

Arrhythmic Mitral Valve Prolapses

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Introduction:

Mitral valve prolapse (MVP) is one of the most common mitral valve abnormalities affecting about 2-3% of the general population (1-4) It is defined as systolic displacement of one or both mitral valve leaflets >2 mm

into the left atrium, with or without leaflet thickening, beyond the long axis of mitral annular plane. (4, 5) It may be sporadic or familial with most data supporting an autosomal dominant mode of inheritance.(6, 7)

MVP is generally considered as a benign condition,(1-3) however, it has been associated with various clinical complications including significant mitral regurgitation requiring surgery, congestive heart failure, infective endocarditis, stroke, ventricular arrhythmias and even sudden cardiac death (SCD).(8-10) Although the association between MVP and SCD has been reported decades ago, it received little attention till recently with several studies reporting a malignant form of MVP associated with complex ventricular arrhythmias (VA) and SCD termed arrhythmic MVP.(11-14)

The reported incidence of SCD due to mitral valve prolapse is variable, with an estimated annual risk of 0.2% to 1.9%, depending on the methods employed to evaluate the cause of death (e.g., autopsy vs. survivors), the study population (e.g., age, athletes) and available clinical data (e.g., electrocardiogram, echocardiogram).(10, 15-17) It is important to identify higher risk MVP patients who need more close follow up or may benefit from early therapeutic intervention.

Risk stratification in MVP:

Multiple risk factors appear to be associated with an increased risk of SCD in patients with MVP. They can be divided into: baseline clinical characteristics, factors detected by non- invasive evaluation (electrocardiography, echocardiographic, and magnetic resonance imaging) and invasive evaluation

(electrophysiological study).

I.Baseline clinical characteristics:

Several observational studies reported that life-threatening VA and SCD are more common in young females,(11, 14) and this may be explained by multiple factors: a) MVP is more common in females, b) they are more likely to have bileaflet prolapse and more valve thickening, and c) less likely to undergo valve surgery.(17) However, a recent cohort of 595 MVP patients found that frequent ventricular arrhythmias were associated with male sex and with increasing arrhythmia severity, there was no significant difference between both genders.(18)

Regarding clinical presentation, patients with arrhythmic MVP frequently suffer from syncopal attacks which is not surprising as syncope is an established cause to search for possible cardiac arrhythmia as the underlying mechanism.(19, 20) In a retrospective study done in 2015 by Clavel et al on MVP phenotypes associated with SCD,(12) the presence of syncope was independently associated with SCD (adjusted odds ratio 13.23[1.64-107.05], P=0.02).

II.Non-invasive evaluation:

1)Electrocardiography (ECG) and Holter monitoring:

A majority of patients (>75%) with MVP-related SCD demonstrate characteristic T-wave abnormalities on the surface ECG with biphasic or inverted T-waves in the inferior leads (II, III, aVF).(11, 14, 21) A recently published study reported that the presence of T-wave inversion/ST-segment depression is one of strongest predictors of ventricular arrhythmia in patients with MVP. (18) However, inverted T waves can be found in up to 40% of MVP patients without a history of sustained VAs,(22) so this finding alone is not enough to consider a patient at high risk and should be correlated with individuals' risk profile.

Premature ventricular contractions (PVC) are a common finding in the general population of MVP patients with and without SCD, (23) with the dominant PVCs morphology are those arising from the papillary muscles region and the outflow tract. (11, 14) The presence of PVCs alone is not enough

to risk stratify a patient as it is a common finding, but it should alert the clinician to consider additional risk stratification. Perhaps a more important marker of SCD is the origin of the PVC. In a series of consecutive bileaflet MVP patients undergoing catheter ablation, a Purkinje origin PVC was identified as the ventricular fibrillation trigger in all 6 of the patients who had a prior history of cardiac arrest.(24) As concluded by the authors, arrhythmic mitral valve prolapse is characterized by fascicular and papillary muscle PVCs that trigger ventricular fibrillation, suggesting a central role of the Purkinje system in this condition.

2) Echocardiography:

Echocardiography plays an important role in risk stratification of MVP patients, with many echocardiographic findings considered to be a marker of arrhythmic MVP.

•Leaflet thickening and redundancy:

Increased leaflet thickness was associated with AMVP in several studies (12, 14) (figure 1A) and increased leaflet thickness/redundancy was an independent predictor of severe VAs in a cohort of 595 patients with MVP. (18)

•Mitral annular disjunction (MAD):

It is defined as detachment of the roots of the annulus from the ventricular myocardium (i.e.,ventriculoannular detachment),which is localized to the base of the posterior leaflet.(25) It is measured as the distance between the left atrial wall-mitral valve posterior leaflet junction and the top of the LV posterior wall at endsystole (figure 1B).

An international multicenter registry that compared 42 patients with history of SCD and MVP who received an implantable cardioverter defibrillator (ICD) with 84 matched controls with MVP, reported the presence of MAD in 100% of SCD group compared to 12% in the control group.(12) Perazzolo Marra et al(13) assessed morphofunctional abnormalities of the mitral annulus in arrhythmic MVP using contrast enhanced cardiac magnetic resonance imaging (CE-CMR) and found that MAD was a constant finding in arrhythmic MVP and LV fibrosis. Moreover, the severity of MAD is associated with VA burden. For example, a disjunction length of >8.5 mm correctly identified 67% of the patients who exhibited non-sustained ventricular tachycardia (VT) on Holter monitoring.(26)

There is an increasing interest in the association between MAD and ventricular arrhythmias and a

study done by Dejgaard et al(27) had reported that MAD itself is arrhythmogenic even in the absence of MVP.

•Bileaflet prolapse:

Bileaflet MVP (figure 1C) has been proposed as a high-risk feature for SCD, but there have been conflicting results regarding long-term prognosis in these patients.(11, 14, 28) A review of 1,200 unexplained out-of-hospital cardiac arrest patients at the Mayo Clinic found a 42% prevalence of bileaflet MVP in a series of 24 young patients who survived an idiopathic out-of-hospital cardiac arrest.(11) However, in another large retrospective series from the same institution, isolated bileaflet MVP, without additional risk factors, did not appear to significantly increase the risk of SCD or need for defibrillator implant compared with single-leaflet MVP, suggesting the importance of confirming the presence of additional risk factors.(28)

•Pickelhaube sign:

Measured by tissue Doppler imaging and defined as peak systolic lateral mitral annulus velocity of ≥ 16 cm/s (Figure 1D).

In a study done by Muthukumar et al,(29) the patients meeting this criterion were more likely to have had a malignant VA (67% vs. 22%; $p < 0.08$). Furthermore, delayed gadolinium enhancement by CMR was only present in the group with the Pickelhaube sign (33%) and not in those without it. The authors concluded that the presence of a Pickelhaube sign may be an indicator of a malignant phenotype of myxomatous bileaflet mitral valve prolapse, but further investigation is needed to confirm their findings.

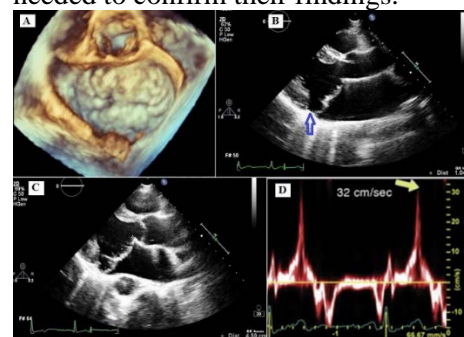


Figure 1: Echocardiographic markers of arrhythmic MVP: A) 3D transoesophageal echocardiography surgical view of mitral valve showing thick redundant leaflets with bileaflet multiscallop prolapse; B) Mitral annular disjunction (blue arrow); C) Bileaflet prolapse; and D) Spiked systolic lateral mitral annular velocities (Pickelhaube sign)

• Mitral regurgitation severity:

Although one observational series(30) found that the presence of moderate to severe mitral regurgitation (MR) was the only independent predictor for occurrence of arrhythmia in MVP, several subsequent studies showed that ventricular arrhythmia can occur in MVP in the absence of significant MR.(11, 14, 19, 31)

3) Cardiac magnetic resonance imaging (CMR):

Two patterns of myocardial fibrosis by CMR have been identified in patients with arrhythmic mitral valve prolapse in literature:

• Focal fibrosis:

Detected by late gadolinium enhancement and usually involving papillary muscles (mainly posteromedial papillary muscle) and adjacent LV myocardium (mainly basal inferior wall).(14, 24, 32) (figure 2)

• Diffuse subclinical interstitial fibrosis:

Bui et al(33) found evidence of diffuse interstitial fibrosis in MVP patients, as suggested by reduced postcontrast T1 times using CE-CMR. In their study, the subset of patients with VA had more pronounced evidence of interstitial fibrosis compared to the control group and only 36% of them had evidence of late gadolinium enhancement (LGE) in the papillary muscles or basal inferolateral wall. They concluded that diffuse interstitial fibrosis is linked to subclinical LV systolic dysfunction and may contribute to Complex VA in MVP, even in the absence of focal fibrosis.

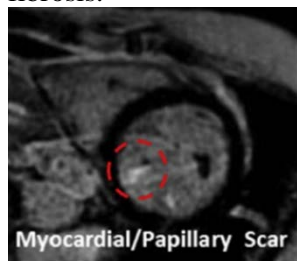


Figure 2: Delayed enhancement CMR showing myocardial scar in the papillary muscle (red-dashed circle)(17)

III. Invasive evaluation:

In patients with multiple risk factors, some clinicians may recommend an electrophysiology study (EPS) to evaluate for inducible sustained ventricular arrhythmias.(17) However, the role of invasive risk stratification is not well established.

Proposed mechanisms of ventricular arrhythmias and SCD:

Despite various studies concerning arrhythmic MVP, the exact mechanism of VA and SCD is not

fully understood with multiple suggested theories. There are two common findings reported in patients with MVP-related SCD: 1) LV myocardial fibrosis; and 2) complex ventricular ectopy.

LV fibrosis is usually located in the basal inferolateral wall or the papillary muscles, which are most vulnerable to the mechanical traction exerted by the prolapsing leaflets.(34) It has been also assumed that friction between the chordae and the LV endocardium can lead to “friction lesions” between the papillary muscle and the annulus.(35) LV fibrosis can act as the substrate that increases the liability to the development and maintenance of sustained VA by either triggered activity or re-entry. Most patients with MVP- related SCD had history of complex PVCs. Acute myocardial stretch can shorten the action potential duration and decrease the resting diastolic potential with subsequent development of stretch-activated early afterdepolarizations. (36, 37) It is the combination of circumstances, such as short-coupled mechanically triggered PVCs from a structural or fibrotic abnormality from the mitral valve apparatus combined with heightened autonomic tone, that sets the stage for the development of SCD in the vulnerable patient.(17)

Treatment of arrhythmic MVP:

1. Sports restriction:

The clinical decision making in a young subject with MVP and symptomatic ventricular arrhythmias is difficult and mostly empiric, depending on the expertise of the medical team in each center. It was demonstrated that only a small proportion of competitive athletes with MVP develop adverse cardiovascular events (0.5% per year).(38) The worst prognosis was reported in those who had both regurgitation and ventricular arrhythmias, suggesting a cautious restriction of competitive sports. However, when MVP is isolated, the prognosis is excellent, and no exercise or sport restriction is required. Noteworthy, SCD in MVP patients usually occurs while at rest or during sleep.(14)

2. Beta blockers (BB) :

Previous studies suggested that autonomic dysfunction in the form of elevated sympathetic and decreased vagal tone is a possible factor that increases the risk of ventricular arrhythmia in MVP.(17, 39) However, no solid evidence has proven this theory till now.

Despite the recommendation on the routine use of BBs in patients with MVP and VAs,(17, 21) the ability of BB to control ventricular

arrhythmias in the setting of MVP is questionable and its role is less established than in many other diseases. In the study by Basso et al on sudden cardiac death (SCD) and MVP, (14) 21% of young adult SCD victims and two living patients had aborted SCD despite beta-blocker therapy.

3. Catheter ablation:

Due to the variable conditions that are involved in initiating malignant VAs in MVP, catheter ablation is reserved for cases where electrical triggers of VT or ventricular fibrillation (VF) can be mapped and identified or for scar-related re-entrant VT.(24, 40) A small case series including 14 patients with bileaflet MVP with and without VF arrest who underwent catheter ablation reported a high rate of acute procedural success (89%) and a significant reduction in implantable cardioverter-defibrillator therapies.(24)

4. Valve surgery:

A retrospective study to assess the effect of mitral valve surgery on ventricular arrhythmias in bileaflet mitral valve prolapse with severe regurgitation(41) found that surgery did not uniformly reduce the frequency of VA, but patients who had >10% reduction in VA frequency post operatively were significantly younger than those who did not. This finding may suggest that early surgical intervention could modify the underlying electrophysiologic substrate.

Conclusions:

- Prospective identification of patients with MVP who may be at risk of SCD is challenging.
- Several factors contribute to the arrhythmic risk in patients with MVP asserting the belief that the occurrence of serious ventricular arrhythmias in MVP is a multifactorial process.
- Multimodality approach including careful clinical assessment, ECG, Holter monitoring, echocardiography and CMR is required for identification of high risk MVP patients.
- Early surgical intervention may be considered in high risk patients with significant regurgitation in attempt to modify the underlying electrophysiologic substrate.

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