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REVIEW ARTICLE

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Mitral valve prolapse and Marfan syndrome

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Abstract

Marfan syndrome is a multisystemic genetic condition affecting connective tissue. It carries a reduced life expectancy, largely dependent on cardiovascular complications. More common cardiac manifestations such as aortic dissection and aortic valve incompetence have been widely documented in the literature. Mitral valve prolapse (MVP), however, has remained poorly documented. This article aims at exploring the existing literature on the pathophysiology and diagnosis of MVP in patients with Marfan syndrome, defining its current management and outlining the future developments surrounding it.

KEYWORDS
Marfan syndrome, mitral valve prolapse

1 | INTRODUCTION

Life expectancy in patients with Marfan syndrome is noticeably reduced, with cardiovascular complications being the most determinant factor.[1] Aortic dissection associated with aortic valve incompetence is the most common cause of mortality and has been widely documented in literature.[2] However, mitral valve prolapse (MVP), a significant cause of morbidity, has received far less attention. This report aims to investigate MVP in patients with Marfan disease, contrast it with findings from a previous study on a murine model and explore the success rates of mitral valve repair.

2 | MARFAN SYNDROME

Marfan syndrome is an autosomal-dominant multisystemic inherited disorder affecting connective tissue. Its pleiotropic clinical manifestations involve the cardiovascular, ocular and skeletal systems.[3] It has a worldwide prevalence of about 1 in 5000 and affects all races equally.[4]

Since the syndrome was first described in a 5-year-old girl in 1896 by Antoine Marfan, diagnostic criteria of Marfan syndrome have been updated.[1] After diagnostic criteria were agreed internationally in 1986 in Berlin, they were subsequently revised and superseded by the Ghent Nosology in 1996. Since some criteria were not applicable to children, it was subsequently revised in 2010, putting more emphasis on aortic root dilatation, ectopia lentis, and FBN1 testing.

3 | MVP

MVP is regarded as the abnormal displacement of an abnormally thickened and redundant mitral valve into the left atrium during systole.[5]

Reports demonstrate that mitral valve dysfunction is present in 80% of patients with Marfan syndrome, and by age 30 years, moderate to severe mitral regurgitation occurs in 1 in 8 of them.[3,6] The impact of this finding is made even more apparent in a study by Brown et al.[7] whereby MVP was found in all the females and nearly all the males (total of 35 patients) with Marfan syndrome in their research. In addition, mitral regurgitation is the principal cause of morbidity and mortality in infants and children with Marfan syndrome.[8–12]

4 | DIAGNOSTIC CRITERIA FOR MVP

In 1963, Barlow et al.[13] published evidence through angiography that systolic clicks and late systolic murmurs were linked to prolapse of the posterior mitral leaflet. However, the invasive nature of angiography has gradually hindered its use as a diagnostic tool. Consequently, studies have suggested echocardiography to be the best noninvasive technique in the imaging of prolapsed mitral valves.[14–16] Brown et al. concluded that all patients with Marfan syndrome who participated in their research and who had mitral clicks and/or murmurs had MVP. Interestingly, another remarkable finding was that half of those patients with mitral prolapse had no abnormal findings on auscultation, thereby leading to the assumption that auscultation lacks sensitivity in assessing mitral valve function in patients with Marfan syndrome.[8,17]

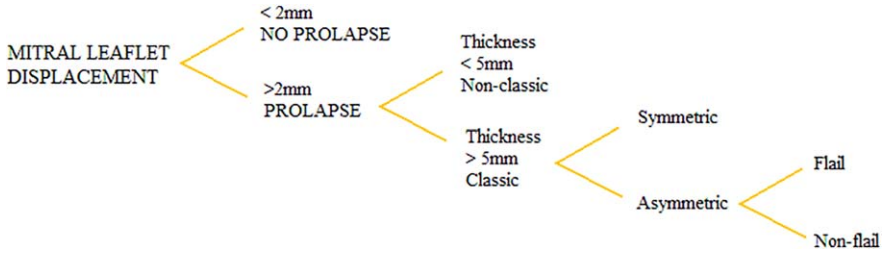

FIGURE 1 Classification of MVP

A study in 2010 by Feuchtner et al.[18] compared the diagnostic performance of echocardiography and cardiac CT angiography in the diagnosis of MVP. Although they noted that combining three-chamber and two-chamber reformations of coronary CT angiographic data produces the highest accuracy of 95% (sensitivity 96%; specificity 93%) for the diagnosis of MVP, radiation exposure and other factors led to the conclusion that echocardiography should be used as the primary diagnostic tool in clinical practice.

Criteria for diagnosing MVP have evolved over the years, mainly due to a better understanding of the three-dimensional (3D) structure of the mitral valve through superior imaging techniques. Recently, Chandra et al.[19] successfully attempted to classify the etiology of MVP using volumetric analysis of real time 3D transesophageal images. This is particularly useful for the presurgical planning of mitral valve repair by distinguishing the degree of valve prolapse.

According to new criteria, prolapse is defined as the displacement of the anterior, posterior or both mitral leaflets by more than 2 mm above the high points of the mitral annulus as recorded in either the parasternal or apical long-axis view. Studies have shown that displacements less than 2 mm are not linked to thickening of leaflets, mitral regurgitation, or valve-related problems.[20] However, leaflet displacements greater than 2 mm enable a further subdivision into classic and nonclassic forms, based on leaflet thickness—classic: >5 mm, nonclassic, ≤ 5mm. Classic prolapse can be further subdivided into symmetric and asymmetric—where leaflets joining at a common point on the annulus is termed symmetric and one leaflet being displaced more toward the atrium is termed asymmetric. Asymmetric coaptation can also be split into flail and nonflail leaflet. Flailing occurs when a leaflet bends outward and becomes concave toward the left atrium.

This classification bears particular importance since it is often indicative of prognosis. Asymmetric prolapse is associated with a greater risk of severe degeneration of the mitral valve, rupture of the chordae tendinae and leading to a flail leaflet—increasing the risk of mitral regurgitation.[21]

A diagrammatic classification is shown below in Figure 1.

5 | COMPLICATIONS OF IDIOPATHIC MVP

Four major complications may occur in patients with MVP: mitral regurgitation, spontaneous rupture of chordae tendinae, infective endocarditis, and sudden death.[22]

Severe regurgitation requiring surgery has been identified as the most common complication of MVP. This has been attributed to progressive myxomatous change in the valve, contributing to the degeneration of the chordae and the valve itself.[23] Jeresaty et al.[24] concluded that in 22 of 25 patients studied (88%), MVP was the only underlying morphologic abnormality leading to ruptured chordae tendinae. The risk of severe mitral valve regurgitation and valve rupture is very small in patients below the age of 50 but rises sharply after, with men more likely to be affected than women above the age of 60.[23] In a case-control study of 56 patients, Hickey et al.[25] estimated that 14 out of every 100,000 adult patients with MVP would go on developing bacterial endocarditis over a 1-year period, compared with three in every 100,000 without any known risk factors for bacterial endocarditis in the population. This interesting finding would lead us to assume that the risk of bacterial endocarditis is 5 times greater in individuals with MVP. Sudden death in young people due to MVP has been related to mitral valve regurgitation and left ventricular dysfunction. It was found by Corrado et al.[26] that MVP was present in nearly 1 in 10 of sudden cardiovascular fatalities in their study.

An important point to consider is Pyeritz's and Wappel's research on patients with Marfan syndrome. They concluded that, in contrast to idiopathic mitral valve regurgitation which occurs mostly after the age of 50, mitral regurgitation is extremely common in young patients with Marfan syndrome.[6]

This puts forward the notion that the prevalence and impact of MVP in Marfan syndrome seems distinct from MVP related to other causes.

6 | MVP AND MARFAN: THE GENETICS

Although MVP can have a sporadic or familial cause, it is more common in patients with connective tissue disorders such as Marfan syndrome, Ehlers-Danlos, osteogenesis imperfecta, dominant cutis laxa pseudoxanthoma elasticum, and the MASS syndrome (MVP, aortic root dilatation, skeletal changes, and skin changes). It has been estimated that about 0.25% of individuals with MVP also have Marfan syndrome, however, this figure could be slightly higher depending on the criteria used to diagnose MVP.[5]

Marfan syndrome is caused by a mutation on chromosome 15q21.1in the gene FBN1, which codes for the glycoprotein fibrillin-1.[27] The autosomal-dominant pattern of inheritance implies that a parent affected with Marfan syndrome will have a 50% chance of passing it

on to the offspring. As well as providing mechanical support for tissues, fibrillin-1 binds to the transforming growth factor beta (TGF-β) family of cytokines, thereby limiting its activation. In Marfan syndrome, fibrillin-1 deficiency leads to excessive amounts of activated TGF-β in the lungs, heart valves, and the aorta causing symptoms of the disease.[28] This pathogenesis was investigated by Habashi et al.[29] who showed that the angiotensin II type 1 receptor blocker, losartan, was successful at preventing aortic aneurysms in a mouse model of Marfan syndrome.

Due to the high proportion of patients with Marfan syndrome with MVP, it was suggested that isolated MVP could also be due to a defect in the FBN1 gene.[30] Ng et al.[31] explored this hypothesis in a murine model of Marfan syndrome. They compared mitral valves in fibrillin-1-deficient mice to those of wild-type mice and noted postnatal architectural changes in mitral valves of the mice with Marfan syndrome. The leaflets displayed excess cell proliferation, reduced apoptosis, and increased TGF-β activation and signaling. Furthermore, the mitral valve phenotype was rescued by TGF-β antagonism in vivo. This fascinating discovery thus validates an association between TGF-β signaling and MVP, laying the foundations for exciting prospects for future research in this matter.

Nevertheless, there exist certain similarities and differences between the murine model and sporadic MVP in humans. Like in humans, the murine model established by Ng et al. exhibits a thickened and degenerated mitral valve prolapsing into the left atrium. However, abnormalities in the FBN1 gene have not been revealed in patients or families with isolated MVP. Furthermore, the valvular manifestation in the murine model and in patients with Marfan syndrome tends to involve the whole valve homogeneously whereas in idiopathic MVP, 1 or both leaflets can be involved and changes can be heterogeneous within the leaflet itself.[32]

7 | MVP AND THE CARDIOVASCULAR SURGEON

MVP can be managed through a medical approach or a surgical approach. Beta adrenergic blockers, calcium channel blockers, and anxiolytics are extensively used to treat symptoms associated with MVP.[33] In addition, antibiotic prophylaxis for infective endocarditis is also indicated.[34]

Surgical management of MVP can involve valve repair or valve replacement. Surgery for mitral valve has evolved significantly over the last decades and is now indicated for pure or predominant mitral regurgitation.[35] However, certain additional issues are involved in the surgical management of MVP in patients with Marfan. Surgery (valve repair versus valve replacement) remains controversial due to the underlying degenerative nature of the connective tissue disease which could compromise repair durability.[36] This idea was adopted by Sirak and Ressallat[37] in 1967 after they attempted mitral valve repair suture annuloplasty and posterior leaflet plication in two patients but subsequently noted recurrence in mitral valve regurgitation.

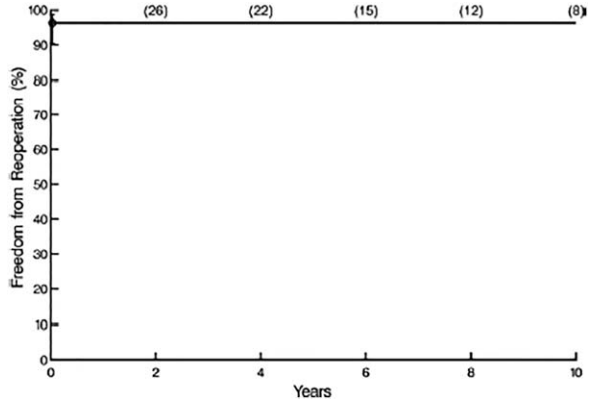

FIGURE 2 Freedom from reoperation after mitral valve surgery in patients with Marfan syndrome. Symbol represents Kaplan-Meier estimate, and vertical bar is 68% confidence limits. Numbers in parentheses represents patients at risk

However, Gillinov et al.[38] published a very detailed study of mitral valve operation in 36 patients with Marfan syndrome between 1983 and 1993. Mitral valve repair was achievable in 29 of 36 patients, where 28 had MVP. The mean age of patients undergoing repair was 26.5 ± 2.6 years (range 9 months-54 years). No operative deaths were noted in patients who underwent mitral valve repair or replacement. After follow-up (mean 26.6 ± 4.8 months with range 1 month-8 years) of patients with mitral valve repair, 3 late deaths were noted. Actuarial 5-year survival after mitral valve repair was 76.7%. Only 1 patient with mitral valve replacement died 2 years after. Actuarial freedom from significant mitral regurgitation (3 or 4+) after mitral valve repair was 88.3%. The 5-year actuarial freedom from reoperation in patients with mitral valve repair was 94%, due to one episode of endocarditis. St. Jude Medical prosthesis (St Jude Medical, Inc., St. Paul, MN) was needed in 1 patient after degeneration of the bioprosthetic valve used for replacement initially. It was concluded that mitral valve repair was possible in 80% of patients with Marfan syndrome.

A more recent study by Bhudia et al.[39] assessed the long-term survival and durability of mitral valve surgery in patients with Marfan syndrome and concluded that valve repair was durable and yielded satisfactory long-term results, even in adults presenting with advanced mitral valve defects. Out of 27 patients studied, 16 needed valve repair (59%) and 11 needed valve replacement (41%). After 12 years of follow-up, two mitral valve reoperations had to be performed. One was done 2 weeks after a mitral valve repair and the other occurred 12 years after mitral valve replacement due to cardiomyopathy.[39] These findings are outlined in Figure 2.

In addition, those results concur with previous studies by Mohty et al.[40] who also noted that long-term durability of mitral valve repair was acceptable but also concluded that repair should be the preferred mode of surgical correction of MVP.

However, the comparison between the above 2 studies bears some limitations. First, the relatively small number of patients in the study by Bhudia et al.[39] might not be adequate to form an accurate judgment. Second, the time frame of this study extended from 1975 to

2000, during which medical and surgical management as well as understanding of MVP evolved. Third, the study by Mohty et al.,[40] although involving a large number of patients, was not limited to MVP in patients with Marfan syndrome solely.

The various cardiac manifestations of Marfan Syndrome imply that MVP also concomitantly exists in patients undergoing aortic root replacement. Kunkala et al.[41] noted that out of their cohort of 166 patients with MVP undergoing aortic root surgery, only 20% underwent simultaneous mitral valve surgery, with a single patient needing reintervention and only 3 patients exhibiting mitral regurgitation grade 2 on follow-up. Operative risk was not found to be increased from undergoing these concomitant procedures.

Timing of the mitral valve surgery has remained a complicated issue that cardiovascular surgeons face because symptoms may be minimal or even not apparent despite severe mitral regurgitation. This can occur due to the left atrium and ventricle adapting and remodeling slowly.[35] If performed too early when the leaking valve is still functional, it can put the patient at unnecessary risk for surgery. On the other hand, if surgery is attempted later, the heart and valve could have potentially already sustained irreversible damage. However, progress in understanding the disease and the impact on left ventricular dysfunction has led to a general preference toward earlier surgery.[35] Optimal surgical management of pediatric Marfan syndrome patients also remains controversial, particularly repair versus replacement. Prognosis is poor with Geva et al.[42] reporting 4 deaths within the first year of life, out of their cohort of 9 patients with infantile-onset Marfan syndrome, with death being largely due to congestive cardiac failure. Surgical options are mainly limited to repair or replacement of the mitral valve. Due to the rapid progression of valve dysfunction, the durability of valve repair can be debatable. Kim et al.[43] concluded that mitral valve repair did not yield durable outcomes and advocated valve replacement instead. Despite morbidity and mortality reported in other studies, valve replacement with mechanical prosthesis was found to be a good option in infantile-onset Marfan syndrome, after 4 out of their 6 pediatric patients who underwent mitral valve replacement experienced no complication related to the prosthetic valve.[43]

8 | MVP: THE FUTURE

In a very recent study in July 2008, Romanelli et al.[44] found that skin biopsy, in parallel with echocardiography, could detect the presence of MVP. This theory was supported by the association between elevated proteoglycan biopsy samples and severe MVP. Eight patients with echocardiographic evidence of MVP and 6 controls were used in the study. Punch biopsies of 4 mm were taken from each participant's forearm skin and tested for proteoglycan mucin levels. Proteoglycan levels in patients with MVP was considerably higher (0.629 mg/g) than those in the control group (0.4 mg/g)

However, although this study still needs to be validated, it could open up a new window of knowledge on MVP which could enable the early identification of patients with suspected severe MVP and appropriate action can be taken to reduce sudden death.

9 | CONCLUSIONS

It is an undeniable fact that after aortic dissection, mitral valve dysfunction is the most important cardiovascular complication in patients with Marfan syndrome and considerably reduces life expectancy. Progress in terms of diagnostic techniques has grown at a considerable rate and has now enabled us to better understand MVP. A fascinating link has been discovered between Marfan syndrome and MVP through the FBN-1 gene and certainly merits further input through research. In addition, the surgical management of MVP has also considerably evolved and new techniques are being developed. Although substantial research has been undergone to explore idiopathic MVP, further attention still needs to be invested into MVP in the context of Marfan syndrome, especially since most original research was carried out in the 1980s and 1990s, when diagnostic criteria were less specific.

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CONFLICT OF INTERESTS

The author declares no conflict of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

AT involved in conceptualization, literature review, analysis, and write-up.

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