ABBREVIATED TITLE PAGE

Prevalence of Mitral Annular Disjunction at Cardiac MRI: Results from a Multicenter Registry

Original research

Summary Statement

Mitral annular disjunction (MAD) was a frequent incidental finding on cardiac MRI examinations performed for various clinical indications. Longer MAD length and coexisting bileaflet mitral valve prolapse were associated with a higher prevalence of arrhythmia.

KEY POINTS

- The prevalence of mitral annular disjunction (MAD) among 2611 patients undergoing cardiac MRI for various clinical indications was 5.44% (142/2611), and MAD was often an incidental finding.

- Patients with arrhythmia showed a higher prevalence of MAD and longer MAD length compared to patients without arrhythmia (57/142, 40% vs 444/2469, 18%;p=.002), with a determined threshold value of 5 mm (OR 3.96 [95% CI, 1.93-8.15], p<.001).

- Patients with MAD and bileaflet-mitral valve prolapse showed higher prevalence of arrhythmia (64.2%, 18/28 vs 34.2%, 39/114, p=.006), systolic curling (75%, 21/28 vs 30.7%, 35/114, p<.001) and myocardial fibrosis (ECV 30%[IQR,28;32] vs 27%[25%;30%]; p=.04).

ABSTRACT

Purpose

To determine the prevalence of MAD in patients undergoing cardiac MRI for various clinical indications and to assess the association of MAD with arrhythmia, mitral valve prolapse (MVP) and myocardial alteration.

Materials and Methods

This study analysed data from a retrospective observational registry of consecutive patients undergoing cardiac MRI for different clinical indications. Cardiac MRI examinations were performed from January 2019 to June 2019 at 13 italian hospitals. Images underwent double reading by expert cardiac-radiologist from enrolling center and core-lab to assess the presence of MAD. Presence and maximum length of MAD and its association to MVP pattern, functional and structural myocardial alteration and arrhythmia were evaluated using nonparametric and parametric tests. Logistic regression models were used to identify predictors of arrhythmia.

Results

Cardiac MRI studies from 2611 consecutive patients (1755, 67% males, median age 53[IQR 39-65] years) were evaluated. Prevalence of MAD was 5.44% (142/2611). MAD was an incidental finding in 74.6% (106/142) of cases. Patients with MAD had a higher prevalence of arrhythmias compared with patients without MAD (40%, 57/142 vs 18%, 444/2469;p<.001). Patients with MAD and bi-leaflet MVP showed longer MAD compared to patients with single-leaflet or absent MVP (7[3;9.5] vs 4[3;5], p<.001), and higher incidence of arrhythmia (64.2%, 18/28 vs 34.2%, 39/114, p=.006).

MAD length ≥5mm independently predicted arrhythmia (OR 3.96 [95% CI, 1.93-8.15], p<.001).

Conclusion

MAD was a frequent incidental finding on cardiac MRI examinations from a multicenter registry. MAD ≥5 mm and when associated to bileaflet-MVP showed a higher risk of arrhythmia.

Abbreviation list:

AF: atrial fibrillation

MAD: mitral annular disjunction

MVP: mitral valve prolapse

NSVT: nonsustained ventricular tachycardia

PVC: premature ventricular contraction

SVT/VF: sustained ventricular tachycardia/ventricular fibrillation

rSCD: resuscitated sudden cardiac death.

MAIN MANUSCRIPT

INTRODUCTION

In recent years, there has been a growing interest in characterizing mitral annular disjunction (MAD) to clarify its pathologic significance. MAD consists of the atrial displacement of the mitral annulus with discernible separation from the ventricular wall (1). Its origin is debated (2). It has been suggested to be the result of mechanical and stretching stress in patients with mitral valve prolapse (MVP) (3), or to be an anatomical variant (4). These hypotheses stem from conflicting findings: some authors have described MAD as an exclusive alteration of MVP (3), supporting the degenerative etiology, while others have reported MAD also in patients without MVP (4–6), supporting the congenital etiology.

In a large autoptic study published in the 1986 (7) MAD was found in almost all patients with MVP (92%) and in 5% of structurally normal hearts. A recent metanalysis published in 2022 including 12 studies, mainly conducted using echocardiography (3), reported MAD in approximately 30% of patients with MVP and in 8.7% of the general population. Conversely, two studies based on cardiac magnetic resonance (cardiac MRI) and CT revealed MAD to be extremely frequent in normal subjects, with a prevalence of 76% and 96%, respectively (8,9).

Irrespective of its origin, MAD seems to be associated to higher arrhythmic risk, but it is not clear when and why. Most of studies reported MAD as a feature of the arrhythmic MVP where, together with systolic curling, lead to excessive mobility of the mitral valve apparatus causing systolic stretch of the myocardium, focal myocardial pseudohypertrophy and fibrosis (10).

The combination of myocardial fibrosis (anatomical substrate) and of mechanical stretch (trigger), seems to elicit ventricular arrhythmia (11,12).

Additionally, recent studies reported arrhythmic events even in patients with MAD and without MVP (13,14)arguing the arrhythmic potential of MAD itself.

Hence, there is an urgent need for further data to increase our capability of differentiate between clinically significant versus insignificant MAD, which is crucial to prevent overdiagnosis in healthy individuals or, conversely, to avoid underestimation of the arrhythmic risk.

cardiac MRI had higher sensitivity in the detection of MAD compared to echocardiography, especially in case of small length MAD (15), and it is also capable of better distinguishing MAD from pseudo-MAD, which consists of the systolic juxtaposition of the belly of the billowing leaflet on the adjacent left atrial wall (14,16). Additionally, cardiac MRI can provide a comprehensive stratification of arrhythmic risk (11,15) based on a multiparametric approach for the evaluation of cardiac morphology, function and fibrosis.

Therefore, the aim of the present study was to investigate the prevalence of MAD in a large registry of patients undergoing cardiac MRI regardless of the clinical suspicion, as well as to assess its association with mitral valve alterations, myocardial remodeling, and arrhythmias.

MATERIAL AND METHODS

STUDY SAMPLE

This study analyzed data from a multicenter observational cross-sectional retrospective registry. The study was approved by the ethics committee (CET 61-2024) and written informed consent waived for its retrospective nature.

Thirteen hospitals participated. Cardiac MRI studies and clinical data of consecutive patients who underwent cardiac MRI from January 2019 to June 2019 were collected. The timeline was selected to avoid the impact of COVID-19 pandemic on cardiac MRI availability, scheduling, and findings (17,18).

Exclusion criteria were pediatric patients (age <18 years-old), cardiac devices, previous MV surgery, lack of late gadolinium enhancement (LGE) images, lack of clinical information about presence of arrhythmias at the time of cardiac MRI.

Demographics (age and sex) and clinical data (known cardiac disease, atrial and ventricular arrhythmias, clinical suspicion before cardiac MRI) at the time of cardiac MRI were retrieved by electronical medical records and collected. The flowchart detailing patient selection is shown in **Figure 1**.

CARDIAC MRI ANALYSIS

Image analysis was performed offline at each center by expert cardiac radiologists with at least 10 years of experience in cardiac MRI according to a standard operating procedure (supplemental material). To assess the intra-observer and inter-observer variability in MAD detection, cardiac MRIs were re-evaluated by the first observer after 6 months to avoid recall bias and by two radiologists from the coordinating center with 10 and 7 years of experience in cardiac imaging (A.P. and D.V.) who were blinded to the initial results.

MAD was considered present when ≥1 mm (19) and recognizable in systolic and diastolic phases. Maximum longitudinal length of MAD was measured in the end-systolic 3-chamber long-axis cine images (19).

MVP was defined as the systolic displacement of any part of the leaflet ≥2 mm from the annular plane into the atrial cavity (16).If present, maximum length of MVP was measured in the end-systolic 3-chamber long-axis images and classified in single-leaflet (sMVP) or bi-leaflet (bMVP).

Mitral valve regurgitation was calculated using the following formula: left ventricular (LV) stroke volume (SV)-aortic forward volume measured by using phase-contrast images (AoPC)/LV-SV)*100.It was classified as mild (<30%), mild-to-moderate (30% to 39%), moderate-to-severe (40% to 49%), and severe (≥50%)(20).

Systolic curling was defined as the excessive end-systolic motion of the inferolateral hinge point of the mural leaflet relative to the ventricular mural summit.

In patients with MAD, data about ventricular volumes and function, atrial volumes, presence and segmental distribution (American Heart Association 16-segment model) of myocardial scar on LGE

images were collected. Mapping sequences, including native T1 mapping, T2 mapping, and extracellular volume (ECV) mapping. Native T1, T2 mapping and ECV global and segmental values were collected. Native T1 values were considered abnormal based on local reference values, while for ECV and T2 mapping, commonly recognized reference values were considered (ECV<27%; T2 ≤ 50 ms) (21).

Statistical analysis

Categorical variables are expressed as counts and percentages, while continuous variables are expressed as median and interquartile ranges.

Comparisons between subgroups of patients based on the presence of MAD (MAD+ vs MAD-), MVP (MVP+,MVP-), arrhythmia and other cardiac MRI parameters were conducted with the Mann-Whitney U test or using the chi-square test or Fisher's exact test, as appropriate.

In analyses involving multiple comparisons, p-values were adjusted with Bonferroni correction.

Cohen kappa coefficient (k) was calculated to assess intra-observer and inter-observer agreement (<0.20: poor; 0.20-0.40: fair; 0.40-0.60: moderate; 0.60-0.80: good; 0.80-1.00: very good agreement) (22). To identify potential predictors of arrhythmia, a univariable logistic regression was implemented on both the entire study sample and the subgroup with MAD. Variables that showed a significant association ($p< 0.05$) in the univariable analysis were included in the multivariable logistic regression model for prediction of arrhythmia incorporating both MVP and MAD as main effects.

The Youden Index was used to identify the best cutoff value of MAD length associated with arrhythmia and logistic regression to assess its arrhythmic predictive value.

All tests were two-tailed, and a P value <0.05 was required for statistical significance. All the analyses were implemented using SAS version 9.4 (SAS Institute).

RESULTS

Patient Characteristics

A total of 2611 consecutive patients undergoing cardiac MRI for various clinical indications were included in the registry. There were mainly male patients (1755/2611, 67.2%) and the median age was 53 (IQR 39-65) years (Figure 2A).

The most frequent clinical indication as well as the most frequent diagnosis at cardiac MRI was ischemic cardiac disease (**Figure 2A**).

Cardiac MRI was performed in most of cases (2513/2611; 96.2%) using a 1.5-T system, in the remaining 98/2611 (3.75%) patients using a 3.0 T scanner.

Native T1 mapping was performed in 452/2611 (17.3%) patients, of which 47/142 (33.1%) with MAD; T2-mapping in 290/2611 (11.1%) patients, of which 33/142 (23.2%) had MAD; and ECV mapping in 261/2611 (10%) patients, of which 37/142 (26.1%) had MAD.

Patient with MAD: prevalence and association to cardiac diseases

The incidence of MAD at cardiac MRI was 5.44% (142/2611) with a median length of 4 [IQR, 3-6] mm. Intra-reader agreement for MAD detection was very good (Cohen's kappa [95% CI]:0.876 [0.770-0.984]), and the inter-reader agreement varied from good (Cohen's kappa [95% CI]:0.798 [0.698-0.898]) to very good (Cohen's kappa [95% CI]: 0.911 [0.834-0.9883]).

Among the 142 patients with MAD (MAD+), a structural and functional evaluation of a mitral valve disease was the reason for cardiac MRI in only 9.86% of patients (14/142). In another 11.9% (17/142) of patients, the main indication to perform cardiac MRI was the search of arrhythmic substrate. The remaining 78.2% (111/142) of patients underwent cardiac MRI for miscellaneous causes (**Figure 2B**). Cardiac MRI showed MAD to be an incidental finding most cases: of 142 total patients with MAD, 30.3% (43/142) had a structurally normal heart, 44.4% (63/142) had various cardiac diseases, and 25.4% (36/142) had an isolated mitral valve disease (**Figure 2B).**

MAD+ vs MAD-

Sex distribution and median age in patients with MAD were similar to that of patients in the non-MAD group (MAD-) (**Table 1**). Compared to MAD-, patients MAD+ more commonly had arrhythmias (57/142, 40.1% vs 444/2469, 17.9%; p<.010), MVP (36.6%, 52/142 vs 5.5%,136/2469;p<.001), curling

(39.4%, 56/142 vs 1.25%, 31/2469; p=.002) and mitral regurgitation (38.7%, 55/142 vs 12.1%, 298/2469; p<.001). Prevalence of LGE was similar in patients MAD+ and MAD-, however, the typical LGE pattern related to mitral valve diseases, with the involvement of subvalvolar inferior and inferolateral mid-basal walls and of the posterior papillary muscle, was more frequent in patients MAD+ (40%, 24/60 vs 3.28%, 36/1097; p<.001).

Association between MAD and Arrhythmia:

Patients with arrhythmia showed a higher prevalence of MAD (11.3%,57/501 vs 4.02%, 85/2110; p<.001), larger MAD length (5 [IQR, 3;6] mm vs 3 [IQR, 3;5] mm; p=.003), higher incidence of curling (8.38%, 42/501 vs 2.36%, 50/2110; p<.001) and MVP (13.3%, 67/501 vs 5.73%, 121/2110; p<.001) (**Table 2**).

Association between MAD and MVP:

Results comparing subgroups of patients according to the presence or absence of MAD and/or MVP are reported in **Table 3.**

Three percent (90/2611, 3.4%) of patients had MAD without MVP (MAD+/MVP-), while 1.99% (52/2611) had MAD and MVP (MAD+/MVP+). For the remaining patients, 5.20% (136/2611) had MVP without MAD (MAD-/MVP+), while the majority (89.3%,2333/2611) had neither MAD nor MVP (MAD-/MVP-).

The rate of arrhythmia was 17.4% (406/2333) in MAD-/MVP- group, 27.9% (38/136) in the MVP+/MAD- group, and 31.1% (28/90) in the MAD+/MVP- group, increasing to 55.7% (29/52) when both MAD and MVP were present (p=.001). The incidence of curling in the same groups was 0% (0/2333), 22.8% (31/136), 20% (18/90) and 73.1% (38/52) respectively (p=.001) **Table 3**. Prevalence of LGE prevalence was similar regardless the presence of MVP and/or MAD, while ECV values were higher in patients with MAD-/MVP- and MAD+/MVP+ (**Table 3**). In the subset of patients with MAD, 36.6% (52/142) had MVP: bMVP in 53.8% (28/52) of patients and sMVP in 46.1% (24/52). Compared with patients with sMVP or MVP-, patients with bMVP had a higher MAD length (7 [IQR, 3;9.5] mm vs 4 [IQR, 3;5] mm; p<.001), higher prevalence of arrhythmias (64%, 18/28 vs 34.2%, 39/114, p=.006) ,and

of sustained ventricular tachycardia(SVT)/ventricular fibrillation (VF) and resuscitated sudden cardiac death (rSCD) (14.3%, 4/28 vs 5%, 6/114;p=.033)(Figure 3).

Patients with bMVP more commonly had moderate-to-severe mitral regurgitation, higher left atrial and left ventricle volumes, and higher rate of LGE in inferolateral mid-basal myocardial wall and in the posterior papillary muscle, and higher ECV values (**Figure 4** and **Table S1**).

Predictors of Arrhythmia

At univariable analysis, the following variables were associated with arrhythmia: MAD presence (OR 2.84 [95%CI, 1.99; 4.04];p<.001), MVP (OR 2.55 [95%CI, 1.85; 3.52];p<.001), curling (OR 3.72 [95%CI, 2.41; 5.73];p<.001), mitral valve regurgitation (OR 1.61 [95%CI, 1.23; 2.11];p<.001), LGE (OR 0.62 [95%CI,0.51;0.77];p<.001), and RV-EF (OR 0.99[95%CI,0.98;0.99];p=.009).

A MAD length ≥5 mm predicted arrhythmia with a sensitivity of 59.6% (46.9%;72.4) and specificity of 72.8% (63.1%;82.5%) (Youden index 0.32) and a OR 3.96 [95% CI 1.93-8.15], p<.001. Presence of MAD was found to be an independent predictor of arrhythmia in the entire sample, in addition to MVP, LGE, curling and right ventricular ejection fraction (**Table S2 and Table 4**). In particular, in patients MAD+ the coexistence of MVP+ further increased the risk (OR 2.34 [95% CI, 1.1;4.98] p=.027) compared to patients MVP- (1.75 [1.05;2.94], p=.033).

DISCUSSION

The clinical significance of MAD is widely debated. It remains unclear whether it represents a “red flag” for life-threatening arrhythmias when present on its own or only when associated with other pathological conditions. Additionally, it is still unclear whether MAD causes MVP, is a degenerative phenomenon related to MVP, or is a completely independent entity. Currently available information varies due to heterogeneity in the analyzed population and imaging methods. Moreover, data on the general population are scarce. Our registry including a large cohort of 2611 consecutive patients undergoing cardiac MRI for various clinical indications showed a 5.44% prevalence of MAD. MAD was an incidental finding in 74.6% (106/142) of patients, of which 30% had a structurally normal heart. The prevalence of MAD reported in this study aligns closely with findings from Hutchins et al (5%) in the

largest autopsy series available accounting for 900 hearts (7), but is slightly lower than the prevalence reported by Konda at al in a echocardiography study on 1439 patients (9%) (23). This discrepancy may be attributed to the higher accuracy of cardiac MRI in the identifying MAD (15) and for the exclusion of pseudo-MAD (4). Isolated MAD in structurally normal hearts has been also previously reported by Angelini et al. at pathological specimen (6) and by Toh et al at CT (9).

We found MVP coexisting to MAD in 36.6% (52/142) of patients. Therefore, MAD appears to be a common but not exclusive feature of MVP phenotype. Similar to our study, Dejgaard L.A et al. (5) also identified MAD in patients without MVP on echocardiography, but reported higher prevalence in those with MVP (78%, 90/116).

In our study, patients MAD+ more commonly had arrhythmias (40.1%, 57/142) compared with patients MAD- (21%, 444/2110; p<.010). The rate of arrhythmia was higher in patients with MAD or MVP and further increased when both MAD and MVP were present (17% vs 30% vs 32% vs 59% respectively; p<.001). Additionally, MAD length was higher in patients with arrhythmia (5 [IQR, 3;6] mm vs 3 [IQR, 3;5] mm; p=.003) as well as in patients with bMVP compared to patients with sMVP and no-MVP (7[3;9.5] vs 4[3;5], p<.001) which had also higher prevalence of arrhythmia (64.2%, 18/28 vs 34.2%, 39/114, p=.006).

Therefore, our results partially support previous hypotheses from Konda and Dejgaard et al (5,23), suggesting the arrhythmic potential of MAD itself. In particular, we support the notion that MAD becomes arrhythmogenic when it exceeds a certain length, with an incremental effect driven by its association with MVP.

The MAD length observed in our cohort in patients without MVP (4 [IQR, 3;5] mm) was similar to that reported by Konda et al at echocardiography (23) and by Toh et al (9) and Tsianaka et al (24) at CT (3–4 mm). MAD length in patients with MVP (7 [IQR, 3 - 9.5] mm) fell within the range of previous cardiac MRI findings in a study from van Wijngaarden et al (8 ± 4 mm) (25).

We found a MAD length> 5 mm to be associated to arrhythmic risk (OR 3.96 [95% CI, 1.93-8.15], p<.001). To date, a definite cut-off for pathological MAD length has not been established, with several

previous attempts yielding values ranging from 4.8 mm (10) to 10 mm (26). Specifically, a MAD distance >8.5 mm has previously been linked to non-sustained ventricular tachycardia (27) , even in patients without mitral regurgitation(10).

Perazzolo Marra et al.(10) firstly described a correlation between the length of MAD and the severity of systolic curling in patients with arrhythmic MVP, suggesting the arrhythmogenic potential of MAD when associated with contractility abnormalities. In agreement with this evidence, we also found higher prevalence of systolic curling in patients with arrhythmia.

The rate of complex arrhythmia observed in our study was higher in patients with bMVP, who also exhibited a higher rate of curling, moderate to severe mitral regurgitation, larger left atrial and left ventricular volume, and higher ECV values. These findings suggest a higher risk of malignant arrhythmias in patients displaying a cardiomyopathic phenotype. This could be partially explained by the coexistence of valve heart diseases and cardiomyopathies in some patients based on genetic predisposition (28) beyond degenerative remodeling (29).

Nonetheless, the underlying arrhythmogenic mechanism of MAD remains elusive. The hypermobility of the atrioventricular junction has been hypothesized to increase myocardial stretch and cause myocardial fibrosis (5,8,30) with a combination of structural and mechanical alteration affecting the valve apparatus and the myocardium that may elicit ventricular arrhythmias (11,12).

LGE is a known predictor of arrhythmias (31) and has been observed to be more prevalent in cases of severe MAD (10). We found higher rate of LGE in the inferolateral mid-basal myocardial wall and in the papillary muscle, as well as higher ECV values, in the group MAD+/bMVP+ which also showed higher prevalence of arrhythmia supporting the role of fibrosis at LGE and mapping in improving risk stratification (32–36).

Our study had several limitations. First, it is a retrospective study; therefore, cardiac MRI protocols were not standardized. Consistent with most of previous literature, MAD was measured as the longitudinal distance over the mitral annulus on a 3-chamber long-axis SSFP cine image. However, MAD length can vary considerably along the annulus circumference, and a cardiac MRI protocol

assessing the mitral annulus at every 30° or a stack of contiguous cines perpendicular to the mitral commissures would provide greater accuracy (5,19). Data regarding arrhythmias were recorded at the time of the cardiac MRI study. Mapping was available for a small subset of participating centers and patients. Finally, follow-up data were not available.

In conclusion, our study demonstrates that MAD may represent a common anatomical variant frequently encountered incidentally on cardiac MRI. When isolated, with a length lower than 5 mm and in absence of any other cardiac alterations, MAD may be considered a benign variant. However, MAD itself may harbor an arrhythmic potential when associated with a more complex structural heart disease including MVP, particularly bMVP, mitral valve degeneration and dysfunction, and myocardial remodeling. Future study including a long-term longitudinal monitoring of cardiac MRI features and arrhythmic profile evolution may further clarify MAD arrhythmic potential and improve early risk stratification.

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