Mitral Valve Prolapse

In 1966 Barlow and Bosman (1) described a constellation of clinical findings consisting of non-ejection 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 pathological 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 tendinae and papillary muscles. The shape of the mitral valve annulus is saddle-like. The mitral valve is functionally bicuspid, but embryologically made up of four cusps. Two cusps are large (the anterior or aortic cusp and the posterior or mural cusp) and two are small commissural cusps (Figure 1). In the case of a normal mitral valve, these commissures are never complete. (3) The posterior leaflet is 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. The chordae tendinae can be divided into three groups. The first two groups originate from or near the apices of the papillary muscles. The chordae of the first order insert into the extreme edge of the valve. The chordae of the second order insert on the ventricular surface of the cusps. The chordae of the third order originate from the ventricular wall much nearer the origin of the cusps. These chordae often form bands or fold-like structures that may contain muscle. Usually there are two papillary muscles (anterior and posterior), which have bifid apices; each receive chordae from both major mitral valve cusps.

DEFINITION, AETIOLOGY AND PATHOLOGY OF MITRAL VALVE PROLAPSE

Normally, the mitral valve billows slightly towards the left atrium; an exaggerated form should be termed “billowing mitral valve”. A “floppy valve” is regarded as an extreme form of billowing. “Prolapse” is defined as the systolic billowing of one or both mitral valve leaflets into the atrium superior to the annular plane, associated with or without regurgitation. A “flail valve” involves chordal rupture and is nearly always 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. More often, a primary disorder of the mitral valve leaflets exists, associated with...
specific pathologic changes causing redundancy of the valve leaflets and their prolapse into the left atrium during systole.

Surgeons differentiate into 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, whereas fibroelastic deficiency has thickening restricted to the prolapsed area(s), with the remaining valve tissue being more transparent, not thickened, without excess tissue and the annulus being dilated or not.(5)

The exact aetiology 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 is observed in its most extreme form in Marfan’s 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 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 pre-existing mitral valve regurgitation. Myxomatous changes in the annulus can cause annular dilatation and calcification, contributing to the severity of the mitral valve regurgitation.

PREVALENCE OF MITRAL VALVE PROLAPSE

Primary MVP is the most frequently diagnosed cardiac valvular abnormality, 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 mostly as an isolated valve dysfunction, but can also be associated with connective tissue diseases such as Marfan’s syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta and muscular dystrophy. In addition, MVP seems also 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 of the patients with primary MVP remain asymptomatic. The diagnosis is often made by a routine cardiac auscultation or by 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, orthostatism and neuropsychiatric symptoms, which are not correlated with mitral valve function, are described as the MVP syndrome.
The cause of these latter symptoms in the MVP syndrome is unknown, but an association between 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 manoeuvres 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 manoeuvre that decreases left ventricular volume, such as Valsalva manoeuvre, sudden standing, early during 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 will be delayed. The sensitivity of a click for diagnosis of MVP is low (19%) but its specificity is high: a mid- or late systolic click can be heard in the absence of MVP in only 1.5% of cases.

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. The electrocardiogram 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. Exercise testing is frequently false-positive with ST-T wave depression, especially in women, even with normal coronary arteries.

The two-dimensional transthoracic or transoesophageal echocardiography is the easiest diagnostic tool to confirm the diagnosis of MVP. 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 > 2 mm to the left atrium of at least one of the mitral valve leaflets during systole and a thickening ≥ 5 mm of the prolapsing valve leaflet during diastole. Dislocation is referred by a hypothetical line through the insertion points of the anterior and the posterior mitral valve leaflet in parasternal and apical long axis view.

The newest generation of two- and three-dimensional transthoracic and transoesophageal echocardiography machines generates exquisite images, allowing one to clearly identify the mechanism of mitral regurgitation and to differentiate Barlow’s disease from fibroelastic deficiency. In patients who require a surgical intervention, the possibilities of reconstructive surgery can be better assessed, ensuring optimal treatment by use of the best technique. Recently, the use of stress or exercise echocardiography has been advocated.

The most typical MVP is characterised 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.

**EARLY MANAGEMENT OF MITRAL VALVE PROLAPSE**

Most patients with MVP require no treatment. Management of MVP (Table 1) should be centered on patient education, symptom recognition and risk management. For those 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 require preventive oral antibiotic prophylaxis. Infective endocarditis is a serious complication of MVP and MVP with regurgitation is considered as the leading predisposing cardiovascular disorder in patients with endocarditis. Although a low incidence of surgical need (7.5%) and lethal outcome (5%), frequent (25%) neurological complications were found associated with infective endocarditis. Even mild hypertension should be treated, as this may aggravate mitral valve dysfunction. Similarly, weight control
should be encouraged. Echocardiographic reevaluation at 2- to 3-year intervals is appropriate.

At highest risk are those who suffer from a moderate-to-severe mitral regurgitation. This group is most likely to require valve surgery, and every effort should be made to reduce factors that increase regurgitation.

High-risk patients require yearly Doppler evaluation. Valve surgery should be considered in patients who have worsening dyspnea and diminishing left ventricular function.

When the presence of arrhythmias is suspected, 24 hours’ ECG recording needs to be performed to determine an antiarrhythmic strategy.

In patients who have symptoms suggestive of MVP, lifestyle modification is the key to 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.17 Orthostatic symptoms related to postural hypotension and tachycardia are best treated with volume expansion, increasing fluid and salt intake.

**TABLE 1: Management of patients with mitral valve prolapse.**

<table>
<thead>
<tr>
<th>Asymptomatic patients</th>
<th>Absence of mitral valve regurgitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up frequency: every 5 years</td>
<td></td>
</tr>
<tr>
<td>Technical examinations</td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td></td>
</tr>
<tr>
<td>Two-dimensional echocardiography and Doppler</td>
<td></td>
</tr>
<tr>
<td>No endocarditis prophylaxis required</td>
<td></td>
</tr>
<tr>
<td>Competitive exercise allowed</td>
<td></td>
</tr>
</tbody>
</table>

| Presence of stable mild mitral valve regurgitation |
| Follow-up frequency: every 2-3 years |
| Technical examinations  |
| Electrocardiogram |
| Two-dimensional echocardiography and Doppler |
| Endocarditis prophylaxis required |
| Moderate static and moderate dynamic competitive sports allowed |

| Presence of progressive mitral valve regurgitation |
| Follow-up frequency: at least every year |
| Technical examinations  |
| Electrocardiogram |
| Two-dimensional echocardiography and Doppler |
| Chest X-ray |
| Endocarditis prophylaxis required |
| Recreational sport allowed |

| Symptomatic patients |
| Not attributable to moderate/severe mitral valve regurgitation |
| Follow-up frequency: every year |
| Technical examinations  |
| Electrocardiogram |
| 24-hour electrocardiographic monitoring |
| Treadmill exercise testing |
| If necessary: anti-arrhythmic drugs (beta-adrenoreceptor blocker) |

| Attributable to moderate/severe mitral valve regurgitation |
| Technical examinations  |
| Invasive hemodynamic evaluation |
| Transoesophageal echocardiogram, 3D |
| Mitral valve surgery |

LATE OUTCOME OF MITRAL VALVE PROLAPSE

When patients with MVP become symptomatic, the symptoms are mostly 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, left atrial or left ventricular enlargement.18

MVP patients with leaflet thickening and redundancy seem to be at highest risk for developing valve regurgitation. The risk of progression of mitral valve regurgitation also increases with age, male sex, elevated blood pressure and high body weight (both of which may explain the male majority).

Leaflet thickening and redundancy put patients at risk for infectious bacterial endocarditis. The risk of developing endocarditis is low (1-3.5%), but oral antibiotic prophylaxis remains important.

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. 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 anti-platelet treatment.

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

Supraventricular arrhythmias are found to be less frequent than ventricular arrhythmias. Premature supraventricular contractions are observed in 35% of those with MVP but also in a similar number of normal individuals. Sinus tachycardia (heart rate greater than 120 beats per minute), paroxysmal atrial tachycardia and intermittent atrial fibrillation are not more common than in control subjects. Nevertheless, atrial fibrillation is seen more frequently in mitral valve prolapse when
mitral regurgitation is present. 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 has been suggested but remains unconfirmed.(19)

The risk of syncope or sudden death is 0.1% per year, hardly any different to that of the rest of the general adult population (0.2%). However, this risk may attain 0.9-2% 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 with MVP are unclear (hemodynamic, neurohumoral, arrhythmic, etc.), although there is evidence in favor of malignant ventricular arrhythmias.(20) Detailed studies have raised doubts as to the direct involvement of the cardiovascular malformation in this mode of fatal outcome. In cases of sudden death linked to MVP, localized or diffuse myocardial disease is often observed in association with MVP (usually asymptomatic or pauci-symptomatic) providing a more plausible cause for sudden death.

LATE MANAGEMENT OPTIONS

When MVP results in significant mitral valve regurgitation, valve surgery is necessary. No clinical data are available proving benefit of long-term vasodilator therapy in symptomatic or non-symptomatic patients with MVP, although salutary hemodynamic effects were noticed during short-term administration of pre- and afterload reduction.

Initially, mitral valve replacement by a mechanical or, less often, biological valve was performed. Currently most patients will be offered reconstructive surgery.(21) Several techniques can be applied: intervention at the leaflet (quadrangular resection, triangular resection, plication, cleft closure), intervention at the annulus (sliding plasty, plication, decalcification), 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.(22) Mitral valve repair currently has low operative mortality (< 1-2%) and is associated with excellent early short-term results, most patients leaving the hospital with residual regurgitation of less than ¼.(23) Follow-up studies suggest a lower risk of thrombosis and endocarditis 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 post-repair. When avoiding subideal techniques (chordal shortening instead of transposition or artificial chordae, the non-use of an annuloplasty ring, and the non-use of a sliding plasty) the recurrence rate of significant mitral regurgitation (colour 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, 24) Freedom from reoperation for fibroelastic deficiency is better (96.6% at 10 years) than for Barlow’s disease (86.1% at 10 years).

PREGNANCY

Primary MVP is considered to be 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 to be one of the most frequent complications during pregnancy in females with MVP and often require treatment with antiarrhythmic drugs. The incidence of preterm delivery is not increased in patients with MVP. Infective endocarditis prophylaxis is recommended as indicated.

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, thought to be related to low intravascular volume. This 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 are as follows\(^{(25)}\):

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 to be 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;
- Prior embolic event.

Athletes with MVP and one or more of the aforementioned criteria can participate in only 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 learnt about the 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.
REFERENCES:


