

Mitral Valve Prolapse, Mitral Regurgitation

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In 1966, Barlow and Bosman¹ described a constellation of clinical findings consisting of nonejection systolic clicks and a late systolic murmur, T-wave abnormalities, and systolic aneurysmal billowing of the posterior mitral leaflet into the left atrium. Since then, in areas without rheumatic heart disease, mitral valve prolapse (MVP) has been portrayed as the most common form of valvular heart disease.² It is characterized by pathologic anatomic and physiologic changes in the mitral valve apparatus affecting mitral leaflet motion and function.

Anatomy of the Mitral Valve

The mitral valve apparatus consists of an annulus, cusps, chordae tendineae, and papillary muscles. The shape of the mitral valve annulus is saddle-like. The mitral valve is functionally bicuspid, but embryologically comprises four cusps. Two cusps are large (the anterior or aortic cusp and the posterior or mural cusp) and two are small commissural cusps (Fig. 33.1). In a normal mitral valve, these commissures are never complete.³ The posterior leaflet is the widest around the annulus and is divided into three scallops: P₁, P₂, and P₃. The opposing sections of the anterior leaflet are designated A₁, A₂, and A₃. The chordae tendineae can be divided into three groups. The first two groups originate from or near the apices of the papillary muscles (Fig. 33.2). The first-order chordae insert into the extreme edge of the valve. The second-order chordae insert on the ventricular surface of the cusps. The third-order chordae originate from the ventricular wall much nearer the origin of the cusps. These chordae often form bands or foldlike structures, which may contain muscle. Usually there are two papillary muscles (anteriolateral and posteromedial), which have bifid apices; each receives chordae from both major mitral valve cusps.

Definition, Etiology, and Pathology of Mitral Valve Prolapse

The term *billowing* valve refers to superior motion of the body of the leaflet. The longer anterior leaflet normally exhibits mild billowing during ventricular systole. Billowing at the base of the leaflet may be considered abnormal when it exceeds 2 mm above the annular plane in a long-axis view (~130 degrees in the midesophageal plane by transesophageal echocardiography) and 5 mm in the four-chamber view (0 degree midesophageal plane). The three scallops of the posterior leaflet have shorter height (length) and normally do not exhibit billowing.

Prolapse is defined as the systolic billowing of the free edge of the mitral valve leaflets into the atrium superior to the annular plane, with or without associated regurgitation. In a *flail valve*, the edge of the leaflet projects toward the atrium,

typically after chordal or papillary muscle rupture, of abnormal elongation of the chordae, excess tissue. It is typically associated with severe mitral regurgitation.

Many conditions may affect components of the mitral valve apparatus and cause secondary prolapse, such as coronary artery disease, rheumatic disease, various cardiomyopathies, and trauma with elongation or rupture of mitral chordae resulting in a flail leaflet. MVP due to primary disorders of connective tissue such as Marfan syndrome is described in another chapter. Usually a primary disorder of the mitral valve leaflets exists, associated with specific pathologic changes that cause redundancy of the valve leaflets and their prolapse into the left atrium during systole.

Surgeons differentiate two different forms of degenerative mitral valve disease: Barlow's disease and fibroelastic deficiency.⁴ Barlow's disease is a more generalized form of valve degeneration and has a myxoid appearance of the whole valve with excess tissue and a dilated annulus. In fibroelastic deficiency, thickening is restricted to the prolapsed area(s) and the remaining valve tissue is more transparent, not thickened, without excess tissue, and the annulus may or may not be dilated.⁵

The exact etiology of primary MVP is unknown. Individuals with MVP are usually of a slender body habitus indicating higher rates of linear growth, suggesting that the connective tissue is of lesser quality and gives less resistance to linear growth. This condition is observed in its most extreme form in Marfan syndrome. MVP might result from a mild imbalance of the growth dynamics of the mitral valve apparatus, especially between the leaflets, the chordae tendineae, and the rest of the heart.⁶ Such imbalance may be transient with complete disappearance of MVP in some patients. In many patients, an abnormal metabolism of collagen associated with an overproduction of mucopolysaccharides results in thickening of one or both mitral valve leaflets and a redundancy of the mitral valve leaflet(s) area.⁷ Indeed, the characteristic microscopic feature of primary MVP is a marked proliferation of the spongiosa, the myxomatous connective tissue between the atrialis and the fibrosa or ventricularis that supports the leaflet. In secondary MVP, no occurrence of myxomatous proliferation of the spongiosa is found.⁸

When the leaflets become grossly abnormal and redundant with increasing quantities of myxoid stroma, they may prolapse. In addition, regions of endothelial disruption occur and become possible sites of thrombus formation or endocarditis. Even the mitral valve annulus and the chordae tendineae can be affected by a myxomatous proliferation, resulting in chordal rupture and worsening of a preexisting mitral valve regurgitation. Myxomatous changes in the annulus can cause annular dilatation and calcification, contributing to the severity of the mitral valve regurgitation.

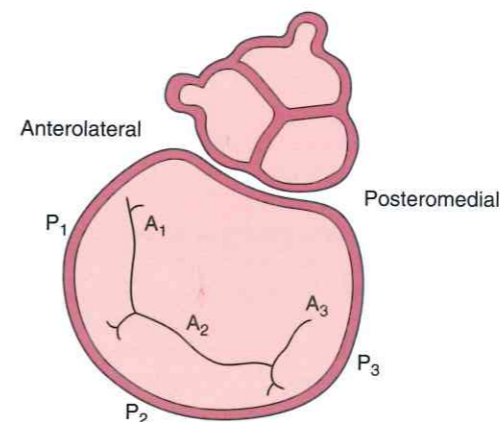


Figure 33.1 Anatomy of the mitral valve. The mitral valve is bicuspid and has four cusps: two large ones (the anterior and posterior cusps) and two small commissural cusps. In a normal mitral valve, the commissures are never complete. The posterior leaflet is the widest around the annulus and divided into three scallops: P₁, P₂, and P₃. The opposing sections of the anterior leaflet are designated A₁, A₂, and A₃.

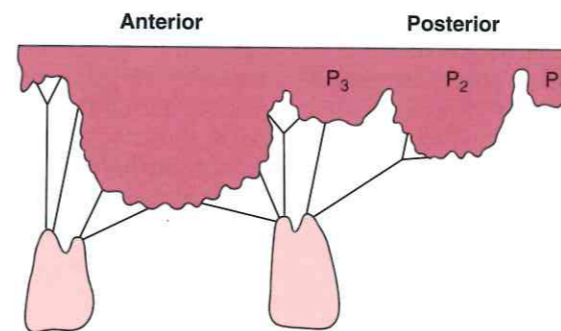


Figure 33.2 Anatomy of the subvalvular apparatus of the mitral valve. The chordae tendineae are divided into three groups. The first two groups originate from or near the apices of the papillary muscles. The third-order chordae originate from the ventricular wall much nearer the origin of the cusps. Usually there are two papillary muscles (anterior and posterior), which have bifid apices; each receives chordae from both major mitral valve cusps.

Prevalence of Mitral Valve Prolapse

Primary MVP is the most frequently diagnosed cardiac valvular abnormality in the developed world, the most frequent cause of significant mitral valve regurgitation, and the most common substrate for mitral valve endocarditis. MVP appears to exhibit a strong hereditary component transmitted as an autosomal trait.⁹ When using strict criteria and adequate diagnostic tools, a prevalence of 2.4% without preponderance in age or gender is observed.⁶

Primary MVP occurs most often as an isolated valve dysfunction, but can be associated with connective tissue diseases such as Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, and muscular dystrophy. In addition, MVP seems to be associated with congenital cardiac abnormalities such as Ebstein malformation of the tricuspid valve, secundum-type atrial septal defect, and Holt-Oram syndrome.

Early Presentation of Mitral Valve Prolapse

Most patients with primary MVP remain asymptomatic. The diagnosis is often made by a routine cardiac auscultation or by an echocardiography performed for other reasons. The

diagnosis of MVP is sometimes considered in patients who have thoracic skeletal abnormalities reflecting suboptimal connective tissue: the most common of these are scoliosis, pectus excavatum, straightened thoracic spine, and narrowed anteroposterior diameter of the chest.

Some patients with primary MVP become symptomatic without significant mitral valve dysfunction. Chest discomfort, anxiety, fatigue, atypical dyspnea with exercise, at rest and nocturnal atypical palpitations, and orthostatic and neuropsychiatric symptoms that are not correlated with the mitral valve function, are described as MVP syndrome (MVPS).¹⁰ The cause of these latter symptoms in MVP syndrome is unknown, but an association between a dysfunction of the autonomous nervous system and MVP is suggested. MVP may be complicated by more serious events such as infective endocarditis, thromboembolic events, atrial and ventricular arrhythmia, and rarely by syncope and sudden cardiac death.

On physical examination, MVP is characterized by an apical mid- or late systolic click, at least 140 ms after the first heart sound, after the beginning of the carotid pulse upstroke; the click can be intermittent and may be aggravated by maneuvers such as squatting or leaning forward. It seems to be caused by the sudden systolic tensing of the mitral valve apparatus as the leaflets billow into the left atrium. Any maneuver that decreases left ventricular volume, such as a Valsalva maneuver, sudden standing, inhalation of amyl nitrate, tachycardia, or augmentation of contractility, results in an earlier occurrence of prolapse during systole. In contrast, when left ventricular volume is augmented, such as during a sudden change from standing to supine position, leg raising, squatting, maximal isometric exercise, decreased contractility, and expiration, the click is delayed. The sensitivity of a click for diagnosis of MVP is low (19%) but its specificity is high: in only 1.5% of cases, can a midsystolic or late systolic click be heard in the absence of MVP.

MVP is often associated with mitral valve regurgitation. Therefore, in one-third of the patients, the midsystolic click is followed by a typical apical late systolic heart murmur.¹¹

The ECG is often normal in patients with MVP. The most common abnormality is the presence of ST-T wave depression or T-wave inversion in the inferior leads.¹² Exercise testing is frequently falsely positive with ST-T wave depression, especially in women, even with normal coronary arteries.¹³

The two-dimensional transthoracic or transesophageal echocardiography is the easiest diagnostic tool to confirm the diagnosis of MVP.¹⁴ Two-dimensional views display the leaflets and the annulus of the mitral valve, but the images must be interpreted in the context of the three-dimensional saddle-like shape of the valve. The nonplanar saddle shape of the normal mitral leaflets can give the appearance of prolapse in certain echocardiographic views. The echocardiographic criteria used for the diagnosis of a classic MVP are a dislocation greater than 2 mm to the left atrium of at least one of the mitral valve leaflets during systole and a thickening greater than or equal to 5 mm of the prolapsing valve leaflet during diastole. Dislocation is referred to by a hypothetical line through the insertion points of the anterior and the posterior mitral valve leaflet in parasternal and apical long-axis views (Fig. 33.3).

The current two- and three-dimensional transthoracic and transesophageal echocardiography machines generate exquisite images, allowing one to clearly identify the mechanism of mitral regurgitation and to differentiate Barlow's disease from fibroelastic deficiency.¹⁵ In patients who require a surgical



Figure 33.3 Prolapse of the posterior leaflet of the mitral valve. The echocardiographic criteria for classic MVP are a dislocation more than 2 mm to the left atrium of a least one of the mitral valve leaflets during systole, and a thickening of 5 mm or more of the prolapsing valve leaflet during diastole. A hypothetical line through the insertion points of the anterior and posterior mitral valve leaflet refers dislocation.

intervention, the possibilities of reconstructive surgery can be better estimated, allowing the patient to be treated by the best technique done by the best surgeon.

The most typical MVP is characterized by important mitral valve regurgitation, significant enlargement of the mitral valve leaflets and annulus, elongation of the chordal apparatus, and loss of leaflet apposition. At the other end of the spectrum, patients with mild bowing and normal-appearing leaflets should be considered as normal variants because their risk of adverse events probably does not differ from that in the general population.

Management of Mitral Valve Prolapse

Most patients with MVP require no treatment. Because there is no cure for MVP, management should concentrate on adequate patient guidance, relief of symptoms, and avoidance of complications (Table 33.1).

Management of MVP should be centered on patient education, symptom recognition, and risk management. For patients with MVP without leaflet thickening and regurgitation, patient education is the only treatment indicated. It should focus on the generally benign nature of the condition and reassure patients that they can live long and healthy normal lives. Oral antibiotic prophylaxis is not required. Follow-up echocardiography in 5 years is reasonable, unless other symptoms warrant evaluation sooner.

Patients with mild regurgitation and/or valve abnormalities may receive preventive oral antibiotic prophylaxis with low cost-to-benefit ratio, but guidelines from the American Heart Association no longer recommend prophylaxis.¹⁶ Although there is a low incidence of surgical need (7.5%) and lethal outcome (5%), frequent (25%) neurologic complications were found associated with infective endocarditis. Even mild hypertension should be treated because this may aggravate mitral valve dysfunction. Similarly, weight control should be encouraged. Echocardiographic reevaluation at 2- to 3-year intervals is appropriate.

Patients with moderate-to-severe mitral regurgitation and symptoms require valve surgery if the risk is acceptable, and

every effort should be made to reduce factors that increase regurgitation. In symptomatic patients with high operative risk, percutaneous procedures such as MitraClip (Abbott Laboratories, Abbott Park, Illinois) or NeoChord (NeoChord, Inc., St. Louis, Minnesota) may be reasonable, considering that watchful waiting may have missed the optimal moment for low-risk surgery.

Not every asymptomatic patient with severe mitral regurgitation (MR) rapidly develops symptoms or adverse sequelae of the disease. In the study by Rosenhek and colleagues, 55% of patients remained free of class I or II triggers 8 years after the diagnosis of severe MR, and trigger incidence did not significantly differ between patients with leaflet flail or leaflet prolapse.¹⁷ In contrast, in the study by Enriquez-Sarano and colleagues, asymptomatic individuals acquired class I or II triggers at a faster rate and more than half of the patients required surgery within 5 years.¹⁸ High-risk patients require Doppler evaluation every 6 to 12 months. Because it may predict symptom onset or ventricular dysfunction, stress testing is emerging as a useful prognostic modality in evaluating asymptomatic patients with MR. In fact, 20% of “asymptomatic” patients may have significantly reduced exercise capacity and should actually be classified as symptomatic.¹⁹ Exacerbation of MR during exercise correlates with poorer symptom-free survival,^{20,21} and impaired contractile reserve during stress testing may predict significant left ventricular dysfunction in medically treated patients.²² Thus, stress testing may identify patients who would benefit most from an early surgery approach if a watchful waiting strategy is used.²³

The best management of asymptomatic severe mitral regurgitation is still debated: early surgery versus watchful waiting.²⁴ In asymptomatic patients without class I triggers (symptoms or ventricular dysfunction), an early surgery approach results in a significant reduction in long-term mortality if performed in an experienced center. This survival benefit is also true in patients without class II triggers (atrial fibrillation or pulmonary hypertension). Higher successful repair rates are achieved with early surgery in experienced centers.²⁵

When the presence of arrhythmias is suggested, 24-hour ECG recording needs to be performed to determine an antiarrhythmic strategy.

In patients who have symptoms suggestive of MVPS, lifestyle modification is key in reducing symptoms. Dietary changes such as avoidance of caffeine may reduce palpitations. In addition, these patients often seem to respond to therapy with beta blockers.²⁶ Orthostatic symptoms related to postural hypotension and tachycardia are best treated with volume expansion, increasing fluid and salt intake.

Late Outcome of Mitral Valve Prolapse

When patients with MVP become symptomatic, the symptoms are most often associated with the complications that cause the dysfunction of the mitral valve. MVP has a complication rate of less than 2% per year, most likely in those patients with a murmur or left atrial or left ventricular enlargement.²⁷

MVP patients with leaflet thickening and redundancy seem to be at highest risk for valve regurgitation. The risk of progression of mitral valve regurgitation also increases with age, male sex, elevated blood pressure, and high body weight.

Leaflet thickening and redundancy put patients at very low risk for infectious bacterial endocarditis (1% to 3.5%), and oral antibiotic prophylaxis has recently been challenged.¹⁶

TABLE 33.1 Management of Patients With Mitral Valve Prolapse

Asymptomatic patients

Absence of mitral valve regurgitation

Follow-up frequency: every 5 years

Tests:

Electrocardiogram

Two-dimensional echocardiography and Doppler

No endocarditis prophylaxis indicated

Competitive exercise allowed

Presence of stable mild mitral valve regurgitation

Follow-up frequency: every 2-3 years

Tests:

Electrocardiogram

Two-dimensional echocardiography and Doppler

Endocarditis prophylaxis reasonable in our opinion

Moderate static and moderate dynamic competitive sports allowed

Presence of progressive mitral valve regurgitation

Follow-up frequency: at least every year

Tests:

Electrocardiogram

Two-dimensional echocardiography and Doppler

Exercise echo

Chest x-ray

Endocarditis prophylaxis indicated

Recreational sports allowed

Symptomatic patients

Not attributable to moderate-severe mitral valve regurgitation

Follow-up frequency: every year

Tests:

Electrocardiogram

24-h electrocardiographic monitoring

Treadmill exercise testing

If necessary: antiarrhythmic drugs (beta-adrenoreceptor blocker)

Attributable to moderate-severe mitral valve regurgitation

Tests:

Invasive hemodynamic evaluation

Transesophageal echocardiogram, 3D

Exercise echo

Mitral valve surgery

High risk: MitraClip

The incidence of stroke in MVP patients is higher than in the general population. The reason is not clearly understood, and currently there are no clinical clues to predict the risk of stroke. Those with severe mitral valve regurgitation seem to be at greater risk, regardless of whether their regurgitation is a result of prolapse. However, the neurologic complications are often associated with shortened platelet survival. Loss of endothelial continuity and tearing of the endocardium overlying the myxomatous valve may initiate platelet aggregation. Patients without symptoms of transient ischemic attacks do not need antiplatelet treatment.

Repetitive atrial arrhythmias and complex ventricular arrhythmias are more common in MVP.

Supraventricular arrhythmias are less frequent than ventricular arrhythmias. Premature supraventricular contractions are observed in 35% of patients with MVP but also in a similar number of normal individuals. Sinus tachycardia, paroxysmal atrial tachycardia, and intermittent atrial fibrillation are less common in MVP patients than in control subjects. However, atrial fibrillation is seen more frequently in MVP with mitral regurgitation or, conversely, in mitral regurgitation due to mitral valve prolapse, more frequently than in mitral regurgitation due to other causes.

Complex premature ventricular complexes correlate with QT dispersion in patients with MVP. Therefore, QT dispersion might be a useful marker of cardiovascular morbidity and mortality due to complex ventricular arrhythmias. A correlation

between QT interval and ventricular arrhythmias in patients with MVP was frequently suggested but not confirmed until recently.²⁸

The risk of syncope or sudden death is 0.1% per year, hardly any different from the risk in the rest of the general adult population (0.2%). However, this risk may attain 0.9% to 2% in patients with mitral valve regurgitation. In addition, between 3% and 5% of cardiac-related sudden deaths during exercise are attributed to MVP. The causes of sudden death related to MVP are unclear (hemodynamic, neurohumoral, arrhythmic, etc.), although there is evidence in favor of malignant ventricular arrhythmias.²⁹ Detailed studies have raised doubts as to the direct responsibility of the vascular malformation in this mode of fatal outcome. On the other hand, localized or diffuse myocardial disease may be observed, a more plausible reason for sudden death.

Late Management Options

When MVP results in significant mitral valve regurgitation, valve surgery is necessary. No clinical data are available to prove the benefit of long-term vasodilator therapy in symptomatic or asymptomatic patients with MVP, although salutary hemodynamic effects were noticed during short-term administration of preload and afterload reducing agents.

Initially, mitral valve replacement by a mechanical or, less often, biologic valve was performed. Currently, most patients are offered reconstructive surgery.³⁰ Several techniques can be applied: intervention at the leaflet (quadrangular resection, triangular resection, plication, cleft closure), intervention at the annulus (sliding plasty, plication, decalcification), intervention at the chordae (shortening, transposition, artificial chordae), shortening of the papillary muscles, and the placement of an annuloplasty ring. Techniques through a small thoracotomy or thoracoscopic approach with robotic assistance or transapical approach have been developed for well selected patients.³¹ Mitral valve repair currently has low operative mortality (<1% to 2%) and is associated with excellent early short-term results. Most patients leave the hospital with no residual regurgitation.³² Follow-up studies suggest a lower risk of thrombosis and endocarditis and longer survival with valve repair rather than valve replacement.

However, myxomatous valve leaflets are structurally, biochemically, physically, and mechanically abnormal, and a certain progression of the disease can be expected postrepair. When avoiding subideal techniques (chordal shortening instead of transposition or artificial chordae, nonuse of an annuloplasty ring, and nonuse of a sliding plasty), the recurrence rate of significant mitral regurgitation (color Doppler grade >2/4) is 2.9% in Barlow's disease and 2.2% in fibroelastic deficiency, which seems related to progression of valve degeneration.^{12,33} Freedom from reoperation for fibroelastic deficiency is better (96.6% at 10 years) than for Barlow's disease (86.1% at 10 years).³⁰

Pregnancy

Primary MVP is considered the most common valvular heart lesion in adult females of reproductive age. In general, pregnancy and labor are well tolerated in patients with hemodynamically stable MVP. Supraventricular and ventricular arrhythmias are considered the most frequent complications during pregnancy in females with MVP and often require treatment with antiarrhythmic drugs. No higher incidence of

preterm delivery is found in patients with MVP. Infective endocarditis prophylaxis is recommended as indicated.¹⁶

Exercise and Mitral Valve Prolapse

Aerobic exercise should be encouraged for all patients with MVP. An aerobic exercise program seems to improve the symptoms and functional capacity of patients with documented MVP. Patients with MVP often have low resting blood pressure, which is thought to be related to low intravascular volume. This condition is of particular importance to athletes with MVP because they may be more sensitive to dehydration induced by vigorous physical activity, and thus at higher risk for exercise-induced syncope.

Current recommendations for athletes are as follows³⁴:

- Athletes with MVP (having a structurally abnormal valve manifested by leaflet thickening and elongation) and without any of the following criteria, can engage in all competitive sports:
 - history of syncope, documented as arrhythmogenic in origin;
 - family history of sudden death associated with MVP;
 - repetitive forms of sustained and nonsustained supraventricular arrhythmias, particularly if exaggerated by exercise;
 - moderate-to-marked mitral regurgitation; or
 - prior embolic event.

- Athletes with MVP and one or more of the aforementioned criteria can only participate in low-intensity competitive sports.
- Exercise recommendations vary for patients who have MVP with mild mitral regurgitation. Athletes in sinus rhythm with normal left ventricular size and function can participate in all competitive sports. Athletes in sinus rhythm or atrial fibrillation with mild left ventricular enlargement and normal left ventricular function at rest can participate in low and moderate static and moderate dynamic competitive sports.
- Athletes with definite left ventricular enlargement or any degree of left ventricular dysfunction at rest should not participate in any competitive sports. Patients on chronic anticoagulation therapy should avoid sports involving body contact.

Conclusions

MVP has caused confusion and concern on the part of both patients and physicians. Over the past two decades, more has been learned about epidemiology, pathophysiology, diagnosis, and treatment of this condition, allowing a rational approach to the management and treatment of patients with MVP. It is important to differentiate between the normal variant forms and the primary form of MVP.

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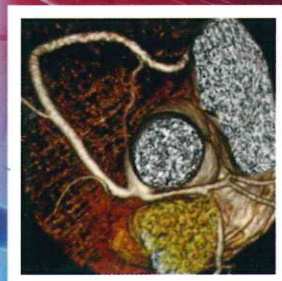
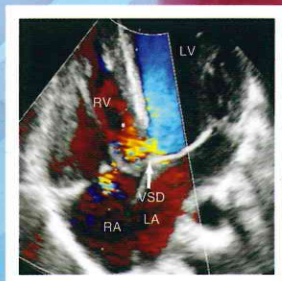
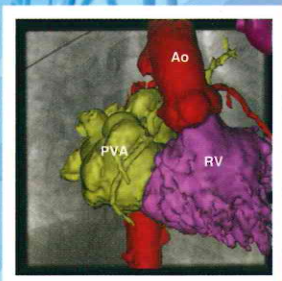
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