Mitral valve prolapse

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Mitral valve prolapse is a common valvular abnormality that is the most common cause of severe non-ischaemic mitral regurgitation in the USA. The overall prognosis of patients with mitral valve prolapse is excellent, but a small subset will develop serious complications, including infective endocarditis, sudden cardiac death, and severe mitral regurgitation. We present a comprehensive review of mitral valve prolapse, examining normal mitral anatomy, the clinical and echocardiographic features of mitral valve prolapse, and the pathophysiology and genetics of the disorder. We discuss the contemporary management of both asymptomatic and symptomatic prolapse, with particular attention to the timing and technique of surgical repair. We conclude that echocardiography is the method of choice for diagnosing mitral valve prolapse, that clinical and echocardiographic features can predict which patients with prolapse are at highest risk for complications, and that mitral valve repair is the treatment of choice for symptomatic prolapse.

Using left ventricular cineangiography in the 1960s, Barlow first recognised the mitral origin of late-systolic murmurs often associated with clicks.[1] Criley subsequently termed this condition mitral valve prolapse.[2] The widespread use of echocardiography in the 1980s led to an apparent epidemic of mitral valve prolapse, especially among young women, and various non-specific symptoms were attributed to the condition. Since that time, our understanding of this valvular abnormality, and of normal mitral anatomy, has evolved greatly. Mitral valve prolapse is much less common than previously believed, and is a heterogeneous disorder with variability in its pathological, clinical, and echocardiographic manifestations. The prognosis of the condition is usually benign, but there can be serious sequelae, the most frequent of which is severe mitral regurgitation. Indeed, myxomatous degeneration of the mitral valve, the most common pathophysiological basis for mitral valve prolapse, is the most common cause of isolated severe mitral regurgitation requiring surgery in the USA.[3,4] The purpose of this paper is to review normal mitral anatomy, define the pathology and complications of mitral valve prolapse, and assess state-of-the-art medical and surgical therapy for this common valve condition.

Defining mitral valve prolapse

Initially mitral valve prolapse was defined as a late systolic murmur associated with "billowing" or prolapse of one or both of the mitral leaflets into the left atrium. With increased use of two-dimensional echocardiography, the diagnosis of mitral valve prolapse became much more prevalent—as high as 38% among teenage girls.[5] In part, this overdiagnosis was due to the erroneous assumption that the mitral valve was planar; thus, any view that showed excursion of the leaflets superior to the mitral annulus was deemed pathological.

Pivotal echocardiography work in the late 1980s redefined normal mitral anatomy.[6–8] Using three-dimensional echo imaging, Levine[6] showed that the mitral annulus was in fact saddle-shaped, with the most superior aspects anteriorly and posteriorly (figure 1). Therefore, in the anterior-posterior axis, the annulus is concave upward, whereas medially-to-laterally, the annulus is concave downward. This geometry creates the possibility that in a four-chamber view the leaflets can appear to break the annular plane, when in reality they are normal (figure 1).[6] Levine found that patients who appeared to have prolapse in a four-chamber view, but not in a long-axis view, were no more likely to have additional features of mitral valve prolapse—for example, mitral regurgitation, left atrial enlargement, or mitral leaflet thickening—than patients who appeared to have no mitral valve prolapse. In short, only valves that showed prolapse in a long-axis view had true mitral valve prolapse.

Echocardiographic mitral valve prolapse has since been defined as single or bileaflet prolapse at least 2 mm beyond the long-axis annular plane, with or without leaflet thickening (figure 2). With this more precise description, the prevalence of prolapse is estimated at 2–3%, and is equally distributed between men and women.[9] Prolapse with thickening of the valve leaflets

Search strategy and selection criteria

To identify the published data on mitral valve prolapse, we searched MEDLINE and PubMed from 1966 to present and selected articles that included the keywords "myxomatous" and "mitral valve prolapse". We restricted our search to articles in English that were about human beings, and included review articles and original research publications. Letters to the editor, commentaries, and case reports were excluded. Further data for the histopathological and biomechanical properties of myxomatous valves were found by searching for keywords "mechanical," "biomechanical," and "biochemical". The references for key reviews and frequently-cited primary research publications were examined to ensure that important sources were not omitted. Additionally, references for articles published in major peer-reviewed journals were reviewed. Publications from non-peer reviewed sources and personal correspondence were not included.

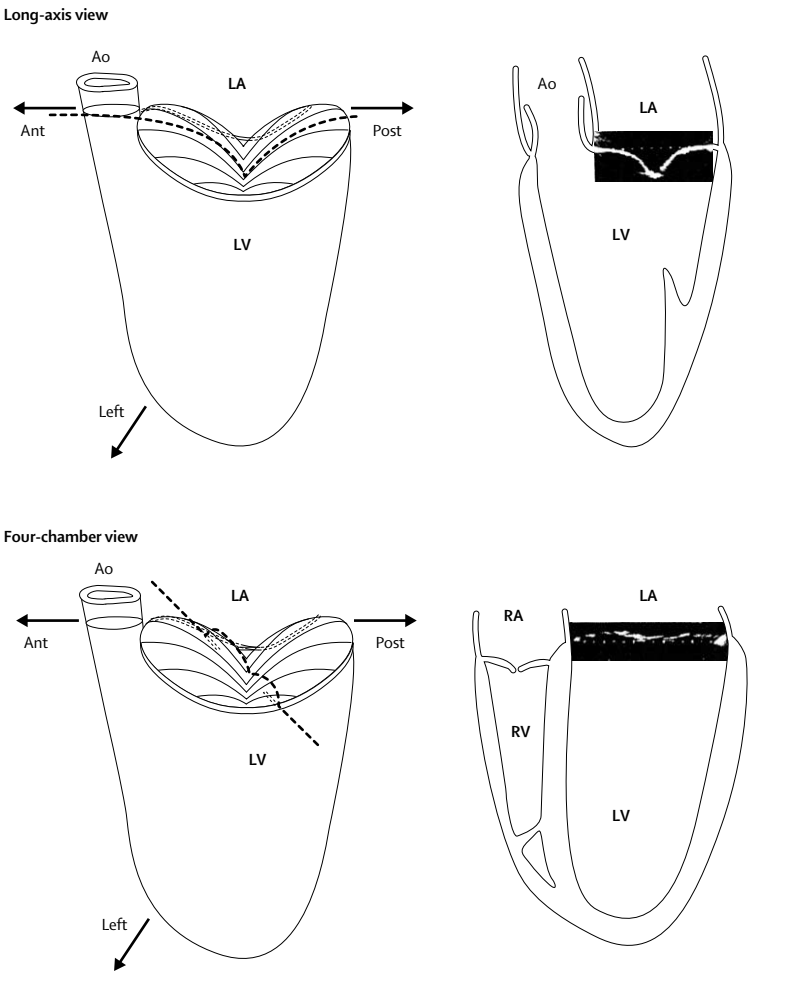

Figure 1: **Long axis and four-chamber diagrams with saddle-shaped annulus, alongside corresponding echocardiographic views**
LV=left ventricle. LA=left atrium. RA=right atrium. Ao=aorta. Ant=anterior. Post=posterior. Reproduced from reference 5 with permission from Lippincott.

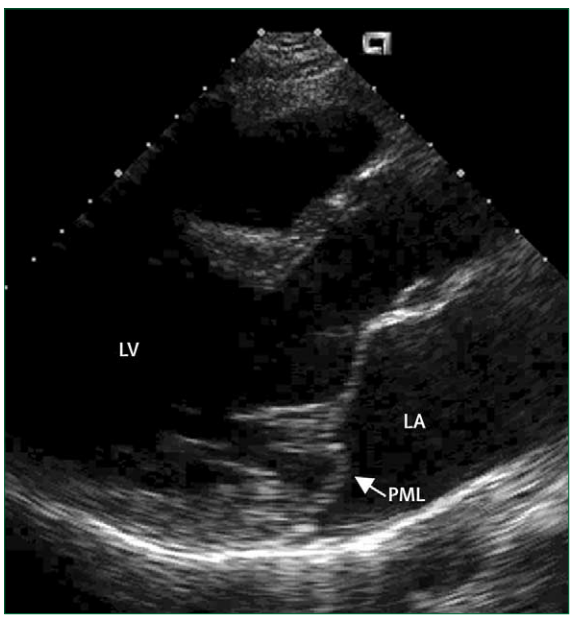

Figure 2: **Transthoracic echocardiographic image in parasternal long-axis view, showing posterior mitral leaflet bowing backward and prolapsing into left atrium during systole**
LV=left ventricle. LA=left atrium. PML=posterior mitral valve leaflet.

greater than 5 mm is termed "classic" prolapse, whereas prolapse with lesser degrees of leaflet thickening is regarded as "non-classic prolapse". Interestingly, longitudinal studies have implicated leaflet thickening as a major predictor of poorer prognosis, with a higher risk of sudden death, endocarditis, and mitral regurgitation in patients with classic prolapse.[10,11] This finding raises the possibility that "non-classic" prolapse is a normal variant, or at least a benign abnormality, of mitral anatomy. Likewise, leaflet prolapse of less than 2 mm does not correlate with other complications of mitral valve prolapse.

Cause and pathology

Mitral valve prolapse is a multifactorial valvular abnormality that can be caused by histological abnormalities of valvular tissue, geometric disparities between the left ventricle and mitral valve, or various connective tissue disorders. Leaflet thickening and redundancy, known as myxomatous degeneration, is the most common and clinically important of these abnormalities. Normal valve tissue is divided into three layers: an inner ventricularis layer, the middle spongiosa, and the outer fibrosa. Myxomatous degeneration is characterised grossly by leaflet thickening and redundancy with interchordal hooding, chordal elongation, and annular dilatation.[3,12–14] Histopathology reveals expansion of the spongiosa layer due to an accumulation of proteoglycans,[12–17] structural alterations of collagen in all components of the leaflet,[13,15,17–19] and structurally abnormal chordae.

The mechanism underlying myxomatous degeneration is not known, but dysregulation of components of the extracellular matrix seems to have a role. The spongiosa layer contains an increased number of interstitial cells, which have properties of activated myofibroblasts.[20] Additionally, these cells express raised concentrations of various proteolytic enzymes, including matrix metalloproteinases, which are responsible for collagen and elastin degradation.[20] Chordae in myxomatous valves do not appear to have increased cellularity, although they do contain increased amounts of glycosaminoglycans. This finding suggests that dysregulation of matrix protein synthesis and degradation, rather than hypercellularity, is to blame for the altered chordal protein composition in myxomatous valve chordae.[21]

The disruption of the load-bearing collagen bundles in myxomatous valves leads to mechanical alterations that

have important implications in the pathogenesis of chordal rupture. Myxoid leaflets and chordae exhibit enhanced extensibility and decreased stiffness compared to normal valves.[22] Additionally, leaflets and particularly chordae show a decrease in the strength at which they fail.[22,23] Chordal rupture is a frequent pathological finding in myxomatous mitral valve disease, and may be secondary to mechanical weakening of the chordae and the abnormal stresses imparted by the redundant leaflet.[3,14] Interestingly, compared with patients with bileaflet prolapse, patients with unileaflet prolapse are more likely to develop a flail leaflet, because their chordae fail at a lower stress and load.[24]

While myxomatous degeneration is the most common reason for mitral valve prolapse, histologically normal valves also may prolapse. Normal mechanical function of the mitral apparatus depends on the relation between the size of the mitral leaflets and the left ventricular cavity. An excess of leaflet tissue, chordal extension, or a disproportionately small left ventricular cavity may lead to auscultatory and echocardiographic signs of mitral valve prolapse. For example, in healthy women a diuretic-induced decrease in left ventricular cavity size may result in echocardiographic mitral valve prolapse,[25] whereas in thin patients the appearance of the condition is probably due to ventricular-mitral disproportion.[26,27] In about 50–80% of patients with unrepaired secundum atrial septal defects, mitral valve prolapse is probably caused by distorted left ventricular geometry and a small left ventricular volume.[28–31] Surgical repair of atrial septal defects usually reduces or eliminates mitral valve prolapse by restoring normal left ventricular shape.[28–31]

Finally, mitral valve prolapse has a well-recognised association with heritable connective tissue disorders including Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum.[32–35] According to current echocardiographic criteria, the prevalence of mitral valve prolapse in patients with Marfan syndrome is 91%, and is due to both left ventricular cavity geometry and histological abnormalities in the valve tissue.[34,36] Whereas earlier M-mode echocardiographic studies reported a high prevalence (78%) of mitral valve prolapse in patients with Ehlers-Danlos syndrome,[35] by present criteria, the prevalence is only 6%.[37] Patients with type IV Ehlers-Danlos syndrome, characterised by abnormal type III collagen synthesis, might be at higher risk for development of mitral valve prolapse.[38]

Genetics

Most cases of myxomatous mitral valve prolapse are sporadic. However, a familial basis for the condition has long been recognised, with an autosomal dominant mode of inheritance, variable penetrance influenced by age and sex, and a marked heterogeneity of clinical presentation even between affected members of the same family.[39–42] In 1999, the first locus for autosomal dominant myxomatous mitral valve prolapse, *MMVP1*, was mapped to chromosome 16p11.2-p12.1.[43] In 2003, Freed and colleagues[44] discovered a second locus, *MMVP2*, on chromosome 11p15.4. Both studies were done with linkage analysis, and to date, the proteins coded by the loci are unknown. Since myxomatous mitral valve prolapse occurs in association with other inherited connective tissue disorders, defects in connective tissue proteins might also be involved in mitral valve prolapse.[45]

Studies on several pedigrees in the 1980s showed that the genes encoding the primary collagens in valve tissue are not linked to autosomal dominant mitral valve prolapse.[46,47] However, more contemporary work has questioned these findings. With single-nucleotide polymorphism analysis, a type III collagen polymorphism has been linked to mitral valve prolapse in Taiwanese patients, although it did not correlate with severity of the prolapse. This polymorphism is located near the mutations that are responsible for type IV Ehlers-Danlos syndrome.[48] Immunohistochemical studies have confirmed marked abnormalities in the distribution and architecture of fibrillin, elastin, collagen I, and collagen III within myxomatous leaflet tissue, suggesting that a genetic abnormality in patients with mitral valve prolapse might be caused by a post-translational defect, rather than in the proteins themselves.[49] Mitral valve prolapse is absent from echocardiographs in newborn babies,[50] suggesting that penetrance of a genetic defect might be age dependent, or, alternatively, that environmental factors have a role in the development of mitral valve prolapse.

Diagnosis

Physical examination and two-dimensional echocardiography are the diagnostic standards for mitral valve prolapse. The classic auscultatory finding is a dynamic, mid-to-late systolic click, frequently associated with a high-pitched, late systolic murmur. Specific manoeuvres—including Valsalva, squatting, and leg raises—are occasionally useful to demonstrate that the click moves within systole as left ventricular volume and loading conditions change. Reduction of end-diastolic volume (eg, Valsalva, standing) results in an earlier click, whereas increasing left ventricular end-diastolic volume (eg, squatting), decreasing contractility, or increasing afterload (eg, hand-grips) will shift the click later into systole.[51,52] A careful physical examination is highly sensitive for echocardiographic mitral valve prolapse, although the specificity is limited.[51] Redundant leaflets or chordae may produce an audible click without echocardiographic prolapse, giving false positive physical findings. Additionally, multiple sources of non-prolapse related systolic clicks have been documented, such as bicuspid aortic stenosis, atrial myxoma, and pericarditis. Of course, echocardiographic prolapse may exist without significant auscultatory findings.[51]

Patients with examination findings that suggest mitral valve prolapse should undergo a two-dimensional echocardiogram to confirm the diagnosis. Early echocardiographic studies in families with mitral valve prolapse showed that about 30% of first-degree relatives of patients with mitral valve prolapse also had the condition.[53,54] Although somewhat controversial, most experts agree that patients with a first-degree relative who has myxomatous mitral valve prolapse should also be screened with echocardiography.[55] This method is also very useful to risk stratify patients with prolapse, as leaflet thickness, redundancy, and increased left-ventricular diameter have all been associated with increased risk of endocarditis, sudden cardiac death, and progression of mitral regurgitation.[10,11,52]

Mitral valve prolapse can be diagnosed when one or both mitral leaflets exhibit at least two millimeters of systolic displacement superior to a line connecting the annular hinge points in a long-axis view. Transthoracic echocardiography, however, may not adequately visualise the entire mitral valve, and thus can miss the diagnosis. Anatomically, the posterior and anterior leaflets of the mitral valve each may be divided into three sections. Carpentier's widely recognised nomenclature describes three posterior leaflet scallops—the lateral (P1), middle (P2), and medial (P3)—and three anterior segments—lateral (A1), middle (A2) and medial (A3; figure 3).[56,57] Most cases of prolapse involve the posterior middle scallop, which is easily identified on long-axis echocardiographic images. Lateral scallop prolapse, however, is not clearly seen on long-axis images; this aspect is best seen in the apical four-chamber view. As noted earlier, superior leaflet displacement in a four-chamber view should not be judged diagnostic of prolapse. Thus, transthoracic echocardiography can confirm the diagnosis of prolapse, but may not be able to exclude lateral scallop prolapse without taking into account several planes of imaging. Alternatively, several studies have shown that transoesophageal echocardiography is very effective in identifying prolapsing segments.[57–59]

Mitral valve prolapse syndrome

Mitral valve prolapse is usually diagnosed on the basis of a classic physical examination, discovered incidentally on an echocardiogram done for another reason, or found once complications of the prolapse are manifest. Various symptoms (including atypical chest pain, exertional dyspnoea, palpitations, syncope, and anxiety) and clinical findings (including low blood pressure, leaner build, and electrocardiographic repolarisation abnormalities) have been associated with mitral valve prolapse and have been termed "mitral valve prolapse syndrome". The misperception that these symptoms frequently occur concomitantly with mitral valve prolapse has led to the practice of obtaining screening echocardiograms on patients who have atypical or non-specific cardiovascular symptoms.

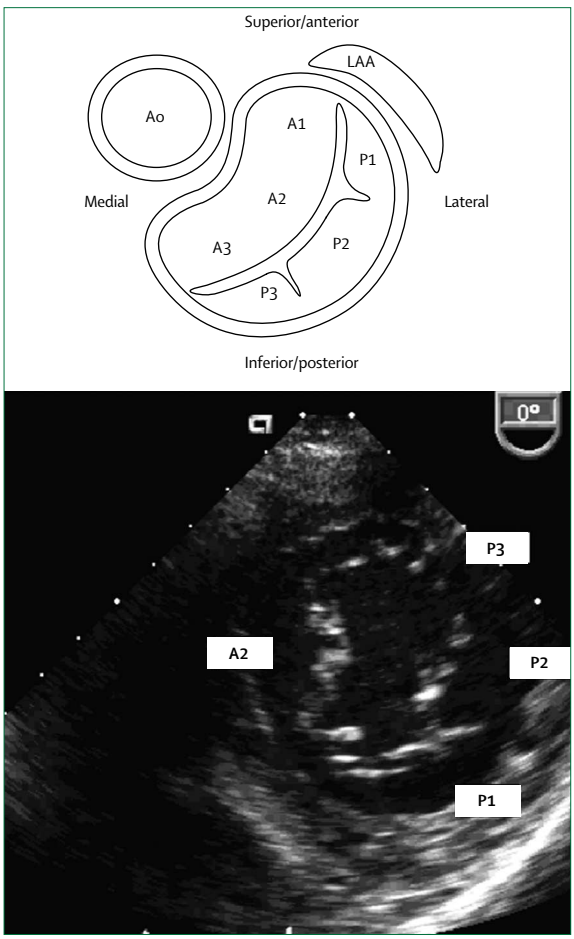

Figure 3: **Anatomy of mitral valve, showing anterior and posterior leaflets**
Ao=aorta. LAA=left atrial appendix. Lower image shows transgastric short axis view of mitral valve with corresponding scallops. Reproduced from reference 57 with permission from *Annals of Thoracic Surgery*/Elsevier.

Recent studies, including an analysis of unselected outpatients participating in the Framingham Heart Study, have reported no excess of psychiatric symptoms or electrocardiographic abnormalities in people with mitral valve prolapse.[9,60,61] Similarly, there were no differences in atypical chest pain, dyspnoea, or panic disorder.[9,60] One study did find that thoracic bony abnormalities (scoliosis, pectus excavatum, decreased anteroposterior diameter), palpitations, leaner body mass, and lower blood pressure were all more likely in patients with prolapse.[60] Only the association with leaner body mass was replicated in the Framingham data.[61] It should be emphasised that, because both conditions are relatively common, chest pain in patients with mitral valve prolapse may be secondary to concomitant coronary artery disease. Due to the frequent occurrence of false-positive exercise stress tests among patients with mitral valve prolapse,[62,63] the use of an imaging modality such as stress electrocardiography or single photon-emission computed tomography myocardial perfusion

imaging may be preferable.[63–65] Postulated mechanisms for electrocardiographic abnormalities in patients with mitral valve prolapse include vasospasm, papillary muscle ischaemia, and microvascular perfusion defects.[66] The exact cause, however, remains unclear; imaging studies and angiography are frequently normal, and coronary flow reserve does not correlate with echocardiographic abnormalities.[62,64,66,67]

It is possible that a complex of unexplained cardiovascular symptoms in a minority of patients with mitral valve prolapse is related to the valvular abnormality, but the mechanism of this association is unknown. Abnormal autonomic function has been reported among symptomatic patients with mitral valve prolapse, including raised circulating concentrations of catecholamines, enhanced β-receptor affinity, increased vasoconstrictor tone, decreased plasma volume, and diminished vagal responsiveness.[68–71] Interestingly, genetic analysis has linked a polymorphism in the angiotensin II receptor with mitral valve prolapse syndrome. Angiotensin II has been shown to affect central sympathetic tone and mediate vagolytic effects in healthy people. A polymorphism at the 1166 position has been associated with postural hypotension and enhanced cardiac vasomotor response, even in healthy people. The polymorphism seems to be more prevalent in patients with prolapse and atypical symptoms than in controls.[72] However, studies that included asymptomatic patients with mitral valve prolapse have shown no evidence of abnormal autonomic or neuroendocrine function either at rest or during tilt-testing.[73,74] Thus, abnormal autonomic function might be responsible for symptoms in some patients with mitral valve prolapse, but it remains unclear whether their prolapse is directly related or incidental.

Managing mitral valve prolapse

Mitral valve prolapse is equally common in men and women, although men seem to have a higher incidence of complications.[3,52,75] Nevertheless, most patients with mitral valve prolapse have an excellent prognosis with an expected survival similar to that of the general population.[11,76,77] Most patients do not develop symptoms or other significant echocardiographic abnormalities.[76] Most asymptomatic patients with mitral valve prolapse can be followed conservatively. Neither their activity level nor lifestyle should be restricted; in fact, routine exercise is preferable. Surveillance echocardiograms are not recommended if patients have only mild regurgitation and stable examination findings. Patients with prolapse are at higher risk for serious complications including infective endocarditis, sudden cardiac death, cerebrovascular ischaemic events, and severe mitral regurgitation. Physicians caring for patients with prolapse should identify patients who are at higher risk for complications, attempt to prevent complications, and optimise the timing for mitral valve surgery, if necessary.

Identification of high-risk patients

Although the rate of serious complications is low, a subset of patients with mitral valve prolapse appears to be at increased risk and can be defined by both clinical and echocardiographic findings. Patients with depressed left ventricular systolic function and moderate-severe mitral regurgitation at baseline have a higher overall mortality rate than those with normal ejection fraction and mild to moderate mitral regurgitation. Risk factors for cardiovascular morbidity (mitral valve surgery, thromboembolic event, congestive heart failure) include mild-moderate mitral regurgitation at baseline, atrial fibrillation, age older than 50 years, and left atrial enlargement (table 1).[77] Multiple studies suggest that patients with mitral leaflet thickness greater than 5 mm—that is, classic prolapse—also represent a higher risk group.[10,11,75,78] Leaflet thickening is associated with a 14-fold higher risk of complications including sudden death, infective endocarditis, or cerebral embolic events.[11] Patients with mitral regurgitation during exercise, but not at rest, also have a higher rate of complications including congestive heart failure, syncope, and progressive mitral regurgitation requiring surgery.[79]

Infective endocarditis

Patients with mitral valve prolapse have a threefold to eightfold higher risk of developing infective endocarditis, with an estimated incidence of about 0·02% per year.[75,80,81] Predictors of increased risk for development of infective endocarditis include male sex, age older than 45 years, the presence of a systolic murmur, and leaflet thickening and redundancy.[10,11,75,81,82] Turbulent flow caused by mitral regurgitation and thickened valve tissue are believed to be the main pathological mechanisms underlying the increased risk of valvular infection. In the absence of mitral regurgitation, the incidence of infective endocarditis is similar to that of the general population, but in patients with mitral valve prolapse and a systolic murmur, the risk increases to about 0·05% per year.[83] Dental procedures are the most common reason for antibiotic prophylaxis, and result in an estimated 78 cases of endocarditis per million procedures.[81,84] Because endocarditis is associated with substantial morbidity and mortality, antibiotic prophylaxis for those with a systolic

	10-year risk of event
0 major and ≤1 minor risk factors	2%
0 major and ≥2 minor risk factors	15%
1–2 major risk factors	78%

Major risk factors: moderate-to severe mitral regurgitation or left ventricular ejection fraction <50%. Minor risk factors: mild mitral regurgitation, flail leaflet, left atrial enlargement, atrial fibrillation, age older than 50 years. Events: heart failure due to mitral regurgitation, mitral valve surgery, endocarditis, death related to mitral valve prolapse. Adapted from reference 77.

Table 1: **Incidence of complications in asymptomatic patients**

murmur has been shown to be a cost-effective measure.[84,85]

Antibiotic prophylaxis remains one of the most important medical interventions for patients with prolapse (table 2, panel).[52] Patients with a systolic click/murmur complex on examination, a systolic click and echocardiographic evidence of mitral valve prolapse with mitral regurgitation, or a click in the setting of high-risk prolapse characteristics on echocardiography, merit prophylaxis. Features indicating high risk include left ventricular dilatation, left atrial enlargement, leaflet thickening, and redundant chordae.[52] Additionally, any patient with myxomatous degeneration and regurgitation on echocardiography should receive prophylaxis, irrespective of the findings of their physical examination. It should be emphasised that mitral regurgitation in patients with prolapse can be dynamic and evanescent. Thus, if patients have additional high-risk features of prolapse, they should receive antibiotic prophylaxis. Conversely, patients with valves of normal appearance that prolapse, but do not leak, do not require prophylaxis, even if they have systolic clicks.[86]

Sudden cardiac death

Sudden cardiac death has long been recognised to occur in patients with myxomatous mitral valve prolapse and is probably due to ventricular tachyarrhythmias.[13,87,88] Although the risk of sudden cardiac death in mitral valve prolapse is very low, with an estimated yearly rate of 40 per 10 000, the incidence is still twice that expected in the general population.[89] Substantial mitral regurgitation,[89] redundant chordae,[11] and depressed left ventricular function[90] increase the risk of sudden cardiac death.

The presence of severe mitral regurgitation with a flail segment appears to carry a higher risk of sudden cardiac death—up to 2% per year.[90,91] Several authors have suggested that an early surgical repair might decrease the risk of sudden cardiac death, and that flail itself, irrespective of symptoms, should be an indication for surgery.[90–92] Follow-up data from the Mayo Clinic lends support to this approach.[92] At present, however, repair of an asymptomatic flail leaflet in the absence of other heart abnormalities carries an American College of Cardiology/American Heart Association (ACC/AHA) IIb recommendation (panel).[52]

The mechanism of sudden death in mitral valve prolapse is not known. Patients with mitral valve prolapse do not have an excess of atrial or ventricular arrhythmias on ambulatory electrocardiograph monitoring.[93,94] However, those with mitral regurgitation of any cause have a higher frequency of complex atrial and ventricular arrhythmias.[95] Additionally, valvular lesions that result in left ventricular volume overload, such as mitral regurgitation, are associated with recurrent ventricular arrhythmias and inducible ventricular tachycardia during electrophysiological study.[96] Increased QT dispersion has been associated with mitral valve prolapse, but the importance of this finding is not known.[97–99]

Cerebrovascular ischaemic events

Early studies showed an association between mitral valve prolapse and cerebrovascular events, especially in young patients.[100–102] The postulated mechanism of cerebral ischaemic events is embolisation of platelet-fibrin thrombi from the surface of myxomatous mitral leaflets, but this finding is rarely demonstrated pathologically.[103,104] Studies of platelet activation in mitral valve prolapse have provided conflicting results, but enhanced platelet activation seems to be associated with the degree of mitral regurgitation rather than the presence of mitral valve prolapse.[105–110]

Recent findings based on current echocardiographic criteria have been mixed; two investigators reported no excess risk of cerebrovascular events among young patients with mitral valve prolapse.[111,112] But a recent analysis from Olmstead County, Minnesota, USA, showed that patients with mitral valve prolapse had a cerebrovascular event rate of 0·7% per year—twice the

	ACC/AHA class
Systolic click and murmur on examination	I
Systolic click and mitral valve prolapse or mitral regurgitation on echo	I
Systolic click and high-risk features of mitral valve prolapse on echo	IIa
Isolated systolic click but no evidence of mitral valve prolapse on echo	III

*Patients, particularly men older than 45 years, who have no mitral regurgitation but who do have echocardiographic evidence of myxomatous valve leaflets, may be at higher risk of bacterial endocarditis. A third of patients with mitral valve prolapse may have mitral regurgitation only with exercise. Moreover, mitral regurgitation may be intermittent. Data on efficacy of antibiotic prophylaxis in these groups of patients are scant; decisions on using prophylaxis should be based on clinical grounds, considering the type of invasive procedure, any previous history of endocarditis, and presence of myxomatous changes on echocardiography. Adapted from ACC/AHA guidelines, reference 52 (and see panel).

Table 2: **Recommendations for antibiotic prophylaxis in patients with mitral valve prolapse**

Panel: **ACC/AHA definitions of class recommendations**

Class I
Recommendations for which there is either evidence or consensus opinion that an intervention is useful and effective

Class II
Recommendations for which there is either conflicting evidence or a disagreement about the usefulness or efficacy of an intervention

IIa
Weight of evidence or opinion is in favour of the intervention

IIb
Usefulness or efficacy of the intervention is less well-established by evidence or opinion

Class III
Recommendations for which there is evidence and/or consensus opinion that an intervention is not beneficial, and may in fact be harmful

expected rate for the community. In multivariable analysis, thickened mitral leaflets, the need for mitral valve surgery, and atrial fibrillation were the most powerful predictors of events; age of 50 years or older was also significant.[113] These data suggest that mitral valve prolapse may confer a small risk of cerebrovascular events, but mainly in older patients with high-risk valve features and advanced mitral regurgitation. Moreover, several studies have shown that among patients with mitral valve prolapse, stroke most frequently occurs in elderly patients with a high prevalence of typical stroke risk factors and identifiable stroke mechanisms.[111,114] Thus, mitral valve prolapse should rarely be judged to be the source of stroke, and its presence should not alter the subsequent medical treatment. Physicians may elect to prescribe prophylactic aspirin treatment to patients with high-risk mitral valve prolapse, but this recommendation is not strongly supported by the available data and carries a IIb recommendation in the ACC guidelines.[115]

Mitral regurgitation

The most important complication of mitral valve prolapse is severe mitral regurgitation, which may result from either progressive myxomatous degeneration or chordal rupture. The risk for developing mitral regurgitation is not uniform among patients with mitral valve prolapse, and both clinical and echocardiographic findings may predict those who are at greater risk. Physicians caring for patients with mitral valve prolapse should recognise individuals who are at increased risk of progressive mitral regurgitation, and assess these patients with vigilance to ensure optimal timing of surgical intervention. Although the prevalence of mitral valve prolapse does not differ by sex, men have a threefold higher risk than women of ultimately needing surgery for severe mitral regurgitation.[3,116] Patients with hypertension and increased body-mass index are likewise at increased risk of developing severe mitral regurgitation, which might explain the preponderance of this condition in men.[117] Age is a final demographic predictor for the development of severe mitral regurgitation, which is infrequent before the fifth decade of life.[118,119]

On echocardiography, the presence of thickened leaflets, posterior leaflet prolapse, and increased left ventricular dimensions predict a greater risk for development of severe mitral regurgitation.[10,11,120] By contrast, individuals with thin leaflets have a very low risk of developing significant mitral regurgitation.[9,10] In patients without mitral regurgitation at rest, the development of mitral regurgitation during exercise has been associated with progressive disease requiring surgery.[79]

The data supporting medical therapy—and in particular, vasodilators—for severe mitral regurgitation are scant, particularly in asymptomatic patients with normal ejection fractions. In fact, decreases in afterload can shift prolapse earlier in the cardiac cycle, paradoxically worsening mitral regurgitation.[121] Very small trials assessing use of angiotensin-converting enzyme inhibitors in asymptomatic patients with normal ejection fractions have shown statistically significant—although relatively modest—reductions in left ventricular mass and regurgitant volumes;[122,123] however, clinically relevant endpoints have not been adequately studied. Furthermore, findings of a recent study in animals suggest that angiotensin receptor blockers may be harmful and might actually exacerbate the deleterious effects of severe mitral regurgitation on left ventricular volumes and contractile function.[124] Additionally, there is a theoretical concern that vasodilators could further mask left ventricular dysfunction and delay mitral valve surgery.[125,126] Therefore, vasodilator therapy is not recommended for the treatment of asymptomatic patients with severe mitral regurgitation and normal left ventricular function.[115]

Timing of surgery

Valve surgery is clearly warranted for patients with symptomatic severe mitral regurgitation, and those who are asymptomatic but have left ventricular enlargement (end-systolic diameter >45 mm) or even mildly reduced systolic function (ejection fraction <60%).[52] Additionally, severe mitral regurgitation accompanied by atrial fibrillation or pulmonary hypertension carries an AHA/ACC Class IIa recommendation for valve surgery (table 3).[52] Mitral valve repair offers several important advantages compared with valve replacement, including lower operative mortality, better long-term survival, lower risk of thromboembolic events or significant haemorrhage, and improved post-operative left ventricular systolic function.[127,128]

The management of asymptomatic patients with preserved left ventricular function remains controversial. However, there is a trend to operate on patients with severe mitral regurgitation at increasingly earlier stages of the disease process. The rationale for aggressive surgical therapy stems from the high success rate and the durability of surgical repair, as well as an expanding body of work that demonstrates improved clinical outcomes with early intervention, irrespective of

	ACC/AHA class
Acute mitral regurgitation in which repair is likely	I
Symptomatic mitral regurgitation with normal LV function and dimensions	I
Mild-moderate LV dysfunction or dilatation, regardless of symptoms	I
Asymptomatic patients, normal LV, with atrial fibrillation	IIa
Pulmonary hypertension (>50 mm Hg at rest, >60 mm Hg with exercise)	IIa
Patients in whom mitral valve repair is likely	IIb
Patients with MVP and refractory ventricular arrhythmias	IIb
Asymptomatic patients, normal LV, in whom repair is unlikely	III

LV=left ventricular. Adapted from ACC/AHA guidelines, reference 52.

Table 3: **Indications for mitral valve surgery in patients with severe mitral regurgitation**

patient symptoms.[129] Occult left ventricular dysfunction frequently predates symptoms in patients with severe mitral regurgitation; this dysfunction may be permanent and has been shown to confer a worse prognosis after valve repair.[130,131] Thus, the medical management of patients with prolapse and severe mitral regurgitation demands vigilant monitoring so that surgical repair may be optimally timed.

In the mid-1990s, Enriquez-Sarano and colleagues[130] found that patients with an ejection fraction of less than 60% or an end-systolic diameter of greater than 45 mm had an increased risk of postoperative left ventricular dysfunction. These findings are reflected in the current ACC/AHA guidelines published in 1998. More recent work[132,133] corroborated these findings, but set a more aggressive threshold for left ventricular systolic diameter at 40 mm. In the latter study, 14% of patients with normal ejection fraction and left ventricular systolic diameter of greater than 40 mm developed postoperative left ventricular dysfunction. Yet, even in this study, seven of 115 patients with normal preoperative ejection fraction and left ventricular size incurred postoperative left ventricular dysfunction. Thus, additional tools are still needed to detect latent left ventricular contractile dysfunction.

One readily available strategy is stress echocardiography in patients with severe mitral regurgitation. Patients with an inadequate increase in ejection fraction or an increased end-systolic volume with exercise are at higher risk for postoperative left ventricular dysfunction, and may benefit from early surgery.[134] Several evolving, non-invasive techniques may soon refine the diagnosis of occult left ventricular dysfunction. Tissue Doppler, which is used to analyse intrinsic myocardial contractile function, has recently been shown to predict post-operative decline in ejection fraction of more than 10% among asymptomatic patients with severe mitral regurgitation and normal ejection fractions.[135] Myocardial strain, which measures the velocity of systolic contraction, can also be assessed with tissue Doppler and can detect very early myopathic changes.[136] This technology may ultimately provide very early evaluation of latent left ventricular systolic dysfuncton in patients with severe valve disease. Currently, however, it is restricted to research facilities.

Severe mitral regurgitation due to a flail mitral leaflet has been associated with adverse clinical outcomes during medical treatment including the development of congestive heart failure and atrial fibrillation, the need for mitral valve surgery, and death.[92,137] Even asymptomatic patients with flail and preserved left ventricular systolic function have been shown to have a poorer survival when compared to age-matched and sex-matched controls without mitral regurgitation.[137] Thus, early valve repair for the treatment of a flail mitral leaflet may be considered for asymptomatic patients, provided that the valve is repairable and the surgeon is very experienced.

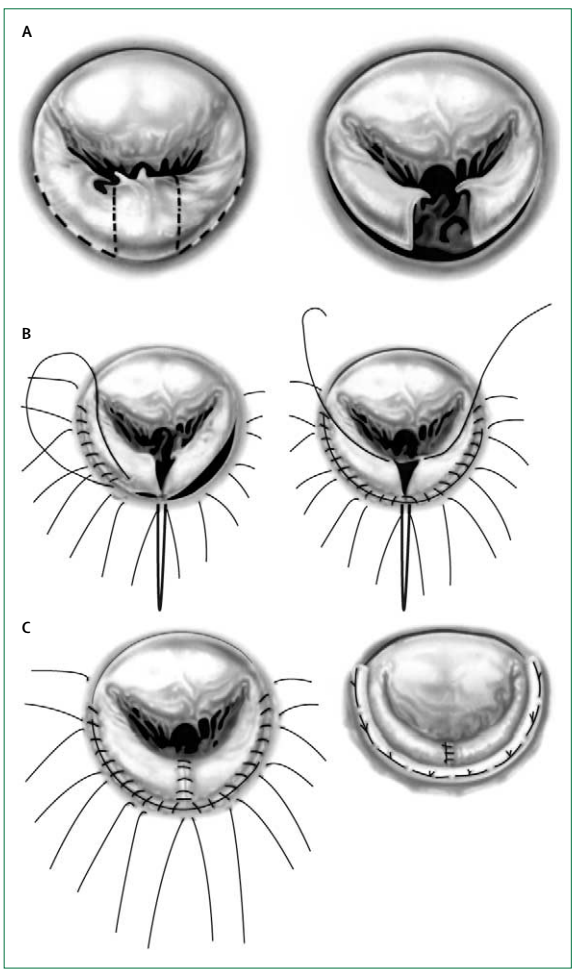

Figure 4: **Mitral valve repair with sliding annuloplasty technique**
(A) Quadrangular section removed from posterior leaflet, remainder of leaflet freed from annulus. (B) Middle scallop re-approximated and sliding repair undertaken by suturing posterior leaflet to annulus, shortening the leaflet. (C) Finally, annuloplasty band applied to reinforce the posterior valve. Reproduced from reference 142 with permission from Elsevier.

Mitral valve repair techniques

The surgical approach, feasibility, and durability of repair are highly dependent on the mechanism of valve dysfunction. Transoesophageal echocardiography can accurately determine which leaflet is involved and, in the setting of bileaflet prolapse, whether significant anterior chordal pathology is present.[59,138] Frequently, more than one segment or scallop is involved, although posterior leaflet dysfunction predominates. A large study assessing patients with transoesophageal echocardiography showed that posterior leaflet prolapse was most common, with defects in the middle scallop (P2) seen in 88% of patients, and middle segment (A2) defects in 65%. The rarest defects were in P1, in 7% of patients, and A1, in 5%.[59] Use of intraoperative transoesophageal echocardiography to determine the mechanism of mitral regurgitation and assess the adequacy of repair has also been associated with improved surgical outcome.[139]

Posterior leaflet prolapse with or without flail has the highest rate of successful repair, with long-term (longer than 10 years) freedom from re-operation rates exceeding 90%.[139–141] Repair usually consists of posterior leaflet quadrangular resection with or without sliding leaflet repair and placement of an annuloplasty ring (figure 4).[142] Flexible (eg, Cosgrove-Edwards and Duran rings) and rigid (eg, Carpentier-Edwards) annuloplasty rings are both widely used. A flexible ring may better preserve normal mitral annular function,[143] but the durability of repair is independent of the type of ring used.[139,144]

Repair of anterior leaflet prolapse is technically more complex and less often feasible than posterior prolapse, although several recent series have reported success rates of 85–90% at a mean follow-up of 3·7–8 years.[145–147] The technique for bileaflet prolapse depends on the extent of the anterior leaflet pathology. In most cases, simply buttressing the posterior leaflet with a standard quadrangular resection and annuloplasty repair will be curative, with long-term success rates reported in excess of 90%.[148] Bileaflet prolapse due to anterior and posterior chordal rupture is rare, occurring in only 5% of patients with degenerative mitral valve disease. Because repair of such valves has only a 40% success rate, mitral valve replacement may be preferable.[139]

Operative risk and durability

In experienced centres, mitral valve repair can be done with an operative mortality of less than 1%.[116,139] Despite the potential presence of residual myxomatous tissue and chordae following valve repair, the rate of reoperation is surprisingly low, with 93% freedom from reoperation at 10 years and 80% at 20 years.[139,149] Compared with mitral valve replacement, repair provides a similar long-term durability and improved long-term survival; life expectancy of patients is similar to that of the general population.[149,150] Repair of anterior leaflet prolapse is associated with a higher risk of reoperation and decreased survival compared with repair of posterior prolapse.[139,149]

Conflict of interest statement

We declare that we have no conflict of interest.

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