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Mitral valve prolapse: From new mechanisms to diagnostic challenges

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ABSTRACT

Mitral valve prolapse (MVP) is the most common primary valvular abnormality, associated with various degrees of incompetence and sequelae, including heart failure and sudden cardiac death. Recent improvements in echocardiographic techniques and new insights into mitral valve anatomy and physiology have rendered the diagnosis of this condition more accurate and reliable. Here we review the genetic etiology, clinical significance, diagnosis, and treatment options for MVP patients.
Key words: echocardiography, genetics, heart valve, mitral valve prolapse

INTRODUCTION

Mitral valve prolapse (MVP) is a common cardiac valvular disorder occurring in 1.2%–3% of the general population. The characteristics' mid-systolic click' was already described in 1887 by Cuffer and Barbillon [1]. In 1936 Barlow further attributed the physical finding to the mitral valve-chordal origin, describing mitral insufficiency in these patients [2]. The prolapse as a distinct syndrome was later described using

surgical and autopsy specimens [3], and since remains a clinical and scientific challenge.

Mitral valve prolapse has at least two histological types. The first MVP is caused by fibromyxomatous changes in the valve leaflets, characterized by alterations in collagen organization and an increase in glycosaminoglycans causing thickening of the leaflets. This gives the valve the pathological appearance designated “myxomatous degeneration”. The second, termed fibroelatci defficienty, is more prevalent in elderly people and is chacarcataised by thickeninc of the spongiosa and accumulaton of collagen [4]. These changes lead to biomechanically impaired leaflets, resulting in redundancy and prolapse into the left atrium (Figure 1) [5, 6]. This further creates abnormal strain on the chordae, which may lead to rupture and worsening the regurgitation.

ETIOLOGY

MVP genetics

Mitral valve prolapse can be classified as sporadic (isolated cardiac presentation), familial or syndromic. Syndromic MVP, also referred to as secondary MVP, is the present of MVP and other known disorders, most commonly a connective tissue disease. The prominent related syndromes include Marfan syndrome [7], Loeys-Dietz syndrome, Ehler-Danlos syndrome, and osteogenesis imperfecta, among others [8]. A summary of the main syndromes is presented in Table 1.

Familial MVP is defined whenever MVP is present as an isolated malformation in a first-degree relative. About 35%–50% of MVP cases are familial, suggesting a strong genetic component in its etiology. The Prevalence of MVP among first-degree relatives is higher than in the general population, estimated at 5%–20%. Familial studies of non-syndromic MVP suggest an autosomal dominant mode of inheritance with incomplete and age-dependent penetrance [9–12].

Genes that were associated with non-syndromic MVP are detailed in Table 2. The first genetic mutation for non-syndromic MVP has been successfully linked to *FLNA* (filamin A mutations) in the family with X-linked inheritance [13]. The *FLNA* gene encodes actin-binding protein that crosslinks actin filaments and links actin filaments to membrane glycoproteins. Later on, mutations in *DCHS1* gene were also identified as causing MVP [14]. *DCHS1* is a member of the cadherin superfamily that encodes calcium-dependent cell-cell adhesion molecules. Using zebrafish and mouse

models, it has been demonstrated that mutated valves exhibit abnormal planar cell polarity architecture in the valve matrix resulting in myxomatous degeneration and prolapse. Six loci reached genome-wide statistical significance in a genome-wide association study (GWAS) of 1 412 MVP cases and 2 439 controls. Through functional analysis, clinical importance was demonstrated for two genes *LMCD1* (LIM and cysteine-rich) and *TNS1* (tensin1) by altered valve phenotype in zebrafish. A recent study found that mutations in the DZIP (DAZ Interacting Zinc Finger Protein 1) gene, involved in primary cilia formation, can cause MVP. Combining analyses of mitral valve development in mice with human genetic data suggested that mitral valve prolapse can be caused by abnormal cilia function [15]. Recent studies have also found epigenetics involvement in the pathogenesis of MVP [16], such as evidence from *in vivo* and *in vitro* studies demonstrating a regulatory role for miRNAs [17]. While these genetic findings point out potential mechanisms for myxomatous degeneration, they currently lack clinical implications.

Structural mechanisms

The mitral valve annulus has a characteristic saddle-shaped shape, with high anterior and posterior points, and concave leaflets toward the left ventricle in the zone of coaptation. This defines the anatomical definition of MVP in which prolapse is define when the leaflet or leaflets prolapse into the left atrium above the line connecting the two annular high points [6]. The practical aspect of this is that prolapse can only be safely diagnosed by echo whenever both the high points (such as in para sternal long axis view on echo cardiography) are in the image planne.

It has been suggested that structural and functional remodeling, as can be evident by cardiac magnetic resonance, may lead to early focal or diffuse fibrosis of the papillary muscles, which play a role in reentry circuits, leading to a high-risk MVP phenotype [18].

CLINICAL SIGNIFICANCE

Mitral valve prolapse is a progressive disease, found with increased rates and severity with age [19]. It has a broad spectrum of clinical presentation, from a silent disease to severe cardiac events. While incorrectly considered by many a benign condition, it often manifests in the 4^{th} to 6^{th} decades of life through the presentation as a severe

cardiac event [9]. Clinical symptoms may include atypical chest pain, exertional dyspnea, palpitations and the classical sign is mid-systolic click. Mitral valve prolapse is the most common cause of isolated mitral regurgitation requiring surgical repair. The lifelong serious adverse complication rate for MVP is 30% [20, 21]. Mitral valve prolapse often results in mitral regurgitation, which can lead to cardiac chamber dilation, arrhythmias, bacterial endocarditis, and congestive heart failure [22].

Importantly, MVP has recently been recognized as a common cause for arrhythmias, including sudden cardiac death (SCD). This life-threatening phenotype is referred as "arrhythmogenic" or "malignant" MVP [23], and its exact prevalence in unclear [24, 25]. In our preliminary results, 9.4% of the MVP families had a history of SCD (unpublished data). The risk of SCD in MVP is estimated to be 3-fold higher than in the general population (0.1% per year) [26]. Four percent of SCDs among young athletes are attributed to MVP [27]. Arrhythmogenic MVP has been associated with abnormalities of the T-waves, which can be a result of the endocardial and mid-myocardial changes of papillary muscles or the left ventricle [24]. Other factors includes bileaflet involvement, polymorphic inferiorely originating ventricular premature beats, mitral annular dysjunction, Picklhaube sign on tissue Doppler tracing of the mitral annulus and female gender [28]. Mitral annulus disjunction (MAD) is an abnormal atrial displacement of the posterior mitral leaflet hinge point. This creates a separation of the mitral valve annulus-left atrial wall. Although MAD is a common finding in MVP and could also be found in normal hearts, it has recently been associated with ventricular arrhythmias and SCD [29]. Few studies have also evaluated the effect of the MAD length, suggesting a cut-off value of 6–8.5 mm in transthoracic echocardiography (TTE) for predication of arrhythmia [30]. Pickelhaube sign is a high-velocity (usually > 16 cm/s) mid-systolic spike in the tissue Doppler velocity profile of the mitral valve annulus in patients with bileaflet MVP.

The high morbidity of MVP leads to a significant economic burden on both the patient and the health system. The annual hospital cost for treating MR in France only was €292 million, including surgical and non-surgical cases [31]. The yearly cost for surgical interventions only was estimated at €80 million.

Due to the described variability, further studies to develop a risk-stratification model for MVP is pertinent to personalized treatment addressing individual risk for adverse outcome, saving unnecessary

DIAGNOSIS

The classic physical auscultatory findings of mid-systolic clicks and/or late systolic murmurs are associated with MVP but are not sufficient for diagnosis.

The first-line and most commonly used imaging modality for MVP is TTE. The sentinel work by Robert Levine on the saddle shape of the mitral valve annulus has lad the American Society of Echocardiography guidelines definition of MVP as displacement of 2 mm or more of the valve leaflets above the annular line in the long-axis view during systole (Figure 1A); the European Society of Cardiology guidelines refer to superiorly displacement of the mitral valve coaptation point relative to the annulus [32, 33].

Transthoracic echocardiography is also the gold standard for assessing the grade of MR severity. Transesophageal echocardiography can define the abnormal relationship of the mitral leaflets to their surrounding structures based on specific and validated criteria (Figure 1B), and can further delineate MAD. Three-dimensional echocardiographic studies [5, 6] have significantly increased the specificity of diagnostic criteria for MVP.

In recent years the role of structural imaging is becoming significant, as it has the potential to identify patients at risk for complications. Risk features for arrhythmia include thickened leaflets, fibrosis of the papillary muscles and inferobasal wall, and MAD as described above. These may be used for early detection of arrhythmias allowing appropriate preventative intervention.

Cardiac magnetic resonance for MVP evaluation is currently gaining popularity. It can facilitate diagnosis [34], and with the use of gadolinium it can benefit in better characterizing the tissue as in the option of detecting myocardial and papillary muscle fibrosis and defining its pattern (macro- or diffuse-fibrosis). Cardiac magnetic resonance is the gold standard for LV and right ventricular volumetric assessment, and can accurately measure regurgitant volume and fraction.

MANAGEMENT

Currently, our arsenal for the management of MVP is mostly surgical. While it is customary to treat MVP with after-load reduction with medication such as angiotensin converting enzyme infhbitors or antiotensin receptor blockers, none of the pharmacologic treatments for MVP were ever proven efficacious in slowing disease progression. The only treatments for MVP that are thought to be efficacious are

surgical and thus palliative. The goal in surgical intervention for MVP is to relieve papillary muscle stretching and facilitate ventricular remodeling, which aim to reduce ventricular arrhythmias. The options include mitral valve repair or replacement, with continuous debate in the literature regarding the best method. These interventions carry significant complication rate and up to 6.5% mortality rate in one study.

For arrhythmic events prevention and treatment, beta-blockers are the first-choice treatment for symptomatic or asymptomatic patients with non-sustained or sustained ventricular arrhythmias. However, high-risk features as ventricular arrhythmias, hypercontractility and fibrosis may prompt further electrophysiologic study investigation [23]. Some authors have entertained ablation protocols to relieve arrythmia burden with high procedural success, although recurrence of ventricular arrythmia were not uncommon [35].

Interestingly, higher levels of soluble suppression of tumorigenicity-2 serum level were associated with MAD and ventricular arrhythmias. This biomarker was suggested to indicate myocardial stretch. It may have a potential in arrhythmogenic MVP diagnosis: the prolapsing leaflets in MVP leads to stretching of the papillary muscles and adjacent myocardium, which has been associated with ventricular arrhythmias.

One of the key questions in treating MVP is whether pharmacological interventions are effective in preventing complications, particularly given that MVP is seen as a structural disease. Recent advances in genetic and molecular techniques may enable the identification of genetic mechanisms leading preventive treatment that reduces disease complications. Marfan syndrome is characterized by high prevalence or mitral valve myxomatous degeneration leading to MVP [36]. Mice with missense mutation in Fbn1 are known to phenocopy Marfan's disease. In one study, both heterozygous and homozygous mice with a fully expressed missense mutation in Fbn1 were compared to wild-type mice. Adult heterozygous mutant mice were shown to have MVP by high-resolution echocardiography. Treatment with a TGFβ-neutralizing antibody successfully normalized morphologic characteristics of myxomatous degeneration both the length and the thickness of the mitral valve leaflets [37]. These data suggest that in the future medical treatment will be used to modify disease progression.

Cascade screening

The familial presentation of MVP raises the question of “cascade screening” for first-degree relatives of MVP index case. Cascade screening refers to common practice to identify individuals at risk for a genetic condition by the process of systematic screening. It is a common practice for MVP in many centers, but has yet to be clearly recommended in guidelines. There are several accepted criteria for screening methods, including clinically significant, cost-effectiveness, acceptable test and option for early treatment. Screening for MVP by echocardiography is a simple procedure that does not involve risk for the patient or radiation exposure as in other imaging modalities. It has the benefit of detection MVP or associated pathologies at an early stage. This will allow appropriate follow-up and timely intervention. On the other hand, the emotional burden on the patient and his family should also be considered. Cost effective data is also lacking as a preliminary stage for systematic screening implantation.

CONCLUSIONS

Mitral valve prolapse clinical variability poses a great challenge to clinicians, while aiming to identify high risk cases at an early stage. In addition to the basic thorough anamnestic, clinical and echocardiographic examination, keys to deeper understanding of the disease development and mechanism may be achieved through combining genetics, structural features on advanced imaging and electrophysiology characteristics.

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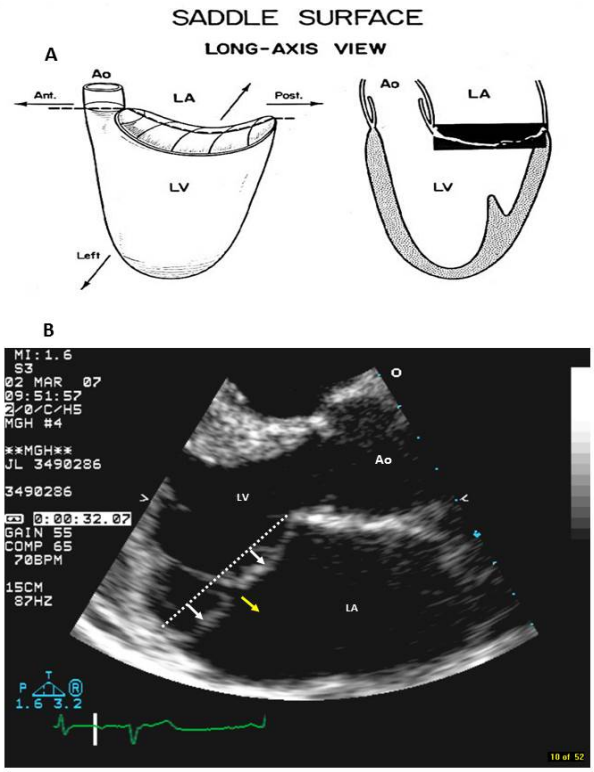

Figure 1. A. Mitral valve prolapse (MVP) is defined by the abnormal relationship of the mitral leaflets to their surrounding structures; cardiac ultrasound is well suited for MVP phenotyping; **B.** Parasternal long axis view of a human with MVP. The leaflets are above the annular line (dotted line) during systole (white arrows). Gap between the leaflets generates potential for regurgitation (yellow arrow). Adapted from [6]

Table 1. Genetics of syndromic mitral valve prolapse (MVP)

	Genes	**Gene's function**	**Present of MVP**	**Inheritance mode**	**Main features**
Marfan syndrome	FBN1	Structural component in the extracellular matrix	40%–80%	AD	MVP is one of the diagnostic criterions

Loeys–Dietz syndrome	TGF-β receptor 1 (TGFBR1); TGFBR2; SMAD3; TGFB2; TGFB3	TGFB singling — well established pathway for connective tissue disorders	25%	AD/AR	Lower rate of MVP in compare to FBN1
Ehlers–Danlos syndrome	COL5A1 or COL5A2 or COL1A1 and TNXB	Connective tissue components		AD	Mainly vascular phenotype, MVP in ~6%
Williams–Beuren syndrome	ELN	Encode major structural protein involved in organization of vascular smooth muscle	6%	AD	Cardiac phenotype includes supravalvular and pulmonary stenosis (45%–75%) and MVP (6%)
Osteogenesis imperfecta	COL1A1, COL1A2, CRTAP, and P3H1	Proteins involved in the extracellular matrix of connective tissues	5.4%	AD	Cardiac phenotype includes aortic root dilatation and aortic valve abnormalities
Trisomies	Trisomies in chromosomes 18, 13, and 15			Most cases are sporadic	Sever global phenotype (including growth retardation and cognitive impairment)

Stickler syndrome	COL2A1, COL11A1, COL11A2, COL9A1, COL9A2, COL9A3	Proteins involved in the extracellular matrix of connective tissues	4%	AD/AR	

The main syndromes which may present with MVP, their genetic origin, and the Prevalence of MVP within each syndrome

Table 2. The main genes associated with non-syndromic mitral valve prolapse

Gene	**Gene function**	**Genetic approach**
DCHS1	Member of the cadherin superfamily that encodes calcium-dependent cell-cell adhesion molecules	Familial segregation study
FLNA	Promotes orthogonal branching of actin filaments and links actin filaments to membrane glycoproteins	Familial segregation study
TNS1	Encodes for tensin 1, actin-binding protein	GWAS
LMCD1	Transcription factor repressor of GATA6	GWAS
DZIP	Role in primary cilium formation	Familial segregation study
LMCD1, NMB, and ALPK3	Known to be involved in cardiomyopathies	GWAS
LTBP2, TGFB2,	Encodes an extracellular matrix protein involved in regulation of TGF-β signaling. LTBP2 is associated with connective tissue disorders	
SPTBN1	Encodes β2-spectrin, a scaffold protein that connects the actin cytoskeleton to the plasma membrane	

Abbreviation: GWAS, genome-wide association study