

The Implication of Left Ventricular Mechanical Dispersion as a Risk Predictor for Ventricular Arrhythmias in Patients with Mitral Valve Prolapse

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Abstract

Background: Mitral valve prolapse (MVP) is considered a benign disorder, although it can be accompanied by ventricular arrhythmias (VA). Speckle tracking echocardiography (STE) can be a promising tool for detecting early derangement. **Objectives:** The aim of this study was to determine whether the left ventricular (LV) mechanical dispersion (MD) derived by STE can be considered a predictor for occurrence of VA in patients with MVP. **Materials and Methods:** This was a cross-sectional study conducted on 63 patients with MVP (37 women and 29 men) presented with palpitation. The patients were divided into two groups: arrhythmic patients with VA (Group 1) and non-arrhythmic patients (Group 2). All of them underwent comprehensive clinical and electrocardiographic examination, cardiac rhythm assessment by Holter monitoring, and comprehensive echocardiographic evaluation including speckle tracking technique. **Results:** VA were detected in 32 of 63 patients. Ventricular bigeminy was the most common type of VA in arrhythmic patients. Unlike other echocardiographic parameters, the LV MD and the mitral annular disjunction (MAD) were found to be significantly higher in arrhythmic versus non-arrhythmic MVP patients ($P < 0.001$). Furthermore, the mean LV MD was higher in patients with frequent ventricular ectopics versus infrequent ones ($P = 0.003$). The cutoff value for LV MD was 35.1 ms or higher (sensitivity 87%, specificity 71%) and for MAD it was 2.7 mm or higher (sensitivity 82%, specificity 60%) in predicting VA in patients with MVP. **Conclusions:** LV MD in addition to MAD can be implemented in risk prediction for VA in patients with MVP presenting with palpitations.

Keywords: Mechanical dispersion, mitral valve prolapse, speckle tracking echocardiography, ventricular arrhythmia

INTRODUCTION

Mitral valve prolapse (MVP), a common valvular heart disease, is defined as the presence of at least 2-mm systolic displacement of mitral valve leaflets above the mitral annulus and has an estimated prevalence of approximately 2%–3% of the general population.^[1,2] It is known to have commonly a good prognosis. However, it can be accompanied in many patients by some sort of dysrhythmia, as they may infrequently develop malignant ventricular arrhythmias (VA) and sudden cardiac death (SCD) with a prevalence of 0.8%–2.5% among patients with MVP.^[3–5] The precise mechanism for the development of such arrhythmias in those patients has not yet been identified, but it has been suggested that papillary muscle fibrosis, chordal rupture, bileaflet prolapse, severe mitral

valve regurgitation, and mitral annular disjunction (MAD) can be associated with an increased risk of arrhythmias in those patients.^[6–10] MAD, which is defined as detachment of the mitral annulus from the basal ventricular myocardium, has been found to be commonly accompanied by papillary muscle fibrosis and VA in individuals with or without MVP.^[9–11]

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Speckle tracking echocardiography (STE) is a modern echo-practice used to evaluate the deformation of the left ventricular (LV) musculature by applying a specialized software technique. It can be used to measure segmental longitudinal strain, global longitudinal strain (GLS), circumferential strain, and mechanical dispersion (MD).^[12,13] Although segmental longitudinal strain is a quantifying measure of the longitudinal contraction of the myocardial wall segments, GLS is a quantifying measure of the total longitudinal contraction of the overall ventricular myocardium, and STE-derived MD is a parameter of heterogeneous desynchronized contraction of the ventricular myocardium. It has been found that MD can be predictive of arrhythmia risk in several cardiac disorders such as ischemic heart disease, hypertrophic or dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy.^[14-16] Similarly, MD has been shown to be correlated with the extent of myocardial fibrosis in many types of arrhythmogenic cardiomyopathies.^[17,18] In contrast, the existence of fibrosis at the papillary muscle and the inferior LV wall was found to be a feature of arrhythmic MVP and it has been proposed as an independent risk factor for VA and SCD.^[19,20] Furthermore, a recent study has indicated that LV MD can be linked to an increased arrhythmic risk and complications in patients with MVP.^[21]

Therefore, this study aimed to determine whether higher LV MD derived by STE is associated with increased incidence of VA in MVP patients presenting with palpitation and whether it can be implemented as a risk predictor for such arrhythmias in these patients.

MATERIALS AND METHODS

This was a cross-sectional study conducted on patients with MVP who presented with palpitation, carried out at the adult echocardiography laboratory in Karbala Center for Heart Diseases from April 1, 2021 to the end of March 2022. All participants were notified about the study procedure and informed consents were taken from each.

The inclusion criteria of the study included patients aged 18–75 years who were diagnosed with isolated MVP. All patients have comprehensive baseline 12-lead electrocardiography (ECG) and cardiac rhythm evaluation by 48-h Holter monitoring, in addition to comprehensive advanced echocardiographic evaluation including speckle tracking technique.

The exclusion criteria of the study included the presence of any other valvular disease, previous cardiac surgery, congenital heart diseases, left bundle branch block or conduction delay, supraventricular dysrhythmia, paced rhythm, or possible alternative cause for arrhythmia (e.g., coronary artery disease, long or short QT syndromes, Brugada syndrome, hypertrophic cardiomyopathy, and electrolyte disturbances).

Sixty-three adult patients with MVP (37 women and 29 men) who presented with palpitation were recruited in this study and divided into two groups: arrhythmic MVP patients (A-MVP) who have VA such as complex ventricular ectopics (VE) or ventricular tachycardia (VT) (Group 1) and non-arrhythmic MVP patients (NA-MVP) who did not have VA (Group 2). The following baseline demographic and clinical information was taken from each participant: age, gender, heart rate, blood pressure, as well as complete medical and medication history. Patients' standard ECGs and 48-h Holter monitoring were reviewed and assessed.

Echocardiography examination was done using General Electric Device (GE VIVID E9, Made in Norway), which includes two-dimensional (2D) mode, M-mode, and Doppler modes, in addition to the advance speckle tracking technique. LV systolic function is measured by ejection fraction (EF), which was evaluated by modified Simpson's biplane method. The LV diastolic function that represents the filling property of the heart during diastole is measured according to the recent American and European guidelines.^[22] Mitral valve (MV) morphology and function were assessed including annular diameters, leaflet thickness, degree of displacement, presence and degree of annular disjunction and severity of mitral regurgitation (MR). MVP was diagnosed as a systolic displacement of the MV leaflet of at least 2 mm beyond the mitral ring toward the left atrium as seen in the parasternal or apical three-chamber long-axis view.^[1] The presence of MAD was measured qualitatively in millimeters in the parasternal or apical long-axis views as the separation between the LV wall and the left atrial wall at the level of the mitral annulus. MR was also quantified using the maximum vena-contracta width measured by 2D color Doppler in the parasternal or apical three-chamber long axis views.

STE analyses were performed on digitally stored film records without knowing the patients' status and arrhythmia characteristics. Standard apical two-chamber, three-chamber, and four-chamber pictures with the best endocardial delineation were selected for each patient. Speckle-tracking by a specialized software for each of the 17 LV segments was performed throughout the cardiac cycle, and minor adjustments were done by the operator when necessary to maximize tracking validity. To obtain the segmental and GLS values, the peak systolic strain was attained for each LV segment and averaged for all 17 segments as a depiction of GLS. The LV MD was identified as the standard deviation (SD) of the time to peak strain, which is the time from onset of QRS wave on ECG to the point of peak strain, in all 17 LV myocardial segments.^[23] Figure 1 shows samples of STE-derived LV MD of two patients with similar GLS and different MD.

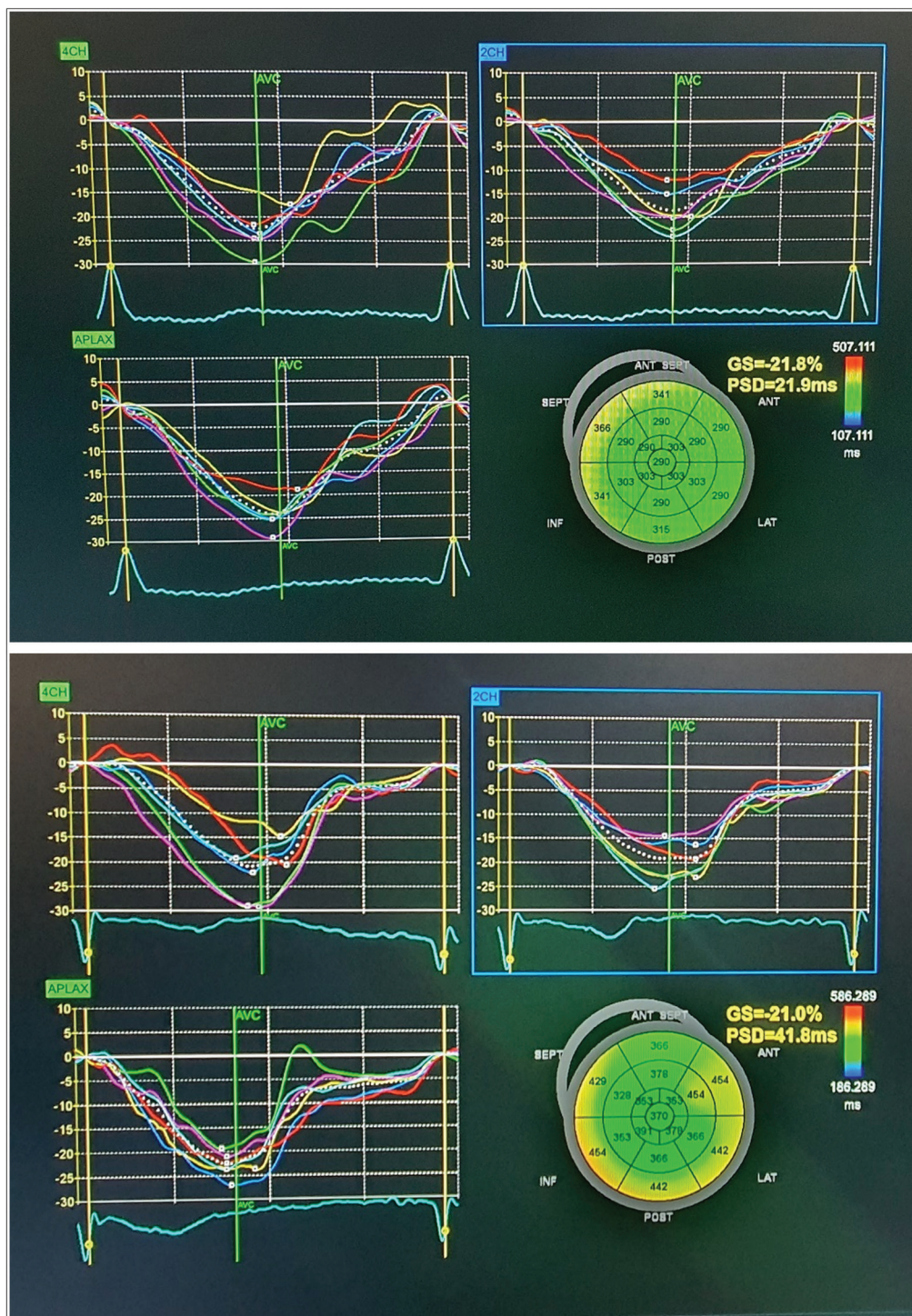


Figure 1: Time to peak-strain standard deviation (PSD) derived from speckle tracking echocardiography technique of two patients with nearly similar GLS value and different PSD (mechanical dispersion SD)

Statistical analysis

For data application, management, and analysis, Microsoft Excel 2010 and Statistical Package for the Social Science (SPSS) version 26.0 were used. Descriptive data were presented as tables and graphics. The quantitative data were evaluated using *t* test and categorical data were investigated using chi-square test. Logistic regression analysis was implemented to estimate the odds ratio (OR)

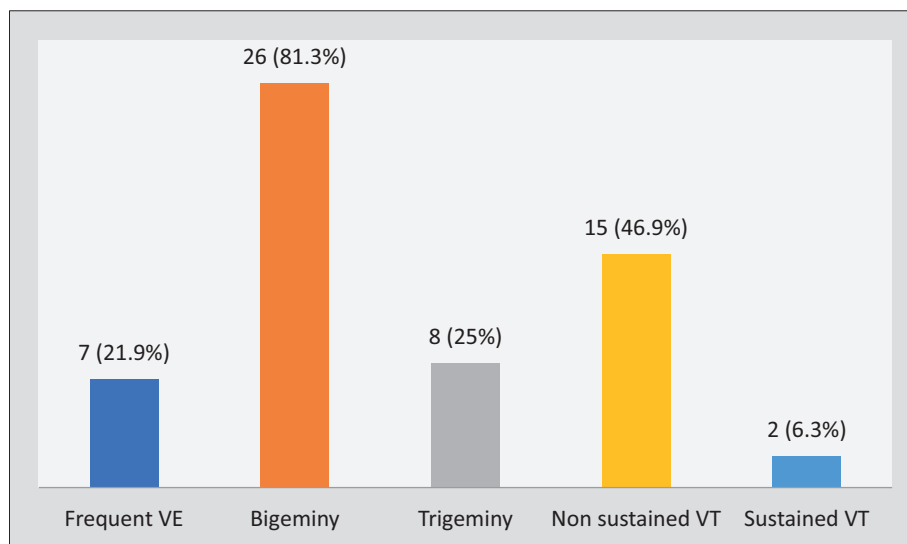
for the prediction of arrhythmic risk in patients with MVP. Receiver-operating characteristic curve (ROC) analysis for diagnostic indices was done. A value of $P < 0.05$ was used to assess the level of significant.

Ethical approval

The study protocol and the patient information and consent form were reviewed and approved by the local

Table 1: Demographic and clinical characteristics of patients in both groups

Parameters		Group 1: Arrhythmic (N = 32)	Group 2: Non-arrhythmic (N = 31)	Total (N = 63)	P Value
Age (mean ± SD)		41.75 ± 13.028	38.38 ± 14.621	40.09 ± 13.826	0.34
Sex	Male	10 (31.3%)	15 (48.4%)	25 (39.7%)	0.2
N (%)	Female	22 (68.8%)	16 (51.6%)	38 (60.3%)	
BMI (mean ± SD)		27.92 ± 5.751	26.42 ± 4.715	27.18 ± 5.259	0.61
BMI	Underweight	1 (3.1%)	0 (0%)	1 (1.6%)	0.31
N (%)	Normal weight	11 (34.4%)	16 (51.6%)	27 (42.9%)	
	Overweight	6 (18.8%)	7 (22.6%)	13 (20.6%)	
	Obese	14 (43.8%)	8 (25.8%)	22 (34.9%)	
BP in mm Hg (mean ± SD)	Systolic	128.59 ± 9.09	125.32 ± 12.97	129.05 ± 11.175	0.25
	Diastolic	77.65 ± 7.618	75.96 ± 6.882	78.01 ± 7.595	0.36
PR in bpm (mean ± SD)		81.22 ± 7.877	79.38 ± 7.260	80.31 ± 7.575	0.34

**Figure 2:** Types of ventricular arrhythmia in arrhythmic group

Institute Review Board (IRB) at the College of Medicine, Al-Nahrain University according to the document number (202012163 on April 4, 2021) and the study was carried out in accordance with the requirements of the 1975 Declaration of Helsinki, as revised in 2008.

RESULTS

VA was detected in 32 of 63 MVP patients, who comprised in Group 1 (A-MVP); and the other 31 patients without VA comprised in Group 2 (NA-MVP). The demographic and clinical characteristics of patients in both groups revealed no significant differences between the two groups as shown in Table 1. Regarding the types of VA in arrhythmic patients, ventricular bigeminy was the most common followed by non-sustained VT then trigeminy, frequent VE and least sustained VT as shown in Figure 2. The distribution of types of VA in arrhythmic patients' group in relation to the gender is given in Table 2, which shows that frequent VE was more common in men, whereas ventricular bigeminy was more in women.

Table 2: Distribution of types of ventricular arrhythmia according to gender in arrhythmic group

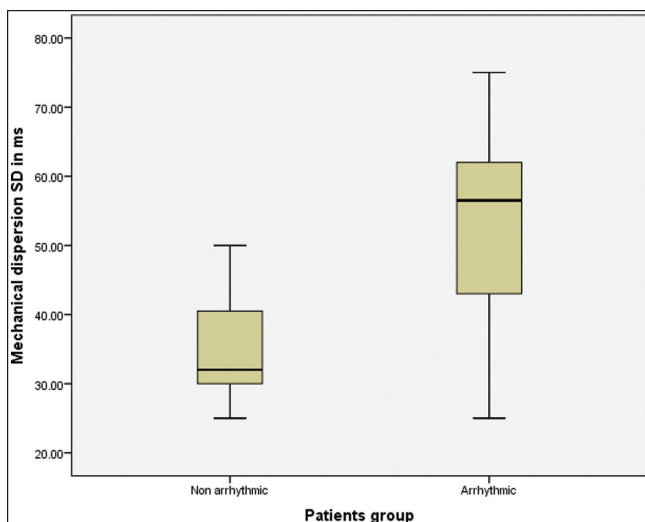
Types of VA	Total No.	Gender				P*
		Male		Female		
		N	%	N	%	
Frequent VE	7	5	71.4%	2	28.6%	0.019
Bigeminy VE	26	7	26.9%	19	73.1%	0.35
Trigeminy VE	8	5	62.5%	3	37.5%	0.07
Non sustained VT	15	6	40.0%	9	60.0%	0.45
Sustained VT	2	0	0.0%	2	100.0%	1

*Fischers' exact test

The echocardiographic findings in both groups, as shown in Table 3, revealed that there were no significant differences in the grading of MVP and MR, in LV systolic and diastolic functions, and in LV GLS between the two groups, whereas the LV MD SD and the degree of MAD were found to be significantly greater in arrhythmic patients as compared with non-arrhythmic patients ($P < 0.001$). Figure 3 shows the comparison of MD SD between arrhythmic and non-arrhythmic

Table 3: Echocardiographic data in patients of both groups

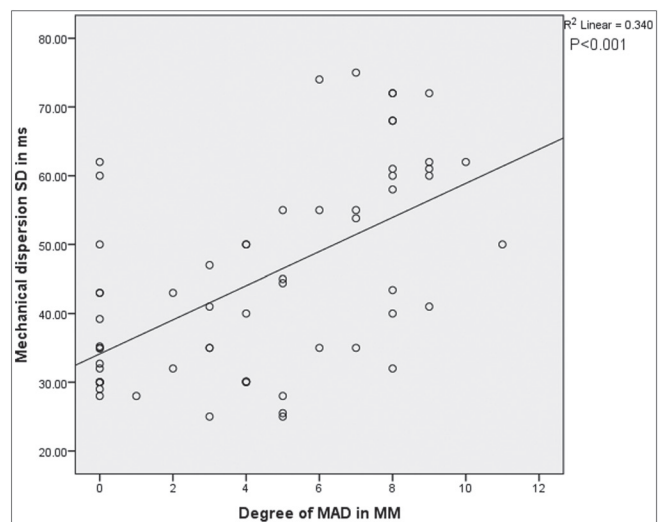
Parameters		Group 1: Arrhythmic (N = 32)		Group 2: Non-arrhythmic (N = 31)		P Value
LV systolic function (EF%) (mean $\pm$ SD)		65.53 $\pm$ 4.02		67.23 $\pm$ 2.81		0.058
LV diastolic function	Normal, N (%)	26	(81.2%)	29	(93.5%)	0.26
	Mild LVDD, N (%)	6	(18.8%)	2	(6.5%)	
MVP grade	Mild, N (%)	28	(87.5%)	29	(93.5%)	0.67
	Mod., N (%)	4	(12.5%)	2	(6.5%)	
	Severe, N (%)	0	(0.0%)	0	(0.0%)	
MR grade	Mild, N (%)	30	(93.7%)	28	(90.3%)	0.61
	Mod., N (%)	2	(6.3%)	3	(9.7%)	
	Severe, N (%)	0	(0.0%)	0	(0.0%)	
Degree of MAD in mm (mean $\pm$ SD)		6.13 $\pm$ 3.260		2.26 $\pm$ 2.463		<0.001
Annular diameter in mm (mean $\pm$ SD)		29.69 $\pm$ 2.78		29.42 $\pm$ 3.16		0.7
Leaflet thickness in mm (mean $\pm$ SD)		2.59 $\pm$ 0.75		2.55 $\pm$ 0.49		0.77
Degree of displacement in mm (mean $\pm$ SD)		2.25 $\pm$ 0.51		2.26 $\pm$ 0.63		0.96
Left atrial dimension in mm (mean $\pm$ SD)		31.62 $\pm$ 3.16		30.48 $\pm$ 4.90		0.27
Left atrial area in cm ² (mean $\pm$ SD)		16.81 $\pm$ 2.985		16.25 $\pm$ 4.057		0.54
GLS in % (mean $\pm$ SD)		18.7 $\pm$ 2.7		19.1 $\pm$ 1.7		0.49
Mechanical dispersion SD in ms (mean $\pm$ SD)		54.16 $\pm$ 14.01		34.68 $\pm$ 6.90		<0.001

**Figure 3:** Comparison of mechanical dispersion SD between arrhythmic and non-arrhythmic group

groups. It was found that there was also a significant positive correlation between the LV MD and the degree of MAD ($P < 0.001$), as shown in Figure 4. Furthermore, the mean of LV MD was noticed to be significantly higher in arrhythmic patients with frequent VE versus those with infrequent VE ($P = 0.003$), as shown in Figure 5.

Reproducibility

Multivariate regression showed that MD and degree of MAD were significant predictors of arrhythmic risk (OR = 1.137, 95% confidence interval [CI] = 1.051–1.230, and $P = 0.001$) and (OR = 1.358, 95% CI = 1.026–1.798, and $P = 0.032$), respectively. However, EF level was

**Figure 4:** Correlation between mechanical dispersion SD and degree of mitral annular disjunction (MAD) in both groups

found to be a protective factor against arrhythmia with significant difference (OR = 0.757, 95% CI = 0.597–0.960, and $P = 0.022$), respectively, as shown in Table 4.

Predictivity

ROC curve analysis for diagnostic indices of MD SD and degree of MAD were used in this study to predict VA in patients with MVP. A comparison of the area under curve revealed that MD SD, and degree of MAD have the widest area under the curve, and they were good predictors (0.873 and 0.818), respectively, with significant association ($P < 0.001$). The cutoff point for MD SD of 35.1 ms or higher may predict VA with sensitivity of 87% and specificity of 71%, while the cutoff point for MAD

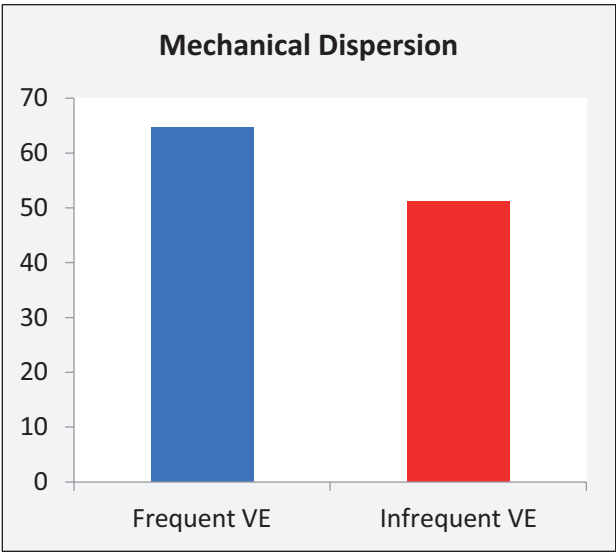


Figure 5: Comparison of mechanical dispersion in arrhythmic patients with frequent VE versus infrequent VE

Table 4: Multivariate regression analysis for the prediction of VA				
Parameter	OR*	95% CI		P Value
		Lower	Upper	
Mechanical dispersion	1.137	1.051	1.230	0.001
Degree of MAD	1.358	1.026	1.798	0.032
Ejection fraction	0.757	0.597	0.960	0.022

* Odds ratio: predicted probability for arrhythmic patients

of 2.7 mm or higher may predict VA with sensitivity of 82% and specificity of 60%, as presented in Table 5 and Figure 6.

DISCUSSION

MVP has recently received increasing attention for identifying high-risk patients due to its association with VAs and the increased risk of SCD.^[4-7,19] This study involved a cohort of MVP patients divided into two groups; with or without VA, in which there were no significant differences in demographic and clinical characteristics between the two groups, which was consistent with the results registered in other similar studies.^[24-26]

Although most patients with MVP have normal resting ECG findings, those with a history of VA or cardiac arrest often show some abnormalities on resting ECG and/or 24-h Holter ECG.^[25-27] In this study, ventricular bigeminy was the most prevalent type of VA in the arrhythmic group, which was also noticed by a research done in Mayo Clinics on MVP patients with out-of-hospital cardiac arrest.^[5] In addition, this study found that frequent VE were more common in men than women, which was consistent with the results reported by another recent research on a large group of patients with MVP.^[25]

Speckle-tracking echocardiography imaging data analysis revealed that LV MD was significantly greater in arrhythmic compared to non-arrhythmic MVP patients ($P < 0.001$) which can be considered as a predictive factor for arrhythmic risk in these patients. This was consistent with other studies stated that arrhythmic MVP patients had greater MD than non-arrhythmic patients.^[21,28] Moreover, this study found that MD was also significantly higher in MVP patients with frequent VE compared to those with infrequent VE ($P = 0.003$). LV MD SD is an indicator of heterogeneity of the LV myocardial regional contraction and strain. The traction effect of prolapsing mitral valve leaflets on the corresponding papillary muscles and the basal segments of LV wall can be the possible reason of strain heterogeneity and hence LV MD.^[21,27] Although the mechanisms of VA in patients with MVP are yet not fully explained, it has been suggested that VA might be caused by valvular trigger acting on a pathological myocardial substrate, such as hypertrophy, or fibrosis.^[20] Also, when the morphologies of premature ventricular contractions (PVCs) in patients with MVP were evaluated, revealed that the dominant form commonly originated from the papillary muscles,^[29] proposing the hypothesis that the prolapsed valve increased the mechanical traction on papillary muscles, which would trigger and induce these PVCs, that may also potentiate progression to malignant VA, particularly if more myocardial fibrosis develops in the papillary muscles. Similarly, recent studies applying cardiac magnetic resonance imaging alongside the findings from autopsies of patients with MVP having SCD showed that a large percentage of these patients had focal myocardial fibrosis of the papillary muscles and in the basal LV myocardium adjacent to the MV.^[30-32] Moreover, electrophysiological studies revealed that PVCs in patients with MVP may originate from the MV apparatus itself or from other nearby areas such as the LV base and outflow tracts.^[29,33] These results and observations suggest that a myocardial substrate for VA may also be embodied by diffuse myopathy and not only by focal changes in the myocardium.^[34,35]

Furthermore, this study revealed no significant differences in the grading of MVP and MR, and in LV systolic and diastolic functions between the arrhythmic and non-arrhythmic groups as also observed in a similar recent study.^[21] Although previous research showed that the presence of moderate to severe MR is an independent predictor for the occurrence of arrhythmia in MVP patients,^[36] several subsequent studies have found that VAs or SCD can occur in MVP patients in the absence of significant MR.^[20,21,24] Additionally, most arrhythmic patients in our study population were having trivial or mild MR, asserting that the association of LV MD with the risk of VAs was independent of the MR grade, and also proposing that it might be a primary rather than

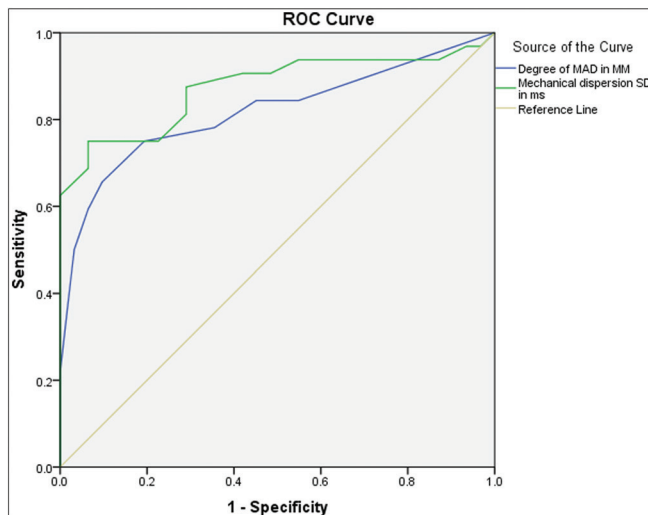
Table 5: ROC analysis for diagnostic indices for prediction of VA in the study groups

Test variables	AUC	Standard error	P-value*	95% CI		Cutoff point	1 – Specificity
				Lower bound	Upper bound		
Mechanical dispersion SD in ms	.873	.048	.000	.780	.967	35.1	0.290
Degree of MAD in mm	.818	.056	.000	.709	.927	2.7	0.400

AUC = area under curve, CI = confidence interval

*Significant $P \leq 0.05$ and high significant at ≤ 0.001

AUC = 1–0.90 (excellent), AUC = 0.90–0.80 (good), AUC = 0.80–0.70 (fair), AUC = 0.60–0.70 (poor), AUC = 0.50–0.60 (fail)

**Figure 6:** ROC analysis of diagnostic indices for prediction of VA in the study groups

an MR-related myopathy could be responsible for the development of VAs in patients with MVP.

In this study, the degree of MAD was significantly greater in the arrhythmic group, which is consistent with that observed by other researchers.^[24,25] Also, the results from another recent study stated that arrhythmic MVP patients had a larger MV annulus, higher degree of MAD and LV posterior wall curling, and indicated that MAD length of >4.8 mm was more associated with myocardial fibrosis and higher risk of arrhythmic events.^[28]

Regarding the prediction of occurrence of VA in patients with MVP, the ROC analysis for diagnostic indices revealed that MD SD and degree of MAD had the widest area under the curve, and highest sensitivity and specificity were achieved when both parameters were included. The cutoff point for the LV MD was 35.1 ms or higher and for the degree of MAD was 2.7 mm or higher, that might predict the risk of VAs. In addition, normal LV MD has been recently evaluated in a cohort of healthy subjects utilizing STE reported to be 34 ± 10 ms.^[37] Based on these findings, an LV MD of 35.1 ms or higher seems to be a reasonable cutoff value for predicting risk of VAs in patients with MVP.

CONCLUSIONS

This study suggests that, in addition to the degree of MAD, LV MD derived from STE can be implemented in risk stratification for VA in patients with MVP presenting with palpitations. The cutoff values for LV MD of ≥ 35.1 ms have a sensitivity of 87% and specificity of 71% and degree of MAD of ≥ 2.7 mm has a sensitivity of 82% and specificity of 60% in the prediction of VA in MVP patients.

Settings

This was a cross-sectional study on patients with MVP who presented with palpitation, carried out at the adult echocardiography lab in Karbala Center for Heart Diseases, in the period from April 2021 to the end of March 2022.

Financial support and sponsorship

Not applicable.

Conflicts of interest

There are no conflicts of interest.

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