



Mitral Valve Prolapse and out-of-hospital cardiac arrest: A case report and literature review

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Abstract

We present the case of a 44-year-old woman who suffered an out of hospital cardiorespiratory arrest. After six direct current shocks and 10 minutes of cardiopulmonary resuscitation she had return of spontaneous circulation and regained consciousness. Transthoracic echocardiography showed normal left ventricular ejection fraction and a mildly dilated left atrium. The mitral valve was thickened with myxomatous degeneration (Barlow's disease) and moderate regurgitation secondary to bileaflet prolapse. Cardiac catheterization showed no coronary artery disease while left ventriculography revealed a mildly dilated left ventricle with preserved systolic function and high-end diastolic pressures. Cardiac MRI revealed an enlarged left ventricle with mitral valve (MV) prolapse and moderate to severe mitral regurgitation (MR). There were no features suggestive of a specific cardiomyopathy other than her valvular heart disease. The patient had an uneventful hospitalization, received an implantable cardioverter defibrillator (ICD), and eventually had MV repair surgery. In this article we also review the literature regarding similar cases and record important data for the epidemiology of the disease and the important research that has been carried out in the identification of prognostic imaging factors and the genetic background of these patients. We emphasize once again that it is especially important to be able to timely identify patients with mitral regurgitation who are at increased risk of sudden cardiac death so that immediate and effective treatment can be offered.

Case

Patient presentation

A 44-year-old patient was transferred to the Accident and Emergency Department of Nicosia General Hospital after suffering an out of hospital cardiorespiratory arrest during anaerobic exercise at the gym. The patient reported weakness and dizziness before she lost consciousness. A bystander nurse initiated cardiopulmonary resuscitation. Ventricular fibrillation was recorded as the initial rhythm upon connecting to an external defibrillator by the paramedics. After six direct current shocks, 10 minutes of CPR, the administration of 2mg adrenaline IV and 300mg amiodarone IV, the patient had return of spontaneous circulation (ROSC) and regained consciousness, upon arrival at the emergency department. She reported a past medical history of mitral valve prolapse and migraines with occasional use of analgesics. She is an active tobacco smoker. She denied any history of chest discomfort, palpitations, and shortness of breath, nausea or vomiting, either at stress or at rest. There was no recent febrile illness, gastroenteritis, or rashes. She is a mother of 5 children and has 1 previous miscarriage. There is no family history of heart disease or sudden cardiac death. On clinical examination she was afebrile; heart rate was 88 beats per minute, blood pressure 122/77mmHg and had oxygen saturation 92% on room air. Her cardiac examination revealed normal S1 and S2 with a mid-systolic click and a late systolic murmur best heard at the apex of the heart. There were normal breathing sounds, no peripheral edema, and normal peripheral pulses. Her neurologic examination was normal with GCS 15/15 and normal cranial nerve exam.

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Initial work up

The electrocardiogram (ECG) revealed sinus rhythm, normal axis with normal QRS and QTc intervals with infrequent ventricular ectopic beats. Shallow negative T waves were noted in lead II, III and aVF (Figure 1). Blood tests were normal with normal arterial blood gases while her chest X ray showed an increased cardiothoracic index. Inpatient Holter monitoring revealed a 2% burden of ventricular ectopy (singlets and couplets) of primarily a single morphology. A transthoracic cardiac ultrasound revealed an Ejection Fraction (EF) of 55-60%, a mildly dilated Left Atrium (LA), normal Right Atrium (RA) and a normal trileaflet Aortic Valve (AV). The mitral valve was thickened with myxomatous degeneration (Barlow's disease) and a moderate Mitral Valve Regurgitation (MR) with a predominately anteriorly directed jet. Moderate bileaflet prolapse was also present. There were only traces of Tricuspid Regurgitation (TR) with normal right ventricular systolic pressure (RVSP). No pericardial effusion was noted (Figure 2). Due to her presentation with an out-of-hospital cardiac arrest, she had an emergency coronary angiogram which showed normal coronary tree anatomy and no coronary lesions of concern. Left ventriculography showed a mildly dilated ventricle with preserved systolic function and high-end diastolic pressures. There was angiographically severe mitral valve regurgitation and a large left atrium (Figure 3).

Diagnosis and Management

Transthoracic and transesophageal echocardiography confirmed that moderate MR was present. The regurgitant volume (Rvol) was 30ml with a Vena Contracta of 0,3cm and Effective Regurgitant Orifice (ERO) of 20mm². The mitral valve was myxomatous with bileaflet prolapse (Figure 4,5). For further

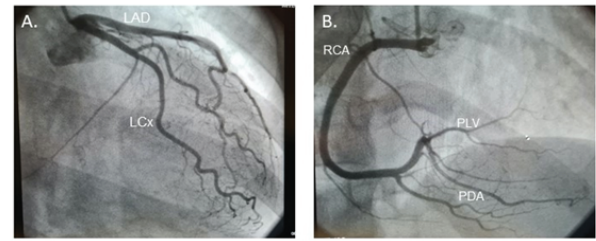


Figure 3: Cardiac Catheterization. The images showed normal coronary arteries while left ventriculography showed a mildly dilated ventricle with preserved systolic. A. Left anterior ascending artery (LAD) and Left Circumflex Artery (LcX). B. Right Coronary Artery (RCA).

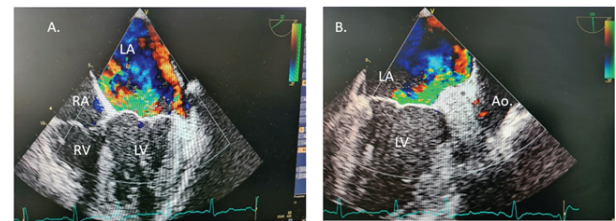


Figure 4: 2D Transesophageal echocardiography. The image shows moderate mitral valve regurgitation. A. Apical Four Chamber View. B. Apical Three Chamber View. LV: Left Ventricle, LA: Left Atrium, Ao: Aortic Root, RA: Right Atrium. RV: Right Ventricle.

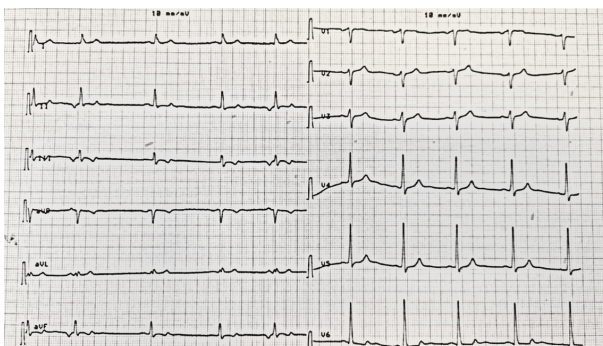


Figure 1: Electrocardiogram (ECG).

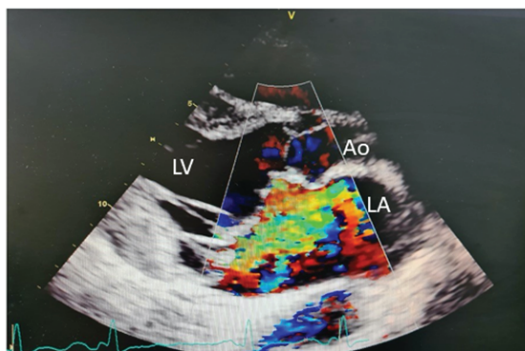


Figure 2: Echocardiographic parasternal long-axis view showing moderate to severe mitral regurgitation. LV: Left Ventricle, LA: Left Atrium, Ao: Aortic Root.

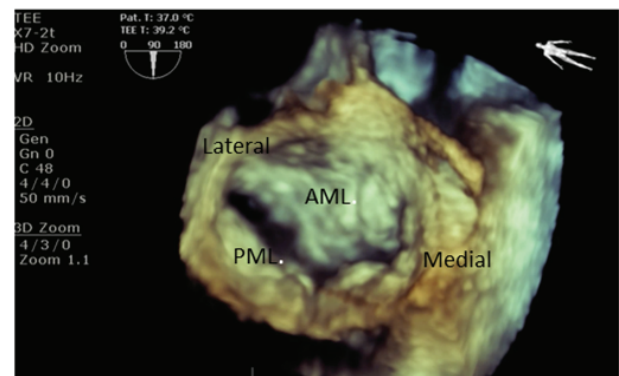


Figure 5: Preoperative Transesophageal echocardiography 3D. AML: Anterior Mitral Leaflet. PML: Posterior Mitral Leaflet.

evaluation of the MR, exercise treadmill testing was utilized using the standard Bruce protocol. The patient was exercised for 6 minutes achieving a maximum heart rate of 95 bpm, whilst on beta blocker therapy. There was normal heart rate and blood pressure response to exercise. The test was stopped at the patient's request. There were multiple PVCs and couplets at peak stress. The echo images showed moderate to severe mitral valve insufficiency at peak exercise and RVSP increased to 50mmHg from 30mmHg at rest. The patient subsequently underwent a cardiac MRI which showed a severely enlarged left ventricle with normal wall thickness and a mildly affected systolic performance. Localized hypokinesia of the mid anterolateral wall segment of the left ventricle was present. The left atrium exhibited increased dimensions. There was leaflet mitral valve prolapse with moderate to severe MR (Barlow disease, Figure 6).

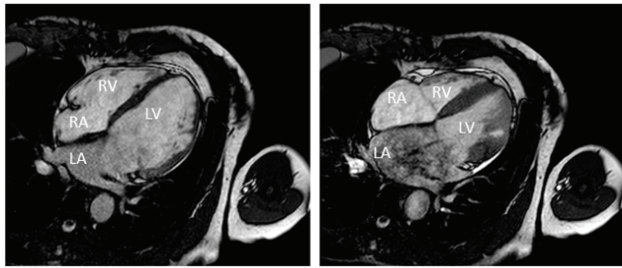


Figure 6: Cardiac magnetic resonance image showing mitral regurgitation. A. CMR showing the four-chamber view in ventricular diastole. B. CMR showing the four chamber in ventricular systole with mitral regurgitation present.

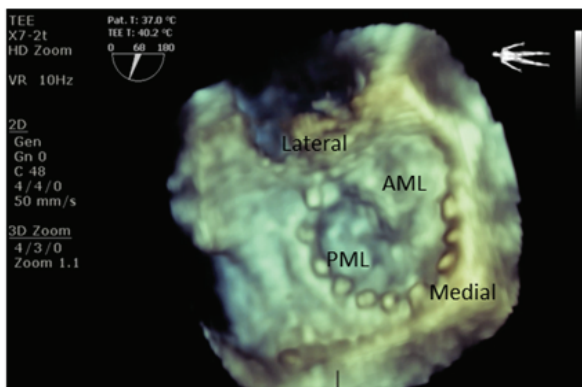


Figure 7: Post Repair Surgery 3D Transesophageal Echocardiography

Follow up

The patient had an uneventful hospitalization, and following a multidisciplinary heart team discussion, an ICD was implanted. The decision for this was based on the circumstances of her presentation with a malignant arrhythmia and the fact that she was a survivor of an arrhythmogenic cardiac arrest. The patient was discharged 12 days after admission and referred for a surgical mitral valve repair. Metoprolol was also prescribed at discharge. The patient eventually had an MV repair surgery with exceptionally good results (Figures 7). With regards to recurrence of significant cardiac arrhythmias, the patient developed recurrent and highly symptomatic episodes of paroxysmal atrial fibrillation, which were successfully suppressed with a combination of bisoprolol and propafenone. There has been no documented recurrence of a notable ventricular arrhythmia following her surgery as seen on her scheduled and frequent ICD checks. Furthermore, her burden of ventricular ectopy remains low. The patient was genetically investigated with Next Generation Sequencing of a panel of 72 genes which are known to be implicated in inherited cardiac conditions (not shown). Two variants were of particular interest, which were further validated by Sanger sequencing (Table 1,2). In the MYPN gene, exon 19, variant c. 3793G>A, p. Ala1265Thr was detected. In Silico analysis shows it is extremely rare and classified as a variant of uncertain significance (VUS) in the Varsome and ClinVar databases. Importantly, a known pathogenic variant reported in the Human Gene Mutation Database (HGMD) affected the same amino acid residue, but substituting alanine with proline, in an Asian female patient with hypertrophic cardiomyopathy [1,2]. She was first diagnosed at age 28-yrs and was compound heterozygote for another variant in the second allele of the same gene, MYPN, thus suggesting recessive

inheritance. A second variant in our patient was in the TMPO gene, exon 4, substituting aspartate with glycine, c. 1970A>G, p. Asp657Gly. Varsome classifies it as likely benign, and Mutation Taster is divided between classifications of polymorphism and disease causing. The mother of the patient carries only mutation in the TMPO gene, and she is healthy at age 68-yrs. Three children of the patient, a son from a first marriage and a son and daughter from a second marriage, aged 28, 21 and 10-yrs respectively, are mainly healthy, with the 21-yo son manifesting mild mitral valve regurgitation. Two other sons, one from each marriage aged 27 and 22-yo, are healthy and have inherited neither of the variants.

It is not easy to attribute causality to either of the two DNA variants, thus reiterating previous similar experience by many authors in this field. Reduced penetrance is certainly a likely explanation of the lack of obvious past family history. If only digenic inheritance is sufficient and necessary to produce a perceptible phenotype, might also explain this lack of past history while the three children who by chance co-inherited both linked variants, may be at increased risk and require close clinical monitoring. Overall, the genetics findings, although not conclusive, might suggest that digenic inheritance is responsible for the phenotype, implicating genes previously linked to dilated cardiomyopathy, thus expanding the phenotypic spectrum of variants and mutations in these genes. An alternative to digenic inheritance might be that the variant in the MYPN gene is pathogenic and the variant in the TMPO gene acts more like a genetic modifier. A genetic modifier is a DNA variant with no effect on its own, but which could exacerbate or even precipitate the phenotype when co-inherited on the background of another condition [3]. A limitation of this work is the absence of unequivocal segregation of the phenotype with the genetic findings, which may be resolved in the future if one or more of the younger members develop pathognomonic clinical features, hopefully not a fatal cardiac arrest. The literature is not particularly helpful in further resolving the genetic uncertainty, as many genes have been shown to be mutated in patients with MVP while incomplete penetrance, or age-dependent penetrance, is the norm. More genes that may play a role either following Mendelian inheritance or following digenic inheritance are to be discovered through contemporary parallel sequencing of panels of genes or through whole exome and whole genome sequencing.

Review of the Literature

Definition of Mitral Valve Prolapse

Mitral valve prolapse (MVP) is a valvular heart disease in which one (asymmetrical) or both (symmetrical) leaflets of the mitral valve are displaced more than 2mm above the mitral annulus into the left atrium during systole. Because of the bulging into the left atrium the valve does not close tightly, causing variable degree of valve regurgitation. According to the thickness of the leaflets, MVP is classified as classic (>5mm) and non-classic (<5mm) MVP. Mitral valve prolapse is also known as click-murmur syndrome, Barlow's syndrome, or floppy valve syndrome [1,4]. During heart auscultation, a mid-systolic click, followed by a late systolic murmur is heard at the apex. The duration of the murmur is prolonged by standing and Valsalva maneuver and the systolic click is heard earlier.

Epidemiology of Mitral Valve Prolapse and Sudden Cardiac Death (SCD)

Mitral Valve prolapse (MVP) affects 2-3% of the general population[5]. Patients may present with a variety of clinical scenarios ranging from mild, nonspecific symptoms to decompensated heart failure, endocarditis, malignant

Gene-Exon	Mutation	dbSNP	MAF	Human Gene Mutation Database (HGMD)	ClinVar
MYPN (Exon 19)	c. 3793G>A, p. Ala1265Thr	rs199476416	0	Hypertrophic cardiomyopathy, reported in female patient with c. 3793G>C, p. A1265P(2)	Uncertain significance
TMPO (Exon 4)	c. 1970A>G, p. Asp657Gly	No data	No data	Not found	No data

Table 1: Variants Detected.

Gene-Exon	Mutation	Varsome	MutationTaster	SIFT	Polyphen	Grantham Score
MYPN (Exon 19)	c. 3793G>A, p. Ala1265Thr	Uncertain significance	Disease causing	0.53	1	58
TMPO (Exon 4)	c. 1970A>G, p. Asp657Gly	Likely benign	Polymorphism, Disease causing	0	0.007	94

Table 2: Prediction

arrhythmias, and sudden cardiac death. The incidence of SCD in patients with MVP in the general population has been calculated up to 0.3-0.4% yearly [6]. MVP has been recognized in a recent study as the third most common cause of sudden cardiac death in young adults <35 years (12%) following arrhythmogenic right ventricular cardiomyopathy (24%), and coronary heart disease (20%) as leading causes [7]. MVP is more frequent in patients with Ehlers-Danlos syndrome, Marfan syndrome, Graves' disease, and polycystic kidney disease [8,9]. Rheumatic heart disease, endocarditis and myocardial ischemia could also be causes of mitral valve prolapse. Barlow's disease is the most prominent form of MVP characterized by myxomatous degeneration of the valve leaflets and increased calcification of the mitral annulus [4].

Identifying patients with MVP at risk for SCD

a) **Electrocardiographic findings:** Patients with MVP often have a normal baseline ECG. However, in patients who had a cardiac arrest, the incidence of inverted or biphasic T waves in the inferolateral leads [5,10] was found to be increased. QT dispersion and QT prolongation have also been described. The presence of premature PVCs originating from the papillary muscle (PM) or fascicular region has been well documented [11]. Arrhythmia's arising from PMs in the left ventricle have right bundle branch morphology in lead V1. More specifically ventricular ectopic originating from the posteromedial PM has a superior axis, which is similar to left posterior fascicular and or perimitral arrhythmias while ventricular ectopic arising from the anterolateral PM has an inferior axis similar to arrhythmias from the left anterior fascicle [12]. Notably a recent study showed how important it is to grade and categorize the burden of ventricular arrhythmia in these patients and presented that severe ventricular arrhythmia is associated with more adverse events. Patients with no VT and PVC frequency below median (<5%) were categorized in the "No/Trivial" group while patients with, PVCs above the median (5%) and/or with documented VT runs no faster than 120 beats/min, with VT runs of 120 to 179 beats/min and with VT >180 beats/min and/or proven history of VT/ventricular fibrillation (VF), indicating a need for an ICD were categorized in "Mild", "Moderate" and "Severe" groups respectively. In addition, in the same study the authors were able to gather the main prognostic factors that were directly correlated with the prognosis of these patients. The most important of these are mitral annular disjunction (MAD), leaflet redundancy and ST-T changes (T wave inversion and ST-depression) [13]. On the same line a recent study that describe the phenotype of forty-two patients with cardiac arrest has found that most patients had PVCs originated mainly from the posterior papillary muscles [14]. MVP may cause alterations

in the mechanical function of the papillary muscles and the left ventricle in extent. This abnormal mechanical function has been associated as a trigger of malignant arrhythmias even in the absence of histological changes [5,15,16].

b) **Echocardiography:** The use of both transthoracic and transesophageal examination is crucial to determine the disease severity. A detailed description of the mitral valve structure should include leaflet thickness or redundancy, annular dilatation, and chordal length. The presence of bileaflet prolapse has been associated with an increased rate of ventricular arrhythmias and sudden cardiac arrest [10,17]. The severity of MR has not been associated with bad prognosis; however its quantification as well as any consequent structure anomalies such as LA dilatation, LV dysfunction, pulmonary flow reversal or pulmonary hypertension should be described. It is important to report that the presence of mitral annular disjunction (MAD) found on echo examination in patients with MPV has been associated with increased prevalence of arrhythmic events. MAD is characterized by the abnormal positioning of the hinge point of the mitral valve away from the ventricular myocardium and has been appointed as an independent factor for the presence of ventricular arrhythmias [18-20]. Accordingly, a study, summarizing findings from subjects of sudden cardiac death and mitral valve prolapse, showed increased prevalence of bileaflet prolapse, subendocardial fibrosis and mitral annulus dilatation [21]. Importantly, a recent study has shown that mechanical dispersion identified by speckle tracking echocardiography was a strong predictor of the presence of malignant arrhythmias. Notably, this was independent of LV function, bileaflet valve prolapse and degree of MR [22].

Cardiac MRI

The most prominent finding in patients with cardiac arrest and MVP is the presence of fibrosis of the papillary muscles and inferobasal segments of the left ventricle that was consistent with histological findings [5]. Consistent with the above researchers have recently reported that by using T1 mapping and late gadolinium enhancement half of the patients with MVP had a degree of papillary muscle fibrosis [23]. It is important to clarify that the absence of fibrosis is not a positive predictive variable since patients without fibrosis still suffer a sudden cardiac death. Probably this is since the fibrosis is a late finding in the disease process and other triggers of malignant arrhythmias are to be blamed. Interestingly a new study has come to support the above theory by demonstrating an undetected until now level of myocardial inflammation in patients with degenerative mitral valve prolapse by using a hybrid method of PET/MRI [24].

Genetics

The genes contribution in the development of MVP has been associated with both the syndromic as well as the nonsyndromic aspect of the genetic spectrum. Trisomies of chromosome 18 (Edwards syndrome), chromosome 13 (Patau syndrome) and chromosome 15 are associated with MVP [23]. In addition, patients with connective tissue diseases such as Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), Ehlers-Danlos syndrome (EDS), Williams-Beuren syndrome (WBS) Pseudoxanthomaelasticum, Osteogenesis imperfecta, Borronedermato-cardio-skeletal syndrome, have been presented with variable degrees of MVP [25-29]. Moreover, isolated non-syndromic familial forms of MVP have also been characterized. These forms are age and sex dependent as well as with different levels of age dependent and age-independent penetrance and phenotypic expression. Also, these forms are present with X-linked recessive inheritance [31] as well as autosomal dominant inheritance [31]. MVP1, MMVP2 and MMVP3 loci in chromosomes 16, 11 and 13 respectively are also associated with the presence of MVP [32-34]. A recent study in patients with left ventricular non-compaction (LVNC) and sinus node dysfunction who present with MVP has found mutations in the FLNC gene that encodes for gamma flamin, a crucial protein interacting with actin filaments in the myocyte structure [35]. Genome-wide association studies have also been conducted. TNS1 gene (encodes tensin 1 which is an actin-binding protein) as well as LCMD1 gene (encodes a transcription factor repressor of GATA 6 which is an important regulator to atrioventricular valves development) are under study to identify their role in the expression of MVP [36,37]. Further studies are needed to identify through genetic analysis those individuals that are in increased risk of malignant MVP and SCD.

Treatment Options

Optimal medical treatment including beta or calcium channel blocker therapy or more complex antiarrhythmic drugs, should be first line treatment in patients with MVP and documented malignant arrhythmias. More importantly the use of ICD therapy as secondary prevention has been related with better prognosis [38]. Furthermore, catheter ablation of PVCs found in patients with MVP has been shown to reduce ICD shocks [11]. The ability of surgical correction to reduce ventricular arrhythmias has been controversial. One study reported a significant reduction in arrhythmic burden after mitral valve surgery, even in the absence of substantial mitral regurgitation [39]. On the other hand, another study failed to show any reduction on the ventricular ectopic burden [40]. At the same time, both emphasize the importance of early surgical intervention for the timely and immediate treatment of possible mechanical and electrophysiological remodeling that the heart may undergo.

Conclusion

While various prognostic factors have been described, no one is sensitive enough to predict these arrhythmias. Overall, there is an increasing need for more studies that will address not only the causative factors leading to sudden cardiac death but also to establish an efficient risk stratification strategy to provide immediate solutions to our patients' problems. Perhaps the early identification of DNA variants that increase the genetic susceptibility to adverse outcomes might be an option, accompanied by closer clinical follow-up. The detection of such variants that demonstrate co-segregation in affected families is a strategy facilitated with contemporary Next Generation Sequencing technologies.

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