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ADULT CARDIOLOGY

Mitral Annular Disjunction in Mitral Leaflet Prolapse: Prevalence, Clinical Profile and Echocardiographic Features at Tertiary Cardiac Care Centre, Rawalpindi

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ABSTRACT

Objective: To determine the prevalence of Echocardiographically-recognizable Mitral Annular Disjunction in patients of Myxomatous Mitral Valve Disease/Mitral Leaflet Prolapse.

Study design: Analytical Cross sectional .

Place & Duration of study: Armed Forces Institute of Cardiology/National Institute of Heart Diseases (AFIC/NIHD), Rawalpindi Pakistan from Jul 2021 to Sep 2021.

Methodology: A total (n=45) diagnosed patients of Myxomatous Mitral Valve disease, were included through non-probability consecutive sampling. Mitral Annular Disjunction (MAD) was assessed by 2D TTE imaging as the distance between the point of insertion of the posterior leaflet into the left atrial wall (upper boundary of the disjunction) and the link between the left atrium and the left ventricle myocardium (lower border of the disjunction)at end-systole in parasternal long axis view. A distance equal to or greater than 2mm was used as a threshold for diagnosing the presence of MAD. The data analysis was done with the help of computer software programme SPSS version 24.

Results: Total number of patients were 45 patients with males being 32 (71.11%) while females being 13 (28.88%), with a mean age of 30.24 + 5.21 years. MAD was present in 26 (57.8%) of the patients with mean length of 2.88mm + 2.77 mm. Patients with MAD had more chest pain, palpitations and dyspnoea than those without MAD. Mitral regurgitation was more severe in patients with MAD than without. The MAD severity correlated with the presence of Non Sustained Ventricular Tachycardia.

Conclusion: MAD is not an uncommon finding in patients having myxomatous mitral valve disease/mitral valve prolapse. The causal relationship between Mitral Valve Prolapse, Mitral Annular Disjunction and Mitral Regurgitation is not fully known but it is apparent that MAD in these patients is associated with clinical implications such as chest pain, dyspnea, palpitations and increased incidence of arrhythmias like Atrial fibrillation and Non-Sustanined Ventricular Tachycardia (NSVT).

Keywords: Mitral Annulus Disjunction, Mitral Leaflet Prolapse, Myxomatous Mitral Valve.

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INTRODUCTION

Mitral annulus disjunction (MAD) is a clinically significant disease characterised by aberrant atrial displacement of the mitral valve's leaflet hinge point and it is easily detectable on echocardiography but often overlooked. Association of MAD has been found with mitral valve prolapse and myxomatous mitral valve.[1] Various morphological changes encompassing various components are involved in myxomatous mitral valve (MMV) which ultimately lead to the mitral valve (MV) functional impairment. MAD was initially described in the 1970s a shift in the mitral valve's hinge point-atrial wall away from left ventricular wall into the left atrium during systole. During systole, the mitral annulus/left atrial wall separates from the base of the inferolateral left ventricular myocardium.[2]

The MV annulus is a three-dimensional (3D) saddle-shaped structure with a complex three-dimensional (3D) structure. The mitral annulus has distinct roles. It electrically separates the left atrium from the ventricle, binds the mitral leaflets to the atrioventricular junction, and connects the left atrium to the ventricular myocardium. The annulus roots are separated from the ventricular myocardium, to which they would typically be linked, in mitral annular disjunction (MAD).[3] The diagnosis cannot be achieved in diastole because the ventricular myocardium is properly positioned under the annulus. As the posterolateral myocardium contracts during systole, the annulus "slides" and separates from the ventricular

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myocardium by a variable distance, ranging from a few millimetres to more than a centimeter.[4] The movement of MV annulus is located near the LV apex in systole and near the LA in diastole. During early systole mitral valve annulus contracts and assumes a deep saddle shape. Both of these factors are important in maintaining MV integrity when the LV contraction is in its early stages.[5] These mitral annulus motions are necessary for an equal and uniform distribution of mechanical load on the MV by the myocardium. MAD results in functional decoupling of annulus from the LV, and the movement of annulus is corresponding to the LA instead of LV throughout the cardiac cycle,[6] Thus, instead of contraction and saddle shape, it expands and assumes a more flattened shape in systole. This flattened MV annulus results in exccess load on the chordae tendinae and mitral leaflets, leading to accelerated degenerative process. Thus MAD results in MV annulus in being hypermobile, further contributing to the myxomatous mitral leaflets' degeneration.[7,8]

MAD has been linked to atrial and ventricular arrhythmias, as well as abrupt cardiac mortality, according to new research (SCD) both in the presence and absence of MVP.[9] However, most of the patients with MVP have a relatively benign course with some having a higher risk of complications. There is a significant correlation between severity of MAD and the detection of NSVT on Holter monitoring. In one study a disjunction distance >8.5 mm was highly predictive for NSVT.[10] The disjunction of mitral annulus poses mechanical stress on the mitral leaflets, and the chordae, and the papillary muscles, and this in turn leads to fibrosis in the long run, serving as a trigger for ventricular arrhythmias. Myocardial fibrosis is one of the independent factors that is associated with adverse clinical outcomes in these patients. Larger the disjunction distance, higher is the prevalence of SCD in these patients with LV fibrosis and MVP.[11]

Carmo *et al.* examined patients with MMVD and MVP by TTE and found a prevalence of MAD to be 55%, 9 Prevalence in women seem to be higher than men.[12] The rate of identification of MAD in studies of MMVD patients was 50.8 percent, and 32.6 percent among patients with MVP, according to a meta-analysis of pooled data of MAD detection rates by using several imaging modalities.[13]

Little attention has been paid to Mitral annulus disjunction, and the clinical profile of these patients and echocardiographic characteristics are by and large unknown. While MAD is associated with mitral valve prolapse (MVP) and myxomatous mitral valve disease, it is unknown which patients with MAD are at higher risk and which additional imaging features may help identify them.

METHODOLOGY

On parasternal long axis view using standard transthoracic echocardiography, myxomatous mitral valve was defined as the presence of extra leaflet tissue and leaflet thickening greater than 5 mm resulting in a prolapse greater than 2 mm into the left atrium. Mitral Valve Prolapse was defined as superior displacement of one or both the mitral leaflets above the mitral annulus into the left atrium by at least 2 mm in the parasternal long-axis view.

A cross-sectional study was carried out from July 2021 to December 2021 at tertiary cardiac care institute.

Sample Size: Using expected prevalence of MAD 55%,[8] and prevalence of MLP 3%, the sample size of n=45 patients was calculated.

Inclusion Criteria: 45 diagnosed patients of Mitral Valve Prolapse aged more than 18 years of both genders were included via non-probability consecutive sampling.

Exclusion Criteria: Patients with active or previous history of Infective Endocarditis were excluded from the study.

After seeking ethical approval from IERB AFIC/ NIHD (IERB Letter#27/6/R&D/2022/105), patients were selected according to inclusion. Informed consent was obtained from the study participants after introducing them to the study and its objectives. Patients were examined for the presence of MAD by 2D Transthoracic echo (2DTTE) in the echo department of AFIC. Name, age, hospital ID number and all the echo parameters were entered in the self-structured Performa.

Data was entered in SPSS version 24. For qualitative factors, frequencies and percentages were determined, like gender and clinical parameters including CAD, chest pain, palpitations, syncope and atrial fibrillation. Stratification was done with regards to presence or absence of MAD and its effect on clinical and echocardiographic parameters by applying Chi-square test . A p-value ≤0.05 was considered significant by taking 95% CI and 5% margin of error.

RESULTS

45 patients were included. Baseline clinical characteristics of the patients are depicted in Table-I. Following results were found. Most of the patients

were symptomatic with a NYHA Class-I of 11(24.47%). 30 (66.7%) patients had NYHA Class-II and 4 (8.9%) patients had NYHA Class-III symptoms. 23 (51.1%) patients had mild MR, 6 (3.3%) patients had moderate MR and 4 (8.9%) patients had severe MR. 2 patients had undergone a mitral valve repair as shown in Table-I.

Table-I: Frequency and Percentages of Baseline Characteristics (n=45**)**

Variables	Frequency (%)	
Gender	Male	32(71.1%)
	Female	13(28.9%)
CAD	Yes	3(6.7%)
	No	13(28.9%)
Chronic AF	Yes	21(46.67%)
	No	24(53.33%)
NSVT	Yes	4(8.9%)
	No	41(91.1%)
CVA	Yes	2(4.4%)
	No	43(95.6%)
Symptomatic	Yes	34(75.6%)
	No	11(24.4%)
Dyspnoea NYHA	I	11(24.4%)
	II	30(66.7%)
	III	4(8.9%)
Chest pain	Yes	10(22.2%)
	No	35(77.8%)
Palpitation	Yes	18(40.0%)
	No	27(60.0%)
Syncope	Yes	5(11.1%)
	No	40(88.9%)
MR	No	12(26.7%)
	Mild	23(51.1%)
	Moderate	6(3.3%)
	Severe	4(8.9%)
Mitral repair surgery	Yes	2(4.4%)
	No	43(95.6%)
Mitral repair & replacement	Yes	2(4.4%)
	No	43(95.6%)
MAD	Yes	26(57.8%)
	No	19(42.2%)

AF=Atrial fibrillation; CAD=Coronary artery disease; NSVT=Nonsustained ventricular tachycardia; CVA = Cerebrovascular accident; NYHA=Newyork heart association dyspnoea; MR=mitral regurgitation; MAD=Mitral annular disjunction

MAD was present in 26 (57.8%) patients and on average measured 2.8 ± 2.77 mm. Patient with most severe MAD had a length of disjunction of 8 mm. MAD was more common in males 18(69.23%) compared to females 8(30.76%). Coronary artery disease(CAD) was more prevalent in patients with MAD 3(11%) .Atrial fibrillation(AF) was documented in 14(53.53%) of the MAD patients and 7(36.84%) of the patients without MAD as shown in Table-II. Chest pain was present in 8(30%) of the patients with MAD and 2(10%) of the patients without MAD. Mitral regurgitation mean grade was 1.5 in patients with MAD and 1.05 in patients without MAD.

There was a high prevalence of palpitations in this population with 18(40%) patients experiencing them. Premature ventricular beats and non-sustained ventricular tachycardia (NSVT) were more commonly found on holter monitoring in mitral annular disjunction patients. 4 patients had an episode of NSVT on holter monitoring. All 4 had MAD. NSVT occurred with a frequency of 15.38% in patietns with MAD. Atrial fibrillation was documented in 21(46.7%) of the patients. 2 (4.4%) patients had a CVA.

We were able to find an association between the presence of disjunction and Mitral regurgitation.

Twenty three (51.11%) patients had grade 1 MR, 14 (60.8%) of these had MAD. 6(13.33%) patients had grade 2 MR, 5 (83.3%) of these had MAD. Four (8.89%) patients had grade 3 MR, all 4 (100%)of these had MAD as shown in Table-II.

Table-II: MAD Association with Gender, CAD, AF, Stroke, Symptomatic, Chest Pain, Palpitations, Syncope , NSVT & MR

Variables	MAD (n=45)			
		Yes	No	*p*-value
Gender	Male	18	14	0.745
	Female	8	5	
CAD	Yes	3	23	0.183
	No	0	19	
Chronic AF	Yes	14	7	0.083
	No	12	12	
CVA	Yes	1	25	0.672
	No	1	18	
Symptomatic	Yes	14	5	0.536
	No	3	9	
Chest pain	Yes	8	18	0.104
	No	2	17	
Palpitations	Yes	13	13	0.109
	No	5	14	
Syncope	Yes	3	23	0.650
	No	2	17	
NSVT	Yes	4	0	0.126
	No	22	19	
MR (Grade)	0	3	9	0.20
	1	14	9	
	2	5	1	
	3	4	0	

AF=Atrial fibrillation; CAD=Coronary artery disease; NSVT= Nonsustained ventricular tachycardia; MR = Mitral regurgitation

Patients with MAD had a larger EROA 0.22±0.15 cm^2 compared to those without it. 0.22±0.15 cm^2 (*p*-value <0.003). Consequently due to effect of MAD on the severity of MR and EROA, patients with MAD had

larger end-diastolic diameter 44.0±9.46 mm and end-diastolic volume 142.3±32.7 ml than those without it 36.3±3.63 mm and 106.7±24.7 respectively as depicted in Table-III.

Table-III: Echocardiographic Parameters ; with MAD and without MAD (n=45)

Echo Parameters	Mean±SD	With MAD	Without MAD	*p*-value
EDD, mm	40.7±8.43	44.0 ± 9.46	36.3 ± 3.63	0.001
EDV, ml	127.2±34.30	142.3 ± 32.7	106.7± 24.7	<0.001
EF, %	58.5±4.47	57.5 ± 5.70	60.0 ± 0.0	0.35
LA, mm	35.2±4.22	36.2 ± 5.17	33.94 ± 1.80	0.45
PASP, mmHg	24.2±10.95	26.6 ± 12.9	21.0 ± 6.45	0.60
EROA, cm^2	0.16±0.15	0.22 ± 0.15	.08 ± 0.10	0.003
MR	-	1.38 ± .89	0.57 ± 0.60	0.002

EDD=End diastolic diameter; EDV=End diastolic volume; EF = Ejection fraction; LA=Left atrial diameter; PASP= Pulmonary artery systolic pressure; EROA = Effective regurgitant orifice area; MR = mitral regurgitation.

DISCUSSION

Mitral annular disjunction is a common entity but little importance has been given to it in patients with Myxomatous mitral valve disease. MAD is seen with high prevalence in this population. In a meta-analysis of pooled data on MAD detection rates using several imaging modalities, researchers found that, the rate of detection of MAD in studies of MMVD patients was 50.8%.[13] Our study found a prevalence of 57.8% (26 patients). The prevalence of MAD varies between different studies because there is no consensus on the specific length that defines MAD. Studies vary with thresholds ranging from 2mm to 5mm for defining MADS.[7,8] Our study used a cutoff of 2mm for 2d TTE measurements. Konda *et al*. analyzed patients having severe MR and in their study they used a ≥2mm cutoff for identification of MAD by TTE.[15] Not all MVP patients have MAD, and MAD can occur without MVP, indicating that MAD and MVP can be distinct disease entities with normal mitral valves in MAD patients.[14]

The maximum distance of disjunction in our patients with MMVD was 8mm, and the main localization of MAD was found in the lateral (P1) region and middle (P2) segments of the posterior mitral leaflet. Significant correlation was detected between the magnitude of the disjunction and number of the segments prolapsing and therefore the severity of MR.[15]

MMVD/MVP and MAD are associated with an increased risk of Ventricular Tachycardias and SCD, according to growing evidence.[9] Symptomatic ventricular arrhythmias are prevalent in patients with MVP, according to Wijngaarden and colleagues.[14] In our group 15% of the patients with MAD had an episode of NSVT on holter monitoring while none of the patients without MAD had any ventricular arrhythmia. Perhaps if long term monitoring like event recorders were to be used ,this frequency of ventricular arrhythmias detection may increase. A study incorporating Cardiac magnetic resonance imaging in patients with MMVD found fibrosis with Left Ventricular late gadolinium enhancement, and the fibrosis was localized mostly to the papillary muscles and the posterolateral wall. MAD emerged as a constant feature of these patients with fibrosis of Left Ventricle.[16]

As a result, it can be deduced that in the presence of MMVD and MVP in the region of the posterior mitral leaflet, which is enhanced by MAD, increased mechanical stress of the papillary muscles and posterolateral wall of the Left Ventricle causes increased mechanical stress of the papillary muscles and posterolateral wall of the Left Ventricle, leading to LV localized myocardial fibrosis, that serves as a morphological substrate of arrhythmias. Our study didn't incorporate CMR to evaluate for fibrosis.[17]

Our study had 2 patients who had a mitral valve repair and had a recurrence of symptoms and MR. According to Newcomb *et al*. the presence of MAD in advanced degenerative myxomatous situations is a significant determinant of MV repair failure, due to deficiency of annuloplasty. In the MAD presence , the annuloplasty ring fails to adequately relieve or decrease the mechanical stress on the mitral apparatus including leaflets, chordae, and papillary muscles. The posterior mitral leaflet must be removed from its location and reattached to the LV's more proximal musculature before being secured with an annuloplasty, making it a time-saving treatment. As a result, MAD is especially important in patients with MMVD and MVP who are undergoing surgery.[18]

Patients with MAD have larger EROA and MR than those without and have larger ventricular dimensions and volumes.[18] Our study supports an association between Severity of MR and presence of MAD. This greater severity leads to ventricular remodeling by dilation and fibrosis eventually, which in turn leads to adverse clinical outcomes.

LIMITATIONS OF STUDY

This study is limited by its retrospective nature, a single centre study and a small population. We used 2D TTE for measurements whereas 3D TTE, CT and CMR provide

superior imaging for detection of MAD as well as areas of annular involvement. CMR can help better define patients particularly at risk of arrhythmias and SCD. Nevertheless MAD remains of paramount importance owing to its clinical implications as well as for surgical management.

CONCLUSION

In patients with MMVD/MVP, MAD is not uncommon. The causal relationship between MVP, MAD and MR is not completely understood but it is apparent that the occurrence of MAD in these patients is associated with clinical implications such as chest pain, dyspnea, palpitations and increased incidence of arrhythmias like Afib and NSVT.

The presence of MAD is independently associated with long-term excess incidence of clinical arrhythmic events. Its recognition on echocardiography is important to better identify these patients who are more at risk of these clinical implications and also to help surgeons in planning the surgical repair. The modification of the surgical repair technique allows better surgical correction of the annular disjunction, which seems to optimize long-term results in these challenging cases.

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Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

MAV: Manuscript writing, drafting, concept and editing

MBS: Study design, concept and critical review

UI: Study design, intellectual contribution and concept

SA: Data collection, data entry and review of article

SAS: Review of article, formatting and critical review

AA: Data management, data collection&manuscript writing

SKS: Proof reading, Intellectual contribution, final approval

AS: Data management, analysis and interpretation

HY: Formatting, critical review and data collection/entry

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Chen TE, Ong K. Three-dimensional echocardiographic assessment of mitral annular physiology in patients with degenerative mitral valve regurgitation undergoing surgical repair: comparison between early-and latestage severe mitral regurgitation. J Am Society Echocar-Diog 2018; 31(11): 1178-1189.
2. Wunderlich NC, Ho SY, Flint N, Siegel RJ. Myxomatous mitral valve disease with mitral valve prolapse and mitral annular disjunction: clinical and functional significance of the coincidence. J Cardio Dev Dis 2021; 8(2): 9-12.
3. Bartko PE, Hülsmann M, Hung J, Pavo N, Levine RA, Pibarot P, et al. Secondary valve regurgitation in patients with heart failure with preserved ejection fraction, heart failure with mid-range ejection fraction, and heart failure with reduced ejection fraction. Eur Heart J 2020; 41(29): 2799-2810.
4. Eriksson MJ, Bitkover CY, Omran AS. Mitral annular disjunction in advanced myxomatous mitral valve disease: Echocardio-graphic detection and surgical correction. J Am Soc Echocardiogr. Off. Publ. Am. Soc. Echo 2005; 18(1): 1014–1022.
5. Newcomb A.E, David T.E, Lad V.S, Bobiarski J, Armstrong S, Maganti M. Mitral valve repair for advanced myxomatous degeneration with posterior displacement of the mitral annulus. J. Thorac. Cardiovasc Surg 2008; 136(1): 1503–1509.
6. Lee A.P, Jin C.N, Fan Y, Wong R.H, Underwood M.J, Wan S. Functional Implication of mitral annular disjunction in mitral valve prolapse: A quantitative dynamic 3D echocardiographic study. Jacc. Cardiovasc. Imaging 2017; 10(1): 1424–1433.
7. Lee AP, Hsiung MC, Salgo IS, Fang F, Xie JM, Zhang YC, Lin QS et al. Quantitative analysis of mitral valve morphology in mitral valve prolapse with real-time 3-dimensional echocar-diography: Importance of annular saddle shape in the patho-genesis of mitral regurgitation. Circulation 2013; 127(1): 832–841
8. Salgo IS, Gorman JH. 3rd, Gorman R.C, Jackson B. Effect of annular shape on leaflet curvature in reducing mitral leaflet stress. Circulation 2002; 106(1): 711–717.
9. Carmo P, Andrade M.J, Aguiar C, Rodrigues R, Gouveia R, Silva J.A, Mitral annular disjunction in myxomatous mitral valve disease: A relevant abnormality recognizable by transthoracic echocardiography. Cardiovasc Ultrasound 2010; 8(1): 53.
10. Topilsky Y, Michelena H, Bichara V, Maalouf J. Mitral valve prolapse with mid-late systolic mitral regurgitation: Pitfalls of evaluation and clinical outcome compared with holosystolic regurgitation. Circulation 2012; 125(1): 1643–1651.
11. Perazzolo Marra M, Basso C, De Lazzari M. Morphofunctional abnormalities of mitral annulus and arrhythmic mitral valve prolapse. Circ Cardiovasc Imaging 2016; 9(1): e005030.
12. Konda T, Tani T, Suganuma N, Nakamura H, Sumida T, Fujii Y, et al. The analysis of mitral annular disjunction detected by echocardiography and comparison with previously reported pathological data. J Echocard 2017; 15(1): 176–185
13. Bennett, S, Thamman, R, Griffiths, T, Oxley C, Khan JN, Phan T. et al. Mitral annular disjunction: a systematic review of the literature. Echocardiograp 2019; 36(1): 1549–1558
14. Van Wijngaarden, A.L. de Riva, M. Hiemstra, Y.L. Parameters associated with ventricular arrhy-thmias in mitral valve prolapse with significant regurgitation. Heart 2021; 107(5): 411-418.
15. Konda. T, Tani. T, Suganuma. N, Fujii. Y, Ota M, Kitai T. Mitral annular disjunction in patients with primary severe mitral regurgitation and mitral valve prolapse. Echocardiography 2020.
16. Sriram CS, Syed FF,. Malignant bileaflet mitral valve prolapse syndrome in patients with otherwise idiopathic out of hospital cardiac arrest. J Am Coll Cardiol 2018; 62(1): 222-230
17. Lee AP, Jin CN, Fan Y, Wong RHL, Underwood MJ, Wan S. Functional implication of mitral annular disjunction in mitral valve prolapse: a quantitative dynamic 3D echocardiographic study J Am Coll Cardiol Imag 2017; 10(1): 1424-1433
18. Antoine C, Mantovani F, Benfari G. Pathophysiology of degenerative mitral regurgitation: new 3-dimensional imaging insights. Circulation: Cardiovas Imag 2018; 11(1): e005971.