Mitral valve prolapse: Old beliefs yield to new knowledge

**ABSTRACT**

Much of the conventional wisdom about the prevalence, causes, diagnosis, symptoms, effects, and treatment of mitral valve prolapse (MVP) is changing. MVP has a benign course and excellent prognosis for most patients, with only a small minority developing serious complications.

**KEY POINTS**

Mitral valve prolapse (MVP) is not as common as once believed, particularly in young women.

Two-dimensional echocardiography (parasternal and apical long-axis views) is the diagnostic test of choice for MVP; cardiac auscultation has a low sensitivity.

Accumulating evidence suggests that the MVP syndrome is not directly linked to the valvular abnormality.

Rarely, MVP is associated with serious complications, but recent data show that, in the absence of mitral regurgitation, it does not increase the risk of arrhythmias, stroke, or sudden death.

MVP is an important cause of progressive severe mitral regurgitation requiring mitral valve surgery, particularly in older men.

Some patients with MVP need antibiotic prophylaxis against infective endocarditis; those with a history of stroke or transient ischemic attack need aspirin or warfarin.

**HOW COMMON IS MVP?**

Previous belief: MVP is very common, especially in young women.

Current knowledge: MVP is not as common as originally thought, with no gender difference in prevalence.

In the United States, the prevalence of MVP is estimated to be 2.4%, based on Framingham data and using the current criteria for diagnosis with two-dimensional echocardiography.

Earlier studies, which used less-specific echocardiographic criteria, had placed the estimate much higher, particularly in young women, for whom the figure was as high as 17%.

Why were the earlier figures so high? Part of the reason is that the earlier studies used less-specific echocardiographic criteria for diagnosis (see Echocardiography, below). Selection bias may also have accounted for the much higher prevalence of MVP among young women with symptoms in earlier, referral-based studies.
A person’s lifetime risk of MVP is more difficult to estimate, as the natural history of its development is unknown.

WHAT CAUSES MVP?

MVP—systolic billowing of one or both mitral leaflets into the left atrium—may result from structural or functional abnormalities of any component of the mitral apparatus, including the leaflets, chordae, papillary muscle, or adjacent left ventricle and atrium.

Primary MVP is characterized by myxomatous degeneration with an increased amount of leaflet tissue and proliferation of the spongiosa layer. We recently found that, compared with normal valves, myxomatous valves contain different proportions of glycosaminoglycan, their leaflets and chordae are stretchier, and their chordae are weaker.

While primary MVP is usually sporadic, familial clustering of MVP has been well described, with autosomal-dominant inheritance modified by age and gender. MVP may also occur in conjunction with certain diseases that affect connective tissue, such as Marfan syndrome and Ehlers-Danlos syndrome. Prolapse of other cardiac valves, most commonly the tricuspid and occasionally the aortic, has been described in patients with MVP.

Secondary MVP refers to prolapse of leaflets that do not show myxomatous change. It may occur when the leaflets are disproportionately large compared with the left ventricular cavity, most often in young women with a relatively small left ventricular cavity in association with a hyperdynamic state. With advancing age, the incidence of secondary MVP among women declines as the size of the ventricle better approximates that of the mitral leaflets.

MVP has also been found in patients with ischemic heart disease, hypertrophic cardiomyopathy, and rheumatic heart disease, but whether these diseases actually cause the MVP is not always clear.

HOW IS MVP BEST DIAGNOSED?

Previous belief: MVP is best diagnosed by auscultation and M-mode echocardiography.

Current knowledge: Auscultation sometimes suffices, but 2-D echocardiography (parasternal and long-axis views) is usually necessary.

The classic finding of MVP on physical examination is a midsystolic click followed by a murmur of varying duration, heard best at the cardiac apex. The click is caused by tensing of the mitral apparatus as the leaflets prolapse in midsystole.

Dynamic maneuvers that diminish preload, such as the Valsalva maneuver or standing, or drugs that decrease afterload, such as amyl nitrate, tend to make the sounds occur earlier in systole. In contrast, the sounds occur later in systole during maneuvers that increase ventricular filling, such as squatting, or increase afterload, such as isometric handgrip (FIGURE 1).

The midsystolic click of MVP should be differentiated from aortic or pulmonic ejection clicks, which occur earlier in systole and the timing of which is not altered by dynamic maneuvers that affect ventricular volume.
Echocardiography
Although the finding of the combination of a midsystolic click and a systolic murmur is relatively specific for MVP, its sensitivity is limited. Furthermore, the finding of either a systolic click without a murmur or a murmur without a click is not well correlated with echocardiographic prolapse or with mitral valve thickening or redundancy. Therefore, transthoracic echocardiography is often necessary for patients suspected of having MVP on the basis of cardiac auscultation.

Even when a patient has the classic auscultatory findings of MVP, echocardiography may have an important role in risk stratification by assessing the degree of regurgitation and chamber enlargement and features of myxomatous mitral valve disease such as leaflet thickening and redundancy. It is also useful in assessing left ventricular systolic function.

Echocardiography can also be used to exclude MVP in first-degree relatives of patients with known myxomatous valve disease; however, there is insufficient evidence to support its general use as a screening test.

Criteria for diagnosis. The echocardiographic diagnosis of MVP should be made only if one or both leaflets are displaced by at least 2 mm above the mitral annulus during systole in either the parasternal or apical long-axis view on two-dimensional imaging (FIGURE 2).

A caveat: in certain two-dimensional echocardiographic views, notably the apical four-chamber view, the mitral leaflets may appear to prolapse while actually remaining below the level of the entire mitral valve, possibly leading to an incorrect diagnosis of MVP. Use of the apical four-chamber view may have contributed to the relatively high prevalence of MVP found in earlier echocardiographic studies.

A detailed three-dimensional echocardiographic analysis has revealed that the mitral annulus is saddle-shaped, not planar, and physicians should look for leaflet displacement above the most superior points of the mitral annulus.

Mitral valve prolapse: Echocardiographic appearance
FIGURE 2. Two-dimensional parasternal long-axis systolic frame showing prolapse of the posterior leaflet (arrow) well behind the plane of the annulus (dotted line). LV = left ventricle, LA = left atrium.

DOES MVP CAUSE THE MVP SYNDROME?

Previous belief: MVP causes a variety of diffuse symptoms.

Current knowledge: Little direct evidence links these symptoms with MVP.

Although most patients with MVP have no symptoms whatsoever, a small subset have a variety of symptoms and signs that are termed the MVP syndrome.

Symptoms of the MVP syndrome include atypical chest pain, dyspnea, palpitations, dizziness, fatigue, and anxiety or panic attacks. However, several studies have shown no true increased frequency of chest pain or dyspnea or other symptoms such as dizziness in patients with MVP. The original descriptions of increased prevalence probably reflected selection bias.

MVP is associated with thin body habitus, pectus excavatum, scoliosis, and low resting blood pressure.

Electrocardiographic abnormalities described in association with MVP include atrial...
al and ventricular arrhythmias, prolonged QTC interval, nonspecific ST-T wave changes, and inferior T-wave inversion. However, other studies have found no increased frequency of electrocardiographic abnormalities in patients with MVP.

Pathophysiology unknown
The pathophysiology of the MVP syndrome is unknown, and the symptoms cannot be explained by the valvular abnormality alone. Several studies have documented abnormal autonomic function in patients with symptomatic MVP, including elevated circulating levels of catecholamines, enhanced beta-adrenergic receptor affinity, increased vasoconstrictor tone, decreased plasma volume, and diminished vagal responsiveness. However, other studies have shown no evidence of abnormal autonomic or neuroendocrine function, either at rest or during tilt-testing, in MVP patients with or without symptoms.

NATURAL HISTORY
AND COMPLICATIONS OF MVP

MVP has a benign course and excellent prognosis for most patients, with a survival rate similar to that in an age-matched and sex-matched population without MVP. However, a minority of patients develop serious complications, including infective endocarditis, cerebrovascular events, progressive severe mitral regurgitation, arrhythmias, and sudden cardiac death.

The risk of complications is highest in men, patients older than 45 years, patients with familial MVP, and patients with a holosystolic murmur or left-sided chamber enlargement. Echocardiographic predictors of increased complications have also been found, including significant mitral regurgitation, leaflet thickening, and leaflet redundancy.

Infected endocarditis
MVP is probably the most common cardiovascular abnormality predisposing to infective bacterial endocarditis. Patients with MVP are at a fivefold to eightfold greater risk of infective endocarditis compared with controls without MVP. However, in prospective studies, the risk that a patient with MVP will develop infective endocarditis has been demonstrated to be very low.

The risk of developing endocarditis is highest in older men and patients with a murmur or those with redundant and thickened valve leaflets. Endocarditis in these patients is associated with considerable morbidity and mortality: the 5-year cumulative incidence of death or mitral valve surgery is estimated to be 60%.

Cerebrovascular events

Previous belief: MVP often causes stroke in young patients.

Current knowledge: Stroke in patients with MVP, regardless of age, is usually due to causes other than MVP.

Whether MVP causes strokes is controversial. Several studies found an association between MVP and cerebrovascular ischemic events, particularly among younger patients without other known risk factors for cerebrovascular disease. Although these events have been attributed to fibrin emboli from the prolapsing mitral leaflet, possibly in association with an underlying prothrombotic state, this has rarely been documented in the literature.

On the other hand, recent population-based and case-control studies demonstrated no increased frequency of MVP among patients with stroke or transient ischemic attacks, including young patients. In addition, patients with MVP who had strokes were similar in age to the general stroke population, and many had other risk factors for strokes, including atrial fibrillation.

Several prospective studies have found that cerebrovascular events occur only rarely in patients with MVP, with an incidence of less than 1% per year.

Mitral regurgitation
Most patients with MVP do not develop significant mitral regurgitation. Nevertheless, MVP is a common cause of progressive, severe mitral regurgitation, which often requires valve repair or replacement.

Several prospective studies have found
that the risk of developing severe mitral regurgitation requiring mitral valve repair or replacement is less than 1% per year.\textsuperscript{22,23,26} The cumulative risk rises with age; an Australian study found that by age 70 it is 4% in men and 1% in women.\textsuperscript{43}

Subsets of patients with MVP who are at higher risk of developing severe mitral regurgitation requiring mitral valve surgery are older men and those with higher systolic pressure and body weight.\textsuperscript{44} Other clinical predictors of the need for mitral valve surgery for mitral regurgitation include a left ventricular diastolic dimension greater than 60 mm and cardiomegaly on chest radiography.\textsuperscript{22} Older patients and those with prolapse of the posterior mitral leaflet have been found to have more severe regurgitation.\textsuperscript{26}

Cardiovascular complications, including atrial fibrillation and congestive heart failure, are much more likely if mitral regurgitation is severe or if it progresses over time.\textsuperscript{26,27}

Severe mitral regurgitation can develop from progressive myxomatous degeneration with an increasing degree of prolapse, or it can be due to chordal rupture. Rupture of chordae tendineae nearly always results in severe mitral regurgitation and a flail leaflet.\textsuperscript{24,42,45}

**Arrhythmias**

**Previous belief:** MVP often causes atrial and ventricular arrhythmias.

**Current knowledge:** No excess of arrhythmias is associated with MVP without regurgitation.

Early studies indicated that many patients with MVP had palpitations and various dysrhythmias, including supraventricular tachycardia and atrial and ventricular premature depolarizations.

However, these studies were likely affected by selection bias, as the subjects typically were patients referred for evaluation of symptoms such as palpitations.

Furthermore, the Framingham investigators\textsuperscript{46} found that these dysrhythmias are also common among people without MVP, and that patients with MVP had no statistically significant excess of dysrhythmias on resting 12-lead electrocardiography, treadmill electrocardiography, or 1-hour or 24-hour ambulatory electrocardiographic monitoring compared with people without MVP.

An exception, however: patients with MVP and mitral regurgitation have a higher prevalence of ventricular dysrhythmias, including ventricular tachycardia.\textsuperscript{47}

**Sudden cardiac death**

Sudden cardiac death is a rare complication of MVP, with an estimated incidence of 0.1% to 0.4% per year, similar to the risk in the general adult population of the United States.\textsuperscript{22,23,48} The risk appears to be greatest in MVP patients with complex ventricular arrhythmias on Holter monitoring, a prolonged QT interval, hemodynamically signifi-
significant mitral regurgitation, and redundant mitral leaflets.22,49

HOW SHOULD MVP BE TREATED?

Patients with MVP who have no symptoms (ie, most patients with MVP) require no specific treatment other than antibiotic prophylaxis in some cases (see below), and should be reassured of their excellent prognosis.

Patients with either syncope or palpitations should be evaluated with Holter ambulatory monitoring to rule out significant supraventricular or ventricular arrhythmias.

Patients without mitral regurgitation should be reexamined every 3 years, and echocardiography should be performed if cardiovascular symptoms develop or a new murmur or mitral regurgitation is found on cardiac auscultation.

Beta-blockers

Beta-blockers may be useful empirically in alleviating symptoms of palpitations, anxiety, and chest pain in some patients.50

Antibiotic prophylaxis

Antibiotic prophylaxis to prevent infective bacterial endocarditis has been shown to be cost-effective ($3,000 per year of life saved) when given to patients with MVP and a systolic murmur.51

Guidelines9,52 call for antibiotic prophylaxis before dental procedures or other invasive procedures for patients with MVP who have either of the following:

• Both a systolic click and murmur on auscultation
• An isolated systolic click and echocardiographic evidence of MVP and mitral regurgitation.

Antibiotic prophylaxis may be considered for those with only a systolic click and no murmur if certain high-risk echocardiographic characteristics are present, such as leaflet redundancy, leaflet thickening, or left atrial or ventricular enlargement.

Antibiotic prophylaxis is not recommend-
ed for those with an isolated systolic click and equivocal or no evidence of MVP on echocardiography.

Anticoagulation

Patients with MVP should receive aspirin (80–325 mg/day) if they have either of the following:

• A history of transient ischemic attacks
• Atrial fibrillation (if they are younger than 65 and have no mitral regurgitation, hypertension, or congestive heart failure).

Patients should receive warfarin (target international normalized ratio 2–3) if they have any of the following:

• Documented stroke
• Recurrent transient ischemic attacks
• Atrial fibrillation with an increased risk of thromboembolism (eg, if they are older than age 65 or have mitral regurgitation, hypertension, or congestive heart failure).

Management of mitral regurgitation

Serial echocardiography is necessary to document changes in left ventricular size and systolic function, which are important indicators of the need for surgery.

Patients with MVP who have mitral regurgitation of mild to moderate severity should undergo echocardiography every year.

Patients with MVP and severe mitral regurgitation should undergo stress echocardiography every 6 to 12 months or more frequently, depending on their clinical condition.

There is no evidence that afterload-reducing drugs favorably alter the natural history of mitral regurgitation if left ventricular function is normal.

The indications for mitral valve surgery when severe mitral regurgitation is present are similar to those for causes of severe mitral regurgitation other than MVP and include the development of symptoms or even mild impairment of left ventricular systolic function. When surgery is required, mitral valve repair is usually feasible (figure 3); the 10-year reoperation-free survival rate is 93% to 96%.53,54

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ADDRESS: Brian Griffin, MD, Department of Cardiovascular Medicine, F15, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail griffib@ccf.org.