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CASE SERIES

Arrhythmogenic Mitral Valve Prolapse and Mitral Annular Disjunction: From Observation to Intervention

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Summary

Ventricular arrhythmias and sudden cardiac death remain rare manifestations of mitral valve prolapse (MVP). Often referred to as arrhythmogenic MVP, this subset of a common valvular pathology has become increasingly recognized and is associated with key characteristics across a variety of imaging modalities. With a better understanding of the relevant anatomical considerations, risk stratification for arrhythmia development is essential to identifying at-risk patients and providing targeted therapies. Patient evaluation should incorporate a thorough review of imaging, including echocardiography and, when necessary, cardiac magnetic resonance imaging, to ensure accurate diagnosis. We present a case series depicting the spectrum of arrhythmogenic MVP severity and methods of risk stratification aimed at identifying characteristics linking valvular pathology to the development of lethal arrhythmias. Based on limited data and our institutional experience, we propose an algorithm for clinical decision-making and management of these patients.

Keywords: Imaging; mitral valve; palpitations; valve replacement; ventricular fibrillation; ventricular tachycardia

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Introduction

Mitral valve prolapse (MVP) is a common valvular heart disease characterized by the superior displacement of one or both mitral valve leaflets into the left atrium during systole. Arrhythmogenic MVP, a subset of MVP, is particularly concerning because of its association with malignant arrhythmias and an increased risk of sudden cardiac death (SCD).[1]

The pathophysiology of MVP involves fibromyxomatous degeneration of the valve leaflets, elongation or disruption of the chordae tendineae, and papillary muscle abnormalities.[1] These structural changes can lead to abnormal valve function and may predispose patients to ventricular arrhythmias. Arrhythmogenic MVP is often associated with mitral annular disjunction (MAD), in which the leaflet root, typically of the posterior leaflet, is displaced from the annulus into the atrium. This is best visualized as separation of the mitral valve insertion point from the ventricular myocardium during systole on echocardiography and cardiac magnetic resonance imaging (CMR).

Echocardiography can identify the Pickelhaube sign, in which traction on the posteromedial papillary muscle by the prolapsing posterior leaflet causes the adjacent left ventricular myocardium to be pulled rapidly toward the apex, resulting in a spike-like lateral annular tissue Doppler velocity signal during systole. CMR can additionally identify valvular or perivalvular late gadolinium enhancement (LGE). The severity of MAD and the presence of LGE correlate with SCD risk, as chronic mechanical stretch and traction of the displaced annulus lead to myxomatous degeneration and fibrosis of the subvalvular apparatus, creating a substrate for scar-mediated ventricular tachyarrhythmias.

Additional risk factors for SCD in patients with arrhythmogenic MVP have been described, including a history of syncope, family history of SCD, inferolateral T-wave inversions on electrocardiography, multifocal or coupled premature ventricular complexes, nonsustained ventricular tachycardia, and severe mitral regurgitation. However, the literature has not demonstrated a consistent risk profile that reliably predicts malignant arrhythmias or SCD, as the relatively low incidence of these events has resulted in a paucity of robust risk stratification models.[1,7]

We present a series of four cases of arrhythmogenic MVP with MAD that encompass a broad spectrum of disease severity and highlight the clinical challenges associated with risk stratification and prevention of SCD. We also propose an algorithm to guide clinical decision-making and management of these patients.

Case 1

A 75-year-old man was referred to the cardiology clinic for evaluation of fatigue in the setting of mild-to-moderate mitral regurgitation and right ventricular (RV) enlargement on transthoracic echocardiography (TTE). Cardiac magnetic resonance imaging was obtained to further assess RV size and demonstrated normal RV dimensions with reduced biventricular systolic function, as well as MAD associated with moderate bileaflet MVP (Figure 1). In retrospect, TTE demonstrated the Pickelhaube sign (Figure 2). No late gadolinium enhancement was identified. Ambulatory Holter monitoring revealed no ventricular arrhythmias.

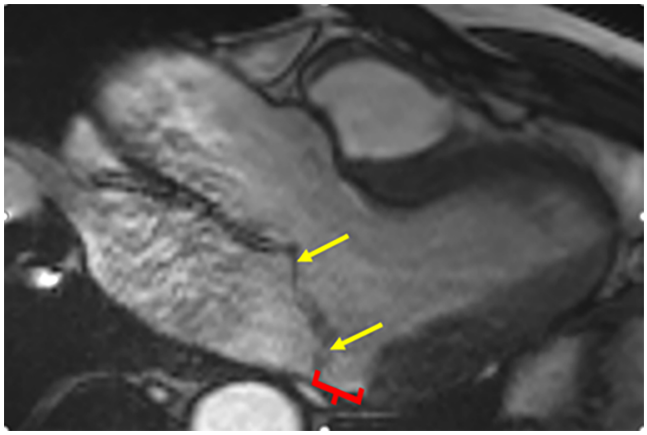

Figure 1. Mitral annular disjunction (red bracket) associated with bileaflet mitral valve prolapse (yellow arrows) on cardiac magnetic resonance imaging in Case 1.

Interpretation

This patient with mild-to-moderate mitral regurgitation and no definitive echocardiographic evidence of MVP underwent CMR, which identified MAD and bileaflet prolapse. This case underscores the clinical challenges in determining when patients with suspected or subtle echocardiographic findings should undergo advanced imaging, as well as identifying asymptomatic phenotypes that warrant further arrhythmic risk stratification. In this instance, concern for right ventricular dysfunction prompted CMR, which revealed MAD and bileaflet prolapse as phenotypic risk factors for ventricular arrhythmias. Given these findings, a strategy of surveillance for ventricular ectopy was pursued despite the absence of symptoms or documented clinical events.

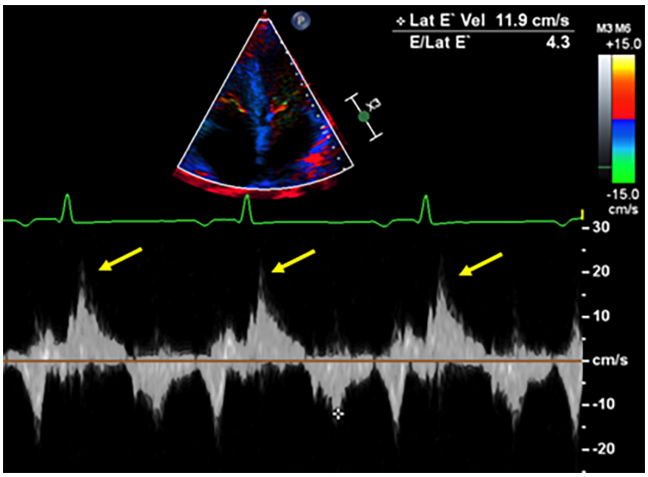

Figure 2. Pickelhaube sign with a spike-like tissue Doppler signal (yellow arrows), reflecting rapid acceleration of the lateral mitral annulus toward the left ventricular apex during systole due to prolapse of the posterior mitral valve leaflet in Case 1.

Case 2

A 45-year-old man with a history of asymptomatic MVP and a family history of SCD in multiple paternal relatives was referred to the cardiology clinic for evaluation of palpitations. Ambulatory Holter monitoring revealed nonsustained ventricular tachycardia (Figure 3), and CMR demonstrated mild bileaflet MVP associated with MAD and trace mitral regurgitation. No late gadolinium enhancement was identified. An electrophysiology study did not induce ventricular arrhythmias; therefore, an implantable cardioverter-defibrillator was not placed. An implantable loop recorder was subsequently placed for long-term monitoring of ventricular arrhythmias. After 18 months of continuous monitoring, no ventricular arrhythmias have been detected.

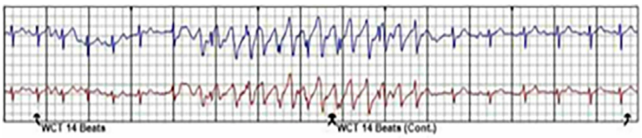

Figure 3. Representative Holter monitor strip demonstrating nonsustained ventricular tachycardia in Case 2.

Interpretation

This patient transitioned from asymptomatic to symptomatic MVP with the development of palpitations and associated nonsustained ventricular tachycardia, in the context of a family history of SCD affecting multiple relatives. Cardiac magnetic resonance imaging identified bileaflet MVP and MAD as high-risk phenotypes. Compared with Case 1, this patient was considered to be at higher risk; accordingly, identification or provocation of malignant ventricular arrhythmias would have prompted consideration of a secondary-prevention implantable cardioverter-defibrillator.

Case 3

A 48-year-old woman with a history of mitral regurgitation and symptomatic ventricular ectopy originating from the posteromedial papillary muscle was referred to the cardiology clinic because of concern for symptoms associated with a severe mitral regurgitation murmur that appeared discrepant with TTE findings of only moderate mitral regurgitation. Six years earlier, she had been evaluated by electrophysiology for symptomatic ventricular ectopy in the setting of CMR demonstrating late gadolinium enhancement of the papillary muscles and submitral valvular apparatus, and she had declined catheter ablation at that time.

She now presented with exertional exercise intolerance and palpitations. Repeat CMR demonstrated moderate-to-severe mitral regurgitation with mildly reduced left ventricular ejection fraction, MAD, and persistent papillary and subvalvular inferolateral late gadolinium enhancement (Figure 4). In retrospect, MAD had also been present on TTE performed 14 months earlier at an outside institution (Figure 5). Cardiopulmonary exercise testing objectively confirmed reduced exercise tolerance.

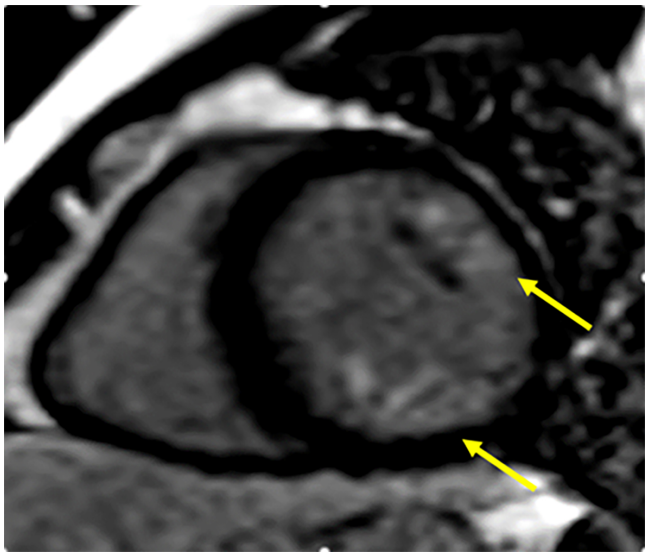

Figure 4. Late gadolinium enhancement (yellow arrows) of the papillary muscles and subvalvular apparatus in a patient with mitral valve prolapse and mitral annular disjunction in Case 3.

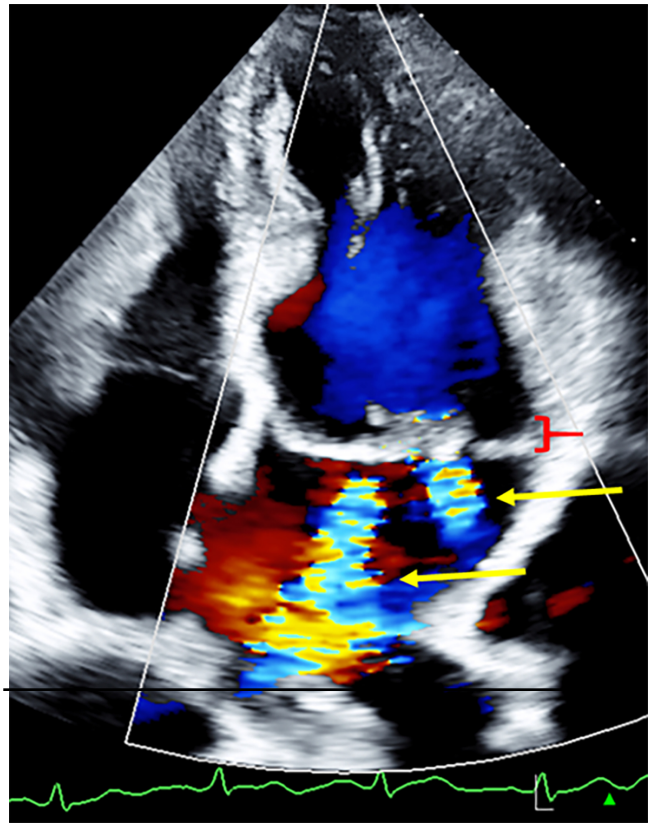

Figure 5. Transthoracic echocardiography demonstrating mitral annular disjunction (red bracket) associated with severe mitral regurgitation (yellow arrows) in Case 3.

Interpretation

This patient initially presented with symptomatic ventricular ectopy and subsequently developed progressive mitral regurgitation in the setting of known perivalvular late gadolinium enhancement and previously unrecognized MAD identified retrospectively six years earlier. Although she had not experienced clinical or subclinical malignant ventricular arrhythmias, she represented a high-risk phenotype characterized by severe mitral regurgitation, ventricular ectopy, reduced left ventricular ejection fraction, and CMR evidence of MAD and late gadolinium enhancement.

Because she met a Class I indication for mitral valve surgery, surgical intervention was pursued first, with the additional rationale of potentially reducing ongoing mechanical traction and progressive fibrosis that could contribute to ventricular ectopy. When her ectopic burden increased despite successful mitral valve surgery, targeted catheter ablation was subsequently offered.

Case 4

A 48-year-old man with a history of atrial fibrillation and MVP presented to the hospital after an out-of-hospital cardiac arrest. He had witnessed a motor vehicle collision and was assisting those involved when he experienced syncope; emergency medical services found him in ventricular fibrillation on initial evaluation. He was successfully resuscitated with external defibrillation, mechanical ventilation, therapeutic hypothermia, and vasopressor support, and subsequently made a full neurological recovery.

Given initial concern for a primary channelopathy as the cause of his cardiac arrest, an electrophysiology study was performed. Polymorphic ventricular tachycardia was induced with epinephrine challenge without associated QT interval shortening, raising concern for catecholaminergic polymorphic ventricular tachycardia rather than congenital long QT syndrome. An implantable cardioverter-defibrillator was placed, and beta-blocker therapy was initiated. Genetic testing at that time was inconclusive. CMR demonstrated bileaflet MVP with mild-to-moderate mitral regurgitation.

Seven years later, the patient developed recurrent device therapies, including antitachycardia pacing and defibrillation, for monomorphic ventricular tachycardia. Transthoracic echocardiography redemonstrated bileaflet prolapse with possible MAD (Figure 6). Repeat CMR confirmed bileaflet prolapse with mitral regurgitation and additionally revealed prominent MAD and basal lateral left ventricular late gadolinium enhancement (Figure 7). Despite aggressive medical therapy for rhythm control, his ventricular tachycardia burden and device therapies continued to escalate, prompting referral for catheter ablation.

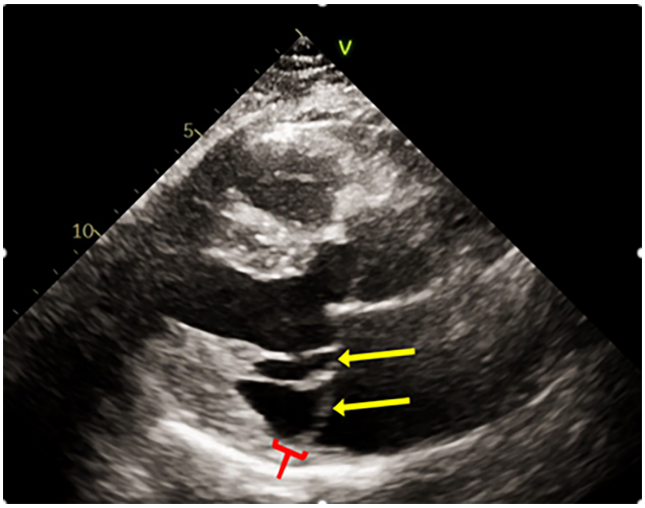

Figure 6. Transthoracic echocardiography demonstrating bileaflet mitral valve prolapse (yellow arrows) and mitral annular disjunction (red bracket) in Case 4.

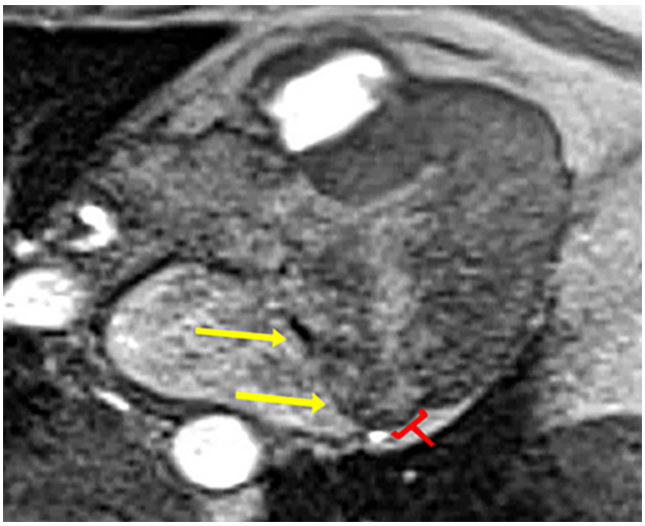

Figure 7. Cardiac magnetic resonance imaging demonstrating bileaflet mitral valve prolapse (yellow arrows) and mitral annular disjunction (red bracket) in Case 4.

Given his prior electrophysiology study complicated by ventricular fibrillation, careful consideration was given to procedural planning to ensure hemodynamic stability during arrhythmia induction. During repeat electrophysiology study, sustained monomorphic ventricular tachycardia was successfully induced using standard pacing maneuvers. Given preserved hemodynamic stability, mapping focused on the basal lateral left ventricular wall corresponding to the region of late gadolinium enhancement. Surface electrocardiography demonstrated a right bundle branch block morphology with a superior axis and lead I negativity, consistent with this anatomic substrate. Entrainment mapping within areas of dense scar identified findings consistent with the clinical tachycardia exit site. Multiple radiofrequency ablation lesions were delivered using an irrigated catheter at 30 W, followed by escalation to 35 W targeting a 10-ohm impedance drop. Following ablation, repeat electrophysiology study demonstrated noninducibility of ventricular arrhythmias.

Subsequent genetic testing identified a likely pathogenic titin (TTN) gene variant, raising further questions regarding the patient's initial diagnosis of catecholaminergic polymorphic ventricular tachycardia.

Interpretation

This patient initially presented with ventricular fibrillation arrest and inducible polymorphic ventricular tachycardia, which was initially characterized as catecholaminergic polymorphic ventricular tachycardia and congenital long QT syndrome following invasive testing. However, the subsequent development of breakthrough monomorphic ventricular tachycardia in the setting of known bileaflet MVP and mitral regurgitation on prior CMR and, in retrospect, previously unrecognized MAD, prompted reconsideration of the underlying mechanism. These findings raised concern for progressive mechanical traction and fibrosis resulting in scar-mediated ventricular tachycardia. Follow-up CMR confirmed this suspicion and guided successful percutaneous ventricular tachycardia ablation. Notably, prior genetic testing initially performed for suspected channelopathy ultimately revealed a mutation later identified as a pathogenic marker associated with arrhythmogenic MVP.

Discussion

Arrhythmogenic MVP has emerged as a recognized cause of SCD, particularly in young adults, with a reported prevalence of 7% in men and 13% in women in one registry, and rates as high as 24% in autopsy series of young adults with SCD. Although there is substantial overlap with hemodynamically significant mitral regurgitation resulting in left ventricular remodeling, autopsy studies of SCD patients with MVP but without significant mitral regurgitation have demonstrated perivalvular myocardial fibrosis, most commonly involving the papillary muscles and adjacent inferobasal and free wall myocardium.

This patchy fibrosis is thought to result from mechanical stretch imposed by MVP and MAD during systole, with repetitive hypercontractility leading to myocyte hypertrophy, injury, and eventual replacement fibrosis. This scarred myocardium can be identified as late gadolinium enhancement on CMR and has been shown to correlate with ventricular ectopy exhibiting right bundle branch block morphology. Although MAD is frequently observed in MVP, not all cases progress to myocardial fibrosis. Available data suggest that fibrosis is more prevalent in high-risk patients, particularly those with significant MAD, ventricular arrhythmias, or late gadolinium enhancement on CMR.

Notably, fibrosis appears to be most common in patients with additional arrhythmogenic substrates, such as prolonged ventricular repolarization or inferolateral myocardial scar detected by late gadolinium enhancement. While fibrosis may develop in patients without significant mitral regurgitation, evidence suggests a synergistic relationship between fibrosis burden and mitral regurgitation severity.[5] In addition, even in the absence of fibrosis, mechanical stretch related to MVP and MAD can result in mechanical and electrical dispersion, which alone may provide an arrhythmogenic substrate. Collectively, these mechanisms explain why MVP, MAD, and late gadolinium enhancement offer overlapping yet distinct prognostic information.[6,8]

The presented cases illustrate how patients with this pathophysiology may manifest a broad phenotypic spectrum of arrhythmogenic MVP, resulting in distinct therapeutic challenges related to disease severity. Our proposed algorithm for clinical decision-making aligns with the 2022 European Heart Rhythm Association guidelines.[9] We strongly advocate for CMR to assess for MAD and late

gadolinium enhancement in patients with MVP who have any risk factors for arrhythmogenic MVP or evidence of structural heart disease on comprehensive echocardiographic evaluation.

In patients with MVP and MAD without a history of syncope, concerning family history, or documented nonsustained ventricular tachycardia, we support periodic ambulatory Holter monitoring. In contrast, for patients with unexplained syncope, a family history of sudden cardiac death, or nonsustained ventricular tachycardia on Holter monitoring, escalation of rhythm surveillance, including more frequent or continuous monitoring, as well as consideration of electrophysiology study for provocation of malignant ventricular arrhythmias may be appropriate to further refine risk stratification. These findings can inform decisions regarding primary prevention implantable cardioverter-defibrillator implantation and/or more aggressive medical or ablative therapies.

When severe or rapidly progressive mitral regurgitation is present, mitral valve repair or replacement should be strongly considered, given the potential benefit of reducing cumulative mechanical traction and progressive myocardial fibrosis.

As evidenced by the association between MVP and SCD, our recommendations are not without limitations. Significant evidence gaps remain regarding the optimal timing of evaluation, surveillance, and intervention. Furthermore, although associations have been demonstrated, there is no "one-size-fits-all" approach to patient assessment, and not all diagnostic modalities discussed, such as CMR, are universally available, making rigid recommendations challenging. When considering intervention, equipoise persists within the medical community regarding mitral valve repair versus replacement, owing to meaningful differences in procedural risks and long-term outcomes.

Key Points

* Arrhythmogenic MVP is mediated by mechanical stretch from leaflet prolapse and MAD, which may result in electromechanical dispersion and/or replacement fibrosis, potentially exacerbated by adverse remodeling from progressive mitral regurgitation.

* Patients with MVP and structural heart disease on comprehensive echocardiography, or with clinical risk factors for arrhythmogenic MVP, should undergo early CMR, which is critical for identifying MAD and late gadolinium enhancement as risk factors for ventricular arrhythmias.

* Detection of ventricular arrhythmias through ambulatory Holter monitoring, continuous rhythm monitoring, or provocation during electrophysiology study further refines risk stratification and informs candidacy for primary-prevention implantable cardioverter-defibrillator implantation and/or aggressive medical or ablative therapy.

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Informed consent

Written informed consent was obtained from the patient for the publication of the manuscript.

Conflict of Interests

None

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