolic basal	1 ± 0.2	0.9 ± 0.2	1.2 ± 0.2	.01	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	.50
Systolic middle	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	.60	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	.60
Diastolic basal	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.1	.60	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	.07
Diastolic middle	0.4 ± 0.1	0.4 ± 0.1	0.3 ± 0.1	.40	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	.20

Data are expressed as mean ± SD.
Bold values indicate significant P values, $P < .05$.

annular detachment, as its fibrotic tissue density decreases progressively away from the trigones under the posterior leaflet. This part of the annulus is normally implanted in the ventricular myocardium and has the potential to slip from its insertion, causing MAD with local consequences located in this posterolateral area. The much higher prevalence of MAD in MVP than in the general population[24] suggests that MAD is indeed an intrinsic component of the myxomatous degeneration of MVP. The sequence of progressive slippage of the annulus over its normal myocardial attachment is remarkably consistent with the suggestion of a genetic MVP phenotype (filamin-A genotype-phenotype in MV dystrophy[25] and a truncating variant in FLNC-encoded filamin C[26]) leading to abnormalities in cellular anchoring proteins. The resulting tissue slippage may ultimately affect outcome.[27] Hence, the heterogeneity in the presence of MAD with MVP complicated by severe MR reflects the known morphologic heterogeneity of MVP, which has been also found in comparison with sex-linked characteristics of MVP.[28] Additional analyses support the evidence that within the heterogeneity of MVP, MAD is one element of the MVP phenotype range with characteristics and consequences that are often concomitant but independent of bileaflet MVP (and vice versa). Our interpretation of the respective impact of MAD versus bileaflet MVP on mitral and LV physiology should remain very preliminary, in particular given the limited power that results from a sample of this size. Irrespective of this MVP heterogeneity concept, when MAD is present, it has important consequences for mitral function that warrant careful examination.

MAD and Valve Dynamics: Focus on End-Systole

The mitral apparatus is a complex, finely coordinated mechanism, which for normal performance requires functional integrity of all anatomic elements: mitral annulus, valve leaflets, chordae tendineae, papillary muscles, posterior left atrial wall, and LV wall.[29] Hence, functional consequences of MAD may affect the shape and function of the mitral annulus and leaflet interaction. Quantitative dynamic analysis on 3D TEE showed that normal mitral annular behavior involves early systolic anteroposterior contraction with fixed intercommissural diameter, yielding early systolic annular area contraction and approximation of anterior and posterior leaflets.[17] Early contraction phase is followed by progressive return of mid to late systolic annular dimensions to diastolic values, while the mitral leaflets are locked by ventricular contraction.[30] MAD associated with MVP does not notably affect early systolic annular behavior, which remains close to normal,[17] but the subsequent excess area enlargement with MAD may contribute to MR (although all patients of the present cohort had severe MR). However, the main features of MAD-associated physiology affect mid to late systolic mitral dynamics. Diffuse myxomatous degeneration (known also as Barlow disease) annular dynamics have been described as displaying late systolic abnormal annular expansion,[31] and valvular dynamics are characterized by considerable mid to late systolic leaflet redundancy, related to leaflet deployment.[32,33] Importantly, although MAD is morphologically associated with fibroelastic disease in some cases, physiologically it is associated with the annular and valvular dynamics of diffuse myxomatous disease,

confirming physiologically the significant morphologic association with bileaflet MVP. Therefore MAD, with the annulus detached from its normal myocardial anchoring in mid to late systole, is probably responsible for the late to systolic increase in annular area. Thus, MAD appears to be one of the manifestations of diffuse myxomatous disease with marked leaflet redundancy exponentially expanding in mid to late systole. It is possible that marked leaflet redundancy augments annular traction during systole and tends to aggravate MAD length, but verifying this will require future longitudinal studies. Hence, MAD is not just a morphologic peculiarity but is directly related to profound dysfunction of mitral apparatus dynamics.

MAD, LV Geometry, and Surgical Outcomes

MAD is associated with distinctive LV characteristics. Although in diastole no difference is noted in LV geometry between patients with and those without MAD, during systole, presence of MAD is associated with excessive wall thickening at the basal level, particularly of the basal PW, as the myocardium detached from its annular anchor bulges in the cavity. This may create the impression of markedly vigorous LV function, which may be misleading for this crucial predictor of late survival[2] and yield overestimation of contractile function.[34] Indeed, the excess LV PW thickening in MAD is rather the result of muscular detachment from its normal anchoring and not a sign of a more vigorous LV contraction. Thus, LV function should not be judged by just one region's kinetics but rather by global volume and function. However, our study shows that after surgery with appropriate annular suture to the posterolateral LV myocardium, MAD collapses. In turn, the excessive wall thickening at the basal level disappears, with all measures of LV size and function similar between patients with and those without MAD. These postoperative changes confirm that the preoperative appearance is indeed misleading and may cause underestimation of the consequences of MR on the left ventricle. Whether MAD area, which may be associated with fibrosis on magnetic resonance imaging[15] and histology,[13] might affect LV function will require long-term postoperative studies. Importantly, MV repair is a major determinant of clinical outcomes in patients with MVP and severe MR,[7,16] and our study shows that the presence of MAD does not impair the feasibility of mitral repair in these patients. Because all patients had severe MR, we cannot affirm that MAD may accentuate MR, but the late systolic annular enlargement certainly contributes to separate the leaflets in systole and may contribute to MR. Furthermore, MAD is also not a cause of poor outcomes of valve repair, as shown by the lack of excess residual MR after repair. However, a small percentage of patients with MAD presented with residual MAD after repair because of insufficient ring sutures that do not reattach the annulus to the PW but rather attach to the annulus or atrial wall. Longer preoperative MAD in patients with versus without residual MAD (9 ± 5 vs 3 ± 4 mm, $P < .0001$) could explain why the annuloplasty itself could not completely collapse the MAD in such cases. A recent outcome study analyzing the link between MAD and subsequent arrhythmic events showed a very strong and independent link, with a trend toward a weaker association with arrhythmia after mitral surgery.[35] Whether postoperative MAD persistence may contribute to LV fibrosis and arrhythmia remains to be demonstrated. Hence, in preparation for valve repair, attracting the surgeon's attention to MAD is crucial to restoring annular attachments.

Study Limitations

MAD is diagnosed easily using long-axis views, but there are no validated methods to measure its extent along the annulus, as MAD may spread variably along the mitral annulus.[9] In the present study, the position and contraction of papillary muscles could not be measured, and their role as shock absorbers[36] remains uncertain. It has been claimed that sudden traction caused by redundant valves on the papillary muscles may cause fibrosis and possibly arrhythmias, but this remains conjectural. The association of MVP clinical outcomes with MAD requires future systematic 3D transesophageal echocardiographic assessments in larger cohorts with adequate follow-up duration. However, although large cohorts with long-term follow-up have confirmed a strong association of MAD with ventricular arrhythmias independent of all other potential determinants,[35,37] the demonstration of highly successful repair with MAD is new and suggests that this anomaly can be fully corrected by appropriate repair.

CONCLUSION

The present study demonstrates that MAD in patients with MVP involves a predominant phenotype of severe diffuse myxomatous disease and causes profound alteration of annular dynamics, with excess annular enlargement in late systole that may contribute to reduced leaflet coaptation associated with severe MR. MAD is not isolated but presents with markedly redundant leaflets and voluminous prolapse, with a dynamic pattern characterized by considerable expansion in mid to late systole. MAD myocardial and annular slippage in systole simulates vigorous LV function, but such hyperdynamic LV function is not observed after surgical annular suturing. However, MAD does not hinder the feasibility and quality of valve repair but requires careful suture of ring to ventricular myocardium, lest residual MAD persists after repair. Thus, MAD should be detected attentively and signaled to cardiac surgeons in patients with MVP and severe MR.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2021.09.004.

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