

Heightening awareness in the detection and management of arrhythmic mitral valve prolapse

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Abstract

Mitral valve prolapse (MVP) is present in 2-3% of the general population. A small percentage of these patients develop sudden cardiac death. Although there have been several clinical, EKG, and imaging findings associated with sudden death in MVP patients, it is not yet known which of the risk factors should be weighed more heavily than other. More importantly, there is no consensus on which patients might benefit from a primary prevention defibrillator. We present a case of a young woman who sustained sudden cardiac arrest, and began recovering after a prolonged resuscitative effort. She ultimately succumbed to opportunistic infection. In hindsight, she had many of the concerning findings of arrhythmic mitral valve prolapse. Raising awareness of this condition can help to reduce risk of sudden death in these patients.

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Abstract

Mitral valve prolapse (MVP) is a well-recognized condition present in 2-3% of the population in the United States, often affecting otherwise healthy young women and overall perceived to be a benign condition. A small fraction of these patients have subtle features ranging from arrhythmias to anatomical changes around the mitral valve apparatus and left ventricle. These are the rare patients that may develop sudden cardiac death (SCD), a condition described as arrhythmic mitral valve prolapse (aMVP). We propose an algorithm to help risk stratify patients with MVP and reduce the chance of SCD.

Introduction

Extracorporeal membrane oxygenation, cardiopulmonary resuscitation, and mitral valve prolapse (MVP) are phrases not typically found in juxtaposition. The former terms reflect a critical resuscitative effort, while the latter denotes a relatively common, typically benign condition present predominantly in young women. We describe a case of aMVP resulting in cardiac arrest, prolonged cardiopulmonary resuscitation, emergent initiation of veno-arterial extracorporeal membrane oxygenation and eventual cardiac and neurologic recovery. However, opportunistic infection led to the demise of this young individual raising the question as to what new knowledge is available to guide clinicians towards a proactive and preventative approach to this rare but fatal condition.

MVP is a condition present in 2-3% of the population in the United States (1, 2), but only a small fraction of these patients suffer sudden cardiac death (SCD). The arrhythmic risk with MVP was described several decades ago first by Barlow et al (3) and later by Nishimura et al (4) who followed 237 patients for a mean of 6 years. They noted that nearly 10% of patients, specifically those with redundant mitral valve leaflets on echocardiogram, had the feared complications of sudden death, infective endocarditis or central cerebral embolism. The risk of SCD was least appreciated and was believed to be exceedingly small given the paucity of data. Dollar et al described clinical and necropsy findings in patients with MVP who died suddenly and compared them with a cohort of patients with MVP that did not die suddenly. They found that the SCD MVP patients were significantly younger (mean age 39 ± 17 years versus 52 ± 15 years; $p=0.01$), were more likely women (67% versus 26%; $p=0.008$), and were without significant mitral regurgitation (7% versus 38%; $p=0.02$), compared to patients who likely died of other cardiac conditions (5). More recent contemporary data as described by Basso et al (6) report the incidence of SCD of patients with MVP varying between 16 to 41 per 10,000 patients per year (0.2% to 0.4% per year)(4,7,8). Of all SCD cases, 11.7% (95% CI 5.8 to 19.1) have been documented to have MVP (9). Features thought to be associated with SCD have included bileaflet prolapse, inferior ST-T wave abnormalities, and complex ventricular ectopy, in addition to several others. Moreover, assessment of survivors of life-threatening arrhythmias have suggested an association exists between hemodynamically uncomplicated MVP and arrhythmic SCD (10,11). The purpose of this report is to heighten awareness to clinicians to the significant symptoms, signs and available diagnostic studies in MVP patients that may be at risk of SCD. Thus far the available literature has listed a number of findings

in mitral valve prolapse patients that might be associated with sudden death. However, no clear guidelines or algorithm exist to help decide how best to manage these patients clinically.

Case report

A previously healthy 60-year-old woman with known MVP was transported to the emergency department undergoing cardiopulmonary resuscitation after a witnessed cardiac arrest in her law office. She previously had noted palpitations which had become worse recently and were associated with "weakness." Approximately one year earlier, her electrocardiogram showed a low voltage QRS, a T wave abnormality non-specific for inferolateral ischemia, and occasional premature ventricular complexes. A treadmill stress echocardiogram was interpreted having normal left ventricular function at baseline but with stress there was believed to be hypokinesis of the distal anterior wall with normal increased wall thickening in the other segments and decreased cavity size. There were no ST segment changes during the stress test. She then underwent a cardiac catheterization which revealed normal epicardial coronary arteries. Her Holter monitoring had previously revealed premature ventricular complexes and several beats of 4-5 of non-sustained ventricular tachycardia. A beta-blocker was prescribed.

At the time of her cardiac arrest, cardiopulmonary resuscitation was instituted immediately by her coworkers. The emergency medical services arrived approximately 10 minutes later and began the Advanced Cardiac Life Support protocol including multiple attempts at defibrillation without return of a sustainable rhythm. On arrival to the emergency department, which was approximately 60 minutes after the initial arrest, fine ventricular fibrillation was noted, and cardiopulmonary resuscitation was continued while further attempts at defibrillation and Advanced Cardiac Life Support protocol were continued. The emergency department contacted the Rapid extracorporeal membrane oxygenation Deployment Team, and she was cannulated for veno-arterial extracorporeal life support. Emergent full body computed tomography scanning was performed, and bilateral hemothoraces were noted and treated with bilateral tube thoracostomies. She underwent placement of an Impella. The transesophageal echocardiogram revealed a nearly akinetic left ventricle, an akinetic right ventricle, and a normal tricuspid valve. The mitral valve was not well visualized in this limited echocardiographic examination on extracorporeal support. She was transferred to the intensive care unit but remained unstable and acidotic, with marginal extracorporeal life support flows. Because of concern for significant intrathoracic bleeding secondary to cardiopulmonary resuscitation related chest trauma, she underwent bilateral thoracotomies and a transverse sternotomy, but only moderate bleeding was noted which was easily controlled. Her extracorporeal membrane oxygenation flows remained low, and an anion gap acidosis persisted. Since she did not have another explanation for the low flows and her examination revealed an extremely firm and distended abdomen, she underwent a decompressive laparotomy which did not demonstrate any evidence of blood loss or ischemic bowel. Extracorporeal membrane oxygenation flows, however, slowly improved and she was returned to the intensive care unit for further management. Although protective hypothermia was initiated, this was discontinued because of the continued concern for bleeding from the right chest cavity. The abdominal incision was managed with a vacuum dressing which over the ensuing week led to complete reduction of the intestines to the abdominal cavity and full fascial closure. Over the next 14 days, she hemodynamically

stabilized with recovery of cardiac function and slow but steady improvement of neurologic function. Over the following six weeks, the patient demonstrated complete cardiac and neurologic recovery, although she had persistent infiltrates thought to be secondary to pulmonary contusion, oozing in her right pleural space secondary to the multiple rib fractures, and adult respiratory distress syndrome. She had multiple subsequent transthoracic echocardiograms which were interpreted as having suboptimal visualization but supposedly a normal mitral valve. Unfortunately, she developed gastrointestinal bleeding, hypotension, and evidence of sepsis. She was found to have Mucormycosis involving the peritoneal cavity, bowel, and abdominal incision. Her Immunoglobulin G level was almost undetectable. She succumbed to the infection despite medical therapy, and her family decided to withdraw support.

Discussion

Prevention of SCD in the MVP population has been a topic of increasing discussion in the cardiology field. Studies published as recently as August, 2020 (12) address the small but definitive incidence of this problem. However, there is no consensus on the level of screening for patients who may be at risk of SCD in the large population of patients with MVP. More importantly, there is no consensus on who might benefit from a primary prevention defibrillator.

Overall, most studies point to the combination of substrate and trigger for the development of malignant arrhythmias in MVP patients. Early in the evaluation of these patients, history and physical examination are the basic steps followed by clinicians. The symptom complex of patients with life-threatening ventricular arrhythmias span the spectrum from asymptomatic, pre-syncope, to full syncope. In our patient, intermittent sensations of fatigue or weakness were the main complaints, albeit infrequent and not sustained. The physical examination, as demonstrated in our patient, may reveal a mid-systolic click, which reflects an abrupt increase in tension in the mitral leaflet caused by the abnormal posterior leaflet systolic curling. A routine 12-lead electrocardiogram may show inferolateral ST-T wave abnormalities or T wave inversions. An ECG may also show complex premature ventricular contractions arising from one or both papillary muscles, fascicles, or outflow tracts. 24-hour Holter monitoring may detect a high burden of premature ventricular contractions: >5% premature ventricular contractions per day or non-sustained ventricular tachycardia predicts a lower survival in this population (12). Faster (approximately 190 beats per minute), polymorphic ventricular tachycardia is also more concerning than slower ventricular tachycardia (12). Our patient underwent a Holter monitor, which showed frequent multifocal premature ventricular contractions (>5%), with a few runs of non-sustained complex ventricular tachycardia lasting 3 to 4 beats. A treadmill stress test to assess for exercise induced ventricular arrhythmias may be helpful. In our patient, however, this study was negative for inducible arrhythmias, but was falsely positive for stress-induced ischemia/regional wall motion abnormalities. This may have been due to a hyperdynamic inferolateral wall and elevated lateral mitral annular velocity, thereby making the anterior wall seem relatively hypokinetic by comparison. Inverted T waves inferolaterally in our patient lead to a cardiac catheterization one year earlier, showing no significant coronary artery disease. In a study of 24 patients with unexplained out of hospital cardiac arrest, 42% of the patients had bileaflet MVP, 78% had biphasic/inverted T waves, and 78% had complex ventricular arrhythmias (13). Similar findings were noted on a study by Basso and colleagues (14). Additionally, Miller et al and others have reported high frequency of T-wave abnormalities (biphasic or inverted T waves in inferior leads) and complex ventricular ectopy as recurrent themes in predicting patients with MVP who are at a higher risk of sudden cardiac death (9)(15). Although bileaflet

prolapse is commonly listed as a risk factor for ventricular arrhythmias and SCD, this finding has not been universally accepted (16).

While electrocardiographic changes and ectopy may be non-specific findings, the use of non-invasive studies such as transthoracic echocardiography and cardiac magnetic resonance imaging (CMR) may help detect patients at risk for SCD from a substrate (myocardial fibrosis) and trigger (mechanical traction) standpoint. Both modalities will show not only the classic finding of MVP, but also the other phenotypical features of aMVP including bileaflet prolapse, mitral annular dysjunction (MAD), hyperkinesia of the inferobasal LV wall, and/or leaflet prolongation/redundancy. Bileaflet prolapse was seen on autopsy in our patient, with significant elongation of the posterior mitral valve leaflet to the same degree as the anterior leaflet (Figure 1). Interestingly, studies have failed to note a correlation between the degree of mitral regurgitation with arrhythmias, as most patients with aMVP and SCD do not have severe mitral regurgitation. Essayagh and colleagues from the Mayo Clinic similarly found the aMVP phenotype to be those patients with MAD, marked leaflet redundancy, inferolateral ST segment and T wave abnormalities, and an enlarged left atrium or left ventricular end systolic dimension (12). In their cohort of 595 patients, MAD was one of the strongest independent predictors of ventricular arrhythmias.

The substrate for the arrhythmia includes regional myocardial hypertrophy and fibrosis, and Purkinje fiber tissue, shown on CMR detecting Late Gadolinium Enhancement (LGE) (17). Kitkungvan et al (17) found myocardial fibrosis was a key element of the substrate for ventricular arrhythmias. They demonstrated that the presence of MVP led to replacement fibrosis in the basal inferolateral segment in approximately one-third of these patients. Histopathological changes in an autopsy study by Han and colleagues, found left ventricular fibrosis in patients with isolated MVP may provide the substrate necessary for the development of malignant arrhythmias (18). Moreover, the addition of the finding of LGE on CMR showed a significant increase in ventricular arrhythmias in MVP patients. CMR with LGE at the inferobasal left ventricular wall and posteromedial papillary muscles is a feature observed in SCD victims (14). A number of MVP patients with complex ventricular arrhythmias may also not have scar histologically (17), as was the case with our patient. Positron emission tomography (PET) scanning may add important information to this algorithm to detect patients with MVP at risk for malignant arrhythmias (19). These patients may have increased uptake of 18F-fluorodeoxyglucose seen on a PET scan, even if there is no late gadolinium enhancement on CMR. This phenomenon is also seen with other conditions such as cardiac sarcoidosis.

While the substrate for malignant arrhythmias appears to lie within the myocardial tissue, the trigger for risk of sudden death in aMVP patients consists of mechanical stretch of the papillary muscles as well as abnormalities of the mitral valve annulus (20). Mitral annular disjunction (MAD), systolic curling, and myxomatous leaflet thickening all contribute to increased arrhythmic risk (20). Studies that can diagnose these triggers are primarily echocardiographically based, although CMR can also reproducibly detect these findings. Proponents of CMR note that MAD may be more reliably measured and visualized on CMR, with near circumferential MAD noted in some patients in this study. MAD, a potentially congenital abnormality of the fibrous mitral annulus, involves a spatial displacement of the point of insertion of the posterior mitral valve leaflet inferior to the true annulus. This anatomic variant leaves the posterior annulus appearing stretched and curtain-like as compared with the normal cord-like structure of collagen fibers that are present along the normal atrioventricular groove (20). Studies have shown an increased frequency of premature ventricular contractions and non-sustained ventricular

tachycardia in patients with MAD as opposed to those without MAD (21,22). MAD and systolic curling of posterior mitral valve leaflets are associated with fibrosis of the surrounding myocardium. Abnormal motion of the mitral apparatus and myocardial stretch by elongated chordae/prolapsing leaflets may incite a fibrotic process by mechanical irritation and stretch triggering ventricular arrhythmias.

Transthoracic echocardiography may demonstrate the classic Pickelhaube sign, a spiked systolic high-velocity signal, from an elevated lateral mitral annular velocity on tissue Doppler imaging. In a study by Muthukumar et al (23), patients with bileaflet MVP and elevated lateral mitral annular velocity had a higher incidence of ventricular tachycardia/fibrillation as compared with patients in the lower velocity group. The former group also showed LGE on CMR in a higher percentage of patients. A later study by these investigators found the presence of the Pickelhaube sign to double the risk of developing ventricular tachycardia (24,25).

It is unclear if aMVP can be passed to subsequent generations, but as genetic testing advances the inheritance patterns will likely become clearer. Mutations have been discovered in *FLNC*-encoded filamin C, which is important in the sarcomere integrity (26). As we learn more about the genetics of aMVP, it is likely that this information can be incorporated into counselling a patient on their particular risk of sudden death. A strong family history of sudden death is concerning, and should be weighed in a shared decision making discussion with the patient about a primary prevention implantable cardioverter defibrillator(ICD).

Available literature thus far has found a number of clinical, electrocardiographic and imaging features that are associated with sudden death in MVP patients. However, there is not enough evidence yet to know which of these factors is more concerning than others. Figure 2 provides several of the risk factors that have been associated with sudden death in aMVP patients. An algorithm to clinically manage these patients is proposed in Figure 3. Similar to arrhythmogenic right ventricular cardiomyopathy, the phenotypic presentation can be variable, leading to difficulties in diagnosis. As more is learned about aMVP, these criteria will likely become streamlined, and risk scores can be developed. There is inevitably a balance between over-implanting primary prevention ICDs in the patients who may never receive appropriate ICD therapy, versus withholding potentially life-saving therapy when pursuing a more conservative strategy. This balance is present when implanting primary prevention ICDs for any condition, and is an important part of the shared decision making discussion with the patient and family. Even in the seminal ScD-HeFT trial the rate of appropriate ICD therapy in a primary prevention group was 21%, or 5.1% per year (27). The rate of appropriate ICD therapy amongst aMVP patients is unknown, and future knowledge of this number can prove valuable in deciding on the need for primary prevention ICDs.

Since MVP is quite common in the general population, performing several cardiac imaging modalities on every MVP patient would have a low yield. However, raising awareness of concerning features on history, electrocardiogram, and a transthoracic echocardiogram could improve the utility of more advanced imaging studies such as a CMR or PET scan, Holter monitoring, and exercise treadmill electrocardiographic tests. Once a diagnosis of aMVP is made, a defined management strategy should be followed. Should all of these patients receive a primary prevention ICD? Electrophysiologic studies are suggested for other arrhythmia syndromes (28), but have an uncertain prognostic role here. Catheter ablation can help mitigate symptoms associated with premature ventricular contractions or runs of nonsustained ventricular tachycardia, or to reduce ICD therapies. If a patient has severe mitral

regurgitation associated with their MVP, surgical repair may be beneficial. Although catheter ablation and mitral valve repair may have a role, they may not be able to obviate the need for an ICD. If aMVP is suspected but the patient does not have higher risk findings, periodic follow up in clinic with serial ECGs and echocardiography could be appropriate. If new symptoms or evolving imaging findings, escalation of diagnostics including repeating a Holter monitor, placement of an implantable loop recorder, or repeating a CMR or PET scan should be considered.

Our case demonstrates the issues facing this rare but often fatal condition of aMVP. The proposed algorithm, if applied to our patient, would have detected bileaflet mitral valve prolapse with an elevated lateral mitral annular velocity, T wave inversions inferolaterally, a >5% PVC burden, and complex runs of non-sustained ventricular tachycardia. More research is certainly needed to determine if the proposed management algorithm is reasonable for evaluation of MVP patients. Ideally a prospective multicenter trial to collect data which may guide clinical evaluation and optimize risk stratification, and lead to validation of a risk score to help clinicians decide about when to recommend further diagnostic studies or when to proceed to a primary prevention ICD.

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Figures

Figure1. View of the heart in the patient described. Left: Left parasagittal view showing the left atrium, mitral valve, left ventricle, aortic valve and proximal aorta. Both mitral leaflets are a bit redundant. Right: Close-up view of the portions of anterior (A) and posterior (P) mitral leaflets. Both leaflets are elongated such that the posterior leaflet is as long as the anterior leaflet. Both leaflets are mildly thickened by fibrous tissue. The heart weighed only 310 grams.

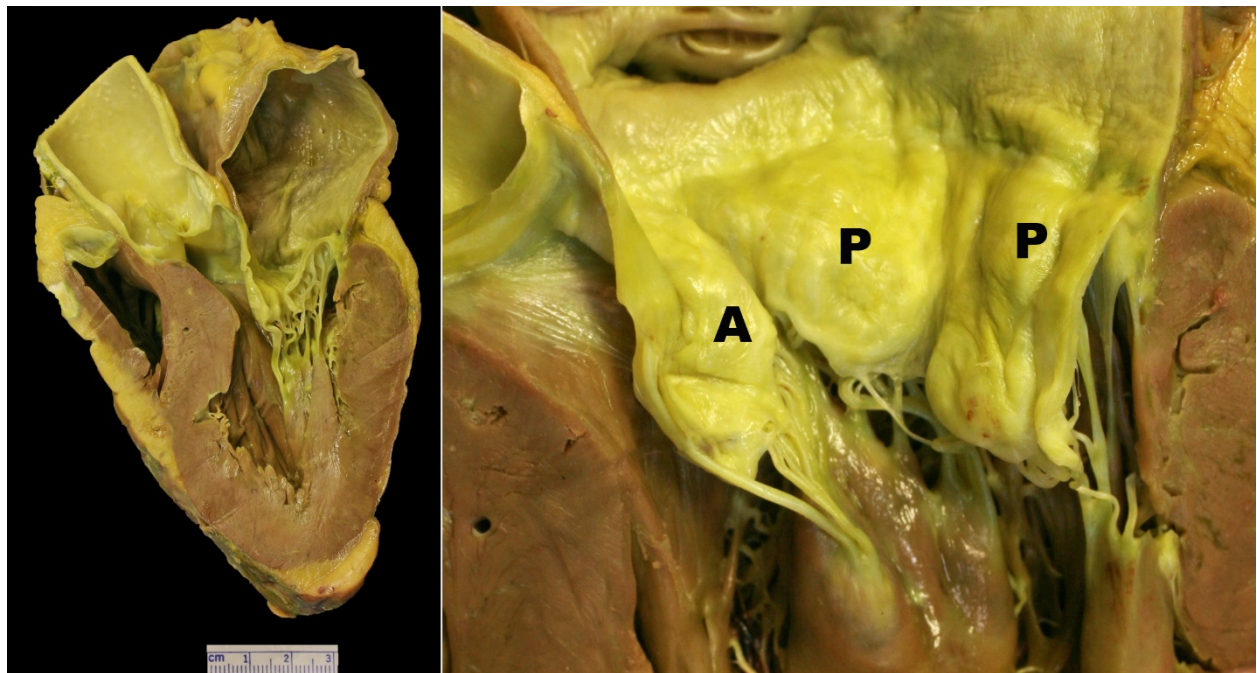


Figure 2. Clinical and diagnostic findings to assist in risk stratification for assessment of aMVP

<u>High Risk Findings</u>	<u>Other Concerning Findings</u>
• Inferior or inferolateral T wave inversions on resting ECG • Mitral annular dysjunction • Complex nonsustained ventricular ectopy or sustained VT (especially if >190bpm) • Positive LGE on cardiac MRI or Positive FDG uptake on cardiac PET scan, especially in inferolateral LV and/or papillary muscles	• Bileaflet mitral valve prolapse • Elongation/redundancy of mitral valve leaflets • High burden of PVCs, particularly from LV papillary muscle or fascicular system • Elevated lateral mitral annular velocity >16cm/s on Tissue Doppler imaging (Pickelhaube sign) • Syncope or palpitations • QT prolongation

Figure 3. Recommended screening protocol for MVP patients

