

Evaluation of left ventricular function in patients with mitral annular disjunction using speckle tracking echocardiography

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Abstract

Background: Mitral annular disjunction (MAD) is a structural abnormality characterized by the systolic detachment of the posterior mitral annulus and the ventricular myocardium. It is usually observed coexistent with mitral valve prolapse (MVP) and associated with a mechanical dysfunction despite preserved electrical isolation function of the mitral annulus. This study aimed to evaluate left ventricular (LV) function using speckle tracking echocardiography in MVP patients with MAD.

Methods: This study was designed as a prospective, single-center study including 103 patients with MVP and 40 age- and sex-matched control subjects. Transthoracic echocardiography and cardiac magnetic resonance imaging were performed to assess LV function and MAD presence.

Results: MAD (+) MVP ($n = 34$), MAD (−) MVP ($n = 69$), and control ($n = 40$) groups were enrolled in the study. Among the MVP patients, 34 (33%) had MAD. T-negativity in the inferior leads on electrocardiography was more frequent in the MAD (+) group than in the MAD (−) patients (4.3% vs. 20.6%, $p = .014$). Mitral regurgitation degree, Pickelhaube sign (17.6% vs. 1.4%, $p = .005$), and late gadolinium enhancement frequency (35.3% vs. 10.6%, $p = .002$) were significantly higher in MAD (+) patients. MAD (+) patients had significantly impaired global longitudinal strain (-23.1 ± 2.1 vs. -23.5 ± 2.3 , $p < .001$), basal longitudinal strain (BLS) (-19.6 ± 1.5 vs. -20.5 ± 1.9 , $p < .001$), Mid-Ventricular Longitudinal Strain (-22.2 ± 1.7 vs. -23.2 ± 2.2 , $p < .001$) and LA strain (-24.5 ± 3.9 vs. -27.2 ± 3.6 , $p < .001$) when compared to MAD (−) MVP patients, despite similar LV ejection fraction. All these values of MVP patients were also significantly lower than the control group. The mean MAD distance was 7.8 ± 3.2 mm in MAD (+) patients. Patients with two or more symptoms were higher in the MAD (+) group than in the MAD (−) group (4.3% vs. 44.1%, $p < .001$).

Conclusion: This study demonstrated a significant decrease in longitudinal strain in MVP patients with MAD, indicating myocardial dysfunction. These findings suggest that MAD may contribute to LV dysfunction and highlight the importance of early

detection in younger patients. Further research is needed to explore the functional implications and long-term outcomes of MAD.

KEYWORDS

left ventricular function, mitral annular disjunction, mitral valve prolapse, myocardial strain, speckle tracking echocardiography

1 | INTRODUCTION

Mitral annular disjunction (MAD) is a structural abnormality of the mitral valve apparatus that is characterized by a separation between the atrial wall of the mitral annulus and the ventricular myocardium.¹ This relatively new entity has been increasingly recognized in cardiac imaging studies in recent years and it is shown to be associated with mitral valve prolapse (MVP), mitral regurgitation, arrhythmic events, and sudden cardiac death (SCD). Its prevalence is found to be over 8% in general population and this number reaches up to four fold in patients with MVP.²

Abnormal atrial attachment of the posterior leaflet and related systolic curling is observed in MAD which accompanies mechanical annular dysfunction.³ MAD may contribute to mitral valve dysfunction by altering the geometry of the mitral valve annulus or by disrupting the continuity of the subvalvular apparatus.⁴ Moreover, it has been suggested that MAD may be associated with myocardial dysfunction that can be detected by abnormal myocardial strain. Separation between the atrial wall of the mitral annulus and the ventricular myocardium may disrupt myocardial mechanics, leading to decreased strain.⁵ Additionally, there may be a direct effect of MAD on the mitral valve, leading to mitral regurgitation and increased afterload on the left ventricle, which may also contribute to myocardial dysfunction.^{2,5}

There are limited number of studies in the literature that examined the strain parameters in MAD and the information about this subject is not enough to define a particular pattern. In the present study, our aim was to investigate the impact of MAD on myocardial strain parameters in patients with MVP.

2 | MATERIAL AND METHODS

2.1 | Patient population

Between September 2020 and October 2021, we conducted a prospective, single-center study including 103 patients with MVP and 40 healthy age- and sex-matched control subjects. Age < 18, history or symptoms of coronary artery disease, heart valve disease with a more-than-mild severity, reduced ejection fraction ($EF \leq 50$), elevated systolic pulmonary arterial pressure (SPAP) at rest (> 50 mm Hg), heart failure and/or atrial fibrillation were regarded as the exclusion criteria. The control group comprised age- and gender-matched healthy subjects. Medical history was obtained for all participants, and each subject underwent physical examination including body surface area (BSA). The local ethics research committee approved the protocol, and

each subject signed an informed consent form. The study complies with the Declaration of Helsinki.

2.2 | Transthoracic echocardiography

Transthoracic echocardiography (TTE) examination was performed using the "Philips Epiq 7 echocardiography device X5-1 transthoracic probe" (Philips Epiq7; Philips Healthcare, Inc., Andover, MA, USA). The standard evaluation included M-mode, two-dimensional (2D), and Doppler studies according to the recommendations of the American Society of Echocardiography. The anatomy of mitral valve apparatus was systematically evaluated to identify prolapsing scallops and/or presence of a flail leaflet; trans esophageal echocardiography was performed when appropriate. Systolic movement of one or both leaflets ≥ 2 mm above the mitral annular plane was accepted as MVP. Although the patients were not divided according to the aetiology of MVP, most patients were having myxomatous MVP rather than fibroelastic deficiency.⁶ The location of the mitral annulus is identified in the long axis view by zooming on the mitral valve at the maximum achievable frame rate. Subsequently, the images were scrutinized on a frame-by-frame basis to accurately view the mitral annulus and to quantify the width of the MAD trench in addition to the extent of the prolapsus depth. Along with these aspects, upper and lower limits of MAD were defined according the expert consensus statement on arrhythmic MVP and MAD.¹ The left ventricular end-diastolic diameters (LVEDDs) and end-systolic diameters (LVESDs) and volumes were measured and indexed to BSA, and EF was calculated using biplane Simpson's method. To assess LV geometry, end-diastolic relative wall thickness, LV mass/BSA (g/m^2), and sphericity index were obtained. Indexed LA area and biplane volumes also were calculated. Myocardial function was assessed with 2D speckle tracking echocardiography with layer specific myocardial deformation quantitative analysis function. End diastole was defined with R wave peak in ECG and end systole was defined as aortic valve closing time. Endocardial borders were observed from end systolic 2D images. Wide myocardial width was calibrated and epicardial borders were evaluated. Mid zone speckles between epicardial and endocardial borders, mid myocardial border were defined automatically. Manual adjustments were carried out in order to obtain correct tracking and 2D speckle tracking width to cover all LV wall thickness if required. Peak systolic strain measurements were performed automatically in each segment via software analysis program (QLAB-CMQ software program of Philips Epiq 7C). Non-traceable segments were excluded after manual adjustment by the operator. Digital cineloops of 2D greyscale LA images were captured during three consecutive

cardiac cycles in both standard apical four- and two-chamber views for the assessment of left atrial (LA) strain. Imaging was conducted during a breath-hold with a stable electrocardiographic recording, and the acquired data were stored for offline analysis. Diligence was exercised to avoid foreshortening of the left atrium and enable reliable delineation of atrial endocardial borders by utilizing standard anatomic landmarks in each view. The frame rate for greyscale imaging was set at 60 frames per second, ensuring adequate spatial definition. Employing the frame-to-frame tracking technique enhanced the feasibility of the analysis for assessing strain.

2.3 | Cardiac magnetic resonance imaging

MAD diagnosis was confirmed with Magnetic Resonance Imaging (CMR) analysis. Systolic displacement of mitral leaflet(s) at least 2 mm away from the annulus was determined as the lowest limit for diagnosis, as defined earlier.¹ MAD length is measured in the sagittal views as the distance between the leaflet insertion on the detached annulus and the left ventricle border. All CMR examinations were performed on a 1.5 T scanner (Aera Siemens Medical system, Erlangen, Germany) using a phased-array body coil. All patients were monitored during the procedure. The sequences were acquired using prospective cardiac gating. All acquisitions used balanced steady-state free precession cine sequence with the following typical parameters: TR/TE 3.8/1–3 ms, slice thickness 8 mm with 2 mm interclase gap, voxel size 1.8 mm × 1.8 mm × 6 mm and acquired temporal resolution 40 ms.

2.4 | Statistical analyses

All statistical tests were conducted using the Statistical Package for the Social Sciences 25.0 for Windows (SPSS Inc., Chicago, IL, USA).

The Kolmogorov–Smirnov test was used to analyze normality of the data. Continuous data are expressed as mean ± SD, and categorical data are expressed as percentages. Student's *t*-test or Mann Whitney *U*-test was used to compare unpaired samples as needed. Chi-square test was used to assess differences in categorical variables between groups. The relationships among parameters were assessed using Pearson's or Spearman's correlation analysis according to normality of the data. Primary analysis used ANOVA to compare all reported data for parametric variables, whereas Kruskal–Wallis test was used for comparison among non-parametric variables between the MAD subjects, MVP subjects and controls. Significance was assumed at a two-sided *p* < .05.

Reproducibility was assessed by reanalyzing 15 randomly selected patients, reported as intraobserver reliability and by calculating from a second independent observer, reported as interobserver reproducibility.

3 | RESULTS

The study included 103 patients with MVP and a control group of 40 people and 34 of these MVP patients (33%) had MAD. Patients were divided into groups as MAD (+) (*n* = 34), MAD (–) (*n* = 69) and control (*n* = 40). The clinical and demographic characteristics of the study groups are shown in Table 1. There was no statistically significant difference between the groups in terms of gender, age, BMI, beta-blocker use and smoking habits. When symptom types such as palpitation, dyspnea, fatigue, chest pain and syncope were compared, no significant difference was found between MAD (+) and MAD (–) groups. However, number of symptoms on admission was not similar. Number of patients with two or more symptoms was higher in the MAD (+) group than in the MAD (–) group (4.3% vs. 44.1%, *p* < .001). T-negativity in the inferior leads on electrocardiography was more frequent in

TABLE 1 The demographic and clinical data of the study population.

Parameters	Control group (<i>n</i> = 40)	MAD (–) (<i>n</i> = 69)	MAD (+) (<i>n</i> = 34)	<i>p</i> (Between groups)
Age, years	35.7 ± 13.7	35.7 ± 14.2	36 ± 12.7	.993
Male, <i>n</i> (%)	10 (25)	25 (36.2)	17 (50)	.084
BMI, (kg/m ²)	24.6 ± 4	23.3 ± 3.6	23.5 ± 3.8	.258
Smoker, <i>n</i> (%)	14 (35)	19 (27.5)	9 (26.5)	.650
Beta Blocker, <i>n</i> (%)	–	13 (18.8)	7 (20.6)	.833
Symptoms and Signs				
Palpitation, <i>n</i> (%)	–	41 (59.4)	20 (58.8)	.954
Fatigue, <i>n</i> (%)	–	11 (15.9)	4 (11.8)	.572
Chest Pain, <i>n</i> (%)	–	22 (31.9)	9 (26.5)	.573
Dyspnea, <i>n</i> (%)	–	16 (23.2)	9 (26.5)	.715
Syncope, <i>n</i> (%)	–	1 (1.4)	3 (8.8)	.104
2+ symptom, <i>n</i> (%)	–	3 (4.3)	15 (44.1)	<.001
Inferior lead T negativity, <i>n</i> (%)	–	3 (4.3)	7 (20.6)	.014

Abbreviations: BMI, body mass index; MAD, mitral annular disjunction.

TABLE 2 Echocardiography and MRI findings of the study population.

Parameters	Control group (n = 40)	MAD (−) (n = 69)	MAD (+) (n = 34)	p (Between groups)
Ejection fraction, (%)	64.7 ± 8.5	62.6 ± 8.9	62.5 ± 6.6	.371
IVS/PW	.95 ± .16	.99 ± .16	1.0 ± .19	.311
PW, (mm)	.95 ± .16	.99 ± .16	.98 ± .17	.021
LVEDD, (mm)	48.7 ± 7.5	45.5 ± 8.0	47.9 ± 8.2	.091
LVESD, (mm)	32.3 ± 5.9	30.1 ± 7.5	30.7 ± 4.7	.231
Mitral annular end-systolic diameter, (mm)	31.1 ± 11.8 ^{***}	41.7 ± 18.9 [*]	44.5 ± 18.5 ^{***}	.002
Mitral annular end-diastolic diameter, (mm)	29.6 ± 10.3 ^{***}	38.3 ± 16.3 [*]	41.5 ± 20.0 ^{**}	.004
MR Degree (25–75 p)	–	0 (0–1)	1 (1–2.2)	.001
LAVI (mL/mm ²)	37.1 ± 11.1 ^{***}	49.2 ± 18.1 ^{***}	60.8 ± 23 ^{***}	<.001
TDI Lateral Sa (cm/s)	10.7 ± 1.6 ^{***}	12.3 ± 2.7 ^{***}	14.5 ± 3.1 ^{***}	<.001
LA strain	−31.1 ± 3.5 ^{***}	−27.2 ± 3.6 ^{***}	−24.5 ± 3.9 ^{***}	<.001
GLS, (%)	−24.5 ± 2.2 ^{***}	−23.5 ± 2.3 ^{***}	−23.1 ± 2.1 ^{***}	<.001
BLS, (%)	−23.3 ± 1.2 ^{***}	−20.5 ± 1.9 ^{***}	−19.6 ± 1.5 ^{***}	<.001
MVLS, (%)	−24.5 ± 1.8 ^{***}	−23.2 ± 2.2 ^{***}	−22.2 ± 1.7 ^{***}	<.001
ALS, (%)	−26.9 ± 3.6	−27.9 ± 3.7	−27.5 ± 3.9	.439
Pickelhaube sign, n (%)	–	1 (1.4)	6 (17.6)	.005
LGE, n (%)	–	7 (10.1)	12 (35.3)	.002
MAD distance (mm)	–		7.8 ± 3.2	

Abbreviations: ALS, apical longitudinal strain; BLS, basal longitudinal strain; GLS, global longitudinal strain; IVS, interventricular septum; LAVI, left atrial volume index; LGE, late gadolinium enhancement; LVEDD, left ventricle end diastolic diameter; LVESD, left ventricle end systolic diameter; MAD, mitral annular disjunction; MRI, magnetic resonance imaging; MVLS, mid-ventricular longitudinal strain; PW, posterior wall; Sa, systolic annular; TDI, tissue doppler imaging.

* $p < .05$ Between control and MAD (−) groups.

** $p < .05$ between control and MAD (+) groups.

*** $p < .05$ between MAD (−) and MAD (+) groups.

the MAD (+) group than in the MAD (−) patients (4.3% vs. 20.6%, $p = .014$).

When the groups were compared in terms of echocardiographic and MRI findings (Table 2), left ventricular ejection fraction (LVEF), posterior wall thickness (PW), interventricular septum to posterior wall ratio (IVS/PW), LVEDD and LVESD, apical longitudinal strain (ALS) levels were similar. Mitral regurgitation degree ($p = .001$), end-systolic and end-diastolic diameter of the mitral annulus, frequency of Pickelhaube sign (17.6% vs. 1.4%, $p = .005$) and LGE (35.3% vs. 10.6%, $p = .002$) were higher in MAD (+) patients compared to MAD (−) patients. When the LA volume index, tissue doppler imaging lateral Systolic Annular, LA strain global longitudinal strain (GLS), basal longitudinal strain (BLS), mid-ventricular longitudinal strain (MVLS) levels were compared, the difference between the three groups was statistically significant. LA strain of the control group -31.1 ± 3.5 and this was -27.2 ± 3.6 for the MAD (−), -24.5 ± 3.9 for the MAD (+) group ($p < .001$). GLS of the MAD (+) group was -23.1 ± 2.1 and this was -23.5 ± 2.3 for the MAD (−), -24.5 ± 2.2 for the control group ($p < .001$). BLS of the MAD (+), MAD (−) and control groups were -19.6 ± 1.5 , -20.5 ± 1.9 -23.3 ± 1.2 , respectively, with a p -value $< .001$. For the BLS of MAD (+), MAD (−) and control groups, these values were -22.2 ± 1.7 , -23.2 ± 2.2 and -24.5 ± 1.8 ; ($p < .001$) and for MVLS, -22.2 ± 1.7 , -23.2 ± 2.2 and -24.5 ± 1.8 ($p < .001$), respectively.

The mean MAD distance was 7.8 ± 3.2 mm in MAD (+) patients (Figure 1).

Table 3 presents the regional strain values across the three groups within the study population, including the control group, MAD (−) group, and MAD (+) group. Across various basal segments, including anteroseptal, inferoseptal, inferior, inferolateral, anterolateral, and anterior, significant differences were observed among the groups ($p < .001$). Notably, the MAD (+) group consistently displayed reduced strain values compared to both the control and MAD (−) groups. Mid-segment strain values demonstrated varying patterns. Mid anteroseptal strain showed significant differences between groups ($p = .009$), with the control group having the highest value ($-25.7\% \pm 3.7\%$) compared to MAD (−) and MAD (+) groups. In contrast, mid inferoseptal, mid inferior, mid inferolateral, mid anterolateral, and mid anterior segments exhibited significant differences ($p < .05$) primarily between the control and MAD (−) groups. At the apical segments, strain values did not exhibit statistically significant differences between the groups (Table 3).

The relationship between GLS level and MAD distance in MAD (+) patients was evaluated by pearson correlation analysis (Figure 2). It was observed that as the GLS level decreased, the MAD distance increased statistically significantly ($r: .694$, $p < .001$). Then, the relationship between BLS level and MAD distance in MAD (+) patients

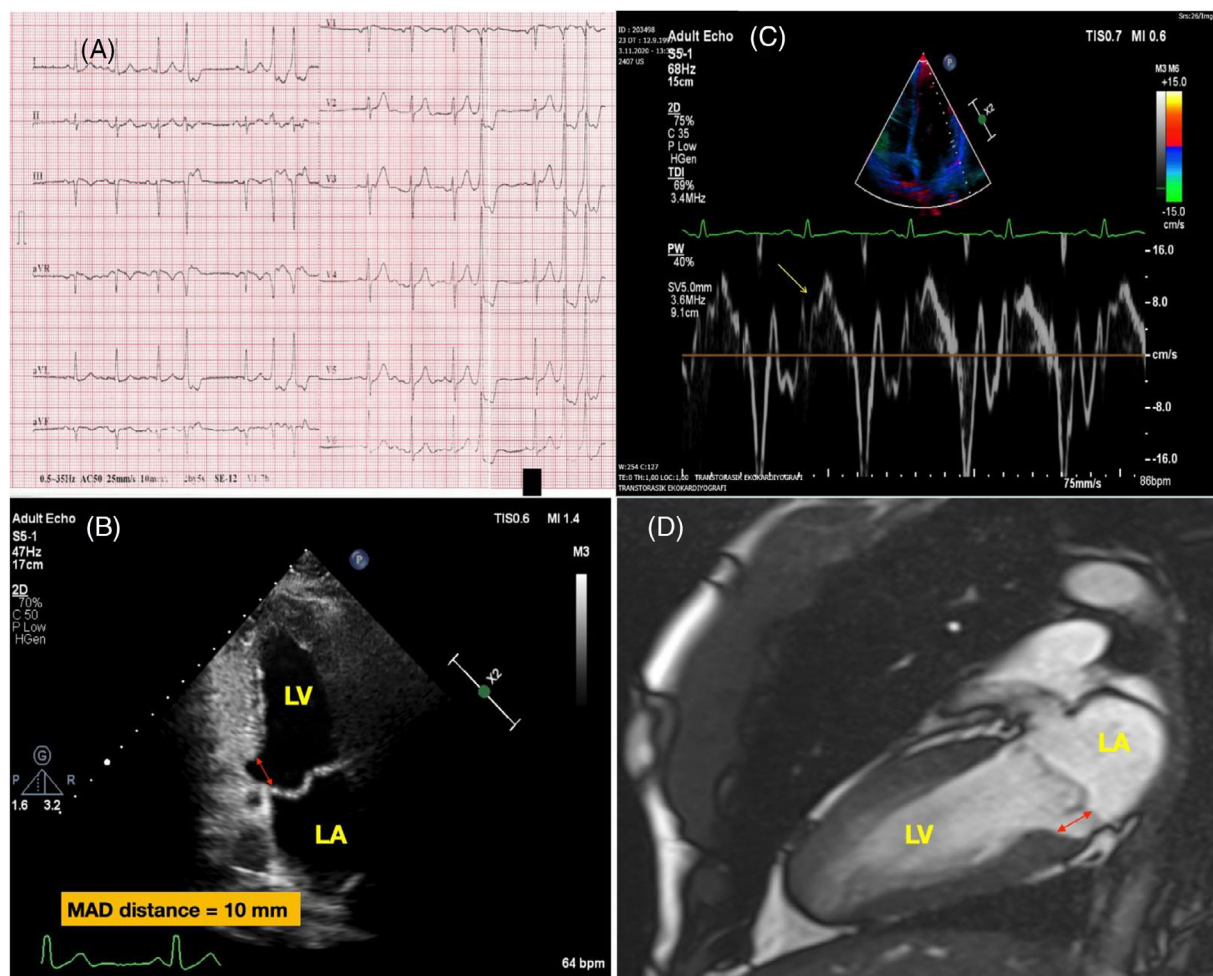


FIGURE 1 A 28-year-old female patient was diagnosed with MAD. (A) Electrocardiography shows the ventricular extrasystoles (wide complex QRS). (B) In TTE examination, the MAD distance was measured as 10 mm in the apical two-chamber view during systole (labeled). (C) TTE shows TDI pattern with high-velocity mid-systolic spike named Pickelhaube Sign. (D) Cardiac magnetic resonance imaging shows the MAD in the two-chamber image (labeled). MAD, mitral annular disjunction; TDI, tissue doppler imaging; TTE, transthoracic echocardiography.

was evaluated by pearson correlation analysis (Figure 3). It was observed that as the BLS level decreased, the MAD distance increased statistically significantly ($r: .715, p < .001$).

3.1 | Reproducibility

A total of 15 patients were randomly selected for inter and intraobserver analysis of variability. Interobserver and intraobserver compatibility of "GLS, BLS, ALS, EF, MY degree" values were calculated. Correlation coefficient for interobserver variability, respectively: GLS, .90 [95% CI, .88–.94]; BLS, .91 [95% CI, .81–.94]; ALS, .85 [95% CI, .75–.92]; EF, .82 [95% CI, .72–.94]; MY degree, .88 [95% CI, .80–.97] was evaluated. Correlation coefficient for intraobserver variability, respectively: GLS, .94 [95% CI, .92–.98]; BLS, .92 [95% CI, .83–.97]; ALS, .89 [95% CI, .78–.94]; EF, .85 [95% CI, .75–.95]; MY degree, .91 [95% CI, .85–.96]; was evaluated.

4 | DISCUSSION

The main finding of our study is the numeric decrease in longitudinal strain in MVP patients with MAD when compared to both MAD (–) MVP and control groups. This difference was detected for both global and segmental longitudinal strain. We interpreted this result as a reflection of partial loss of basal support during systole for the ventricular myocardium in significant MAD. The normal mitral annulus has roots located within the ventricular myocardium and these roots provide tight anchoring of the annulus to the ventricular myocardium.⁷ MAD occurs when these roots of the mitral annulus separate from the ventricular myocardium or fail to adhere sufficiently. However, the data about the functional implications of MAD and related ventricular dysfunction in the literature is scarce. First study in Medline about this subject was reported by Lee et al which investigated the 3D structure of MAD and its functional importance. In their study 42% of the 101 MVP patients were having MAD and mean dislodgement distance was

TABLE 3 Regional strain values in the three groups of the study population.

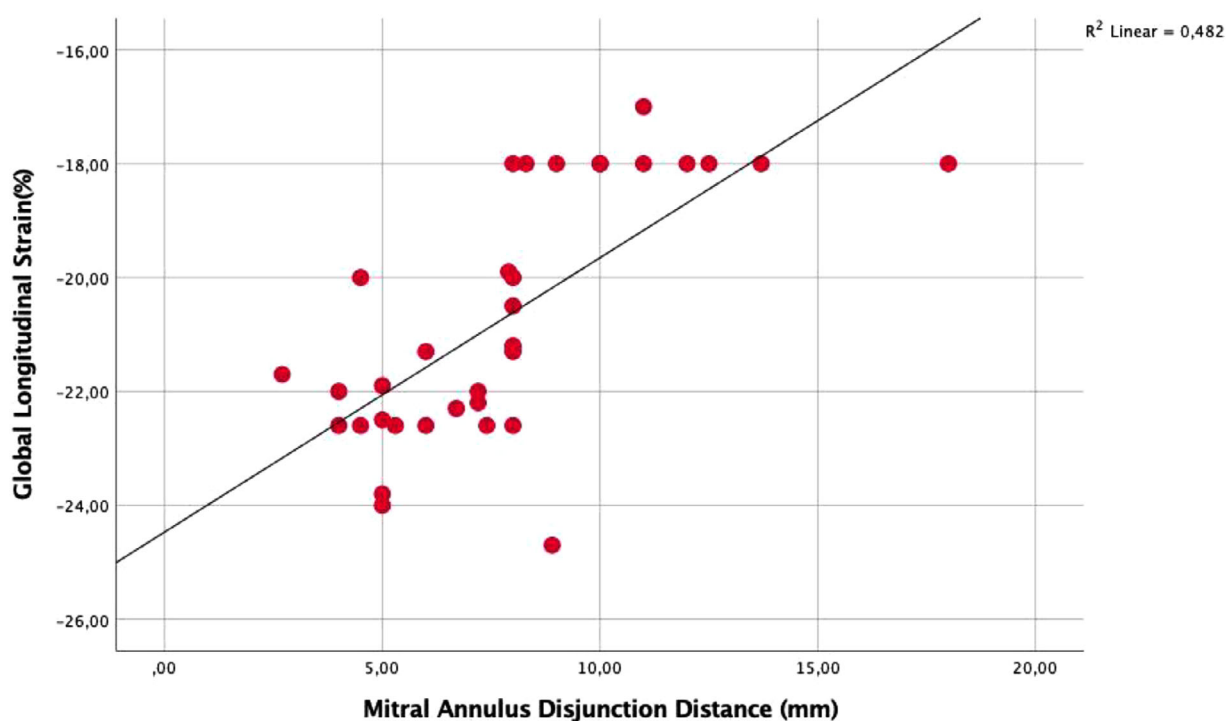
Paremeters	Control group (n = 40)	MAD (–) (n = 69)	MAD (+) (n = 34)	p (Between groups)
GLS, (%)	–24.5 ± 2.2 ^{*,**}	–23.5 ± 2.3 ^{*,***}	–23.1 ± 2.1 ^{*,***}	<.001
Basal anteroseptal (%)	–24.6 ± 2.2 ^{*,**}	–22.8 ± 3.2 ^{*,***}	–19.9 ± 2.2 ^{*,***}	<.001
Basal inferoseptal (%)	–24.0 ± 2.1 ^{*,**}	–20.3 ± 3.3 ^{*,***}	–19.9 ± 3.3 ^{*,***}	<.001
Basal inferior (%)	–22.9 ± 2.5 ^{*,**}	–19.8 ± 2.6 ^{*,***}	–18.8 ± 2.1 ^{*,***}	<.001
Basal inferolateral (%)	–24.6 ± 2.2 ^{*,**}	–18.9 ± 2.6 ^{*,***}	–17.8 ± 2.5 ^{*,***}	<.001
Basal anterolateral (%)	–22.4 ± 4.1	–21.5 ± 3.9	–20.5 ± 3.4	.143
Basal anterior (%)	–22.9 ± 2.4 ^{*,**}	–20.2 ± 3.1 ^{*,***}	–19.8 ± 3.0 ^{*,***}	<.001
Mid anteroseptal (%)	–25.7 ± 3.7 ^{*,**}	–24.1 ± 3.0 [*]	–24.4 ± 3.3 ^{**}	.009
Mid inferoseptal (%)	–25.2 ± 2.7 ^{*,**}	24.5 ± 2.7 ^{*,***}	–22.5 ± 2.8 ^{*,***}	<.001
Mid inferior (%)	–25.6 ± 2.2 ^{**}	–24.5 ± 3.6	–23.2 ± 3.1 ^{**}	.030
Mid inferolateral (%)	–23.8 ± 2.6	–23.5 ± 2.4	–22.5 ± 2.4	.447
Mid anterolateral (%)	–25.0 ± 3.1 ^{**}	–23.7 ± 3.7	–22.9 ± 2.8 ^{**}	.032
Mid anterior (%)	–24.7 ± 4.8	–24.2 ± 1.6	–22.5 ± 2.6	.103
Apical septal (%)	–25.3 ± 3.8	–27.7 ± 2.2	–27.9 ± 2.1	.059
Apical inferior (%)	–27.5 ± 2.5	–27.8 ± 2.3	–27.6 ± 2.9	.971
Apical lateral (%)	–27.0 ± 2.4	–27.5 ± 2.0	–26.2 ± 3.0	.475
Apical anterior	–27.4 ± 1.7	–28.2 ± 1.4	–26.0 ± 2.2	.171
Apex	–27.4 ± 1.7	–28.2 ± 1.5	–27.4 ± 2.1	.539

Abbreviations: GLS, global longitudinal strain; MAD, mitral annular disjunction.

* $p < .05$ Between control and MAD (–) groups.

** $p < .05$ between control and MAD (+) groups.

*** $p < .05$ between MAD (–) and MAD (+) groups.

**FIGURE 2** The relationship between GLS level and MAD distance. GLS, global longitudinal strain; MAD, mitral annular disjunction.

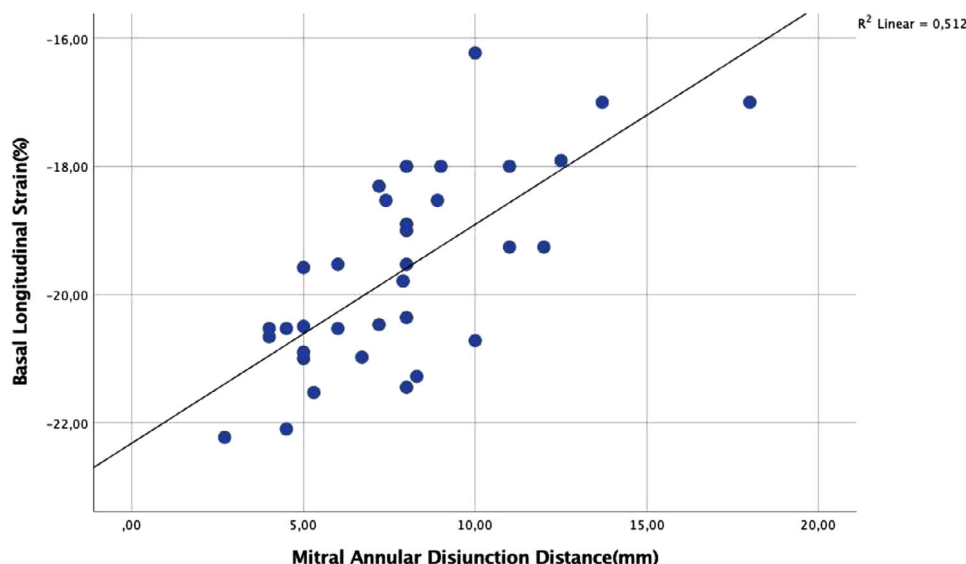


FIGURE 3 The relationship between BLS level and MAD distance. BLS, basal longitudinal strain; MAD, mitral annular disjunction.

8.9 mm. Both results were compatible with ours. However, they found that although MVP had a reductive effect on left ventricular global longitudinal strain (LV-GLS) when compared to the control group with normal mitral valve, MAD positivity did not have any additional effect on LV-GLS. This result was opposing our main finding. One of the main differences between our and their study population was age. Mean age of our and their MAD+ MVP groups were 35.7 ± 14.2 and 56 ± 13 respectively. A systematic review defining the features of MAD has revealed that average age of these patients was 62 years in the literature. Therefore, our study population is younger, mostly composed of Barlow's disease, suggesting that functional effects of MAD may show different characteristics according to the age period in which it is detected, and this may be due to etiological differences.⁸

A case-control study by Wang et al. examined the strain parameters of 21 MAD (+) and 21 MAD (−) MVP patients. MAD was causing a significant decrease in BLS by TTE, basal inferolateral (BIL), basal circumferential and basal radial strain by cardiac magnetic resonance imaging (CMRI). Moreover, they concluded that global circumferential strain by CMR was independently associated with the diagnosis of MAD. They claimed the difference between TTE and CMR as the TTE strain analysis could not catch the significant difference in strain parameters of MAD+ and MAD− MVP patients however CMR could. These results may be attributable to some confounding factors as the relatively small sample size and study design. In our study, all the strain differences were found by TTE evaluation.⁵ More recently, Sanoglion et al. analyzed 93 MVP patients, 34.4% of which were MAD (+) and showed significantly impaired LV-GLS (-17.2 ± 1.4 vs. $-19.4 \pm 3.0\%$, $p < .001$) and LV-GCS (-16.3 ± 4.1 vs. -20.4 ± 4.9 , $p < .001$) in MAD+ MVP patients compared to MAD− MVP cases, despite similar LVEF.⁹

In our study 103 MVP patients and 40 control subjects were included and MAD was detected in 34 (33%) of the MVP patients, compatible with most other studies in the literature. MAD is detected in 20%–58% of the patients diagnosed with MVP and the prevalence is

even higher in myxomatous MVP.¹ Nonetheless, 21% of MAD patients do not have MVP.⁴ In our study, all MAD patients were having MVP.

As indicated in the EHRA expert consensus statement, longitudinal strain proves valuable in evaluating the interplay between the mitral leaflets and the myocardium, as well as illustrating alterations in the temporal pattern of myocardial deformation. The fulfillment of these parameters has been proposed as a potential indicator for identifying an elevated risk of ventricular arrhythmias (VA).¹

Our results provided that longitudinal strain is significantly affected in MAD (+) patients when compared to MAD (−) MVP patients. Longitudinal strain and especially the GLS provides information about the functioning of longitudinal fibres and LV remodeling. It is known to be a predictor of cardiovascular outcome.¹⁰ Therefore, our results are important in terms of detecting early myocardial dysfunction related to MAD especially in the younger patients. Moreover, in our study MVP patients with MAD had more severe mitral insufficiency when compared to the MAD (−) group. This result may be explained by the changes observed in annulus dynamics in patients with MAD. The mitral annulus enlarge more at the end of the systole (paradoxical systolic dilatation) and flattening of the annulus rather than physiologic saddling (paradoxical annular unsaddling) is a feature of MAD. It has been shown that MAD is associated with deformity of mitral leaflets and chordae tendineae. Furthermore, extend of disjunction and degree of mitral regurgitation are shown to be correlated.⁸ Likewise, Dumont et al. have proved that annular dilatation due to MAD (+) Barlow's mitral valve disease causes more severe mitral regurgitation.¹¹

All the above mentioned features of MAD positivity in patients with MAD also may explain the increased number of symptoms in this group, another finding of our study, when compared to MAD (−) group, owing to more severe functional deformation.

Malignant MVP is characterized with increased SCD risk, bileaflet prolapse, ECG repolarization abnormalities, papillary muscle and inferobasal wall fibrosis and its main echo finding is MAD. This entity

also includes another term arrhythmic MVP (AMVP) which usually presents with frequent premature ventricular contractions and T-wave inversion in the inferolateral leads.¹² Although we did not define a subgroup as malignant MVP of AMVP, our results were compatible with the literature such that T-wave inversion in the inferolateral leads was detected in 20.6% of MAD (+) group that was significantly more common than the MAD (−) group (4.3%) ($p = .014$).

CMR can effectively identify prolapsed scallops using a series of cine images, making it particularly suitable for the risk stratification of VA in patients with MVP. This suitability stems from its unique ability to noninvasively detect focal myocardial fibrosis through late gadolinium enhancement (LGE). Several studies have suggested an association between LGE at the midwall of the papillary muscles or patchy myocardial fibrosis (nonischemic pattern) in the LV infero-basal region and the occurrence of complex VA.¹

In a recent study, 2607 participants were included in the study, the authors identified MAD in 1990 cases (76%), most frequently observed at the anterior and inferior ventricular wall. Clinically significant inferolateral disjunction was reported in 134 cases (5%). Positive associations were found between systolic curling and disjunction at any site and systolic curling and prolapse.¹³

LV fibrosis especially at the papillary muscles and inferobasal wall of the left ventricle can be detected as LGE in patients with MAD and previous reports showed that LGE can be seen as high as 40%–47% of these patients.^{5,14} Likewise, in our study 35.3% of MAD+ MVP patients had LGE in CMR whereas this percentage was only 10% for MAD (−) MVP patients. Actually these areas of LGE in MAD (+) MVP patients were found to be related with unipolar low voltage areas which are accepted as a potential substrate for VA and SCD.¹⁵ This relationship between LGE and VA and SCD in patients with MVP was also supported by other studies.^{3,16}

Another important finding of our study was the higher frequency of Pickelhaube sign in MAD+ MVP patients. This sign is a high velocity midsystolic spike gathered from the lateral mitral annulus by tissue Doppler imaging, due to the stretching effect of prolapsing leaflet on posteromedial papillary muscle. As LGE, this sign was found to be a noninvasive imaging marker associated with SCD in MVP in previous studies.¹⁷ We detected this sign in 17.6% of MAD (+) MVP patients whereas only 1.4% of the MAD (−) MVP group had this sign on TTE.

In our study, mean disjunction distance was 7.8 ± 3.2 mm. There is no limit to define the movement of annulus as disjunction. In fact, detachment of the mitral annulus from myocardium may range between a few millimeters to more than 1 cm in the literature.¹⁸ Increased distance also increases the risk of SCD and it is reported that disjunction > 8.5 mm was predictive of VA.¹⁹

4.1 | Study limitations

Relatively small sample size, observational cross-sectional design additional to the lack of blinding and long term follow-up of the clinical outcomes are the main limitations of our study. The subjects were recruited from a single center, which may be associated with a selection

bias. Although performed by experienced professionals, the echocardiography and CMRI techniques used to assess myocardial function and measure MAD have inherent limitations and potential variability in measurements. More comprehensive strain analysis may provide a more precise assessment of LV function. Limited information on MAD aetiology is another limitation since different aetiologies or underlying mechanisms of MAD could influence the study outcomes and interpretation of the results.

5 | CONCLUSION

MAD is a structural abnormality of the mitral annulus which is usually accompanying MVP. Our study suggests that MAD may impair both regional and global LV functions that can be detected with strain analysis. We conclude that longitudinal strain parameters are affected and T-wave inversion in ECG, increased dislodgement distance and LGE are important parameters that can inform about more severe MVP cases with MAD. MAD is a relatively new entity and further studies are necessary to determine the optimal management strategy for patients with MAD.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

All the authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author on request.

PATIENT CONSENT STATEMENT

All participants gave written consent.

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