Received: 30 May 2019 | Revised: 22 June 2019 | Accepted: 4 July 2019

DOI: 10.1111/echo.14437

REVIEW

Echocardiography WILEY

Mitral annular disjunction: A systematic review of the literature

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Abstract

Background: Mitral annular disjunction (MAD) is a structural abnormality where there is a separation between the mitral valve annulus and the left atrial wall which is not well understood.

Methods: We conducted a systematic review to evaluate the prevalence of MAD, factors associated with MAD and clinical outcomes among patients with MAD.

Results: A total of 19 studies were included in this review, and the number of noncase report studies had between 23 and 1439 patients. The pooled rate of MAD in studies of myxomatous mitral valve patients was 66/130 (50.8%, 3 studies), and among patients with mitral valve prolapse was 95/291 (32.6%, 3 studies). One study suggests that 78% of patients with MAD had mitral valve prolapse, and another suggested it was strongly associated with myxomatous mitral valve disease (HR 5.04 95% CI 1.66–15.31). In terms of clinical significance, it has been reported that MAD with disjunction > 8.5 mm was associated with nonsustained ventricular tachycardia (OR 10 95% CI 1.28–78.1). There is also evidence that gadolinium enhancement in papillary muscle (OR 4.09 95% CI 1.28–13.05) and longitudinal MAD distance in posterolateral wall (OR 1.16 95% CI 1.02–1.33) was predictive of ventricular arrhythmia and late gadolinium enhancement in anterolateral papillary muscle was strongly associated with serious arrhythmic event (OR 7.35 95% CI 1.15–47.02).

Conclusions: Mitral annular disjunction appears to be common in myxomatous mitral valve disease and mitral valve prolapse which can be detected on cardiac imaging and may be important because of its association with ventricular arrhythmias and sudden cardiac death.

KEYWORDS

cardiac magnetic resonance imaging, echocardiography, mitral annular disjunction

1 | INTRODUCTION

Mitral annular disjunction (MAD) is a structural abnormality whereby there is a distinct separation of the mitral valve annulus—left atrial wall continuum and the basal portion of the posterolateral ventricular myocardium, a region which would normally be attached. It is a localized abnormality usually affecting the ventricular myocardium directly under the posterior mitral valve leaflet, typically in the region of the P1 and P2 mitral valve scallops.[1] MAD is detectable during ventricular systole only when the mitral annulus "slides" and detaches from the ventricular myocardium by a variable distance ranging from a few millimeters to more than 10 mm is distance.[2]

Mitral annular disjunction was initially described over 30 years ago in an autopsy report of 900 hearts.[3] This evaluation found that 92% of the 25 hearts with mitral valve prolapse had MAD. At that time, MAD was not attributed to clinically adverse outcomes and as such it received little attention. In more recent years, there has been an increasing number of studies examining the different aspects of MAD,[4-7] with a general theme that MAD maybe of more clinical significance than previously thought. In particular, MAD leads to hypermobility and myxomatous degeneration of the mitral valve leaflets and there is growing evidence that MAD may be associated with ventricular arrhythmias and sudden cardiac death.[1]

Although MAD is not a well-known entity within the cardiac imaging community, it can be detectable on noninvasive imaging modalities including transthoracic echocardiography, transesophageal echocardiography, and cardiac magnetic resonance (CMR) imaging. Imaging can detect not only the presence of MAD but also its location and extent along with assessing the severity of associated myxomatous mitral valve disease and mitral regurgitation if present. The presence of MAD is detected as an absence of myocardium during systole between the posterior mitral valve annulus and adjacent basal segments of the ventricular wall. On echocardiography, this is most commonly seen in the parasternal long-axis view (Figure 1A in systole showing disjunction and B in diastole with disjunction not seen) and to a lesser extent from the apical four-chamber view and apical two-chamber view in the systolic phase. The equivalent image projections on CMR are also able to detect the presence, extent, and location of MAD in the systolic phase (Figure 2A in systole showing disjunction and B in diastole). CMR has additional benefits of assessing for myocardial and papillary muscle fibrosis which may also be present.

In view of the importance of understanding MAD, we conducted a systematic review of the literature to evaluate what is currently known about MAD. In particular, we were interested in rates of MAD in different populations, clinical and imaging correlations with MAD and adverse outcomes associated with MAD.

2 | METHODS

We conducted a systematic review to evaluate the current literature on MAD. Cohort studies, case-control studies, cross-sectional studies, and case reports which evaluated patients with MAD were included. We were particularly interested in studies that reported the prevalence of MAD, variables associated with MAD and clinical outcomes among patients with MAD. Studies that analyzed the same cohort as an included study were excluded to avoid duplication of results. Both full publications and conference abstracts were included.

A search of MEDLINE and EMBASE was performed on OVID® using the search term "mitral annular disjunction" in March 2018. After deduplication, there were 23 publications. An additional search of PubMed was performed to identify literature that was accepted and published ahead of print using the same search term. This search yields 9 results.

The search results were independently reviewed for inclusion by two reviewers (SB and CSK). Full texts of potentially relevant studies were downloaded and reviewed for final inclusion. Data extractions were performed by two independent reviewers (SB and CSK). Extracted information included study design, year, number of patients, mean age of participants, percentage of male participants, participant inclusion criteria, imaging methods used, rate of MAD in the cohort, clinical findings for the MAD and non-MAD cohort and clinical outcomes associated with the MAD and non-MAD cohort.

Results from the extractions are presented in Tables. A figure was used to show the pooled rate of MAD in different cohorts. The results were narratively synthesized.

3 | RESULTS

A total of 19 studies were included in the review (Figure 3).[1,2,4-20] These studies included 14 retrospective cohort studies, 2 matched case-control studies, 1 cross-sectional study and 2 case reports (Table 1). The studies were conducted between 1995 and 2018. The number of patients included in the noncase report studies ranged between 23 and 1439. From 13 studies that reported mean age of participants, the average age overall was 53 years and among the 11 studies that reported the sex of the participants, overall the mean percentage of male participants was 41%. The inclusion criteria for participants among the included studies varied considerably which included participants with myxomatous mitral valve disease, mitral valve prolapse, established MAD, participants with implantable cardioverter-defibrillator implant for idiopathic ventricular fibrillation, survivors of sudden death, and those general patients referred for echocardiographic evaluation. The imaging modalities

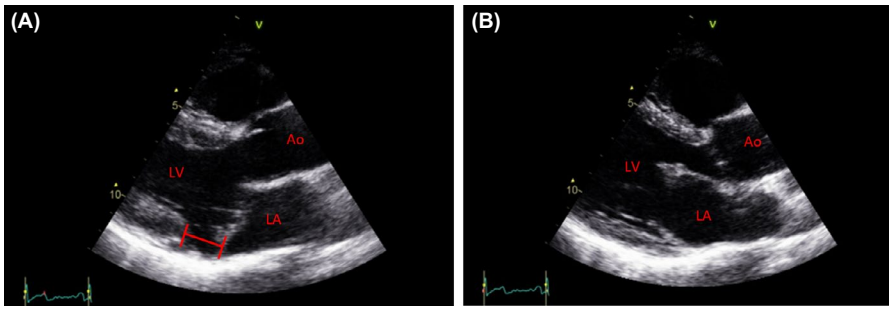

FIGURE 1 Parasternal long-axis view on transthoracic echocardiography showing mitral annular disjunction in ventricular systole (A) which is not present in diastole (B)

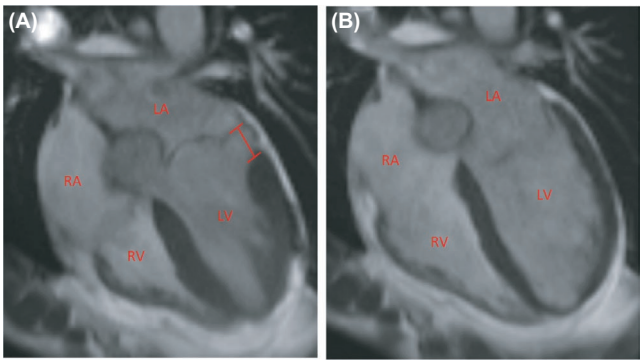

FIGURE 2 Cardiac magnetic resonance image showing mitral annular disjunction in ventricular systole (A) which is not present in diastole (B)

to detect and quantify MAD were transthoracic echocardiography, transesophageal echocardiography and CMR imaging.

Table 2 shows the studies that evaluated the rate of MAD. Four studies evaluated patients with myxomatous mitral valve disease. Five studies evaluated patients with mitral valve prolapse or floppy mitral valve and another two studies evaluated patients who underwent transthoracic echocardiography. One other study evaluated patients with idiopathic ventricular fibrillation who had an ICD implanted. The imaging methods used to identify MAD were 2D echocardiography (7 studies), 3D transthoracic echocardiography (2 studies), and CMR imaging (2 studies). The pooled rate of MAD in different patient groups is shown in Figure 4. The pooled rate of MAD in the 3 studies of myxomatous mitral valve was 66/130 (50.8%). Among patients with mitral valve prolapse, the pooled rate of 3 studies was 95/291 (32.6%). A single study of severe mitral regurgitation with a floppy mitral valve reported a rate of 48/185 (25.9%). In a general cohort of transthoracic echocardiography patients, the two studies by Konda reported a rate of 170/2157 (7.9%). In the postventricular fibrillation and arrest cohort, the rate of MAD was 5/32 (15.6%).

The clinical and imaging features associated with MAD are shown in Table 3. Dejgaard et al evaluated the reasons for imaging for patients who were found to have MAD and 34% had valvular heart disease and were followed up, 27% had arrhythmias, 12% had palpitations, 10% had heart murmur, 9% had aborted cardiac arrest, and 2% had syncope or presyncope. They also reported mitral valve prolapse to be present in 78% of patients with MAD.[4] Essayah et al reported that myxomatous mitral valve disease was a strongly associated with MAD (HR 5.04 95% CI 1.66–15.31), and other significant variables included mitral regurgitation severity (HR 3.12 95% CI 1.002–9.806) and mitral annulus diameter end-systolic 2-chamber length (HR 1.17 95% CI 1.05–1.30).[11] Konda et al reported that mitral valve prolapse was associated with MAD (OR 3.65 95% CI 1.70–7.83).[7] In the study by Torras 2018, all patients with MAD had bi-leaflet prolapse and all patients with myxomatous mitral valve prolapse and sudden death had larger MAD distance (10.3 ± 1.5 vs 6.9 ± 1.7 mm).[18] The observation about sudden cardiac death with longer MAD was also reported by Parazzollo Marra et al.[5]

Table 4 shows the outcomes associated with MAD that are reported by patients. Carmo et al[1] found no sustained ventricular tachycardia among MAD patients but a disjunction of >8.5 mm was predictive of nonsustained ventricular tachycardia (OR 10 95% CI 1.28–78.1). Clavel et al[10] studied mitral valve prolapse patients, and all the patients with sudden death and implantable cardioverter-defibrillator had MAD while 12% had MAD in the control group. Dejgaard et al studied MAD patients and found that gadolinium enhancement in papillary muscle (OR 4.09 95% CI 1.28–13.05) and longitudinal MAD distance in posterolateral wall (OR 1.16 95% CI 1.02–1.33) was predictive of ventricular arrhythmia and late gadolinium enhancement in anterolateral papillary muscle was strongly associated with serious arrhythmic event (OR 7.35 95% CI 1.15–47.02).[4] Essayah et al reported the MAD was associated with ventricular arrhythmias.[12] Perazzolo Marra et al[5] reported that longer MAD was present in 50 sudden deaths with MVP and fibrosis compared to 20 sudden deaths in patients without mitral valve prolapse. Zienciuk et al[20] reported 5 patients with MAD among 32 patients with idiopathic ventricular fibrillation.

4 | DISCUSSION

Our review of MAD has several key findings. First, there is evidence that in some populations such as myxomatous mitral valve disease and mitral valve prolapse, MAD is common and the posterior mitral valve annulus should be inspected carefully and MAD should

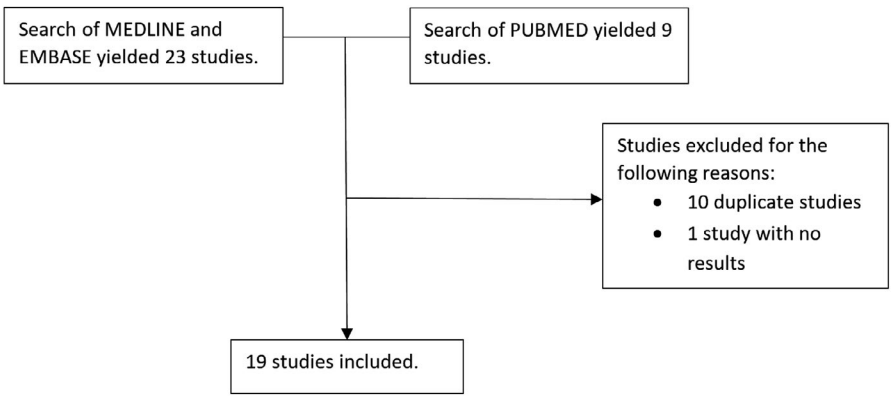

FIGURE 3 Flow diagram of study inclusion

TABLE 1 Description of studies of mitral annular disjunction

Study ID	Study design	Year	No. of patients	Mean age	% Male	Inclusion criteria
Augello 2017	Case report	Published 2017	1	46	0	Case report of patient with disappearance of electrographic abnormalities after surgical mitral valve repair in patient with MVP and MAD.
Carmo 2010	Retrospective cohort study	2003–2006	38	57	53	Patients with myxomatous mitral valve disease who underwent transthoracic echocardiogram.
Christiansen 2010	Retrospective cohort study	Published 2010	31	56	61	Patients with MVP who underwent CMR.
Clavel 2015	Matched case-control study	Published 2015	126	–	–	Patients who survived sudden death with ICD and no cause other than MVP and 84 controls with MVP.
Dejgaard 2018	Cross-sectional study	2015–2017	116	49	40	Patients with MAD identified on echocardiogram or CMR.
Eriksson 2005	Retrospective cohort study	1995–1999	67	52	66	Patients with advanced myxomatous mitral valve disease who underwent mitral valve repair with or without correction of MAD.
Essayah 2019	Retrospective cohort study	Published 2019	89	64	29	Patients with mitral valve prolapse which was myxomatous or fibroelastic disease who underwent CMR.
Jin 2014	Matched case-control study	Published 2014	120	–	–	Patients with MVP and severe mitral regurgitation undergoing repair and age, sex-matched controls with 3D TOE.
Konda 2013	Retrospective cohort study	2010	718	65	–	Patients referred for echocardiography.
Konda 2017	Retrospective cohort study	2014	1439	65	58	Patients referred for echocardiography.
Lee 2017	Retrospective cohort study	Published 2017	156	59	74	Patients with MVP, heart failure with functional mitral regurgitation and controls who underwent 3D TOE.
Mantovani 2017a	Retrospective cohort study	Published 2017	61	–	–	Patients with myxomatous valve disease and severe regurgitation on 3D TOE.
Mantovani 2017b	Retrospective cohort study	2017	61	52	–	Patients with MAD assessed for left ventricular abnormalities pre- and postmitral valve repair with sutured annuloplasty ring.
Perazzolo Marra 2016	Retrospective cohort study	2010–2014	36	44	25	Patients with right bundle branch block or polymorphic ventricular arrhythmia referred for clinic with echocardiographic evidence of MVP with CMR.
Tani 2015	Retrospective cohort	2009–2010	185	–	–	Patients with severe MR causing floppy mitral valve.
Toki 2019	Retrospective cohort study	Published 2018	23	–	–	Patients with mitral valve prolapse and 3D TOE.
Torras 2018	Retrospective cohort study	2016–2017	101	59	50	Patients with myxomatous MVP and patients with fibroelastic deficiency who underwent echocardiogram.
Uchikawa 2018	Case report	2018	1	24	0	Patient with constrictive pericarditis and worsening MAD after long-term chylopericardium.
Zienciuk 2018	Retrospective cohort study	1998–2018	32	–	–	Patients with idiopathic ventricular fibrillation with ICD implantation and echocardiogram.

Abbreviations: CMR = cardiac magnetic resonance imaging; ICD = implantable cardioverter-defibrillator; MAD = mitral annular disjunction; MVP = mitral valve prolapse; TOE = transesophageal echocardiogram.

TABLE 2 Prevalence of mitral annular disjunction

Study ID	Cohort description	Imaging used	Sample size	Rate (%)
Carmo 2010	Myxomatous mitral valve disease	Transthoracic echocardiogram	38	21/38 (55%)
Christiansen 2010	Mitral valve prolapse	Cardiac magnetic resonance imaging	31	18/31 (58%)
Essayagh 2019	Mitral valve prolapse and myxomatous mitral valve disease or fibroelastic disease	Cardiac magnetic resonance imaging	89	31/89 (35%)
Konda 2013	Referred for echocardiogram	Echocardiogram	718	45/718 (6%)
Konda 2017	Referred for echocardiogram	Echocardiogram	1439	125/1439 (9%)
Lee 2017	Mitral valve prolapse, normal mitral valve and heart failure patients with function mitral regurgitation.	3D transesophageal echocardiogram	156	42/156 (27%) but among mitral valve prolapse 42/101 (42%). None of FMR group had MAD
Mantovani 2017a	Myxomatous mitral valve disease	3D transesophageal echocardiogram	61	27/61 (44%)
Mantovani 2017b	Myxomatous mitral valve disease	2D echocardiogram	61	27/61 (44%)
Tani 2018	Severe MR causing floppy mitral valve	2D echocardiogram	185	[a]Type 0/No MAD—14 (7.6%) Type I—123(66.5%) Type II—47 (25.4%) Type III—1 (0.5%)
Torras 2019	Mitral valve prolapse	2D echocardiogram	101	22/101 (22%)
Zienciuk 2018	Idiopathic VF arrest with ICD	2D echocardiogram	32	5 (15.6%)

[a]Type I—hypermobile basal LV segment with no MAD, type II—MAD < 5 mm, type III MAD—>5 mm.

be considered for routine evaluation when reporting on imaging. Second, MAD appears to be associated with ventricular arrhythmias so once detected, it may be of clinical importance but more studies are needed to better understand its clinical significance. Third, there is growing evidence that among patients with cardiac arrest and there is no identified cause and identification of MAD may be important as it may be associated with arrhythmias that could have precipitated the event. Collectively, the findings from this review are that more research and education about MAD is needed.

The exact mechanism for the development of MAD and its rates in different patient cohorts is unclear. It is unknown if it is a congenital, degenerative, or acquired structural abnormality. A key finding of this review is that there is a higher proportion of patients with MAD who have a myxomatous mitral valve compared to patients with a structurally normal heart. It has been suggested by Hutchins et al that the increased tissue formation and leaflet mobility in the form of bowing and prolapsing segments is thought to be due to the increased mechanical stress and stretch placed

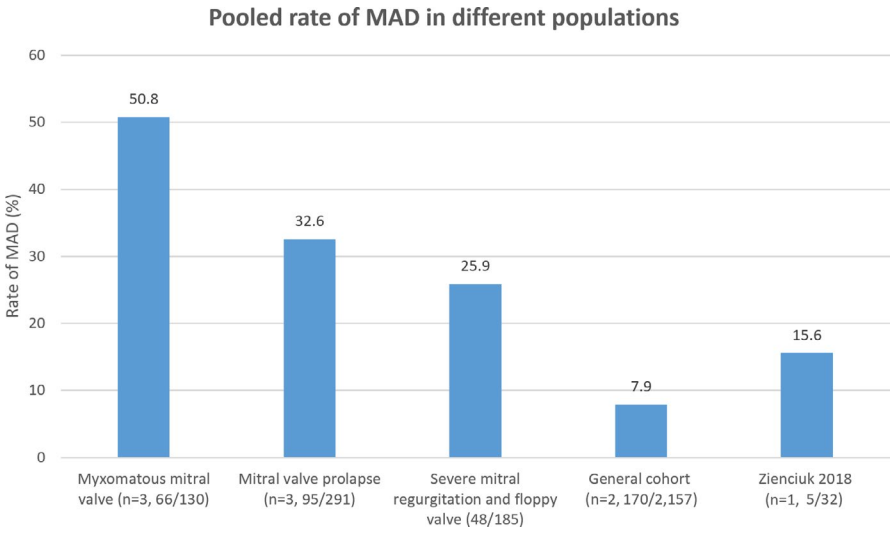

FIGURE 4 Pooled rate of mitral annular disjunction in different cohorts

TABLE 3 Clinical and imaging features associated with mitral annular disjunction

Study ID	Imaging	Findings
Carmo 2010	Echocardiogram	Comparing MAD to no MAD:
		Age 60 ± 15 vs 55 ± 15.
		Female sex 13/21 vs 5/17.
		Coronary artery disease 1/21 vs 0/17.
		Atrial fibrillation 6/21 vs 4/17.
		Stroke 3/21 vs 0/17.
		Endocarditis 0/21 vs 2/17.
		Symptomatic 21/21 vs 14/17.
		Mean NYHA class: 1.4 ± 0.9 vs 1.2 ± 1.0.
		Syncope 2/21 vs 3/17.
		Palpitations 6/21 vs 6/17.
		Chest pain 9/21 vs 2/17.
		Mitral repair surgery 1/21 vs 3/17.
		Mitral prosthesis only 3/21 vs 2/17.
		Mitral repair and replacement 1/21 vs 1/17.
		No difference in left ventricular end-diastolic diameter, left ventricular end-diastolic volume, ejection fraction, fractional shortening, left atrial diameter, pulmonary artery systolic pressure, mitral regurgitation and effective regurgitant orifice area comparing MAD to no MAD.
		MAD group had reduced diastolic-to-systolic mitral annulus diameter difference of −4.6 ± 4.7 mm compared to 3.4 ± 1.1 mm in no MAD group.
Dejgaard 2018	Echocardiogram/ CMR	Reasons for echo was:
		Valvular heart disease follow-up 39 (34%).
		Evaluation for arrhythmias 27 (23%).
		Palpitations 14 (12%).
		Heart murmur 11 (10%).
		Aborted cardiac arrest 10 (9%).
		Syncope or presyncope 2 (2%).
		Dyspnea 2 (2%).
		Other 11 (10%).
		MVP present in 90/116 (78%) of patients with MAD.
Essayah 2019	CMR	Independent predictors of MAD:
		Myxomatous mitral valve disease (HR 5.04 95%CI 1.66–15.31).
		Mitral regurgitation severity (HR 3.12 95%CI 1.002–9.806).
		Mitral annulus diameter end-systolic 2-chamber length (HR 1.17 95%CI 1.05–1.30).
		MAD was also associated with enlarged basal left ventricular systolic diameter, mitral annulus and left ventricular fibrosis at the level of papillary muscle.
Jin 2014	3D TOE	Difference between MAD and no MAD:
		Commissural width (CW) (mm) 41.8 ± 6.1 vs 37.8 ± 4.6, $P < 0.001$.
		Anteroposterior diameter (mm) 36.4 ± 6.2 vs 36.3 ± 4.6, $P < 0.001$.
		AP-to-CW ratio (%) 0.87 ± 0.08 vs 0.96 ± 0.08, $P < 0.001$.
		Annular height (mm) 4.8 ± 1.3 vs 5.6 ± 1.5, $P < 0.001$.
		AH-to-CW ratio (%) 11.5 ± 2.7 vs 14.9 ± 4.2, $P < 0.001$.
		Annular unsaddling (%): 18 (90) vs 35 (46), $P < 0.001$.
		Annual circumference (mm): 128.2 ± 19.5 vs 121.3 ± 13.6, $P < 0.001$.
		Annular area (mm^2): 121 ± 390 vs 1088 ± 255, $P < 0.001$.

(Continues)

TABLE 3 (Continued)

Study ID	Imaging	Findings
		Leaflet billowing volume (mL): 1.91 ± 1.99 vs 0.70 ± 0.74, $P < 0.001$.
		Chordal length (anterolateral) (mm) 25.9 ± 4.0 vs 22.6 ± 5.3, $P < 0.001$.
		Chordal length (posteromedial) (mm) 27.8 ± 5.2 vs 24.5 ± 6.1, $P < 0.001$.
Konda 2013	Echocardiogram	LA diameter smaller with MAD (3.0 ± 0.38 vs 3.66 ± 0.53).
		Septal, lateral and posterior TDI significantly higher in MAD.
		Variation in degree of MAD: 5 had MAD diameter > 5 mm, 11 < 5 mm, 26 no measurable distance by hypermobility seen.
Konda 2017	Echocardiogram	Differences between MAD and no MAD:
		Age 55 ± 21 vs 66 ± 16, $P < 0.0001$.
		Female 57.6% vs 40.6%, $P = 0.0002$.
		LV diastolic dimension (cm) 4.42 ± 0.51 vs 4.59 ± 0.65, $P = 0.005$.
		LV systolic dimension (cm) 2.76 ± 0.47 vs 3.00 ± 0.73, $P < 0.0001$.
		Left atrial dimension (cm) 3.14 ± 0.60 vs 3.63 ± 0.68, $P < 0.0001$.
		Left atrial volume (mL) 49.7 ± 21.1 vs 64.0 ± 27.8, $P < 0.0001$.
		Left atrial volume index (mL/m^2) 31.7 ± 12.3 vs 39.6 ± 18.1, $P < 0.001$.
		Left atrial ejection fraction (%) 48.3 ± 11.4 vs 45.8 ± 13.0, $P = 0.04$.
		End-systolic volume (mL) 26.6 ± 8.87 vs 32.1 ± 22.7, $P = 0.008$.
		Ejection fraction (%) 62.2 ± 5.64 vs 60.0 ± 9.8, $P = 0.01$.
		Left ventricular wall motion index: 1.07 ± 0.21 vs 1.18 ± 0.37, $P = 0.002$.
		E/A 1.20 ± 0.52 vs 1.06 ± 0.56, $P = 0.009$.
		Deceleration time of the early mitral filling wave (ms) 220.3 ± 54.9 vs 234.1 ± 70.4, $P = 0.033$.
		Mitral valve prolapse 12% vs 2.9%, $P < 0.001$.
		Multivariate predictors of MAD:
		Age OR 0.98 (0.96–0.99), $P = 0.001$.
		Gender OR 2.03 (1.24–3.32), $P = 0.005$.
		Left ventricular dimension diastole OR 2.33 (1.13–4.83), $P = 0.022$.
		Left ventricular dimension systole OR 0.39 (0.18–0.85), $P = 0.018$.
		Left atrial dimension OR 0.47 (0.29–0.77), $P = 0.003$.
		Mitral valve prolapse OR 3.65 (1.70–7.83), $P = 0.001$.
Lee 2017	3D TOE	Differences between MAD and no MAD:
		Age 56 ± 13 vs 60 ± 9.
		Men 74% vs 71%.
		Body surface area (m^2) 1.7 ± 0.1 vs 1.7 ± 0.2.
		Heart rate 73 ± 13 vs 76 ± 14.
		Ejection fraction (%) 62 ± 8 vs 62 ± 7.
		End-diastolic volume (mL) 133 ± 37 vs 139 ± 42.
		End-systolic volume (mL) 51 ± 22 vs 52 ± 20.
		Left atrial volume (mL) 132 ± 74 vs 133 ± 64.
		Effective regurgitant orfice (mm^2) 56 (32–76) vs 50 (30–65).
		Number of prolapsed segments 3.8 ± 2.2 vs 1.2 ± 0.4.
		Chordal rupture 52% vs 73%.
		Average intercommissural width (mm) 40.4 ± 5.5 ± 37.6 ± 4.5.
		Average anteroposterior diameter (mm) 36.7 ± 6.1 vs 35.2 ± 4.7.
		Average circumference (mm) 131 ± 18 vs 123 ± 15.
		Average area (mm^2) 1198 ± 340 vs 1066 ± 253.

(Continues)

TABLE 3 (Continued)

Study ID	Imaging	Findings
		Average height (mm) 6.3 ± 1.4 vs 6.8 ± 1.4.
		Annular height-to-intercommisural width ratio (%) 16 ± 3 vs 18 ± 4.
		MAD not seen functional mitral regurgitation group.
		Max MAD located most frequently at P2 & P1 and less at P3.
		MAD associated with more severe chordae deformity, larger MV leaflet area, billow height and volume and longer papillary muscle to coaptation lengths.
		MAD had no difference in strain/LVEF and LV strain did not correlate with any annular dynamics in MAD group.
Mantovani 2017b	2D TOE	Differences between MAD and no MAD:
		Regurgitant volume (mL) 83 ± 31 vs 90 ± 57, $P = 0.57$.
		Left atrial volume index 60 ± 17 vs 60 ± 17, $P = 0.91$.
		No difference in diastolic measures of basal and mid-left ventricular diameter and wall thickness.
		In systole basal posterior wall increased in MAD (mm) 19.1 ± 2.2 vs 15.2 ± 2.2, $P < 0.001$ and in systole wall thickening was higher for basal posterior wall (%) 74 ± 27 vs 50 ± 28, $P < 0.001$.
		Rate of basal (posterior wall and interventricular septum thickness/diameter) was higher in MAD (1.06 ± 0.24 vs 0.91 ± 0.21, $P = 0.01$), $P = 0.01$.
		No difference in interventricular septum thickness and ejection fraction 65 ± 4 vs 62 ± 8, $P = 0.13$.
		Systolic ratio wall thickness/diameter higher in basal segment than in mid-segment in MAD ($P < 0.001$).
		Cavity deformation was larger in MAD ($P = 0.004$).
		Postsurgical repair with suture annuloplasty ring, left ventricular diameters and wall thicknesses were no different for MAD vs no MAD but wall thicknesses declined in all segments ($P > 0.50$).
Perazzolo Marra 2016	CMR	MVP with late gadolinium enhancement had longer MAD and higher prevalence of curling (94% vs 19%).
		Bi-leaflet prolapse had longer MAD (4.8 vs 2.5, $P < 0.001$).
		Sudden cardiac death patients had a longer MAD.
Tani 2018	2D echocardiogram	Majority of prolapse site was posterior leaflet.
		MAD was detected in patients with severe MR.
Toki 2019	3D TOE	Late systolic prolapse had greater circumferential extent of MAD (180 ± 39 vs 51 ± 28 degrees, $P < 0.001$), MAD distance 7.4 ± 3.3 vs 5.0 ± 1.8 mm, $P = 0.039$ and MAD index (1388 ± 690 vs 269 ± 179, $P < 0.001$) compared to holosystolic prolapse.
		Rate of systole expansion of the mitral valve annulus positively correlated with MAD index ($P = 0.038$).
Torras 2018	2D Echocardiogram	All MAD patients had bi-leaflet prolapse.
		All severe myxomatous MVP with sudden death had larger MAD distance (10.3 ± 1.5 vs 6.9 ± 1.7 mm).

upon the mitral valve annulus and apparatus.[2] This would explain why patients with myxomatous mitral valve may have MAD but it does not explain the case of patients with myxomatous mitral valve who do not have MAD. It has been reported by Tani el al that there are different degrees of MAD and they classified them as type 0/no MAD, type I (hypermobile basal left ventricular segment with no MAD), type II (<5 mm MAD), and type III (>5 mm MAD). If MAD is a degenerative process and potentially progressive in myxomatous mitral valve, it may not be seen at the early stage and there may be a minimum threshold for MAD distance before it can be seen.[16] Furthermore, as the patients with MAD but no mitral valve prolapse were younger compared to other patients, the hypermobility from the MAD may not have enough time to cause the myxomatous changes.

Our review highlights the evidence regarding the association between ventricular arrhythmias and MAD. Several studies show that the occurrence of ventricular arrhythmias was higher with a greater extent of MAD distance and circumferential area suggesting there to be a greater the risk of electrical instability with a greater extent of MAD.[4,11] Secondly, the occurrence of MAD and late gadolinium enhancement may indicate myocardial scarring and fibrosis, a known cause for ventricular arrhythmias. Perazzolo Marra et al found that there was a greater extent of late gadolinium enhancement within the left ventricle with longer MAD diameters in sudden cardiac death patients. But the location and extent of late gadolinium was not consistent in the two studies of MAD with CMR assessment.[4] In Essayagh et al study, 84% of patients with late gadolinium enhancement was located within the papillary muscles.[11] Furthermore, this does not explain the small patient group who have ventricular arrhythmia without scarring or fibrosis of the papillary muscle. The results of Syed et al suggested that the hypermobility of the basal posterolateral and anterolateral left ventricular regions may cause

TABLE 4 Outcomes associated with mitral annular disjunction

Study ID	Findings
Carmo 2010	On Holter monitoring no sustained VT. MAD group more ventricular extra beats and nonsustained VT but not statistically significant. Disjunction > 8.5 mm was predictive of NSVT sensitivity 67% and specificity 83%, with odds ratio (10 95% CI 1.28–78.1).
Clavel 2015	Among MVP patients, 100% of patients in sudden death with ICD group had MAD while 12% had MAD in control group.
Dejgaard 2018	Predictors of ventricular arrhythmia: Longitudinal MAD distance in posterolateral wall OR 1.16 95% CI 1.02–1.33, $P = 0.03$. Gadolinium enhancement in papillary muscle OR 4.09 95% CI 1.28–13.05, $P = 0.02$. Predictors of serious arrhythmic event in MAD patients: Age OR 0.93 95% CI 0.89–0.98, $P = 0.002$. Ejection fraction OR 0.86 (0.7–0.96), $P = 0.008$. Mitral valve prolapse (ASE) OR 0.22 95% CI 0.06–0.75, $P = 0.02$. Late gadolinium enhancement in anterolateral papillary muscle OR 7.35 95% CI 1.15–47.02, $P = 0.04$.
Essayah 2019	MAD associated with ventricular arrhythmias ($P = 0.037$).
Eriksson 2005	During follow-up of 5.9 y, there were 2 deaths from cerebrovascular accident and cerebral atrophy. Survival was 94.7% in normal operation and 96.8% in MAD correction (not statistically significant $P = 0.28$).
Perazzolo Marra 2016	Histology of the mitral annulus showed a longer MAD in 50 sudden death patients with MVP and LV fibrosis than in 20 patients without MVP.
Zienciuk 2018	Patients with idiopathic VF 32 review of echo and 5 had MAD and systolic curling.

excessive mechanical stress on the mitral valve annulus resulting in myocyte hypertrophy and fibrosis, which may subsequently result in electrical instability, this hypermobility and presence of ventricular arrhythmia was also evidence in the absence of late gadolinium enhancement.[21] The hypermobility and hypertrophied myocytes may also explain the increase left ventricular wall thickness as is seen in Mantovani et al[15] The Picklehaube's sign (lateral MV annular systolic velocity > 16 cm) is observed during the excessive pulling motion of the posterolateral left ventricular wall, the presence of the Picklehaube's sign may prove useful in detecting significant hypermobility which may predispose patients with MAD to ventricular arrhythmias.[22]

Our review highlights the few high-quality studies of MAD but it is apparent the evidence is limited and more studies are needed. While our review included 19 studies, some studies were only in abstract form or were case reports. In addition, the sample sizes of the studies were small as the largest study had 1439 patients and many studies were retrospective in design. Several specific questions remain unanswered. First, the prevalence of MAD in the general cohort, as well as high prevalence populations such as myxomatous mitral valve and mitral valve prolapse, needs to be studied in larger population. Second, the clinical significance of MAD requires evaluation with not only a larger sample size but longer follow-up. Third, it is not clear what should be done in terms of management for these patients with MAD. Fourth, the prognostically significant clinical and imaging features of MAD on echocardiography and CMR need to be further investigated. We believe that there is a need for more education on MAD as it is not well-known and better understanding of MAD may improve patient care.

In conclusion, MAD is structural abnormality which is commonly seen in patients with myxomatous mitral valve disease and mitral valve prolapse. If specifically looked for on imaging, it can be easily detected on echocardiography and CMR, but requires a keen eye as it is only detectable during ventricular systole. There is growing literature about its importance as there is literature to suggest its association with ventricular arrhythmias and sudden cardiac death. It is clear from this review that much still remains unknown regarding MAD and there is a definite need for further research into MAD and its potential effect on patient management and treatment options. More education on MAD within the cardiovascular imaging arena is also needed to improve the detection and reporting rates within clinical practice, this will also aid future research.

ACKNOWLEDGMENTS

None.

CONFLICTS OF INTEREST

None.

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How to cite this article: Bennett S, Thamman R, Griffith T, et al. Mitral annular disjunction: A systematic review of the literature. *Echocardiography*. 2019;00:1–10. https://doi.org/10.1111/echo.14437