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STATE-OF-THE-ART REVIEW

Mitral Annular Disjunction in the Context of Mitral Valve Prolapse

Identifying the At-Risk Patient

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ABSTRACT

Mitral annular disjunction (MAD), a separation between the left atrium/mitral valve annulus and the left ventricular myocardium, is frequently seen in patients with arrhythmic mitral valve prolapse. Although an association exists between MAD and ventricular arrhythmias, little is known regarding the identification of individuals at high risk. Multimodality imaging including echocardiography, computed tomography, cardiac magnetic resonance, and positron emission tomography can play an important role in both the diagnosis and risk stratification of MAD. Due to a paucity of data, clinical decision making in a patient with MAD is challenging and remains largely empirical. Although MAD itself can be corrected surgically, the prevention and treatment of associated arrhythmias may require medical therapy, catheter ablation, and an implantable cardioverter-defibrillator. Prospective data are required to define the role of implantable cardioverter-defibrillators, targeted catheter ablation, and surgical correction in selected, at-risk patients. (JACC Cardiovasc Imaging. 2024;17:1229–1245) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Mitral valve prolapse (MVP) is the most common cause of primary mitral regurgitation (MR) with a prevalence of approximately 2% to 3% in the general population.[1] The prognosis of patients with MVP is typically determined by the presence and severity of MR and its consequences, but is generally favorable when surgery is performed in a timely manner.[2,3] However, in a small subgroup of patients, the presence of MVP is associated with an increased risk of malignant ventricular arrhythmias and sudden cardiac death, independent of the degree of MR, which suggests the presence of an arrhythmic MVP phenotype.[4,5] Mitral annular disjunction (MAD), defined as a distinct separation between the left atrium/mitral valve annulus and the left ventricular (LV) myocardium, is frequently present in patients with arrhythmic MVP. MAD is thought to play a pivotal role in the

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

CT = computed tomography

FDG = fluorodeoxyglucose

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LV = left ventricle

MAD = mitral annular disjunction

MD = mechanical dispersion

MR = mitral regurgitation

MVP = mitral valve prolapse

PVC = premature ventricular complex

pathophysiology of arrhythmic MVP, whereas an association between MAD and the development of ventricular arrhythmias has been noted in some reports.[6-8] It is postulated that MAD leads to excessive mobility of the mitral valve (MV) apparatus, which in turn causes traction on the papillary muscles and the posterobasal LV myocardium, serving as the trigger for ventricular arrhythmias. This increased traction causes repetitive mechanical injuries to the myocardium, activating apoptosis pathways and inducing papillary muscle and LV fibrosis (the arrhythmic substrate).[9] The combination of a substrate and a trigger provokes early after-depolarizations, which can lead to premature ventricular complexes (PVCs), ventricular arrhythmias, and sudden cardiac death.[4,9]

Multimodality imaging, including echocardiography and cardiac magnetic resonance (CMR) imaging, may play an important role in the diagnosis and risk stratification of MAD and has proven useful in elucidating the underlying mechanisms of ventricular arrhythmias in these patients. Although there is growing interest in the entity of MAD, little is known about the identification and management of patients who are at increased risk of a ventricular arrhythmic event. In this review, we provide a summary of the current published reports on MAD and we explore the role of multimodality imaging in the diagnosis and risk stratification of patients with MAD. Subsequently, we provide an overview of a clinical screening approach for individuals who might be at risk for ventricular arrhythmias. Finally, we conclude with a summary of the most up-to-date evidence for managing these patients.

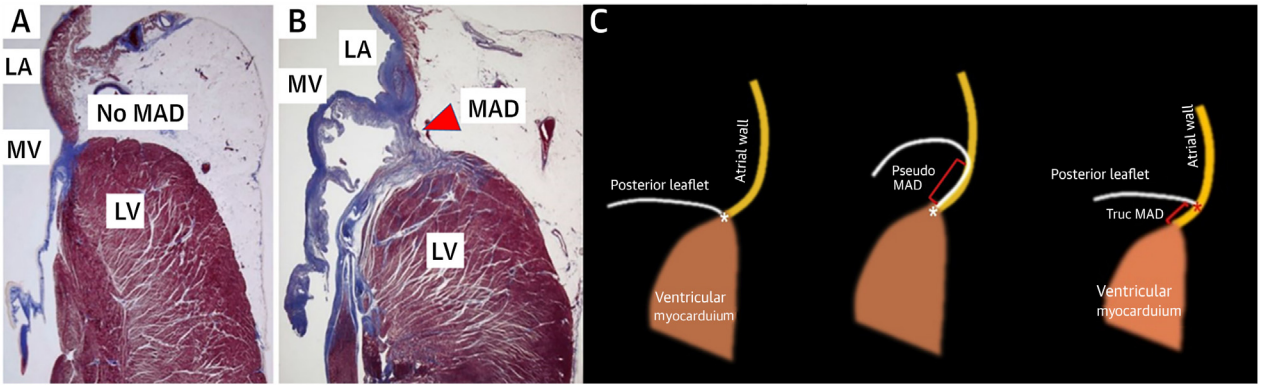
PATHOLOGY OF MAD

Adequate MV function requires structural and physiologic integrity of all components of the MV complex, including the leaflets, chordae, mitral annulus, papillary muscles, and the LV. Histologically, accumulation of proteoglycans is the most common cause of MVP, causing leaflet redundancy, chordal elongation, and annular dilatation.[10] Although these findings can explain the higher incidence of MR and mechanical complications in patients with MVP, the pathogenesis of ventricular arrhythmias and sudden cardiac death is less well explained by these abnormalities. The "mitral annulus" does not represent a complete, rigid ring but rather a complex, D-shaped structure consisting of fibrous, muscular, and adipose tissue components. Histologic studies have shown that a fibrous, cord-like structure supports the posterior mitral leaflet but that it is discontinuous,[11-13] allowing the posterior leaflet to insert directly into the crest of the LV myocardium. Separation of the attachment of the MV to the atrial wall on cardiac imaging, is known as MAD (**Figure 1**).

The first recognized report of MAD was in 1876 by Henle[16] who used the term "Filum coronarium." In 1966, Zimmerman[17] referred to the "four fila coronaria of Henle," describing fibrous strings extending from the fibrous trigones to the "free rims" of the mitral and tricuspid orifices. Whereas these "fila" represent fibrous tissue interposed between the atria and ventricles (implying separation of these structures), they reflect normal anatomical structures, and no specific mention is made of a separation between the atrium and ventricle. In 1975, McAlpine[11] published a description of a "subvalvular membrane," making reference to both Henle[16] and Zimmerman.[11] In 1984, Hutchins et al[18] performed sections of 900 adult hearts and found a separation between the left atrioventricular junction and the LV free wall in 65 specimens. They termed this "disjunction," which occurred as an isolated phenomenon in some hearts, whereas it was associated with "floppy mitral valves" in others.[18] The investigators did not describe if myocardial or fibrous tissue filled the potential space.[15] A potential limitation of the study by Hutchins et al[18] was the fact that only a single block of atrioventricular tissue was histologically examined. Angelini et al[19] investigated the entire atrioventricular junction in 13 hearts: MAD was found in all but 1, suggesting that disjunction is a normal anatomic variant.

In many cases, this apparent separation may be ascribed to the posterior MV leaflet abutting the left atrial wall during systole, a phenomenon which has been termed "pseudo-MAD" (**Figure 1**), and which can only exist in the presence of MVP.[15] The insertion of the posterior leaflet may also be displaced superiorly into the atrium ("true MAD"), which could potentially exist in the absence of MVP (**Figure 1**).[15] Pseudo-MAD and true MAD have also been shown to coexist in some individuals.[20] Although it is associated with MVP, MAD often occurs in isolation.[19] In a study of more than 600 individuals without known cardiovascular disease or risk factors for cardiac disease, MAD was identified in 80%.[20] However, only 5% of MAD cases were posteriorly located, with the majority being inferior, anterior, or anterolaterally with

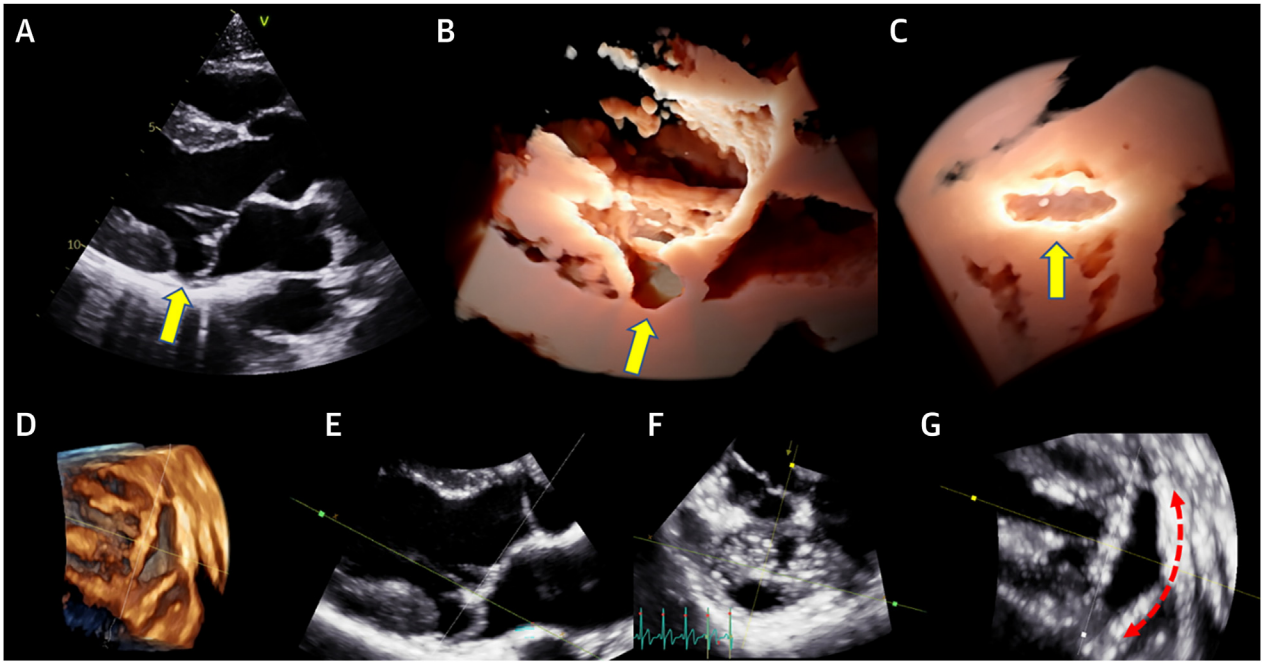
FIGURE 1 Anatomy of MAD



Histologic sections showing the convergence of the left atrium (LA), mitral valve (MV), and left ventricle (LV) in a person (A) without and (B) with mitral annular disjunction (MAD). (C) The difference between pseudo-MAD and true MAD. Figures 1A and 1B are modified with permission from Perazzolo Marra et al.[14] Figure 1C has been reproduced with permission from Faletra et al.[15]

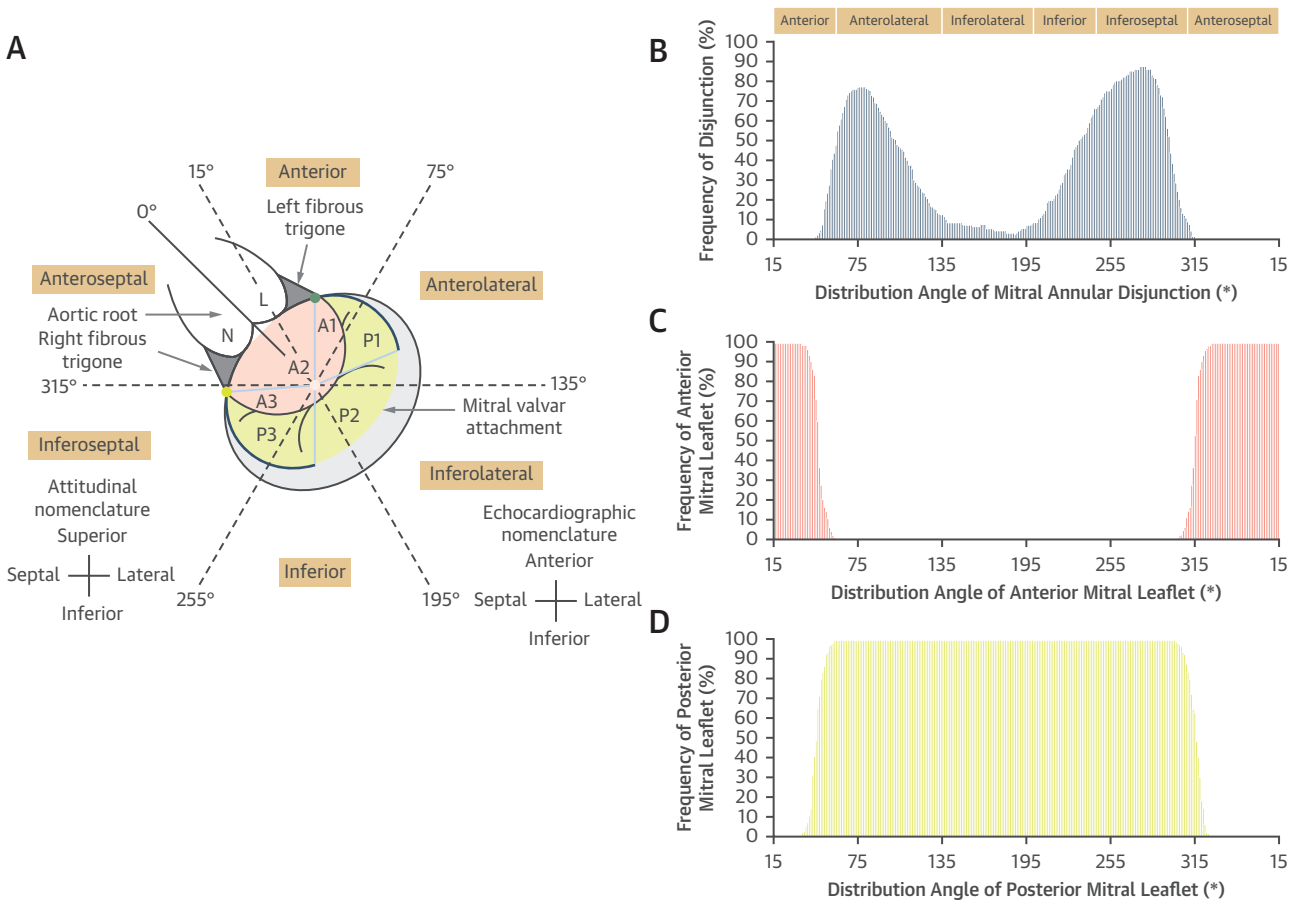
respect to the mitral annulus.[21] It is thought that "evolutional MAD" occurs mostly in the commissural regions, whereas "pathogenic MAD" is seen posteriorly. Rigorous identification of MVP by dynamic frame-by-frame analysis of the mitral annulus throughout the cardiac cycle is mandatory to ascertain posterior MV annular detachment from the adjacent myocardium.

FIGURE 2 Echocardiographic Visualization of MAD



(A) Parasternal, 2D view showing MAD during systole (yellow arrow). (B) 3D, volume-rendered view transecting the area of MAD (yellow arrow). (C) 3D, volume-rendered, en face view of MAD (yellow arrow). (D) 3D data set subjected to slice-rendering (E to G) to show the annular extent of MAD (G, red arrow).
2D = 2-dimensional; 3D = 3-dimensional; other abbreviation as in Figure 1.

FIGURE 3 Distribution of MAD in Normal Hearts



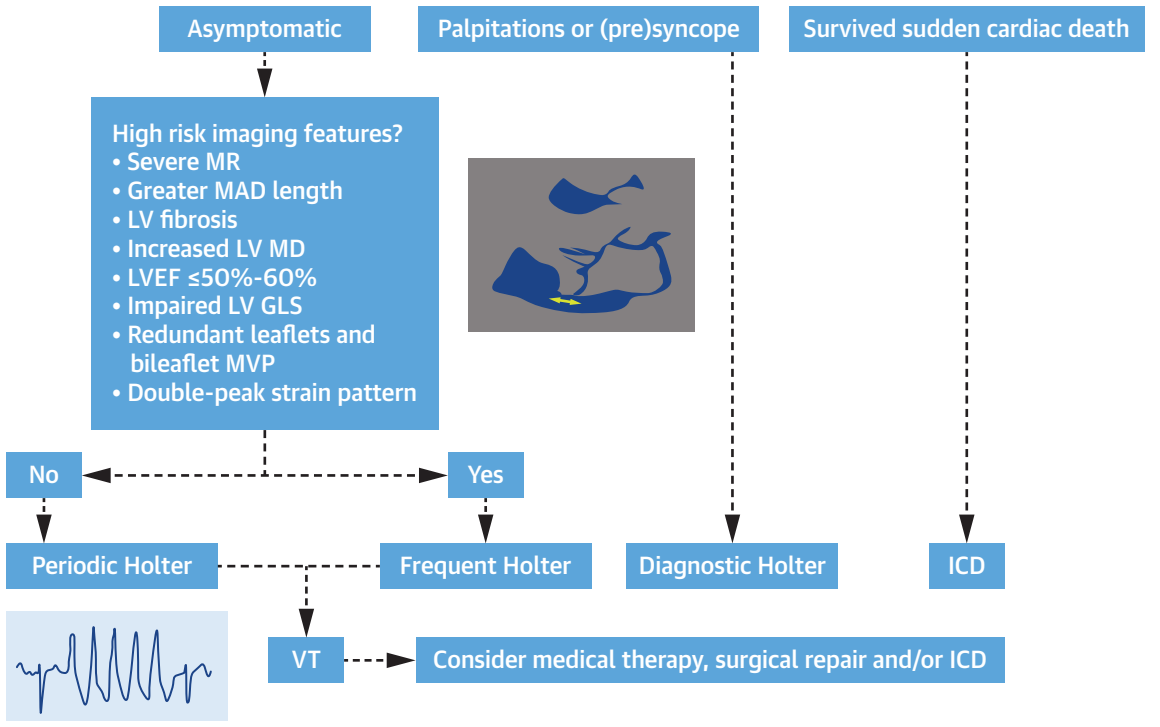
(A) An apical view of the mitral valve and annulus showing the anterior leaflet and scallops (peach), the posterior leaflet and scallops (yellow), and the most common areas where MAD occurs in normal hearts (blue). MAD occurring in these regions (blue) may be considered evolutional in contrast to pathogenic MAD, which occurs mostly posteriorly. (B to D) The bimodal distribution of MAD in normal hearts is shown in a frequency histogram. Reproduced with permission from Toh et al.[22] Abbreviation as in Figure 1.

ROLE OF MULTIMODALITY IMAGING IN MAD

ECHOCARDIOGRAPHY. MAD can be visualized on both 2-dimensional (2D) and 3-dimensional (3D) transthoracic and transesophageal echocardiography (Figure 2). The distribution of MAD along the mitral annulus can be bimodal (P1/P3 scallops) or more evenly distributed along the annulus (P1-P3), and it can therefore only be diagnosed in most persons on 2D echocardiography when standard imaging planes transect its distribution (Figure 3).[20,22] MAD is infrequently observed in the posterior wall and is therefore likely often missed when the diagnosis relies on a parasternal long-axis view only.[22] 3D echocardiography has a geographic advantage over 2D echocardiography in that slice rendering of 3D data sets can be performed to diagnose MAD which is present in any position along the posterior mitral annulus (Figure 3). The axial resolution of transthoracic echocardiography (2-3 MHz) may be inadequate for visualization of pseudo-MAD, where one would have to distinguish the prolapsing mitral valve tissue from the atrial wall.[15] Even the higher resolution of transesophageal echocardiography (5-7 MHz) may not be sufficient for this purpose because the leaflet and atrial wall are both aligned with the ultrasound beam.[15] CMR has a higher resolution than echocardiography, which might allow the distinction of pseudo-MAD from true MAD.[15,23]

Because of the profound disruption of the LV and MV architecture, it is not surprising that MAD causes a number of dynamic, mechanical abnormalities. MVP

CENTRAL ILLUSTRATION **Proposed Algorithm for Integration of Cardiac Imaging in Risk Stratification and Managing Patients With MAD and MVP**



Van der Bijl P, et al. JACC Cardiovasc Imaging. 2024;17(10):1229–1245.

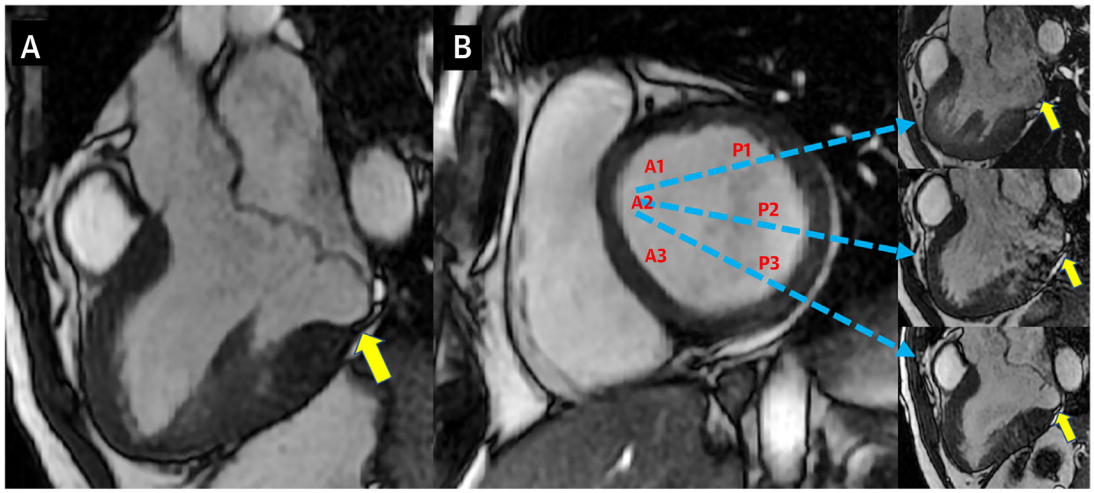
Various imaging biomarkers have been associated with the risk for life-threatening arrhythmias, although their relative merits and prognostic value remain to be defined. GLS = global longitudinal strain; ICD = implantable cardioverter-defibrillator; LV = left ventricle; LVEF = left ventricular ejection fraction; MAD = mitral annular disjunction; MD = mechanical dispersion; MR = mitral regurgitation; MVP = mitral valve prolapse; VT = ventricular tachycardia.

and MAD are associated with a curling motion of the posterior mitral annulus, which can be clearly seen on echocardiography, and which has shown a linear correlation with the MAD length in a CMR imaging study, suggesting that it plays an important role in the pathophysiology of this phenomenon.[14] During mid to late systole, the mitral annulus detaches from the LV myocardium, accompanied by an increase in annular area.[24] Excessive (posterobasal) LV wall thickening occurs in the presence of MAD, which may lead to a visual overestimation of systolic function.[24] Therefore, it is of the utmost importance to assess LV systolic function globally in patients demonstrating MAD and not to rely on a visual impression of regional wall motion.

In conjunction with defining the presence and extent of MAD, the mechanism and severity of coexisting MR (which does not correlate with the presence of MAD) should be described. Downstream consequences of MR (ie, left atrial and LV dilatation and dysfunction) are integral to preoperative assessment. MAD is associated with disproportionate LV enlargement in excess of what is accounted for by the MR caused by MVP.[6] Posterolateral, basal hypertrophy has been documented in patients with MAD, which has been variably attributed to hypermobility of the annulus or a forme fruste of hypertrophic cardiomyopathy.[25,26] LV basal longitudinal strain appears to be of greater magnitude in patients with MVP compared to normal individuals, but it does not differ significantly between those with and without MAD.[27]

Some, but not all patients with MAD are at risk of life-threatening arrhythmias. A recent consensus document has proposed risk stratification strategies.[28] Although risk stratification involves taking into account clinical and electrocardiographic markers, some echocardiographic features may be useful to identify individuals at higher risk (**Central Illustration**). LV mechanical dispersion (MD) (the SD of the time from onset of the QRS complex to speckle

FIGURE 4 Evaluation of MAD With CMR Imaging



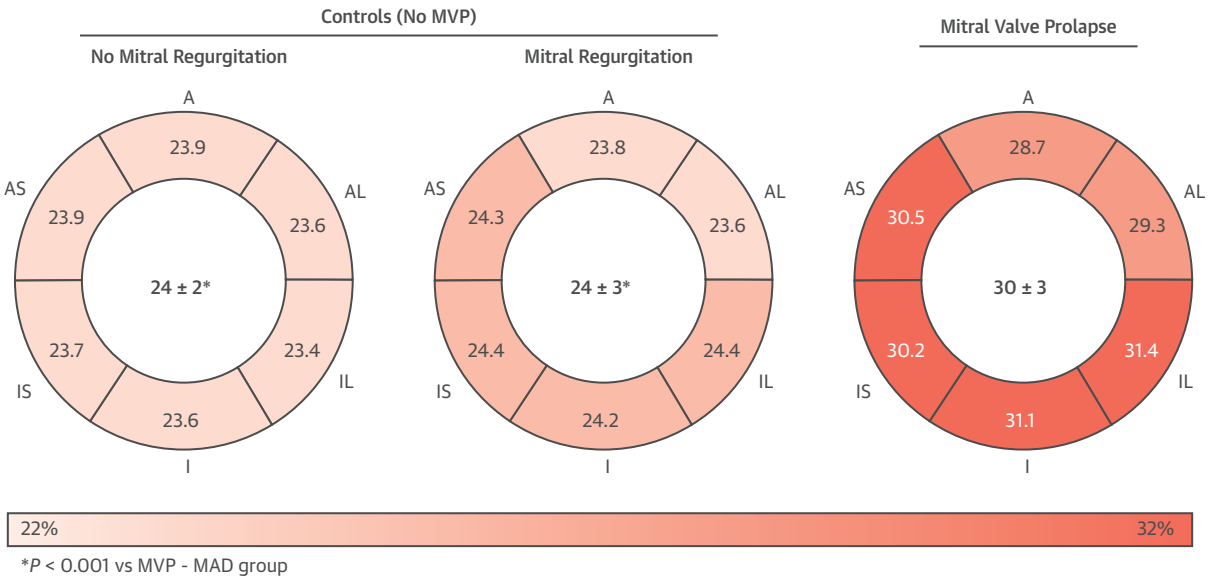
(A) Steady-state free precession, long-axis, 3-chamber view of the left ventricle showing MAD during systole (yellow arrow). (B) Imaging planes proscribed along the direction of the anterior and posterior mitral valve leaflet scallops showing MAD along the entire length of the posterior mitral annulus (yellow arrows). CMR = cardiac magnetic resonance; other abbreviation as in Figure 1.

tracking-derived peak strain in 17 LV segments) reflects electromechanical dyssynchrony, which has been shown to promote the expression of proarrhythmogenic genes in a preclinical model.[29] LV MD is a promising echocardiographic marker of arrythmia risk, which is calculated automatically on many postprocessing platforms when analyzing speckle tracking strain. It has shown associations with outcomes in a variety of ischemic and nonischemic cardiomyopathies. Increased LV MD has been independently associated with arrhythmic risk in MVP, but it has not been specifically investigated in the context of MAD.[30] LV postsystolic shortening is another (semi-)automatically derived marker of ventricular arrhythmias in patients with MVP, but MAD-specific data are not available.[29] Posterolateral, basal hypertrophy may be associated with risk of sudden cardiac death, although this remains speculative.[25] Recently, a "double-peak" (just before and just after end-systole) strain pattern, detected on speckle tracking echocardiography in the inferolateral, basal wall of the LV, has been linked to ventricular arrhythmias in patients with MVP.[31] It is postulated that the first peak occurs due to normal myocardial shortening, the nadir by late systolic lengthening (caused by annular expansion and leaflet displacement caused by papillary muscle traction), and the second peak by postsystolic shortening.[31]

CARDIAC MAGNETIC RESONANCE. CMR imaging is well suited to evaluate the mitral annulus and to characterize MAD. Imaging planes can be proscribed along any direction, soft tissue resolution is high, and its acquisition is not limited by body habitus. MAD has been reported to be common in a recent population study.[21] However, the location of MAD in the inferolateral wall seems to be rare and is associated with MVP and curling of the lateral wall.[32] Importantly, CMR can also detect the presence of LV replacement fibrosis at the level of the papillary muscles or adjacent LV myocardium, which has prognostic implications. Despite these strengths, only a few CMR studies have been performed where MAD was specifically investigated.[7,14,33] In a study from Essayagh et al[33] including 89 patients with MVP, MAD was identified in 35% of the population. Similarly, in another CMR study which included 80 patients with MVP, the frequency of MAD was 42%.[26] The extent and distribution of annular involvement in MAD can be ascertained with CMR by scanning a number of segments transecting the mitral annulus (Figure 4).

CMR is currently the noninvasive gold standard for cardiac chamber quantification, and it has been applied to investigate LV structure and function in patients with MAD. Basal hypertrophy is more common in the lateral and septal walls in patients with MAD vs patients without MAD.[33] The exact

FIGURE 5 Distribution of Left Ventricular Extracellular Volume on CMR in Patients With MAD

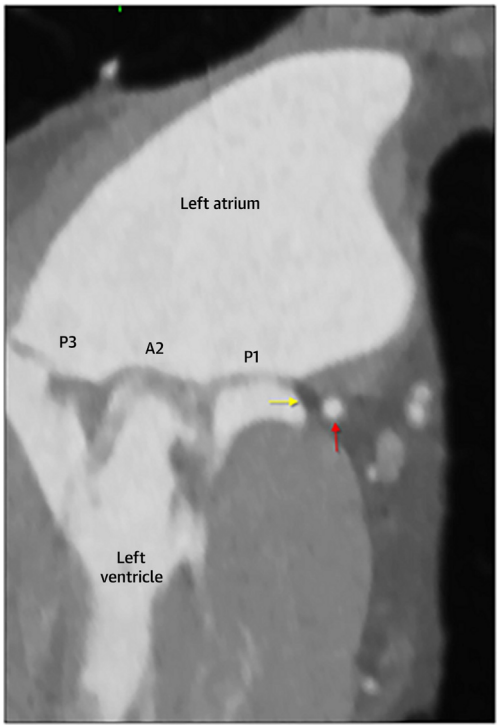


Left ventricular extracellular volume detected with CMR was compared between normal controls, patients with mitral regurgitation without prolapse, and patients with mitral regurgitation, prolapse, and MAD. Patients with mitral valve prolapse (MVP) and concomitant MAD had higher percentages of left ventricular extracellular volume than patients without mitral valve prolapse/MAD. Reproduced with permission from Pavon et al.[35] A = anterior; AL = anterolateral; AS = anteroseptal; I = inferior; IL = inferolateral; IS = inferoseptal; other abbreviations as in Figures 1 and 4.

mechanism of LV basal hypertrophy in MAD is still unknown, but it may relate to changes in myocardial energetics in response to repetitive traction by MAD and/or MVP.[34] In addition, although MR volume was similar between MVP patients with and without MAD, papillary muscle late gadolinium enhancement (LGE) was more common in those with MAD.[33] This observation may reflect the formation of myocardial fibrosis caused by the repetitive mechanical injury caused by the curling motion of the posterior MV leaflet in the presence of MAD.[33] Increased extracellular volume has also been noted in patients with MAD, although no direct comparison has been performed between MVP patients with and without MAD (Figure 5).[35] Perazzolo Marra et al[14] performed a unique imaging study where patients with arrhythmic MVP but without significant MR underwent CMR. Patients with MVP and LV LGE demonstrated greater MAD lengths than those without LGE,[14] and a clear association was observed between MAD length and systolic curling of the posterior mitral valve leaflet.[14] LV ejection fraction was found to be statistically lower in patients with MVP and MAD than in those without MAD. However, the clinical relevance of this observation is still uncertain.[33] Although transthoracic echocardiography did not show any difference in LV speckle tracking strain parameters between patients with MVP and MAD or no MAD, CMR showed significant differences in radial and circumferential strain in the basal segments between these individuals.[27] Accordingly, CMR may perhaps be more sensitive to detect the functional consequences of MAD when compared to echocardiography.

COMPUTED TOMOGRAPHY. Although MAD is most commonly assessed with echocardiography and CMR, the evaluation of the actual prevalence and extent of MAD according to these imaging modalities remains largely unknown due to the lack of comprehensive 3D data on the distribution of MAD in the absence of other cardiac pathology. Because computed tomography (CT) has the highest spatial resolution, it has the potential to reveal millimetric MAD, which may not be detectable with other imaging techniques (ie, echocardiography and CMR) (Figure 6). Recently, Toh et al[22] investigated the prevalence and extent of MAD with multiplanar reconstruction of data sets obtained from cardiac CT in 98 patients with structurally

FIGURE 6 Evaluation of MAD With Computed Tomography

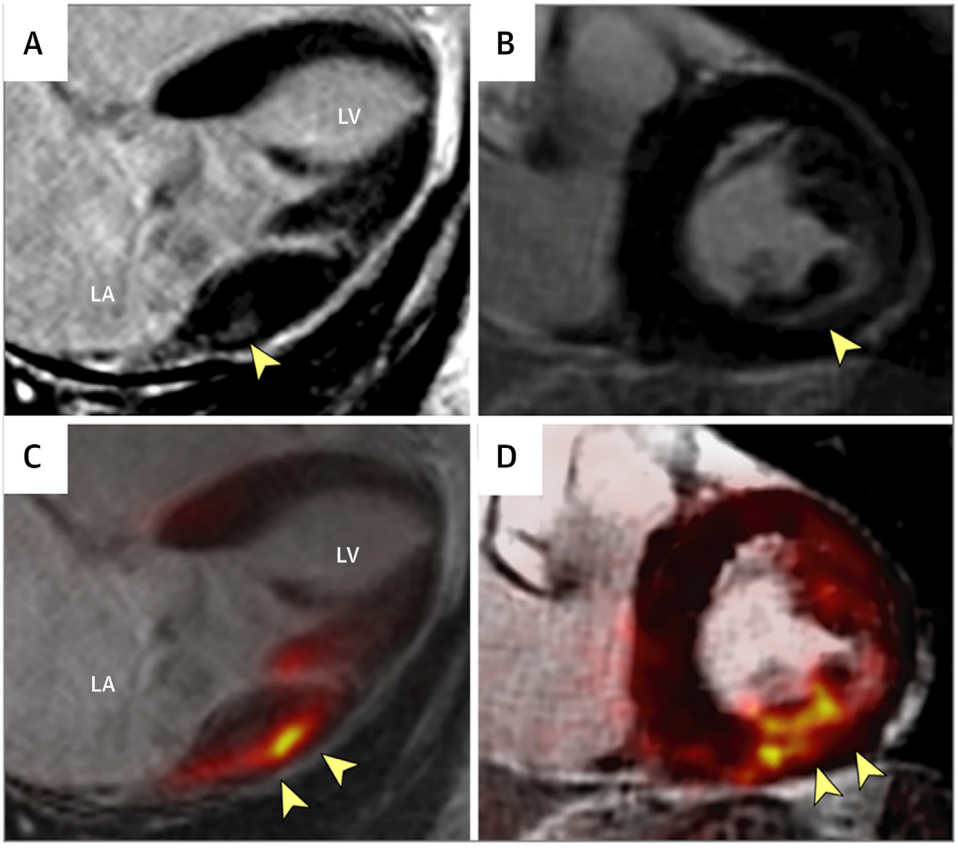


MAD (yellow arrow) seen on computed tomography. Reproduced with permission from Toh et al.[22] Abbreviation as in Figure 1.

normal hearts. Scans were evaluated during systole because MAD cannot be adequately diagnosed during diastole, which mandated exclusion of the majority of CTs screened for analysis.[22] MAD was a common finding in patients with a normal MV apparatus (96% of the study population).[22] The median value of the maximal height of disjunction was 3.0 mm (IQR: 1.5-7.0 mm) and its distribution corresponded to approximately two-fifths of the attachment of the posterior MV leaflet. The disjunction height of 3.0 mm is less than what has been shown for patients in whom MAD is associated with MVP (5.2-10 mm).[22] Individuals with MVP who experience arrhythmias appear to have greater disjunction heights than those who do not, suggesting a potential link between the "severity" of MAD and arrhythmogenesis.[22] MAD showed a characteristic bimodal distribution, which was confirmed by Saremi et al[36] (Figure 3). In 80% of cases, MAD was found septally (P3 scallop) and laterally (P1 scallop), whereas in 16% it was limited to the septal or lateral side.[22] Only 4% of scans showed no MAD.[22] Toh et al[22] have shown that MAD is a common finding in the normal adult heart, and also that it can be easily overlooked when only standard echocardiography views are used (eg, a parasternal long axis). Although MAD is most often described in the central region of the posterior annulus in patients with MVP, it is commonly observed in the commissural regions in patients with a normal MV apparatus. As such, evolutional MAD in a normal valve apparatus (being more prevalent in the commissural regions) should perhaps be distinguished from the more "pathogenic" variant observed in patients with MVP (being more prevalent in the central part of the posterior leaflet). These findings may also clarify why the presence of MAD alone is insufficient to explain the higher incidence of ventricular arrhythmias and risk of sudden cardiac death seen in a subpopulation of individuals with MAD. Therefore, not only the distribution, but also the height of MAD may distinguish normality from pathology. Whether pathologic MAD is congenital or acquired, or if the distribution can evolve in an individual, remains unknown.[22] The pathogenesis of arrhythmias may rather be caused by a combination of a substrate (MAD) and a trigger (excessive stretch due to the MVP), provoking early afterdepolarizations, PVCs, and ventricular arrhythmias.

POSITRON EMISSION TOMOGRAPHY. Until recently, it was unknown whether there are also detectable changes in myocardial metabolism that accompany the development of fibrosis in patients with MVP and MAD. In a prospective study of patients with MVP, significant MR, and PVCs, hybrid positron emission tomography/CMR was used to characterize the burden and distribution of ^{18}F-fluorodeoxyglucose (FDG) uptake (a surrogate marker of myocardial inflammation) and LGE.[37] ^{18}F-FDG uptake was detected in 17 of 20 (85%) patients and colocalized with areas of LGE on CMR in 14 (70%) patients (Figure 7). These surrogates of myocardial inflammation and fibrosis were also found in asymptomatic patients with significant MR without any indication for MV surgery, suggesting an association between arrhythmic MVP and myocardial inflammation. Activated myofibroblasts and inflammatory markers were identified in the peripapillary regions of a histologic study from patients with MVP and a murine MVP model.[38] This lends support to the role of inflammation in the pathogenesis of fibrosis in MVP patients.[38]

FIGURE 7 ^{18}F-FDG Uptake and LGE in a Patient With MVP



Example of an asymptomatic patient with MVP and severe mitral regurgitation showing ^{18}F-fludeoxyglucose (FDG) uptake in the inferobasal region (A, B) coexisting with areas of late gadolinium enhancement (LGE) on CMR (C, D). Reproduced with permission from Miller et al.[37] Abbreviations as in Figure 1.

PROGNOSTIC VALUE OF MAD IN THE CONTEXT OF "ARRHYTHMIC MITRAL VALVE PROLAPSE"

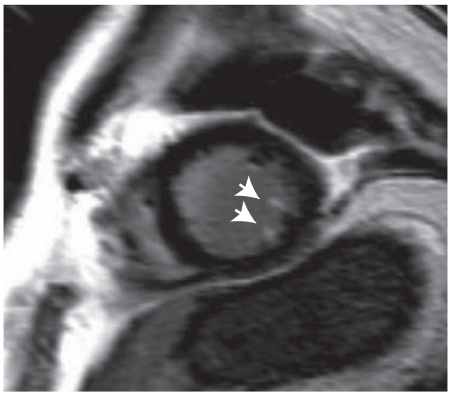
ASSOCIATION OF MAD WITH LV REMODELING. Patients with MVP and MAD present with structural changes that are different from having MVP but no MAD.[6] This includes LV remodeling, with larger LV dimensions (disproportionate in relation to the degree of MR) which is not related to age.[6,24,33] This observation may be explained by de-anchoring of the LV myocardium from the root of the mitral annulus,[39] causing inefficient ventricular contraction and thereby increasing the LV end-systolic dimension.[40] The annular detachment may also induce LV atrophy and/or fibrosis at the level of the posterobasal wall[4] which could further promote LV remodeling and which permits permanent, MAD-induced, adverse LV remodeling. Alternative hypotheses for disproportionate LV remodeling in the presence of MAD include volume overload caused by the prolapse volume,[41] the presence of a concomitant cardiomyopathy,[42,43] the development of a PVC-induced cardiomyopathy, and an underlying genetic substrate.[44,45] Besides syndromic forms of MVP (eg, Marfan and Loeys-Dietz syndromes), there is a growing body of evidence supporting the fact that nonsyndromic MVP may be genetic in origin, characterized by autosomal dominant or X-linked inheritance.[45-48] Whether a MAD phenotype-genotype link exists, however, remains speculative.[18]

ASSOCIATION OF MAD WITH VENTRICULAR ARRHYTHMIAS. Arrhythmias that have been linked to MVP range from brady-arrhythmias to malignant ventricular arrhythmias, causing sudden cardiac

arrest.[49,50] Although the frequency of sudden cardiac death in MVP is low, estimates ranging between 0.2% and 4% have been reported.[4,51,52] The wide range published for the prevalence of sudden cardiac death in MVP is at least partly due to variations in the definition of sudden cardiac death. A recent, prospective, continuous, long-term cardiac monitoring study showed that yearly incidence rates of severe ventricular arrhythmias (including aborted cardiac arrest, ventricular fibrillation, appropriate or aborted implantable cardioverter-defibrillator (ICD) therapy, sustained ventricular tachycardia, or nonsustained ventricular tachycardia with hemodynamic instability) were as high as 4% in patients with arrhythmic MVP with no previous severe events.[53] Another recent study revealed that 29% of athletes with MVP who were partaking of competitive sports had evidence of ventricular arrhythmias.[54] Athletes with MVP and ventricular arrhythmias had larger LV and left atrial sizes (with comparable LV systolic function) and a higher prevalence of MAD (16% vs 3%; $P < 0.001$) compared to athletes with MVP but without ventricular arrhythmias. The incidence of serious adverse events (including MV surgery, ischemic stroke, atrial fibrillation, and sudden cardiac death) in these patients was low (0.5% per year), yet all those who experienced events had evidence of ventricular arrhythmias at baseline. In addition, MAD was more common in athletes with events than in those without (38% vs 6%; $P = 0.012$).

Volume overload of the LV caused by severe MR is related to ventricular arrhythmias in patients with MVP.[55,56] Although patients with LV systolic dysfunction caused by severe MR may account for a significant proportion of the observed ventricular arrhythmias, life-threatening ventricular arrhythmias and sudden cardiac death have also been observed in patients with MVP who had no or mild MR.[57] Autopsy reports from patients with sudden cardiac death without an enlarged LV and left atrium suggest that mechanisms other than volume overload may play a role in malignant arrhythmia onset.[4,14] Important mechanisms for malignant arrhythmias in patients with MVP include regional myocardial hypertrophy and fibrosis, as well as Purkinje fibers which are triggered by mechanical stretch.[4] LV myocardial fibrosis may cause electric instability and act as a substrate for ventricular arrhythmias.[9,58,59] Myocardial stretch on the LV inferobasal segment and posterior papillary muscle is caused by MAD and the attendant systolic curling motion.[4] Repeated stretch injury may cause fibrosis over time and facilitate the development of ventricular arrhythmias. A recent study has shown that inferolateral myocardial fibrosis detected by T1 mapping on CMR corresponded to T-wave inversion in the same areas in patients with arrhythmic MVP.[60] Therefore, myocardial fibrosis may be the underlying cause of electrical abnormalities seen on the surface electrocardiogram (**Figure 8**). Not only focal, but also diffuse lateral wall fibrosis, has been associated with ventricular arrhythmias, even in the absence of LGE.[60] LV MD has been shown to be a risk marker of ventricular arrhythmias in MVP, but has not been studied specifically in MAD (**Figure 9**).[62]

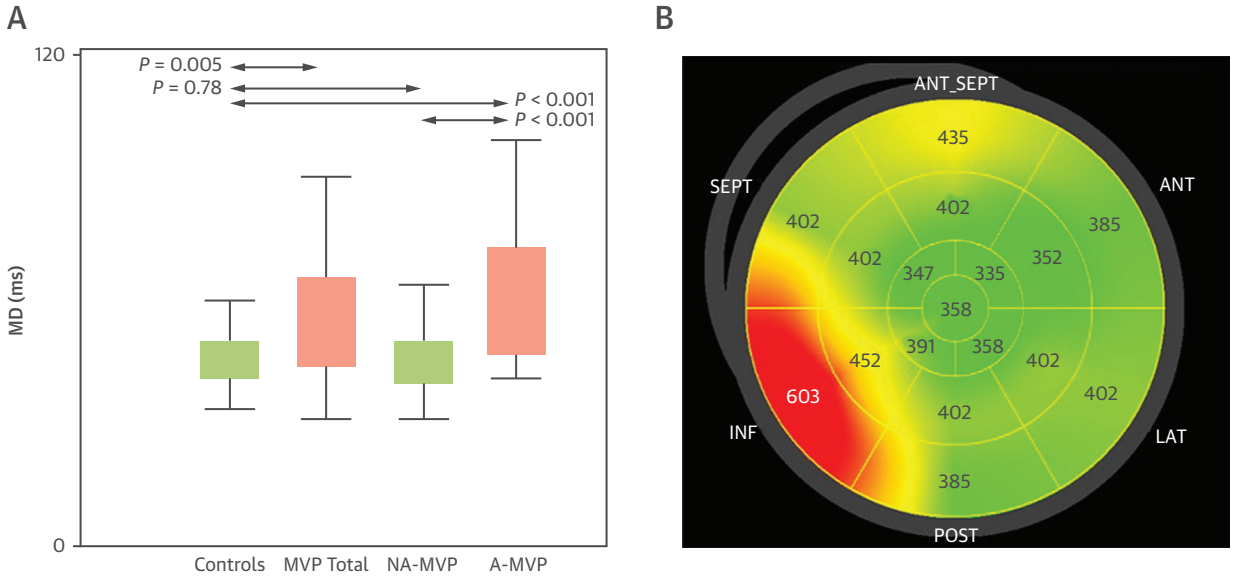
FIGURE 8 Papillary Muscle Fibrosis



LGE CMR showing papillary muscle tips on a short-axis, steady-state free-precession image of a patient with MVP. Reproduced with permission from Van der Bijl et al.[61] Abbreviations as in **Figures 4, 5, and 7**.

MAD is generally accepted to be a risk marker for arrhythmic events in patients with arrhythmic MVP, although data remain inconsistent regarding the independent association of MAD with arrhythmias. In a study by Dejgaard et al[7] including 116 patients with MAD, severe ventricular arrhythmias were present in 12% of patients with MAD. Twenty-six (22%) patients with MAD did not have MVP, and MVP alone was not associated with arrhythmic events. These findings suggest that MAD itself may contribute to the arrhythmic substrate. The maximal leaflet displacement from the LV myocardium in MVP has been termed “billowing excursion” and was found to be independently associated with ventricular arrhythmias in a study of patients without severe MR.[63] Carmo et al[64] showed that a greater MAD length (>8.5 mm) was a strong predictor of nonsustained ventricular tachycardia (**Figure 10**). MAD length in patients with MVP has also been linked to myocardial fibrosis and cardiac death.[14] MAD has been independently associated with a higher risk of arrhythmic

FIGURE 9 LV MD and MAD



Comparison of LV mechanical dispersion (MD) between controls, all patients with MVP (MVP total), patients with MVP but without cardiac arrhythmias (NA-MVP) and patients with MVP and cardiac arrhythmias (A-MVP). (A) Patients with MVP and cardiac arrhythmias had greater LV MD than those with MVP but without cardiac arrhythmias. (B) A patient with MVP and an increased LV MD of 60 ms displayed as a parametric map. Figure 9A has been redrawn from Ermakov et al.[30] ANT = anterior wall; ANT_SEPT = anterior septum; INF = inferior wall; LAT = lateral wall; POST = posterior wall; SEPT = septal wall; other abbreviations as in Figures 1 and 5.

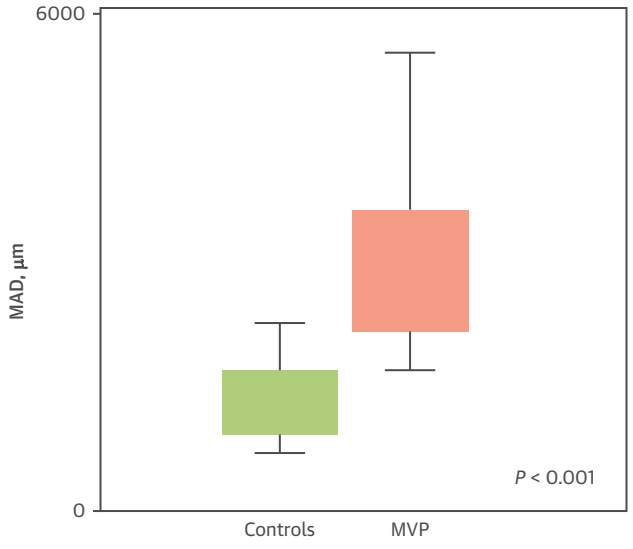
events when compared to MVP in isolation.[6,65] However, MAD was not associated with a higher mortality. In a recent study of 474 patients with MVP and moderate or severe MR, MAD was no longer predictive of a combined endpoint of ventricular tachycardia, sudden cardiac death, and unexplained syncope when LGE was present.[52] In general, individuals with MVP but without evidence of arrhythmias are at low risk.

There are few studies which included a large enough number of patients to allow extensive multivariable testing, and none considering an array of alternative etiologies of sudden cardiac death (eg, the severity of MR, LV function, heart failure, coronary disease, and channelopathies). Such data would be invaluable and would allow a better understanding of the true association between MAD and sudden cardiac death.

PATIENT MANAGEMENT AND FOLLOW-UP: FUTURE PERSPECTIVES ON THERAPEUTIC INTERVENTIONS

NATURAL COURSE OF THE DISEASE. Knowledge about the evolution of MAD over time, unfortunately, remains largely unknown. Mitral annular abnormalities often precede the development of significant MR in MVP, suggesting pathology of the annulus as the common denominator.[66] Although the progression of MAD over time remains to be demonstrated, the link between MAD and progressive development of ventricular arrhythmias is well established.[6] In patients without serious ventricular arrhythmias at the time of MVP diagnosis, those with MAD are at higher risk of developing significant arrhythmias during follow-up. According to the study from Essayagh et al,[8] almost one-third of patients with MAD but without ventricular arrhythmias at baseline developed significant arrhythmias (defined as ventricular tachycardia, ablation for ventricular tachycardia or PVCs, ICD insertion, and sudden cardiac death) at 5-year follow-up. This percentage further increased to 58% at 10-year follow-up. In contrast, only 15% and 38% of patients without MAD developed significant arrhythmias at 5- and 10-year follow-up, respectively. Although the development of ventricular arrhythmias is progressive and accumulates over time, MAD does not appear to be associated with excess mortality within the first 10 years after diagnosis (Figure 11). In contrast, once ventricular arrhythmias occur (often years after the initial diagnosis of MVP and MAD),

FIGURE 10 MAD Length and Sudden Cardiac Death



Among patients who experienced sudden cardiac death, the length of MAD is greater in those with MVP compared to those without. Redrawn from Perazzolo Marra et al.[14] Abbreviations as in Figures 1 and 5.

they are independently associated with excess mortality.[8] Progressive myocardial fibrosis may accumulate over time in patients with the MAD-MVP phenotype and may be associated with a delayed emergence of arrhythmias.

MONITORING FOR VENTRICULAR ARRHYTHMIAS. Because ventricular arrhythmias often arise only in the long run, rhythm monitoring should be repeated during follow-up. The frequency of screening or institution of a therapeutic intervention for ventricular arrhythmias should be based on symptoms, Holter monitoring, the severity of the ventricular arrhythmia detected on Holter monitoring, and the presence of other risk markers of "arrhythmic MVP" (Central Illustration). In the absence of ventricular arrhythmias and when MAD is not part of an arrhythmic MVP phenotype, Holter monitoring can be episodic. In the absence of ventricular arrhythmias, but when MAD is part of an arrhythmic MVP phenotype, Holter monitoring should be performed frequently (eg, yearly), although the exact frequency remains uncertain. In contrast, an immediate therapeutic intervention is indicated in the presence of severe ventricular arrhythmias, such as fast ventricular tachycardia, especially when these arrhythmias are associated with syncope or presyncope.[67] In the context of MVP with MAD and suspected ventricular arrhythmias, the role of electrophysiologic testing is unknown but should not be used to replace Holter or loop recorder monitoring when screening for ventricular arrhythmias. Electrophysiologic testing should also not be routinely used for risk stratification.

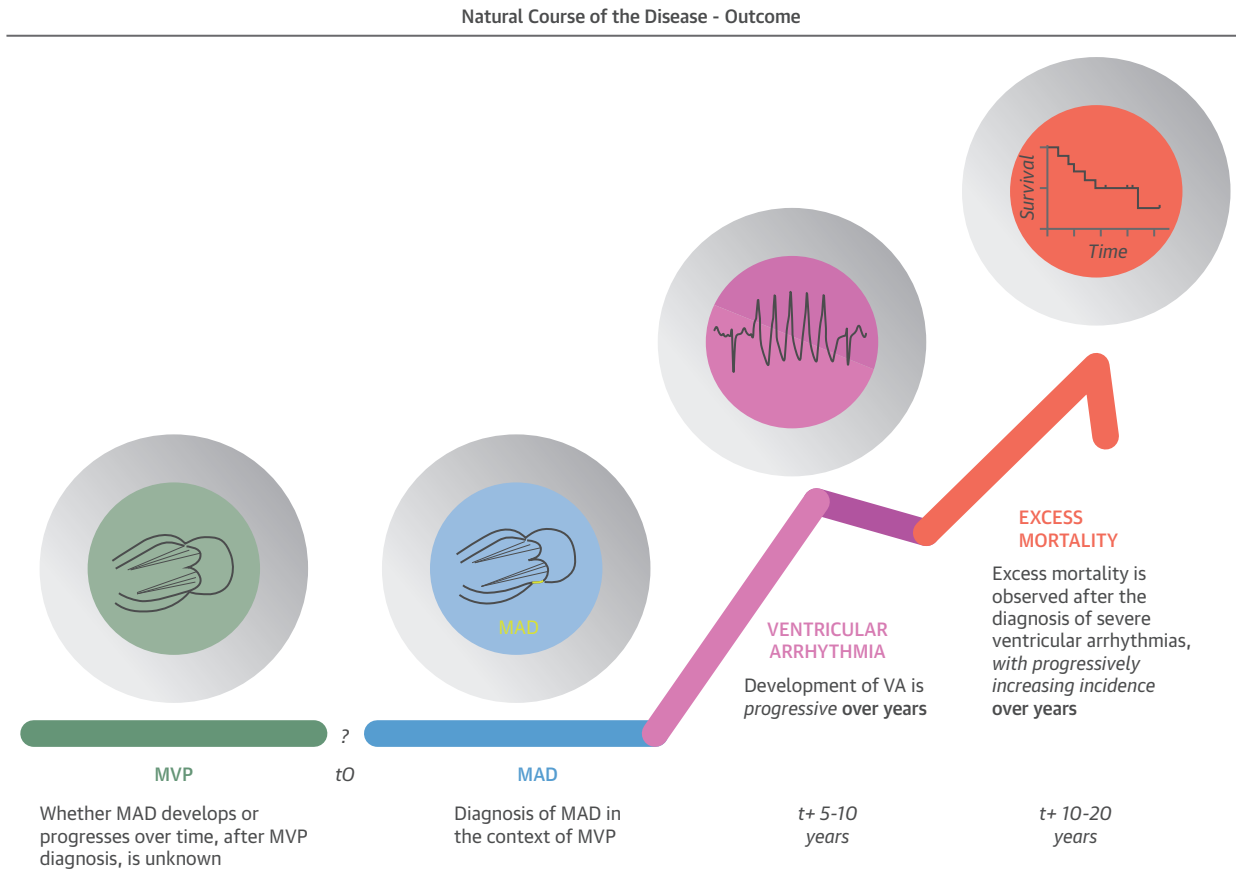
TREATMENT

Due to a paucity of data, clinical decision making in a patient with MAD is challenging and remains largely empirical. Although several management options are available, both the decision to intervene and the treatment choice should be considered carefully by a multidisciplinary heart team consisting of imaging specialists, electrophysiologists, and cardiac surgeons.

MEDICAL THERAPY. Medical therapy comprises beta-blockers, calcium channel antagonists, and other antiarrhythmic drugs which may be beneficial in selected patients by reducing the burden of ventricular arrhythmias. Although randomized studies of medical therapy are lacking in patients with MVP and MAD, its carefully monitored use should be considered, either as primary or as adjunctive therapy. A case series has drawn attention to the potential value of flecainide, in addition to beta-blocker therapy.[68]

RADIOFREQUENCY CATHETER ABLATION. On invasive electrophysiologic testing, the location of origin of ventricular arrhythmias has been mapped to the papillary muscles, the LV outflow tract, and the mitral annulus. PVCs from these sites could trigger ventricular fibrillation in individual patients with MVP and MAD. Radiofrequency substrate modification is feasible in patients with MVP and symptomatic, drug-refractory ventricular arrhythmias.[69] An immediate reduction in the burden of ventricular ectopy has been shown in noncardiac arrest patients after ablation, whereas 86% reported a reduction in symptoms. Although the burden of ventricular ectopy is not reduced in patients who experienced cardiac arrest, catheter ablation causes a significant reduction in the number of appropriate ICD shocks. In 25 patients with MVP and ventricular ectopy mapped to the level of the papillary muscles, Enriquez et al[70] showed a complete elimination of ventricular ectopy in 19 (76%) and a significant reduction of ventricular ectopy in 2 (8%). Successful ablation improved LV systolic function in those who had depressed LV ejection fraction before the ablation. Catheter ablation in patients with MVP and MAD can be technically challenging due to catheter instability, deep intramural sites of origin, and the need to ablate the papillary muscle base.[4,71,72] Long-term follow-up is required postablation because of late recurrence from

FIGURE 11 Natural Course of MAD



The natural history of MAD is not well described, and whether MAD undergoes evolution from a mild to a more severe form over time is unknown. Once MAD is diagnosed, the incidence of ventricular arrhythmias is progressive and excess mortality is a relatively late phenomenon. Abbreviations as in Figures 1 and 5.

arrhythmic foci that were not targeted during the initial procedure or progression of the underlying arrhythmogenic substrate (eg, due to mechanical stress and myocardial fibrosis). These mechanisms provide a potential explanation for the high recurrence rate of ventricular arrhythmias (26%-32%) after successful ablation.[69,70,73] Although catheter ablation can reduce the burden of PVCs and improve LV function, its role in preventing sudden arrhythmic death is unproven.

ICD. ICD insertion is recommended for secondary prevention in patients who experienced an episode of aborted sudden cardiac death even though data on ICD efficacy and recurrence rate of cardiac arrest in such patients are not available. In a retrospective analysis of 42 patients with MVP who underwent ICD insertion after cardiac arrest, appropriate ICD therapy occurred in 16 (38%) and 22 (52%) patients for recurrent ventricular fibrillation and ventricular tachycardia, respectively, during a median follow-up of 63 months. There are currently no data to support a role for primary prevention ICD in patients with MAD who may be at risk of sudden cardiac death.

MV SURGERY. MV surgery is indicated for patients with MVP and severe MR who are symptomatic or have LV systolic dysfunction.[74,75] Durable MV repair or replacement addresses LV volume overload and may result in a reduction of the ventricular arrhythmia burden. Patients with MAD but without an indication for MV surgery to correct regurgitation may derive benefit from repair of MAD per se by insertion of a ring/prosthesis which reconnects the mitral annulus to the LV myocardium. This relieves the excessive stretch on the papillary muscles, thereby eliminating the trigger for ventricular arrhythmias. Retrospective data have shown a signal

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TABLE 1 Different Imaging Modalities Used for Diagnosing and Risk Stratifying MAD, MVP, and MR

	Imaging Modality	Technique	Risk-Stratification Parameter
MAD	Echocardiography	2D 3D	Presence of MAD MAD length[64]
	CMR	Anatomical (eg, SSFP)	Presence of MAD MAD length
	CT	–	Presence of MAD
MVP	Echocardiography	2D 3D Speckle tracking strain	Mechanical dispersion[62] LVEF ≤50% to 60%[56] Redundant leaflets and bileaflet MVP[81] Impaired LV GLS[62] Double-peak strain pattern[31]
	CMR	Anatomical (eg, SSFP and LGE) Functional (eg, feature tracking)	LV fibrosis[60]
	CT	–	–
MR	Echocardiography	2D 3D Doppler	Severity of MR[55,56]
	CMR	Phase contrast	

2D = 2-dimensional; 3D = 3-dimensional; CMR = cardiac magnetic resonance; CT = computed tomography; GLS = global longitudinal strain; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; MAD = mitral annular disjunction; MR = mitral regurgitation; MVP = mitral valve prolapse; SSFP = steady-state free precession.

toward reduction of ventricular arrhythmia burden post-MV repair.[76-78] In a study by Essayagh et al,[6] the risk of ventricular tachycardia after MV surgery in patients with MAD became insignificant. Naksuk et al[76] reported the intriguing observation that MV surgery only reduced ventricular arrhythmias in younger (ie, <60 years of age) but not in older patients. The progressive nature of MAD, with the formation of an arrhythmic substrate (ie, myocardial fibrosis) over time, ties in with the age-dependent benefit of MV intervention. A corollary is that the benefit of MV surgery may be limited in patients with malignant arrhythmias in whom an area of myocardial fibrosis has already been established. Although surgical MV repair is the preferred treatment option in patients with MAD and severe MR with malignant ventricular arrhythmias, survival benefit and risk reduction of sudden cardiac death remain to be shown.

Although transcatheter edge-to-edge MV repair has been shown to improve survival in high-risk patients with MVP and severe MR,[79] it is unable to correct the annular-myocardial separation which is intrinsic to MAD. Therefore, surgical MV repair remains the standard of care for patients with MVP and MAD who suffer from ventricular arrhythmias. The role of surgical cryoablation during MV surgery also merits further investigation.[80]

CONCLUSIONS

Modern imaging techniques have highlighted the frequent presence of MAD in patients with MVP. Emerging evidence supports the fact that MAD is associated with ventricular arrhythmias and sudden cardiac death, occurring because of a trigger (increased mechanical stretch) acting upon a substrate (LV/papillary muscle fibrosis). This provokes early after-depolarizations, leading to ventricular ectopy and malignant ventricular arrhythmias. Various imaging biomarkers have been associated with the risk for life-threatening arrhythmias (Table 1), although their relative merits and prognostic value remain to be defined. A more detailed analysis of the specific MAD phenotype (eg, pseudo-/true MAD and the distribution along the mitral annulus [ie, evolutional MAD and pathogenic MAD) which is associated with arrhythmias, is required. Individuals in whom MAD is diagnosed but without an indication for MV surgery should be investigated with multimodality cardiac imaging and followed up with ambulatory electrocardiographic monitoring. Prospective data are also required to define the role of

HIGHLIGHTS

- MAD is associated with ventricular arrhythmias, but little is known regarding risk stratification.
- Multimodality imaging may be useful in identifying high-risk patients with MAD.
- Prospective data are required to define the role of prevention and treatment in at-risk patients.

ICD insertion, targeted catheter ablation, and surgical MV repair/replacement in selected patients who are at high risk of lethal arrhythmias. In the interim, multicenter registries may be valuable to provide more data.

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