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Review

Mitral Valve Prolapse and Mitral Annular Disjunction Arrhythmic Syndromes: Diagnosis, Risk Stratification and Management

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Abstract

Although mitral valve prolapse (MVP) is usually considered a benign clinical condition, it has been linked with ventricular arrhythmias and sudden cardiac death in patients with a certain "arrhythmic" phenotype, raising awareness and mandating a specific risk stratification protocol. Mitral annular disjunction (MAD) is considered a "red flag" in malignant MVP syndrome along with bileaflet myxomatous prolapse, female gender, negative or biphasic T waves in the inferior leads, fibrosis in the papillary muscles or inferobasal wall detected by cardiac magnetic resonance imaging and complex arrhythmias of right bundle branch morphology. MAD seems to play a critical role in the chain of morphofunctional abnormalities which lead to increased mechanical stretch and subsequent fibrosis mainly in the papillary muscles, forming the vulnerable anatomic substrate prone to arrhythmogenesis, and associated with long-term severe ventricular arrhythmias. Arrhythmogenesis in MVP/MAD patients is not fully understood but a combination between a substrate and a trigger has been established with premature ventricular contraction triggered ventricular fibrillation being the main mechanism of sudden cardiac death (SCD). Certain characteristics mostly recognized by non-invasive imaging modalities serve as risk factors and can be used to diagnose and identify high risk patients with MAD, while treatment options include catheter ablation, device therapy and surgical intervention. This review focuses on the clinical presentation, the arrhythmogenic substrate, and the incidence of ventricular arrhythmias and SCD in MAD population. The current risk stratification tools in MAD arrhythmogenic entity are discussed.

Keywords: mitral annular disjunction; mitral valve prolapse; ventricular arrhythmias; sudden cardiac death

1. Introduction

Mitral annular disjunction (MAD) is an anatomic abnormality which refers to a wide separation between the left atrial wall-mitral valve junction and the basal posterolateral ventricular myocardium that has been recently associated with malignant arrhythmias and sudden cardiac death (SCD) [1–5]. MAD as a sole entity as well as in the setting of the broader classification of "malignant mitral valve prolapse (MVP) syndrome" are considered potentially arrhythmogenic entitles [6].

In the original description from Hutchins *et al.* [1] in the 1980s in 900 hearts with "floppy" mitral valves, MAD was defined as a wide separation $\geq$5 mm between the posterior leaflet insertion into the left atrial wall and the LV attachment was found in 92%, suggesting a correlation between this anatomic variant and myxomatous degeneration of the mitral valve. MAD has been reported to exist in 6% of normal hearts, as a normal anatomic variant [1]. The first echocardiographic description comes from Erikson *et al.* [2] in 2005 where MAD was observed by transesophageal echocardiography in 99% of patients, referred for surgical repair for advanced mitral valve (MV) disease. To that point, MAD was only studied as an anatomic variant in the context of MVP, possibly accelerating the degenerative process of the MV [1]. Hypermobility and systolic elongation of the posterior mitral annulus as a consequence of MAD was thought to increase mechanical stretch on the valvular apparatus and subsequently lead to myxomatous degeneration [1]. During last decades MAD has been associated with malignant ventricular arrhythmias in the setting of MVP [3,5]. However, recent evidence supports its arrhythmogenic entity even in subjects without MVP [6].

Thus, MAD is now considered a "red flag" in malignant MVP syndrome along with bileaflet myxomatous prolapse, female gender, negative or biphasic T waves in the inferior leads, fibrosis in the papillary muscles or inferobasal wall detected by cardiac magnetic resonance (CMR) and complex arrhythmias of right bundle branch morphology, while its role in arrhythmogenesis remains to be clarified [3,6–8]. This review focuses on the clinical presentation, the arrhythmogenic substrate, and the incidence of ventricular arrhythmias and SCD in MAD population. The current risk stratification tools in this new arrhythmogenic entity are discussed.

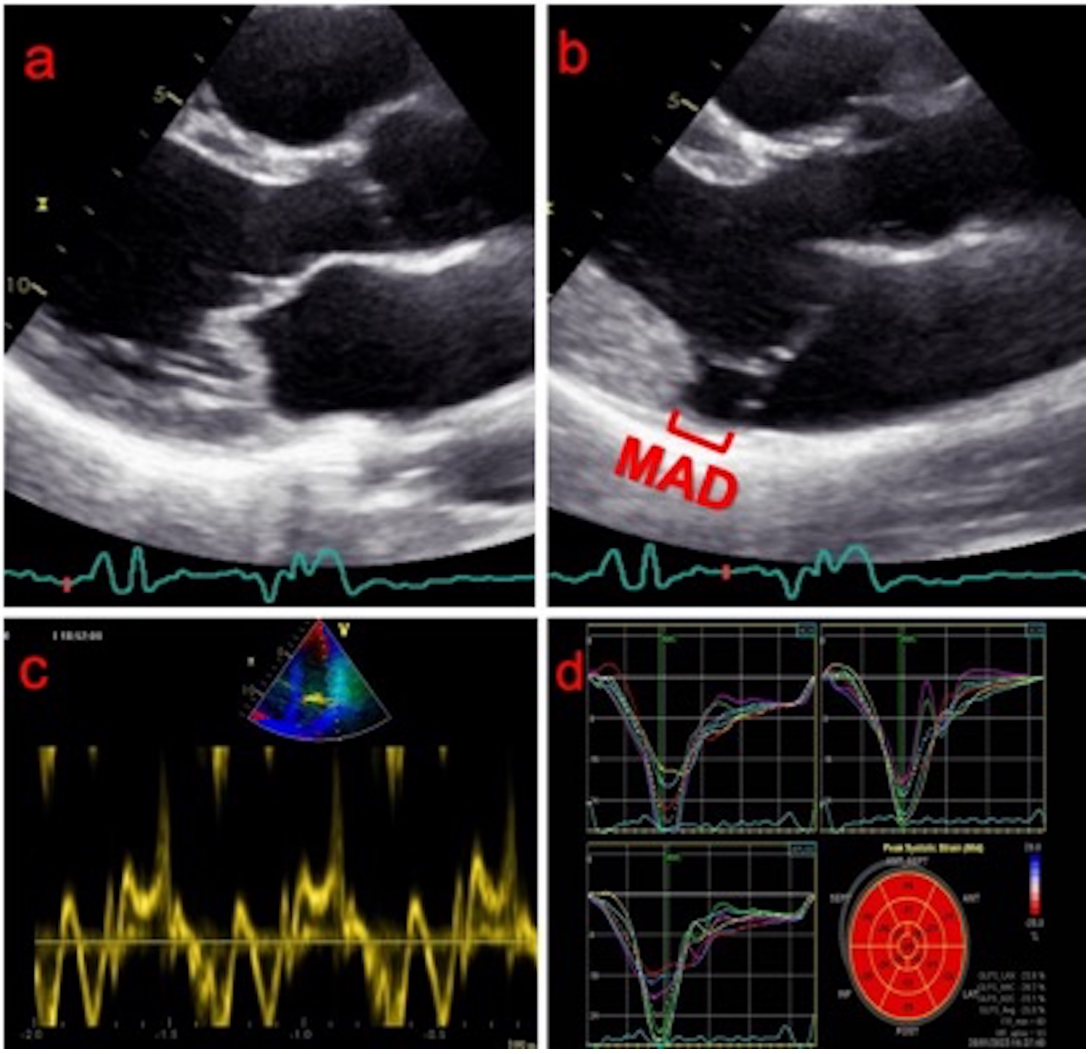

Fig. 1. Echocardiographic findings of mitral valve prolapse and mitral annular disjunction. (a) Transthoracic parasternal long axis echocardiographic view of a bileaflet mitral valve prolapse during end-diastole. (b) Mitral annular disjunction is revealed during end-systole. (c) The "Pickelhaube" sign (spiked systolic lateral mitral annular velocity >16 cm/s) may serve as an early indicator of mechanical stress even in the absence of fibrosis. (d) Longitudinal strain (GLS) with supranormal values in the basic inferior/lateral wall of the left ventricle.

2. Definition and Diagnosis

MVP affects 1–3% of the general population [9] and is classically defined as a superior displacement of MV leaflets above the mitral annulus >2 mm, measured echocardiographically in the parasternal long axis view during systole [10]. There are two phenotypes described. The first one refers to the classic form of Barlow's disease which is characterized by myxomatous degeneration of the MV, with bileaflet prolapse of redundant and thickened leaflets (≥5 mm) (Fig. 1a), while the second one is characterized by fibroelastic deficiency (FED) resulting in thinner leaflets with segmental prolapse due to connective tissue abnormalities [11,12]. There are also familial and genetic patterns described, with filamin C (FLNC) gene mutations being related to arrhythmogenic forms of MVP.

In pathological studies, MAD has been mainly related to MVP with floppy mitral valve and myxomatous degeneration rather than FED [1,13,14]. MAD can be easily detected by transthoracic echocardiography (TTE) [2], and measured in the parasternal long axis view during end-systole (Fig. 1b). It mainly affects the area under the posterior mitral leaflet, which is more prone to mechanical stretch as opposed to the more rigid aorto-mitral continuity [14]. A threshold ≥5 mm was first adopted [1], but a cutoff of 2 mm has been also proposed and used in some studies [14]. Longitudinal MAD distance and circumferential extension can be accurately identified by CMR [15] with reports of MAD area ranging between 30°–240° (median 150°), corresponding to merely 2/3 of the annular circumference [6] (Fig. 2a). Cardiac computed tomography (CT) is also used in certain studies to characterize MAD [16].

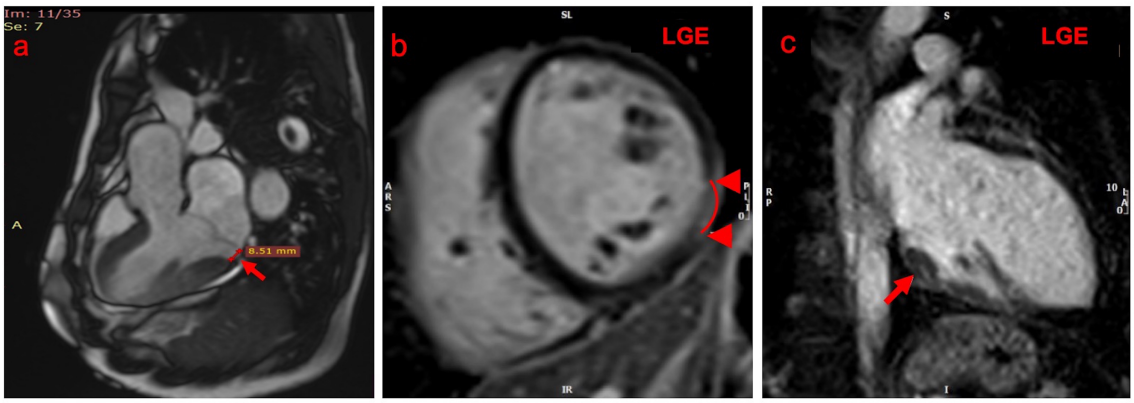

Fig. 2. Cardiac magnetic resonance findings of mitral annular disjunction (MAD) arrhythmic syndrome. (a) MAD with a distance of 8.51 mm in the posterolateral wall (red arrow). (b,c) Late gadolinium enhancement (LGE) localized at the posteromedial papillary muscle and at the inferior wall of the left ventricle (red arrows).

A clear description of the patho-morphological substrate of MAD is still lacking. In a recent study, Faletra *et al*. [17] evaluated MVP patients with an echocardiographic diagnosis of MAD by CMR, and based on the hinge line of posterior leaflet in the diastolic phase concluded to two possible anatomic phenotypes: "pseudo"-MAD and true MAD. The first refers to the juxtaposition of posterior leaflet on the atrial wall in systole which imitates MAD, although the insertion point of the leaflet is normal, while the second one refers to true displacement of the hinge point into the atrial wall, also observed in diastole. This true MAD area is formed from a subannular membrane [18] and it is not clarified whether MVP patients share the one or the other phenotype [17].

In recent studies, MAD was identified in approximately 16–55% of MVP patients, with varying results but lower prevalence than previously reported, maybe due to different imaging modalities used and populations studied [19,20]. In a series of 185 patients, Konda *et al*. [14] reported that MAD is detected in 24% of patients with severe mitral regurgitation and in 90% of patients with Barlow's syndrome, while in a recently published review where 19 studies where included, MAD prevalence was reported to be 50.8% in patients with myxomatous mitral valve, 32.6% in patients with MVP and 25.9% in patients with a floppy mitral valve and severe mitral regurgitation [21]. Of note, in a recent retrospective study where cardiac CTs of structurally normal hearts were 3D analyzed, MAD was seen in 96% of patients as a normal "phenomenon" of the mitral annulus formation [16].

3. SCD Prevalence

The prevalence of SCD in MVP population is low and estimated to be between 16 to 41 per 10000 per year (0.2% to 0.4%) [22]. Yet the real prevalence is difficult to be determined. Among patients with MVP, only a few will suffer SCD, however given the prevalence of MVP in the general population [23], the total number of patients at risk is significant. In Italian autopsy series, as reported by Basso *et al*. [22], MVP was identified as the cause of death in 7% of young adults <40 years, and in 13% amongst females, representing the first fatal cause in this second group. Autopsy studies often report MVP as a cardiac finding in an otherwise structurally normal heart, but due to the uncertain cause-effect relationship between MVP finding at autopsy and SCD, it is not classified as a fatal structural abnormality [24]. This observation is further supported by a meta-analysis of autopsy studies where 22% of deaths were reported unexplained and 11.7% of them exhibited MVP [23]. Yet, the arrhythmic prevalence of MAD itself remains to be determined taking into consideration that in the recent 10-year cohort of MAD patients, this clinical entity was not linked to excess mortality, but it was significantly correlated with severe ventricular arrhythmias in long-term follow-up [25].

4. Ventricular Arrhythmias in MAD: Origin, Triggers and Anatomic Substrate

Arrhythmogenesis in MVP/MAD patients is not fully understood but a combination between a substrate and a trigger has been established with PVC triggered VF being the main mechanism of SCD [26]. There is a wide spectrum of ventricular arrhythmias in MVP-MAD population ranging from premature ventricular complexes (PVCs) to sustained ventricular arrhythmias [ventricular tachycardia/ventricular fibrillation (VT/VF)] [27]. In the recently announced EHRA consensus statement on arrhythmic MVP/MAD complex, "arrhythmogenic MVP" was defined as the presence of MVP, with or without MAD, in patients with frequent (≥5% of total PVC burden) or complex arrhythmias (NSVT/VT/VF) in the absence of any other well-defined arrhythmic substrate [28]. On the other hand, it has been recently reported that MAD arrhythmic syndrome can be the manifestation of a concealed proar-

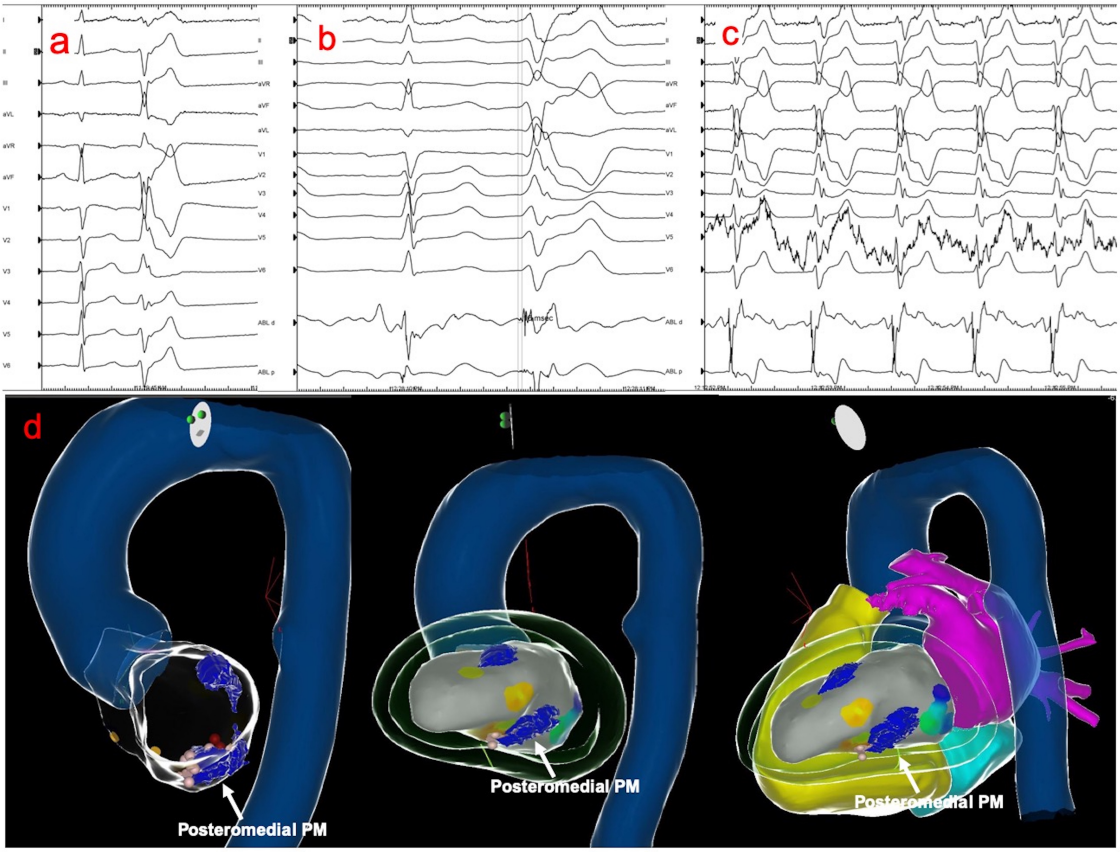

Fig. 3. Electroanatomical mapping and ablation of premature ventricular contraction (PVC) arising from the posteromedial papillary muscle. (a) Typical PVC arising from the posteromedial papillary muscle (left superior axis with RBBB morphology). (b) PVC mapping demonstrating Purkinje potentials preceding the local ventricular activation. (c) Catheter ablation at the earliest activation site led to "warm-up" effect with the same PVC morphology. (d) Merge of electroanatomical 3-D and cardiac CT models demonstrating the papillary muscles (marked in blue). The posteromedial papillary muscle along with the ablation points are shown in multiple views (white arrows).

rhythmic genetic substrate which underlies, and mechanical stretch can serve as the trigger for arrhythmias on this vulnerable-in the presence of fibrosis-substrate [29]. The incidence of PVCs in MVP population has been reported to be between 49 and 85% [26], while in a recent cohort of 595 MVP patients ventricular arrhythmias occurred in 43% [30]. Localized reentry, triggered activity and autonomic system abnormalities has been proposed to be implicated in arrhythmogenesis of MVP/MAD population [26,27,31].

Until now, malignant arrhythmias and SCD in MVP patients has been linked to severe mitral regurgitation and subsequent left ventricular remodeling [26]. However, in out of hospital cardiac arrest (OHCA) survivors with bileaflet MVP, Sriram *et al*. [7] have demonstrated an association between MVP phenotype and arrhythmic SCD even in the absence of significant mitral regurgitation. In addition, in a study of Essayagh *et al*. [30] which included 595 MVP patients, severe ventricular arrhythmia was not associated with mitral valve regurgitation severity.

The origin of arrhythmias mainly involves the papillary muscles (PM) and the outflow tract in areas near the MV apparatus [7,32,33]. Among survivors of OHCA with documented VT/VF, patients with bileaflet MVP had higher burden of PVCs and complex ventricular arrhythmias originating from the outflow tract and PM or fascicles, in an alternating fashion [7,8]. The close proximity of the arrhythmogenic ectopic activity to the MV apparatus suggests an association between an anatomic substrate (mechanical stretch of the PM due to hypermobile mitral annulus and consequent fibrosis) and arrhythmogenesis [26,33]. The development of fibrosis in the left ventricular myocardium close to the MV apparatus (100% patchy replacement-type fibrosis at the level of PM and 80% sub-endocardial and mid-mural fibrosis at the infero-basal wall) has been associated with ventricular arrhythmias of Right Bundle Branch Block (RBBB) morphology and SCD in MVP cases [3]. More precisely, the posterior PM seems to be the main origin of arrhythmias in MVP patients (Fig. 3a) and has been correlated with late gadolinium enhancement (LGE) in CMR [32].

MAD seems to play a central role in the structural substrate predisposing to malignant arrhythmias [26]. First, Carmo *et al*. [5] in 2010 demonstrated that MAD, is associated with frequent PVCs and non-sustained ventricular tachycardia (NSVT) in a population of MVP patients in comparison to those with MVP but without MAD. More precisely they correlated MAD length >8.5 mm with the occurrence of NSVT, suggesting a critical role of this variant in the chain of morphofunctional abnormalities of the mitral valve annulus which form the suitable anatomic substrate for malignant ventricular arrhythmias. Deijgaard *et al*. [6] went a step further by describing the MAD arrhythmic syndrome in 116 patients with MAD, where 12% of them suffered severe arrhythmic events that were not linked to MVP, thus revealing MAD itself as an arrhythmogenic entity. The chain of morphofunctional annular abnormalities in MVP patients with MAD led to Padhua hypothesis [26]. When MAD is present, functionally the mitral valve annulus is decoupled from the left ventricular myocardium [34]. This disruption of the ventriculo-mitral unit leads to hypermobility and paradoxical systolic motion of the annulus [34]. Normally the annulus follows contraction of the left ventricle during cardiac cycle [35]. In MAD, the annulus moves according to left atrium and instead of deepening its saddle shape in systole, it expands and flattens forcing the left ventricular basal myocardium to move outwards in systole and inwards in diastole [34,36]. The flattening of the mitral annulus increases mechanical stretch on the mitral leaflets [37] and PM causing PM elongation and resulting in leaflet degeneration, regional hypertrophy and subsequent fibrosis [4,38]. This hypothesis is further supported by CMR findings where LGE enhancement is confirmed in the areas prone to mechanical stretch [3,15] (Fig. 2). Enhanced basal left ventricular systolic deformation (supranormal in inferolateral segments) along with high tissue velocities in the basal lateral wall, regional hypertrophy and left ventricular dilatation both in CMR and echocardiographic studies of MVP and MAD population suggest that MAD is a disease not only of the MV but also of the adjacent myocardium [15,39,40]. There are reports that fibrosis can present later in the course of the disease and arrhythmias have been documented even in the absence of LGE in CMR [7,33] in few cardiac arrest survivors. This finding underlines mechanical stretch as the main arrhythmic trigger.

A traumatized fibrotic myocardium and/or a diseased Purkinje tissue are mutually involved in arrythmogenesis [26], the first acting as the vulnerable substrate and the latter as the trigger by means of afterdepolarizations and abnormal automaticity [7,31,41]. PVCs arising from Purkinje fibers were identified as VF trigger in the electrophysiological study (EPS) in 6 out of 6 cardiac arrest survivors and as the dominant ventricular ectopy site in 5 out of 8 patients with complex arrhythmias, all with bileaflet MVP [33]. Previous publications suggest that papillary muscles represent an anatomic structure potentially triggering VF even in the normal heart [42]. More specifically, in idiopathic VF populations short coupled ventricular extrasystoles from PMs were preceded by Purkinje-like potentials (PLPs) and were the main mechanism initiating VF [32,43]. The Purkinje fibers are the terminal part of the ventricular conducting system lying at the subendocardium and extending from the interventricular septum to PMs and the lateral ventricular walls [44]. They are characterized by fast conducting properties and automaticity while their complex architecture favors re-entrant circuits and maintenance of ventricular arrhythmias and VF [41,45]. In cardiac arrest survivors with documented VF and MVP, PLPs were recorded in the PMs [33]. In the series of Syed *et al*. [33], the presence of diseased fascicular/Purkinje system was confirmed by the presence of fractionated and abnormal split potentials in asymptomatic MVP patients with inducible VF in the standard EPS, underlying the Purkinje tissue disease as the main electrophysiologic abnormality implicated in arrhythmogenesis. Mechanical stretch to the PMs from hypermobile mitral annulus in patients with MAD may alter the electrophysiologic properties of surrounding tissue shortening the action potential duration and prolonging the ventricular refractory period [7,44], thus facilitating re-entry in areas of fibrotic myocardium and triggered activity by stretch-activated afterdepolarizations in the local Purkinje tissue [43]. This case is supported by EPS findings which revealed areas of slow conduction in close proximity with MV [33]. Autonomic nervous system dysfunction seems to contribute in arrhythmogenesis with most of PM ventricular arrhythmias being catecholamine sensitive [46]. High sympathetic tone predisposes to increased ventricular ectopy, while enhanced catecholamine levels lead to alterations in Ca+ levels in sarcoplasmatic reticulum [7]. As a result, delayed afterdepolarizations and ventricular ectopy emerge [41].

5. Risk Stratification

Risk stratification in this population is highly demanding. The incidence of SCD is relatively low, but overrepresentation of MVP in unexplained SCD cohorts along with the high prevalence of MVP in the general population indicates a large population at risk [20], which remains to be identified. There are several risk factors reported including ECG abnormalities, morphofunctional characteristics, echocardiographic and CMR findings [7,8,26]. The emerging role of EPS is yet to be clarified and added to a risk stratification model aiming to identify the “high risk“ patient.

SCD seems to be of great importance in the young and female patients with MVP [7,8]. Conflicting evidence concerning the prevalence of SCD according to age exist [8,25]. Studies in cardiac arrest survivors established a certain high risk clinical profile in young women with syncope, bileaflet myxomatous MVP, MAD, mild or mild-to-moderate mitral regurgitation, biphasic or inverted T waves in the inferior leads and frequent PVCs originating from outflow tract or

papillary muscle [7,8].

In unpublished data from our group, fibrosis detected by CMR, PVCs morphology (RBBB with left superior axis) and positive programmed ventricular stimulation during EPS seem to be the high risk features. In the largest cohort of MAD-MVP patients published in 2021, Essayagh *et al*. [25] concluded that the presence of MAD is independently associated with long term excess incidence of clinical arrhythmic events proving the progressive course of the substrate and mandating careful monitoring for malignant arrhythmias in the long term. These findings that are suggestive of a "progressive disease" are in line with a catheter ablation study in MVP patients where 5 out of 15 patients with successful ablation of dominant PVC foci presented during follow up with hemodynamically significant VT/VF arising from a different site [47]. Of note, all of these patients had inducible VF in prior EPS [47].

MAD seems to correlate with regional fibrosis as represented by LGE enhancement in the adjacent myocardium [15,48,49] and PMs [46] and these patients are more prone to arrhythmic events as stated by pathologic and EPS studies [3,6]. Myocardial extracellular volume (ECVsyn) also plays a role in revealing interstitial myocardial fibrosis in MAD-MVP patients [48]. Increased ECVsyn of the basal LV segments was found to have a strong association with MAD and OHCA even in the absence of LGE [48]. Thus CMR with pre- and post-T1 mapping and ECVsyn calculation should be a basic tool in risk stratification of this population [15,48,49].

The origin of ventricular ectopic activity strongly correlates with malignant arrhythmia burden and SCD [7,33]. The prevalence of PVCs in the MVP population is high but complex VTs are more common among SCD population [7]. As previously discussed ventricular ectopy seems to be mainly of LV origin since all SCD victims displayed RBBB morphology ventricular arrhythmias [3]. More robust investigation revealed as the dominant PVC morphology in MVP patients with complex arrhythmias, the one originating from posterior PM [32]. Thus PVCs originating from this area should be considered as a "red flag" and added to risk stratification algorithm [32].

Biphasic and inverted T waves in inferior leads are considered a high risk marker possibly reflecting repolarization abnormalities due to altered contractility in the basal LV segments adjacent to MAD [6,7,26]. There are reports of longer corrected QT intervals among arrhythmia patients with MVP but this is not a constant finding with reports varying from 9% to 26% [26,50]. QT dispersion is also reported to be higher in these patients but both these parameters cannot be strongly associated with arrhythmic risk [51].

Longitudinal MAD distance both in echo [5,6] and CMR along with systolic curling motion of the posterior mitral annulus [52] correlate with increased risk of ventricular arrhythmia. Precisely, a disjunction length $>$8.5 mm was associated with NSVT on holter monitoring in a cohort of 38 MVP patients [5] while circumferential area and greater longitudinal MAD distance measured in CMR was an independent risk factor for arrhythmias [6]. Novel echocardiographic findings have also been reported in the MAD-MVP population [13,53,54]. Higher annular tissue velocities in the basal lateral segment depicted in the "Pickelhaube" sign [39] as a spiked configuration with velocities $>$16 cm/s reflect the mechanical stretch on these myocardial regions and can serve as an early indicator of mechanical stress even in the absence of fibrosis (Fig. 1c). Heterogeneity of longitudinal strain has also been reported with supranormal values in basal inferolateral regions [53,55] reflecting hypercontractility along with higher myocardial work in the same regions [56] (Fig. 1d). Basal to mid LV wall thickness ratio $>$1.5 were also higher in MVP patients with late gadolinium enhancement than in those without [4]. These findings can be explained by constant stretch leading to increased oxygen demand and oxidative stress but remains to be further confirmed. Mechanical dispersion, already associated with ventricular arrhythmias in patients with cardiac diseases [57], was also found to be higher in arrhythmogenic MVP patients [58].

The role of EPS in MVP population has not been clearly established and remains controversial since the induction of VF is considered a non-specific finding in patients with complex ventricular arrhythmias. Studies in MVP cardiac arrest survivors and ablation population revealed hemodynamically significant VT/VF even in the absence of myocardial scar [8,33]. These patients had a high burden of PVCs and complex arrhythmias from PM and outflow tract [7,8]. Therefore, in patients with MAD and frequent symptomatic arrhythmias of PM origin, a more aggressive protocol should be employed independently of LV fibrosis in CMR. Syncope patients may be candidates for EPS, and they should be carefully monitored for progressive disease thereafter, as proposed in the Essayagh *et al*. [25] study, possibly via implantation of loop recorders [7]. However, further studies are needed to strengthen the prognostic significance of EPS in this population.

All these parameters contribute to elucidating the association between the substrate and the trigger in this arrhythmic syndrome and serve as risk markers but as discussed earlier we focus on the presence of MAD, fibrosis, PVC origin and the "positive" EPS as the strongest correlators with malignant arrhythmias and thus SCD risk predictors.

The following protocol can be used for risk stratification of MAD patients. All patients with echocardiographically detected MAD accompanied by signs of mechanical stretch (high longitudinal strain values in basal inferolateral wall/"Pickelhaube" sign, inverted T waves in inferior leads) and frequent ventricular arrhythmias arising from posterior PM/outflow tract (12-lead ECG Holter monitoring and treadmill test), should be further tested with CMR to detect myocardial or PM fibrosis. In cases of symptomatic VTs

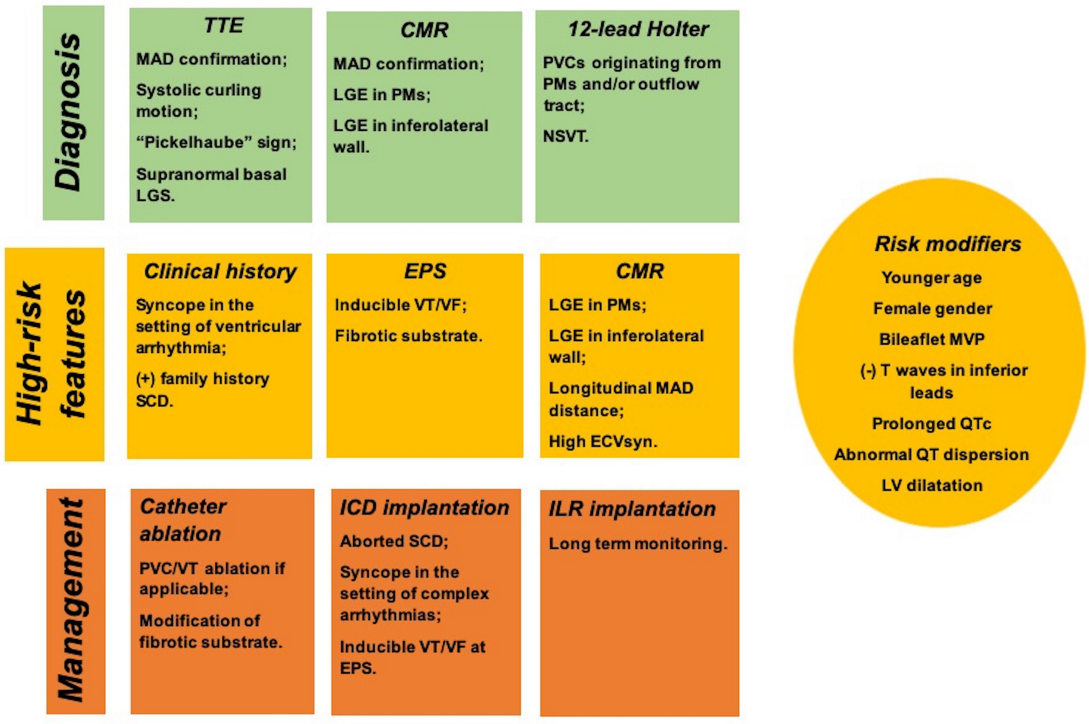

Fig. 4. Diagnosis, risk stratification and management of mitral annular disjunction (MAD) arrhythmic syndrome. Abbreviations: CMR, cardiac magnetic resonance imaging; EPS, electrophysiological study; GLS, global longitudinal strain; ICD, implantable cardioverter defibrillator; ILR, implantable loop recorder; LV, left ventricle; LGE, late gadolinium enhancement; MVP, mitral valve prolapse; NSVT, non-sustained VT; PVC, premature ventricular complex; QTc, corrected QT interval; SCD, sudden cardiac death; TTE, transthoracic echocardiography; VT/VF, ventricular tachycardia/ventricular fibrillation.

or LGE/diffuse fibrosis, EPS should be performed to further map the site of ectopic activity and to reveal possible multifocality, along with programmed ventricular stimulation. Patients with "positive" EPS should be referred for implantable cardioverter defibrillator (ICD) implantation. In accordance with the recently announced risk stratification algorithm of EHRA, asymptomatic patients without complex ventricular may be further monitored with an ILR, while MVP patients with no documented arrhythmias, but other malignant phenotypic characteristics (as previously described) may be candidates for ILR, or frequent monitoring [28]. These data are depicted in Fig. 4.

6. Management

Management of ventricular arrhythmias in MVP patient includes anti-arrhythmic drug therapy, catheter ablation, surgical intervention and prevention of SCD with device therapy, as discussed earlier [26]. Currently, no antiarrhythmic medication has been reported to be highly effective in this population [59]. In a recent cohort, MAD strongly correlated with arrhythmic events even in patients under medication [25]. Beta-blockers are the main category used acting by reducing hypercontractility responsible for mechanical stretch to the mitral subvalvular apparatus and adjacent myocardium, but also by adjusting the catecholamine levels [26,59].

In current practice, catheter ablation is reserved for patients with frequent symptomatic PVCs, sustained ventricular arrhythmias and VF [31]. PVC-triggered VF is the main mechanism of SCD in bileaflet MVP patients [33] and thus, identification and ablation of dominant PVC foci can be a useful strategy in this population. Ablation of idiopathic VF was first reported by Haisaguerre *et al*. [60,61] where PVCs with short coupling interval were mapped and ablated. These PVCs where often preceded by PLPs, same as in cardiac arrest survivors with bileaflet MVP, and mainly located in PMs or fascicular tissue adjacent to PMs [33,42].

Catheter ablation of the dominant PVC foci in MVP patient has been proved to reduce the arrhythmic burden and ICD shocks, and should be recommended, especially in patients with monomorphic PVCs [7,33]. The PMs are the most common ablation target with varying acute success rate ranging from 60–100% both in MVP patients [47,62,63] and in patients with ventricular arrhythmias from PMs of other etiology, with less promising long term success rate of about 60% [46]. Other possible sites of ectopic activity amenable to radiofrequency (RF) ablation are the outflow tract and the mitral annulus [33,47,64]. Acti-

vation mapping of spontaneous or inducible PVCs is the main strategy [33]. The site of earliest activation located by the bipolar catheter is compared with the surface QRS of the PVC and targeted for ablation [33]. Pace mapping can also be used, taking into consideration both the morphology and latency of capture, in case of non-inducible ventricular arrhythmias [47]. An example of catheter ablation of a PVC arising from the posteromedial PM is shown in Fig. 3. RF ablation of PVCs arising from PMs poses certain limitations and repeat procedures along with late recurrence are reported in MVP patients [30,47,62]. In particular, RF ablation of the PMs can be extremely challenging due to difficulty in maintaining catheter stability and intracavitary position of PMs [33,46,65], often leading to a need for multiple procedures. Intracardiac echocardiography catheter (ICE) is commonly used to guide the procedure [65], enabling direct visualization of anatomic structures and confirming adequate ablation catheter contact at the site of earliest activation [33,47,62]. Cryoablation has been proposed in refractory cases for better catheter contact to the PM [43,63,66]. Although effective in reducing PVC burden, ablation therapy may not prevent fatal arrhythmias in MVP patients, as it is suggested in the study of Marano *et al*. [47] where 33% of patients presented with hemodynamically significant VT/VF after index ablation [47]. Interestingly, all patients who required repeat ablation had PVCs of different foci than the index procedure which is consistent with the progressive nature of the arrhythmic substrate, especially in patients with multifocal PVCs. On the other hand, EPS seems to accurately identify "high risk" patients since all of them had inducible VF in prior programmed ventricular stimulation [47]. The progressive clinical course of the substrate is also underlined in the recently published 10 year study of MAD/MVP patients where MAD correlated with long-term excess incidence of clinical arrhythmia [25].

There is a lack of evidence concerning surgical replacement or mitral valve repair and arrhythmia outcomes, with data deriving mostly from small single-center series and isolated cases [67,68]. To date, surgical repair is indicated in severe mitral regurgitation targeting repair of the prolapsing leaflets. This is supposed to relieve, at least to some degree, the mechanical stretch to the subvalvular apparatus which acts as a trigger for arrhythmic events [68]. On the other hand, severe arrhythmias are frequently presented in patients with mild and moderate mitral regurgitation, who are not candidates for surgical intervention [6,7]. Surgical repair cannot reverse the natural course of the disease especially when considering the involvement of fibrosis and the progressive arrhythmogenic substrate [25,26], and thus terminate the arrhythmia circle. However, there are reports of reduction of arrhythmic burden after surgical intervention, but this may be attributed to left ventricular remodeling and load volume restoration [69]. From a technical aspect, in MAD cases, the posterior leaflet needs to be repositioned and attached to basal myocardium and further secured with an annuloplasty ring, with a reported success rate of 87% [68].

In all patients with documented VT/VF as well as in cardiac arrest survivors an ICD should be implanted as secondary prevention, in accordance with international guidelines. No specific guidance exists for primary prevention in this population. A proposed algorithm based on the available risk stratification tools for the management of patients with MAD is depicted in Fig. 4.

7. Conclusions

MAD is a novel "high-risk" marker among patients with or without MVP, as it is associated with malignant ventricular arrhythmias. Yet the real arrhythmic prevalence needs to be determined. Recent studies suggest the progressive course of this arrhythmic substrate, mandating careful monitoring of these patients and the need for more aggressive risk stratification protocols. The longitudinal MAD distance as well as the detection of fibrotic arrhythmogenic substrate with CMR are of prognostic significance for arrhythmias. EPS appears to have a good correlation with identification of "high-risk" patients suitable for ICD implantation, and in that direction more prospective studies are needed to further establish its role in the primary prevention strategy.

Author Contributions

PN and KPL drafted the manuscript. PN, EP, IL, KV, AC, GT, ME, EN, and KPL performed the research and reviewed the manuscript. GT and KPL approved the final version. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest. Konstantinos P. Letsas is serving as one of the Editorial Board members and Guest editors of this journal. Konstantinos Vlachos and Gary Tse are serving as the Guest editors of this journal. We declare that Konstantinos P. Letsas, Konstantinos Vlachos, and Gary Tse had no involvement in the peer review of this article and have no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Alessandro Zorzi.

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