REVIEW

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 incompetent function 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 of mid-systolic click were 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 then, it has remained a clinical and scientific challenge.

MVP 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 fibroelastic deficiency, is more prevalent in elderly people and is characterized by thickening of the spongiosa and accumulation 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 worsen the regurgitation.

ETIOLOGY

MVP genetics

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

Familial MVP is diagnosed 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 and is estimated at 5%–20%. Familial studies of non-syndromic MVP suggest an autosomal

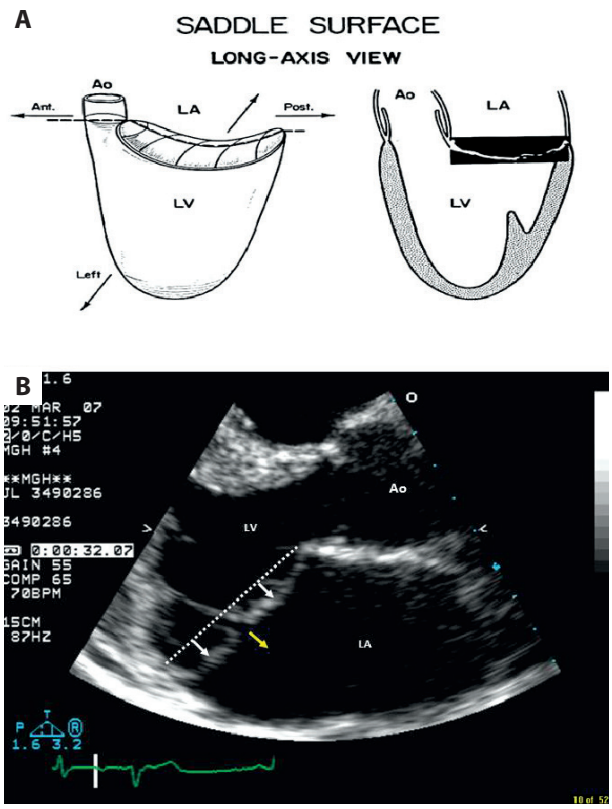

Figure 1. A. Mitral valve prolapse (MVP) is defined by the abnormal position of the mitral leaflets to their surrounding structures. Cardiac ultrasound is well suited for MVP phenotyping. **B.** Parasternal long-axis view of a human heart with MVP. The leaflets are above the annular line (the dotted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

Abbreviations: Ao, aorta; LA, left atrium; LV, left ventricle

dominant mode of inheritance with incomplete and age-dependent penetrance [9–12].

Genes that are 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 an actin-binding protein that crosslinks actin filaments and links them to membrane glycoproteins. Later on, mutations in the *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 1412 MVP cases and 2439 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 MVP 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 microRNAs (miRNAs) [17]. While these genetic findings point out potential mechanisms for myxomatous degeneration, they currently lack clinical implications.

Table 1. Genetics of syndromic mitral valve prolapse

	Genes	Gene's function	Presence of MVP	Inheritance mode	Main features
Marfan syndrome	FBN1	Structural component in the extracellular matrix	40%–80%	AD	MVP is one of the diagnostic criteria
Loeys–Dietz syndrome	TGF-β receptor 1 (*TGFBR1*); *TGFBR2*; *SMAD3*; *TGFB2*; *TGFB3*	TGF-β singling — well-established pathway for connective tissue disorders	25%	AD/AR	Lower rate of MVP in comparison 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

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; TGF-β, transforming growth factor β; other — see Figure 1

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; other — see Table 1

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 determines the anatomical definition of MVP in which prolapse is defined 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 echocardiography (such as in parasternal long-axis view on echocardiography) whenever both high points are in the image plane.

It has been suggested that structural and functional remodeling, as shown 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

MVP is a progressive disease, found with increased rates and severity with age [19]. It has a broad spectrum of clinical presentations, from silent disease to severe cardiac events. While incorrectly considered by many a benign condition, it often manifests from the fourth to sixth decades of life as a severe cardiac event [9]. Clinical symptoms may include atypical chest pain, exertional dyspnea, palpitations, and the classical sign is mid-systolic click. MVP is the most common cause of isolated mitral regurgitation requiring surgical repair. The lifelong serious adverse complication rate for MVP is 30% [20, 21]. MVP 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 of arrhythmias, including sudden cardiac death (SCD). This life-threatening phenotype is referred to as "arrhythmogenic" or "malignant" MVP [23], and its exact prevalence is 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 T-waves, which can be a result of the endocardial and mid-myocardial changes of the papillary muscles or the left ventricle [24]. Other factors include bileaflet involvement, polymorphic inferiorly triggering ventricular premature beats, mitral annular disjunction, Pickelhaube sign on tissue Doppler tracing of the mitral annulus, and female sex [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 on transthoracic echocardiography (TTE) for the 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 for both the patient and the healthcare system. The annual hospitalization cost for treating mitral regurgitation 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 are pertinent. This will allow personalized treatment that could address individual risks for adverse outcomes, saving unnecessary interventions.

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 seminal work by Robert Levine on the saddle shape of the mitral valve annulus informed the definition of MVP in the American Society of Echocardiography guidelines 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 (ESC) guidelines refer to the superior 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 position 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 of 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 for 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 offer benefits in better characterizing the tissue, for example detecting myocardial and papillary muscle fibrosis and defining its pattern (macro or diffuse fibrosis). Cardiac magnetic resonance is the gold standard for left ventricular 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 medications such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, none of the pharmacologic treatments for MVP have ever been shown efficacious in slowing disease progression. The only treatments for MVP that are thought to be efficacious are surgical and thus palliative. The goal of surgical intervention for MVP is to relieve papillary muscle stretching and facilitate ventricular remodeling, which aims 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 a 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 such as ventricular arrhythmias, hypercontractility, and fibrosis may prompt further electrophysiologic study investigations [23]. Some authors have considered ablation protocols to relieve the arrhythmia burden with high procedural success, although recurrence of ventricular arrhythmia was not uncommon [35].

Interestingly, higher levels of soluble suppression of tumorigenicity-2 serum levels 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 lead 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 to preventive treatment that reduces disease complications. Marfan syndrome is characterized by a high prevalence of mitral valve myxomatous degeneration leading to MVP [36]. Mice with a missense mutation in *FBN1* are known to phenocopy Marfan syndrome. 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 in 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 the MVP index case. Cascade screening refers to the common practice of identifying individuals at risk of a genetic condition through the process of systematic screening. It is a common practice for MVP in many centers but has yet to be recommended in guidelines. There are several accepted criteria for screening methods, including clinical significance, cost-effectiveness, test acceptability, and options 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 detecting MVP or associated pathologies at an early stage. This allows 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 in this preliminary stage for systematic screening implantation.

CONCLUSIONS

MVP clinical variability poses a great challenge to clinicians who aim to identify high-risk cases at an early stage. In addition to the basic thorough anamnestic, clinical, and echocardiographic examination, a deeper understanding of the disease development and mechanism may be achieved through combining information about genetics,

structural features on advanced imaging, and electrophysiological characteristics.

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REFERENCES

1. Cuffer M, Barbillion M. New investigations on the gallop rhythm [article in French]. Arch Gen Med. 1887; 19: 129–149.
2. Barlow JB, Pocock WA, Marchand P, et al. The significance of late systolic murmurs. Am Heart J. 1963; 66(4): 443–452, doi: 10.1016/0002-8703(63)90375-2.
3. Muthukumar L, Jahangir A, Jan MF, et al. Association between malignant mitral valve prolapse and sudden cardiac death: A review. JAMA Cardiol. 2020; 5(9): 1053–1061, doi: 10.1001/jamacardio.2020.1412, indexed in Pubmed: 32936277.
4. Hjortnaes J, Keegan J, Bruneval P, et al. Comparative histopathological analysis of mitral valves in barlow disease and fibroelastic deficiency. Semin Thorac Cardiovasc Surg. 2016; 28(4): 757–767, doi: 10.1053/j.semtcvs.2016.08.015, indexed in Pubmed: 28417861.
5. Levine R, Stathogiannis E, Newell J, et al. Reconsideration of echocardiographic standards for mitral valve prolapse: Lack of association between leaflet displacement isolated to the apical four chamber view and independent echocardiographic evidence of abnormality. J Am Coll Cardiol. 1988; 11(5): 1010–1019, doi: 10.1016/s0735-1097(98)90059-6, indexed in Pubmed: 3281989.
6. Levine RA, Triulzi MO, Harrigan P, et al. The relationship of mitral annular shape to the diagnosis of mitral valve prolapse. Circulation. 1987; 75(4): 756–767, doi: 10.1161/01.cir.75.4.756, indexed in Pubmed: 3829339.
7. Malcolm AD. Mitral valve prolapse associated with other disorders. Casual coincidence, common link, or fundamental genetic disturbance? Br Heart J. 1985; 53(4): 353–362, doi: 10.1136/hrt.53.4.353, indexed in Pubmed: 3885977.
8. Kyndt F, Gueffet JP, Probst V, et al. Mutations in the gene encoding filamin A as a cause for familial cardiac valvular dystrophy. Circulation. 2007; 115(1): 40–49, doi: 10.1161/CIRCULATIONAHA.106.622621, indexed in Pubmed: 17190868.
9. Devereux RB, Kramer-Fox R, Brown WT, et al. Relation between clinical features of the mitral prolapse syndrome and echocardiographically documented mitral valve prolapse. J Am Coll Cardiol. 1986; 8(4): 763–772, doi: 10.1016/s0735-1097(86)80415-6, indexed in Pubmed: 3760352.
10. Strahan NV, Murphy EA, Fortuin NJ, et al. Inheritance of the mitral valve prolapse syndrome. Discussion of a three-dimensional penetrance model. Am J Med. 1983; 74(6): 967–972, doi: 10.1016/0002-9343(83)90791-x, indexed in Pubmed: 6859065.
11. Disse S, Abergel E, Berrebi A, et al. Mapping of a first locus for autosomal dominant myxomatous mitral-valve prolapse to chromosome 16p11.2-p12.1. Am J Hum Genet. 1999; 65(5): 1242–1251, doi: 10.1086/302624, indexed in Pubmed: 10521289.
12. Freed LA, Acierno JS, Dai D, et al. A locus for autosomal dominant mitral valve prolapse on chromosome 11p15.4. Am J Hum Genet. 2003; 72(6): 1551–1559, doi: 10.1086/375452, indexed in Pubmed: 12707861.
13. Le Tourneau T, Le Scouarnec S, Cueff C, et al. New insights into mitral valve dystrophy: a Filamin-A genotype-phenotype and outcome study. Eur Heart J. 2018; 39(15): 1269–1277, doi: 10.1093/eurheartj/ehx505, indexed in Pubmed: 29020406.
14. Durst R, Sauls K, Peal DS, et al. Mutations in DCHS1 cause mitral valve prolapse. Nature. 2015; 525(7567): 109–113, doi: 10.1038/nature14670, indexed in Pubmed: 26258302.
15. Toomer KA, Yu M, Fulmer D, et al. Primary cilia defects causing mitral valve prolapse. Sci Transl Med. 2019; 11(493), doi: 10.1126/scitranslmed.aax0290, indexed in Pubmed: 31118289.
16. Roselli C, Yu M, Nauffal V, et al. Genome-wide association study reveals novel genetic loci: a new polygenic risk score for mitral valve prolapse. Eur Heart J. 2022; 43(17): 1668–1680, doi: 10.1093/eurheartj/ehac049, indexed in Pubmed: 35245370.
17. Nappi F, Iervolino A, Avtaar Singh SS, et al. MicroRNAs in valvular heart diseases: Biological regulators, prognostic markers and therapeutical targets. Int J Mol Sci. 2021; 22(22), doi: 10.3390/ijms222212132, indexed in Pubmed: 34830016.
18. Bui AnH, Roujol S, Foppa M, et al. Diffuse myocardial fibrosis in patients with mitral valve prolapse and ventricular arrhythmia. Heart. 2017; 103(3): 204–209, doi: 10.1136/heartjnl-2016-309303, indexed in Pubmed: 27515954.
19. Hickey AJ, Wilcken DE. Age and the clinical profile of idiopathic mitral valve prolapse. Br Heart J. 1986; 55(6): 582–586, doi: 10.1136/hrt.55.6.582, indexed in Pubmed: 3718797.
20. Düren DR, Becker AE, Dunning AJ. Long-term follow-up of idiopathic mitral valve prolapse in 300 patients: a prospective study. J Am Coll Cardiol. 1988; 11(1): 42–47, doi: 10.1016/0735-1097(88)90164-7, indexed in Pubmed: 3335704.
21. Iung B, Baron G, Tornos P, et al. Valvular heart disease in the community: a European experience. Curr Probl Cardiol. 2007; 32(11): 609–661, doi: 10.1016/j.cpcardiol.2007.07.002, indexed in Pubmed: 17976510.
22. Nishimura RA, McGoon MD. Perspectives on mitral-valve prolapse. N Engl J Med. 1999; 341(1): 48–50, doi: 10.1056/NEJM199907013410109, indexed in Pubmed: 10387961.
23. Alenazy A, Eltayeb A, Alotaibi MK, et al. Diagnosis of mitral valve prolapse: much more than simple prolapse. Multimodality approach to risk stratification and therapeutic management. J Clin Med. 2022; 11(2), doi: 10.3390/jcm11020455, indexed in Pubmed: 35054149.
24. Basso C, Perazzolo Marra M, Rizzo S, et al. Arrhythmic mitral valve prolapse and sudden cardiac death. Circulation. 2015; 132(7): 556–566, doi: 10.1161/CIRCULATIONAHA.115.016291, indexed in Pubmed: 26160859.
25. Essayagh B, Sabbag A, Benfari G, et al. Presentation and outcome of arrhythmic mitral valve prolapse. J Am Coll Cardiol. 2020; 76(6): 637–649, doi: 10.1016/j.jacc.2020.06.029, indexed in Pubmed: 32762897.
26. Maron BJ, Rowin EJ, Maron MS. Paradigm of sudden death prevention in hypertrophic cardiomyopathy. Circ Res. 2019; 125(4): 370–378, doi: 10.1161/circresaha.119.315159, indexed in Pubmed: 31518168.
27. Maron BJ, Haas TS, Ahluwalia A, et al. Demographics and epidemiology of sudden deaths in young competitive athletes: from the United States national registry. Am J Med. 2016; 129(11): 1170–1177, doi: 10.1016/j.amjmed.2016.02.031, indexed in Pubmed: 27039955.
28. Reinier K, Chugh SS. Sudden death associated with mitral valve prolapse. JACC: Clinical Electrophysiology. 2021; 7(8): 1035–1037, doi: 10.1016/j.jacep.2021.03.009.
29. Bennett S, Thamman R, Griffiths T, et al. Mitral annular disjunction: A systematic review of the literature. Echocardiography. 2019; 36(8): 1549–1558, doi: 10.1111/echo.14437, indexed in Pubmed: 31385360.
30. Muthukumar L, Rahman F, Jan MF, et al. The pickelhaube sign: novel echocardiographic risk marker for malignant mitral valve prolapse syndrome. JACC Cardiovasc Imaging. 2017; 10(9): 1078–1080, doi: 10.1016/j.jcmg.2016.09.016, indexed in Pubmed: 28017396.
31. Trochu JN, Le Tourneau T, Obadia JF, et al. Economic burden of functional and organic mitral valve regurgitation. Arch Cardiovasc Dis. 2015; 108(2): 88–96, doi: 10.1016/j.acvd.2014.09.008, indexed in Pubmed: 25662004.
32. Freed LA, Levy D, Levine RA, et al. Prevalence and clinical outcome of mitral-valve prolapse. N Engl J Med. 1999; 341(1): 1–7, doi: 10.1056/NEJM199907013410101, indexed in Pubmed: 10387935.
33. Gilon D, Buonanno FS, Joffe MM, et al. Lack of evidence of an association between mitral-valve prolapse and stroke in young patients. N Engl J

Med. 1999; 341(1): 8–13, doi: 10.1056/NEJM199907013410102, indexed in Pubmed: 10387936.
34. Musella F, Azzu A, Antonopoulos AS, et al. Comprehensive mitral valve prolapse assessment by cardiovascular MRI. Clin Radiol. 2022; 77(2): e120–e129, doi: 10.1016/j.crad.2021.11.004, indexed in Pubmed: 34895911.
35. Wibawa K, Ivan I, Jessica G, et al. The outcome of ventricular arrhythmias associated with mitral valve prolapse after catheter ablation: a systematic review and meta-analysis. Cureus. 2021; 13(12): e20310, doi: 10.7759/cureus.20310, indexed in Pubmed: 35024259.
36. Judge DP, Rouf R, Habashi J, et al. Mitral valve disease in Marfan syndrome and related disorders. J Cardiovasc Transl Res. 2011; 4(6): 741–747, doi: 10.1007/s12265-011-9314-y, indexed in Pubmed: 21866385.
37. Ng C, Cheng A, Myers L, et al. TGF-β–dependent pathogenesis of mitral valve prolapse in a mouse model of Marfan syndrome. J Clin Invest. 2004; 114(11): 1586–1592, doi: 10.1172/jci200422715, indexed in Pubmed: 15546004.