Mitral Annulus Disjunction: Diagnostic Modalities, Clinical Implications, and Prognostic Progression

Disjunção do Anel Mitral: Modalidades Diagnósticas, Implicações Clínicas e Evolução Prognóstica

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Abstract

Mitral annulus disjunction (MAD) is an abnormal insertion of the flexion line of the mitral annulus into the atrial wall. The annulus presents a separation (disjunction) between the posterior leaflet–atrial wall junction and the left ventricular myocardial crest.[1] MAD was first described more than 30 years ago in an autopsy study and is reportedly related to mitral valve prolapse (MVP) in 92% of cases.[2] Since then, several studies have been conducted, and reports on the prevalence of MAD in patients with MVP have varied. Ultimately, it may or may not be associated with mitral regurgitation.

Transthoracic echocardiography is part of initial MVP assessment, allowing its diagnosis and the assessment of related complications. As new diagnostic methods emerged, cardiac magnetic resonance imaging and transesophageal echocardiography improved the assessment of this pathology in terms of its diagnosis, extension, and location.

However, the phenotypic characteristics of MVP that are more closely associated with MAD remain uncertain mainly due to the limited number of patients in classic studies on the subject.

Patients with MAD may develop symptoms related to ventricular arrhythmias, configuring the MAD arrhythmic syndrome, which may progress to sudden death.

The literature presents conflicting prognostic data among several studies on the subject from clear diagnostic criteria and best imaging method to be used to treatment and prognosis. This review describes MAD characteristics associated (or not) with valve prolapse to improve the diagnosis and management of this important pathology.

Mitral annulus disjunction and diagnostic imaging modalities

Mitral annulus disjunction (MAD) has been suggested as a structural abnormality often associated with mitral valve prolapse (MVP) and malignant arrhythmias. To date, transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and cardiac magnetic resonance imaging (CMRI) have been used to assess MAD. However, none of these modalities has been adopted as a standard reference for the diagnosis of this entity.[3]

Mitral annulus disjunction analysis by transthoracic echocardiography and transthoracic echocardiography

MAD can be diagnosed by TTE in the parasternal longitudinal view and, less commonly, in the apical four- and two-chamber views. MAD distance is usually measured on TTE from the junction of the mitral valve and the left atrial wall to the base of the left ventricular wall during end-systole and in the parasternal long-axis view defined as the longitudinal distance of the MAD inferolateral wall. Equivalent CMRI projections can also detect MAD presence, extent, and location in the systolic phase.[4]

Although the two-chamber view is rarely analyzed in MAD assessments, it seems plausible that it can be clinically identified by echocardiographic imaging along the lower left ventricular (LV) wall similarly to the way it is identified in the inferolateral wall since pathological studies describe MAD at any point around the mitral valve annulus. These observations further reinforce the importance of a routine assessment of the MAD that includes the entire circumference of the valve annulus.

Another important aspect that must be analyzed on TTE is the presence of the Pickelhaube sign (Figure 1). This is an S wave with a high-velocity systolic peak on mitral annulus tissue Doppler (annular systolic velocity > 16 cm/s) that may be useful for detecting significant mitral valve annulus hypermobility. Although consistent data are still lacking in the literature, some studies label it as a risk marker for the arrhythmogenic syndrome associated with MAD.[5]

The study by Tan et al. (2018) analyzed TTE results of 185 patients with severe mitral regurgitation (MR) due to MVP. In this analysis, the researchers classified patients into four subtypes based on valve annulus mobility: type 0, no MAD; type I, hypermobile basal left ventricular segment without MAD; type II, MAD < 5 mm; and type III, MAD > 5 mm. In this scenario, 66.5% of patients were classified as type I, 25.4% as type II, 7.6% as type 0, and only 0.5% as type III.[6] However, these findings may be underestimated due to the greater accuracy of CMRI at detecting MAD, especially when close to 2 mm.[4]

LV ejection fraction (LVEF) should be cautiously measured during TTE using the Simpson method as the disjunction region does not include myocardium and should be excluded from the analysis. Thus, although some case series demonstrate

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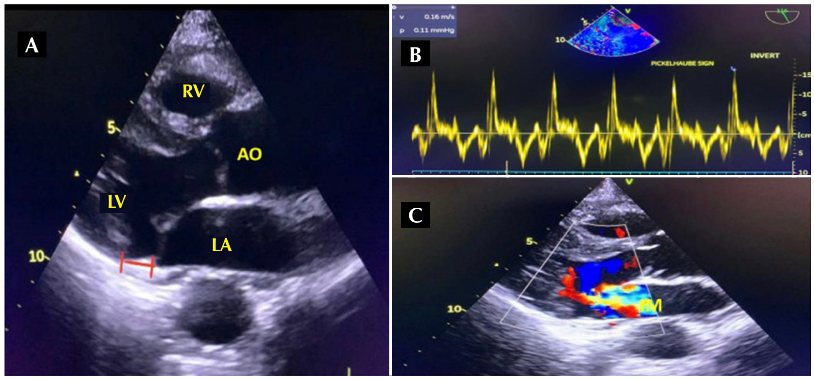


AO, aorta; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; RV, right ventricle. Images cordially provided by Hospital São Rafael - BA.

Figure 1 – *Images A and C demonstrate the presence of MAD associated with mitral regurgitation. B. Pickelhaube sign.*

a decreased LVEF in these patients, this may actually be due to miscalculation. In these cases, it is also important to consider that a decreased LVEF may be more closely related to concomitant MR.[3]

In clinical practice, TEE is requested mainly in patients with inconclusive or technically difficult TTE to better define mitral valve anatomy before surgery. However, it is not routinely used to assess MAD due to its semi-invasive nature.[7]

Mitral annulus disjunction analysis by cardiac magnetic resonance imaging

The ability to visualize the valve annulus and its disjunction varies between different imaging techniques. CMRI can distinguish adjacent structures and characterize myocardial tissue, detecting a minimal disjunction of up to 01 mm from the posterior mitral valve annulus of the left ventricle (LV) wall (Figure 2). In addition, it can accurately identify the presence of myocardial fibrosis in the posterior region of the papillary muscle and in the inferior basal segment of the LV by late gadolinium enhancement.[4]

Dejgaard et al. studied patients with MAD by CMRI and found that gadolinium enhancement in the papillary muscle and the longitudinal MAD distance in the inferolateral wall were predictive of the presence of ventricular arrhythmia. Furthermore, the study reported that late gadolinium enhancement in the anterolateral papillary muscle was strongly associated with a severe arrhythmic event.[3]

Comparison of echocardiography and resonance analysis of Mitral annulus disjunction

Mantegazza et al. studied 130 patients with MVP and MAD to analyze the agreement between the findings documented by the three imaging modalities (TTE, TEE, and CMRI). Their study established a disjunction ≥ 2 mm detected by CMRI as MAD. In this scenario, 88.7% of patients diagnosed with MAD by CMRI were also diagnosed by TTE and 94.7% were also diagnosed by TEE. TTE and TEE accuracy improved to 97.0% and 96.5%% assuming a cutoff value for MAD length by CMRI ≥ 6 mm and ≥ 4 mm, respectively.[4]

The lower MAD detection rate by TTE can be justified by different mechanisms such as inadequate acoustic window, shading or reverberations caused by posterior calcification of the mitral valve annulus, and lower spatial resolution compared to CMRI.[7]

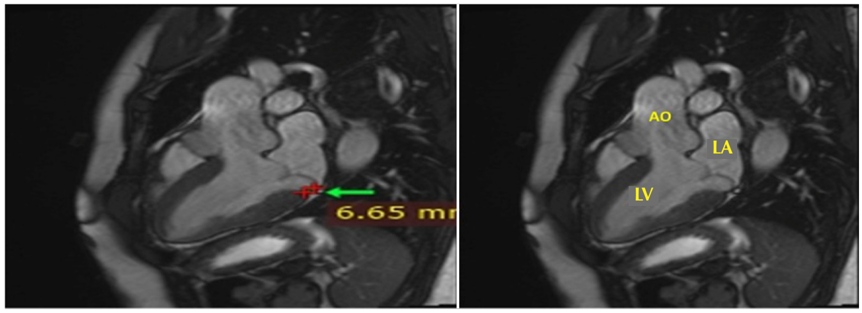
Large-scale studies showed that small disjunctions (< 4 mm) can cause malignant ventricular events; thus, CMRI may be a desirable test that can better identify the presence of MAD and MVP with high arrhythmogenic risk.[8]

MAD myocardial deformation analysis via different methods

MAD may be associated with different left ventricular myocardial deformation due to reduced cardiac muscle in the disjunction segment, such as in the inferolateral basal segment (Figure 3). Accordingly, Wang et al. (2021) analyzed global, radial, and circumferential longitudinal strain using TTE and CMRI in 63 patients divided into three groups of equal numbers of participants (group I, patients with MAD and MVP; group II, patients with MVP only; and group III, patients with no structural cardiac changes).[8]

A strain analysis by CMRI showed that patients with MAD and MVP have statistically lower values in the basal segments, especially in the inferolateral segment in circumferential and radial strain analyses. Although not statistically significant, there was a similar trend of a lower magnitude in the basal segments by longitudinal strain in the group of patients with MAD and MVP compared to the other groups (Figure 4). The CMRI global circumferential strain cutoff point was -18.0%, with a sensitivity of 76% and specificity of 76% for identifying MAD (area under the curve, 0.75). These observations on myocardial deformation by CMRI in patients with MVP and MAD can be explained by the disjunction segments being dragged in the longitudinal and apical direction by the rest of the myocardium during systole, although with less vigorous deformation and contraction in the circumferential or radial direction.[9]

Literature findings show that patients with MAD present unique strain patterns compared to those with MVP but without MAD, especially in the basal segments.[8] In addition, CMRI may be better able than TTE to assess LV characteristics associated with MAD.[9] Longitudinal, circumferential, and radial strain values by TTE were lower in patients with MAD in both studies; however, the differences were not statistically



AO, aorta; LA, left atrium; LV, left ventricle.

Figure 2 – *CMRI image showing a MAD measuring 6.65 mm during ventricular systole (red marks).*

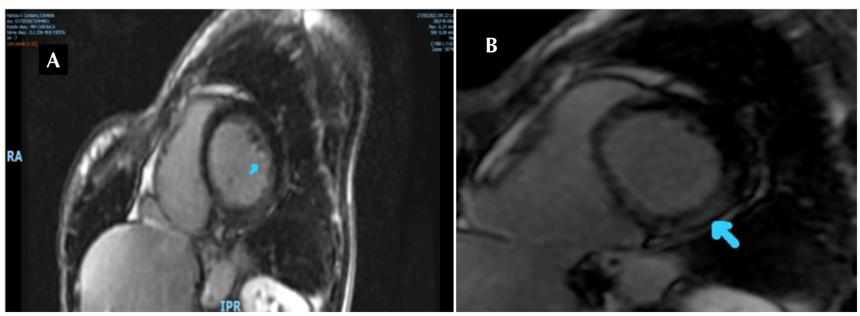
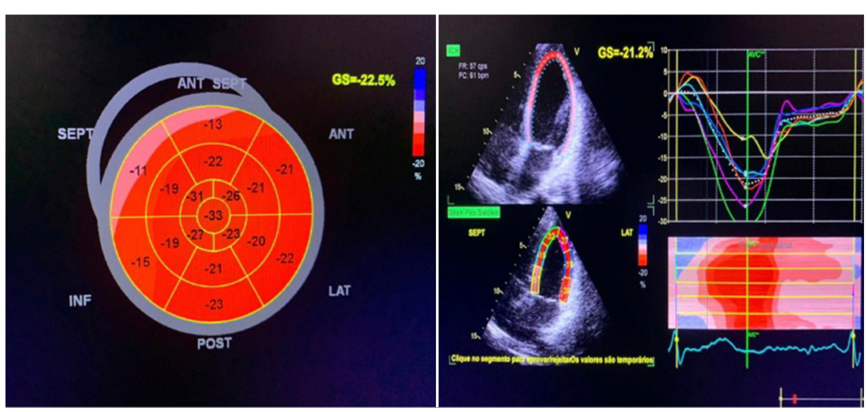


Figure 3 – *Cardiac magnetic resonance image of a patient with mitral annulus disjunction. A. Late enhancement showing fibrosis in the anterolateral papillary muscle. B. Late enhancement showing fibrosis in the inferolateral wall.*



Images cordially provided by Hospital São Rafael – BA.

Figure 4 – *Global longitudinal strain (GLS) in a patient with mitral annulus disjunction. This example shows regional impairment (basal septum) with a preserved GLS.*

significant. Future prospective imaging studies with larger cohorts are necessary to confirm these findings and further assess the usefulness of the strain technique by TTE and CMRI in patients with MAD.

MAD in the normal heart

MAD anatomical findings have received increasing focus in recent studies. Complementary imaging methods play a fundamental role in better characterizing the mitral annulus in the diagnosis of MAD.[10] However, controversy persists about the prevalence of MAD in healthy people, as it remains unclear whether the anatomical diagnosis alone has a prognostic relationship regardless of MVP and associated valve regurgitation. Further prospective studies are necessary to better understand the role of MAD in normal hearts.

Tricuspid annulus disjunction

Tricuspid annulus disjunction (TAD) involves separation between the tricuspid valve annulus and the basal myocardium of the right ventricle (RV) at the end of systole. It can be associated with tricuspid valve prolapse (TVP) and MVP and has a high correlation with MAD, being present in 50% of cases. This strong correlation can be explained by the presence of fibrous annulus disease in this group of patients.[11,12]

Aebal et al. evaluated the right side of the heart in 84 patients previously diagnosed with MAD and reported the presence of TAD in 42 of them. In that study, TAD was defined by CMRI as a longitudinal distance greater than 1 mm between the tricuspid leaflet and the basal segment of the free wall of the RV both in the lateral (four-chamber window) and in the inferior region of the free wall of the RV (inlet and outlet).

There was a strong association between the presence of bi-annulus disjunction and older age, greater MAD distance, circumferential mitral disjunction, and MVP. However, there was no association with cardiac arrhythmias, which may be a selection bias, showing the need for more studies to evaluate TVP and TAD.[11]

Clinical implications

The clinical course of MAD remains a controversial topic that has generated more studies due to its association with arrhythmias and sudden death in the presence or absence of MVP, which is called MAD arrhythmic syndrome and includes the signs and symptoms of arrhythmias present in patients with MAD. Palpitations is the most common clinical presentation, but pre-syncope, syncope, and documented ventricular arrhythmias are also included.[3]

MAD can be detected both in patients with MVP and in those without structural changes on echocardiography. However, MAD is more frequently encountered in patients with TVP. Retrospective studies reported a MAD prevalence of 16–71% in patients with MVP.[13]

Several factors may be associated with a higher MAD frequency in patients with MVP. Putnam et al. retrospectively investigated 90 patients with severe MVP and MR who underwent preoperative computed tomography. MAD was detected in 20% of these patients, being most often associated with female sex, smaller mitral annulus size, and greater posterior leaflet length.[14]

The presence of MAD in patients with MVP is also related to an increased risk of arrhythmias and sudden death. One of the mechanisms studied is that greater leaflet mobility leads to mechanical stress in the inferolateral wall and papillary muscles of the LV, resulting in hypertrophy and subsequent myocardial fibrosis.[2]

A previous study by Perazollo et al. reported a significant correlation between longer MAD and the presence of late enhancement on CMRI in patients with MVP ($R = 0.61$, $p < 0.001$). An anatomopathological analysis of sudden death cases showed a longer MAD in 50 cases with MVP and myocardial fibrosis and in 20 cases without MVP.[15]

MAD extension is significantly related to the presence of non-sustained ventricular tachycardia, with an extension greater than 8.5 mm being a predictor.[5]

Dejgaard et al.[3] studied 116 patients with MAD diagnosed by echocardiography and CMRI. Palpitations were the most common symptom (71% of cases), and severe ventricular arrhythmias were detected in 12% of cases. Cases of arrhythmias were more common in younger patients with a lower LVEF and higher frequency of papillary muscle fibrosis. Greater MAD extension in the inferolateral wall by CMRI was an independent risk factor for ventricular arrhythmias. MVP was detected in 78% of these patients, but there was no association with ventricular arrhythmias, suggesting that MAD is related to symptoms and arrhythmias regardless of MVP status.[3]

The presence of MR and MVP should increase the degree of suspicion of the possibility of associated MAD. However, it can also be present alone, especially in the young population with unexplained ventricular extrasystole.

CMRI may be useful in risk stratification for detecting papillary muscle fibrosis and measuring longitudinal MAD distance in the inferolateral wall.[16,17] However, the clinical course of MAD remains a controversial topic still in the knowledge construction phase.

Predictive factors in surgical repair

Surgical repair in patients with MVP and MR is already a well-established procedure in clinical practice with proven safety and efficacy. However, the increasing ability to diagnose MAD has raised questions about its surgical prognosis and immediate and late results. The real effects of changed lateral mitral annulus dynamics on the subvalvular apparatus in these situations and its influence on final mitral repair result remains uncertain. Thus, better understanding is important to enable surgical planning.

MAD is usually related to MVP with the phenotypic expression of severe diffuse myxomatous disease, profound annular dynamics changes, and excessive annulus dilation at the end of systole, which may reduce the coaptation of its leaflets and be associated with severe MR. However, MAD does not impair valve repair viability and quality, requiring careful suturing of the annulus to the LV so that residual MAD does not persist after repair. Thus, MAD must be diagnosed in the preoperative evaluation and the condition shared with the surgeon and heart team of patients with MVP and severe MR.[18]

A recent study analyzed patients with MVP associated with severe MR eligible for mitral valve repair. The surgical outcome was studied in patients with MAD associated or not with MVP, and the groups were compared for surgical success. MAD was observed in approximately 40% of patients with MVP, with involvement of the two cusps being the most frequent type and invariable involvement of the P2 segment. Mitral repair was performed in 60 patients (98%), and leaflet resection was required more frequently in patients with versus without MAD. There was no intergroup difference in cord implantation, presence or absence of residual MR, or time of aortic clamping. The factors with statistically significant differences that influenced the surgical outcomes of patients with or without MAD were intercommissural diameter, leaflet area, and prolapse volume.[18]

After almost two decades of studies and debates, the annulus in MR correction is used at the surgeon's discretion. However, large series in centers of excellence demonstrated the effectiveness of the annulus in preventing late MR recurrence. DiBardino et al. and Gillinov et al. confirmed the significant advantage of ring annuloplasty over ringless mitral repair in terms of reconstruction durability.[19,20]

A rigid saddle-shaped mitral annulus ring has been widely recognized as able to prevent MR recurrence in cases of MVP.[21] In fact ringless repair is an independent risk factor for postoperative MR recurrence.[22]

Jensen et al. showed that saddle-shaped rigid ring annuloplasty can uniformly distribute tension forces compared to flexible rings and can maintain the medial alignment of the papillary muscles, improving leaflet coaptation and presenting greater repair durability.[23–25]

To date, consensus is lacking on the effectiveness of surgical repair in the presence of MAD, only reports that the use of rigid saddle-shaped rings by experienced surgeons would theoretically increase life expectancy.[9]

Final considerations

MAD is frequently associated with MVP, and its diagnosis is based on multimodal cardiovascular imaging. Echocardiography and CMRI play a complementary role in diagnostic assessments and prognostic characterization. Although the clinical course can vary, part of the growing importance of this diagnosis stems from the possible association with ventricular arrhythmias and sudden death.

Authors' contributions

Souza AC: article conception and final review; Carvalho MVSF: diagnostic modalities in mitral annulus disjunction; Sales MA: surgical treatment; Bezerra SL: organization and collection of images provided by the São Rafael Hospital, Salvador, BA, Brazil. Torreão JA: discussion of cardiac resonance and its diagnostic and prognostic contribution; Macedo CT: discussion of prognostic progression.

Conflict of interest

The authors have declared that they have no conflict of interest.

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