REVIEW ARTICLE

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Mitral Valve Prolapse

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MITRAL valve prolapse (MVP) is defined as the billowing of mitral leaflets superior and posterior into the left atrium (LA) during systole. It is currently the most commonly diagnosed cardiac valve abnormality, and progressive degeneration of this valve now represents the primary cause for mitral valve (MV) dysfunction that requires replacement or repair.[1] Although the incidence has varied widely, depending primarily on the mode of diagnosis, in most studies, it was found that approximately 5% of the population has MVP, with a slightly higher incidence in women.[2] In the Framingham study, MVP was found in 17% of women aged 20–29 yr, though in other studies, the incidence rate among women was as low as 2%.[3–5] As noted in a previous review,[6] there is a striking decrease in female prevalence from the third decade on, to as low as a 1% incidence in women in their ninth decade. No such change in male incidence occurs after adolescence. Pini *et al.*[7] suggest that MVP occurs in two phenotypic patterns: first, an anatomic form, characterized by thickened, billowing mitral leaflets, which accounts for progressive valve pathology, and second, a functional form, in which there is dynamic systolic expansion of the mitral annulus. The high incidence of MVP together with the low incidence of progression to severe MV dysfunction that requires repair or replacement prompted Boudoulas *et al.* to stratify patients into two groups at high or low risk for progression. These groups correspond to the anatomic form and the largely functional form of MVP, respectively.[8]

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Pathophysiology, Clinical Features, and Natural History

Anatomic Mitral Valve Prolapse

The form of MVP with the most significant consequences is that associated with myxomatous MVs. It is characterized by weakening of the central pars fibrosa of the valve cusp, which, in turn, allows the cusp to expand and become redundant, whereas the chordae tendinae become elongated. Davies et al.[5] showed that collagen dissolution was present in valves of MVP patients with severe mitral regurgitation (MR). These changes are limited to the posterior leaflet in two thirds of cases, and found on both leaflets in most of the remaining cases. Maximum destruction of the MV occurs around sites of chordal insertion and into the body of the cusp, often resulting in rupture of the chordae and loss of tethering of the leaflet.[9,10]

This anatomic group composes 15–20% of patients with MVP, and represents those who experience progressive valve deterioration and significant MR and those who ultimately require MV replacement.[11] The majority of complications from MVP appear in men after age 45.[11,12] The myxomatous degeneration of the MV results in a characteristic progression from the asymptomatic presence of systolic clicks and murmurs to left-side cardiac chamber dilation, progressive dyspnea, atrial fibrillation, pulmonary edema, and complications, including infective endocarditis (IE) and embolic phenomena. Symptoms and complications among these patients are directly proportional to the degree of valvular pathology.[8] Frequently, this condition is inherited in a characteristic autosomal dominant pattern, with age- and sex-variability in expression.[13] Though not included in Boudoulas' classification *per se,* it is likely that MVP that occurs as part of an inherited group of tissue disorders, such as Marfan or Ehlers-Danlos syndrome, can be classified among this anatomic group. These secondary causes of MVP probably compose less than 5% of all cases (table 1).

In studies from industrialized nations, anatomically based MVP was the most common cause of severe, isolated MR, responsible for 38–64% of all cases.[14,15] The usual history of the patient with an anatomically significant myxomatous valve is that of a very slow (decades) onset of symptoms secondary to a chronically degenerative myxomatous MV. Kolibash *et al.* showed, in their follow-up of 86 patients with severe MR and MVP diagnosed by clinical, surgical, and pathologic findings, that, on average, it was 25 yr from diagnosis of MVP until severe MR developed. Once significant MR developed, MV surgery was required within 1 yr in almost all of the patients.[16]

In the vast majority of cases, MR develops when the chordae tendinae which tether the edge of the valve leaflet, rupture,[9,10] allowing some portion of the valve leaflet to flail. If the regurgitant flow is limited because the flail segment is small, pulmonary venous congestion may be limited, because the LA absorbs the volume. During diastole, the distended LA can fill the left ventricle (LV) more completely. Hemodynamic studies show an increase in the rate and extent of LV early diastolic filling, which increases left ventricular end-diastolic volume and results in greater ventricular ejection. Over time, the LV dilates and hypertrophies to compensate for the increased volume load, with decreases in LV compliance evidenced by rightward displacement of the end-diastolic pressure-diameter curve.[17] As MR progressively worsens because of ongoing chordae rupture and the mitral annular dilation that accompanies LV dilation, further LA and LV dilation will occur. Ongoing ventricular dilation leads to unfavorable loading conditions, with the increased LV radius requiring a greater wall stress for any given systolic pressure.[18,19] As assessed by various measures, LV function deteriorates,[17,20] which decreases the efficiency of ventriculovascular coupling.[17] In addition to ventric-

Table 1. Conditions Associated with Mitral Valve Prolapse

- Cardiac
  - Ostium secundum atrial septal defect
  - Hypertrophic cardiomyopathy
  - Ebstein's anomaly
  - Wolf-Parkinson-White syndrome
  - Tricuspid valve prolapse
  - Coronary artery vasospasm
  - Rheumatic endocarditis
  - Ischemic heart disease
  - Myocarditis
- Connective tissue
  - Marfan syndrome
  - Ehlers-Danlos syndrome
  - Thoracic abnormalities
    - Pectus excavatum
    - Pectus carinatum
    - Straight back syndrome
    - Narrow anterior-posterior chest diameter
    - Scoliosis
  - Pseudoxanthoma elasticum
  - Osteogenesis imperfecta
  - Menkes kinky-hair syndrome
  - Cutis laxa
  - Disorders of the temperomandibular joint
  - Scleroderma/CREST syndrome
- Others
  - Turners syndrome
  - von Willebrand's disease
  - Adult polycystic kidney disease
  - Acromegaly
  - Duchenne's muscular dystrophy
  - Myotonic dystrophy
  - Homocystinuria
  - Fragile X syndrome
  - Graves' disease
  - Mucopolysaccharidoses
  - Anorexia nervosa
  - Systemic lupus erythematosis
  - Relapsing polychondritis
  - Polyarteritis nodosa

Collated from various sources.

ular dysfunction, the chronically distended LA is at increased risk of fibrillation.

A factor that contributes to the variability in the onset of symptomatic failure and to the severity of symptoms may be the amount of systemic hypertension. Increased systemic vascular resistance (SVR) will worsen regurgitant flow into the LA, and increased intraventricular pressure will increase stress on the chordae tendinae, hastening their rupture and the consequent hemodynamic deterioration.[21] Whereas small, incremental increases in regurgitant flow may permit gradual compensatory increases in LA and LV size, primary chordal rupture in the setting of systemic hypertension may result in the acute decompensation sometimes seen with MVP-associated MR.

Acute and chronic MR with associated LV dysfunction are well-known causes of pulmonary hypertension. Patients with MVP that progresses to require MV surgery typically have pulmonary artery (PA) pressures greater than 30 mmHg, with moderately depressed cardiac indices (table 2).[22–24] In studies, it was found that even in the presence of preserved LV systolic function, chronic MR is associated with pulmonary hypertension (usually mild) in as many as 76% of cases.[25] In the presence of MR, right ventricular performance deteriorates with an increase of PA pressure,[26] and deterioration in right ventricular ejection fraction was proposed as a useful predictor of progressive deterioration in cardiac function.[27]

In multiple long-term follow-up studies of MVP patients, it was found that a variety of complications occur in the subgroup of patients with anatomic disease. Patients with hemodynamically significant MR are those at greatest risk for endocarditis and arrhythmias, in addition to being the most likely to require MV surgery.[28]

Table 2. Comparison of Preoperative Hemodynamic Data from Three Studies of Patients with Mitral Valve Prolapse Requiring Surgical Correction

Measured	Yacoub *et al.*[22]	Salomon *et al.*[24]	Old *et al.*[23]
PAP	31	34.3 ± 12.4	36
PCWP	18–20	22.6 ± 7.6	21
CI	NA	2.1 ± 0.6	2.3
LVEDP	NA	15.3 ± 5.9	16.6

Data are average values, with standard deviations when available.

PAP = mean pulmonary artery pressure (mmHg); PCWP = pulmonary capillary wedge pressure (mmHg); CO = cardiac output (l/min); CI = cardiac index (l/min per m^2); LVEDP = left ventricular end-diastolic pressure (mmHg); NA = not applicable.

In Düren *et al.*'s long-term prospective follow-up of 300 patients with idiopathic MVP diagnosed by cineangiography or transthoracic echocardiography (TTE) (with a mean age of 42 yr and an average follow-up of 6 yr), 50% of patients had a stable course, except for supraventricular tachycardia and mild MR. Of the remaining 150 patients, three suffered sudden death, ventricular fibrillation developed in 2, ventricular tachycardia in 56, and IE in 18, while 28 underwent MV repair, 11 suffered cerebrovascular accidents, and 8 suffered from severe MR.[29] The high incidence of complications in this study probably represents significant referral bias, with overrepresentation of highly symptomatic patients.

In a retrospective study of 456 patients with MVP, Marks *et al.*[11] compared those with and those without thickened and redundant MVs diagnosed by TTE. They found that those with thickened and redundant valves had an increased risk of IE, MR, and MV repair. There was, however, no increase in the incidence of cerebrovascular accident.[11] Finally, Nishimura *et al.*[30] conducted a prospective study of 237 minimally symptomatic MVP patients with an average age of 44 yr during a mean follow-up period of 6 yr. They found that the presence or absence of redundant MV leaflets was the only variable associated with sudden death. Of this group, 10 patients suffered cerebrovascular accidents, 3 experienced IE, and 17 underwent MV replacement. They also found that an LV end-diastolic diameter of greater than 60 mm was the best TTE predictor of the subsequent need for MV replacement. Notably, of the 20 patients diagnosed solely by TTE without auscultatory findings of MVP, none went on to have complications during follow-up. Overall mortality among this group equaled that of the general population; but, again, these patients were selected to be free of symptoms or minimally symptomatic.

Mitral Valve Prolapse—The Syndrome

The disappearance of MVP with aging, particularly in women, could mean that a largely functional form of the disease occurs in which factors other than valve structure *per se* may be important. Therefore, Boudoulas describes a second classification of MVP as the "syndrome." Much evidence has been established linking MVP to the variable relation between LV size and mitral annulus size.[31] These findings suggest that prolapse results as LV size is sufficiently decreased, or that as LV shape is sufficiently altered, maintenance of normal leaflet coaptation during systole is impossible.[32] A larger mitral leaflet and annulus in relation to body size in normal women may contribute to more consistent expression in this population. A decreased LV volume is the likely cause of the high incidence of MVP in secundum-type atrial septal defect[33] and in anorexia nervosa, which generally results in a decrease in LV size. Repair by surgery in atrial septal defect and weight gain in anorexia were shown to predictably eliminate MVP.[34,35]

Patients with clinically evident MVP syndrome often have symptoms that include chest pain, palpitations, arryhthmias, fatigue, dyspnea, and autonomic imbalances that manifest as postural phenomena, which include syncope and pre-syncope. The chest pain of MVP often has been described as atypical for angina pectoris, being left precordial, sharp, cyclic, unrelated to exertion, and unrelieved by nitroglycerin.[36] Proposed etiologies of this chest pain are excessive stretch on chordae tendinae causing focal areas of decreased subendocardial blood flow, and coronary vasospasm, microembolism to the coronary circulation, decreased diastolic perfusion with tachycardia and increased inotropy, and esophageal motility disorder.[8,37–40] Patients with MVP documented by echocardiography, along with the patients' first-degree relatives, had no greater incidence of chest pain, palpitations, or dyspnea than patients without MVP who were referred for evaluation of these symptoms.[2,41] Nevertheless, the presence of MVP was associated with auscultatory clicks and murmurs, thoracic bony abnormalities, decreased blood pressure, and palpitations.[2] Although an association also was suggested between panic disorder and MVP, the majority of recent studies conclude that panic disorder, which is diagnosed in 5% of the population, and MVP are two common disorders that frequently coexist.[42,43]

Studies show a variety of adrenergic abnormalities in the MVP syndrome. These include an increase in symptoms with isoproterenol infusion, an increase in urinary epinephrine and norepinephrine in symptomatic patients, "supercoupling" of β-adrenergic receptors, and β-adrenergic hypersensitivity.[44–46] Whether such increased β-adrenergic sensitivity can account for decreased ventricular dimensions is unknown, and other studies fail to find any autonomic difference between MVP patients and control subjects.[47–49]

Though patients with MVP "syndrome" compose the majority of patients with MVP (80%), they have significantly fewer complications than those with the anatomic variant. The majority of these patients are young women with symptoms referable to autonomic regulation abnormalities, which ultimately appear to resolve spontaneously.

Diagnosis of Mitral Valve Prolapse

Clinical Examination

The presence of a non-ejection systolic click with or without a late systolic murmur describes the auscultatory diagnosis of MVP, regardless of etiology.[50] The click is usually mid-to-late systolic, with a murmur either absent, late-systolic, or, as is often the case in the severe anatomic form, pansystolic. When valve function deteriorates and progresses to severe MR, the click may disappear. The physical examination and history may reveal an S3 gallop, rales, dyspnea, and fatigability and other symptoms of congestive heart failure that imply more severe or advanced disease. In a minority of patients, the examination may reveal bony or other connective tissue abnormalities characteristic of the various disorders listed in table 1.

Echocardiography

By providing clear, noninvasive images of the structure and function of the MV, two-dimensional echocardiography is invaluable in the evaluation of MVP. The clinical diagnosis of MVP is confirmed by echocardiographic demonstration of displacement of the mitral leaflets from their normal position or relation to surrounding structures. In cases of pure prolapse, there is posterior systolic motion of the continuously juxtaposed MV leaflets behind the line that connects the valve's closure and opening points (the C-D line), as indicated in figure 1.[12] Generally accepted criteria require a posterior systolic motion of at least 2 mm in late systole, or at least 3 mm for holosystolic prolapse.[51]

The original TTE criteria for MVP diagnosis were based on the parasternal view that produces a long-axis image of the LV in the antero-posterior plane. Leaflet displacement above the mitral annular hinge points in this plane and into the LA correlates with angiographic prolapse.[52] Later, the apical four-chamber view also was used in the diagnosis of MVP, because this image runs perpendicular to the mitral leaflets and facilitates imaging of the annulus. However, as compared with the parasternal long-axis view, use of the apical four-chamber view in MVP diagnosis resulted in positive findings in a surprisingly high percentage (as much as 34%) of individuals who carry none of the auscultatory

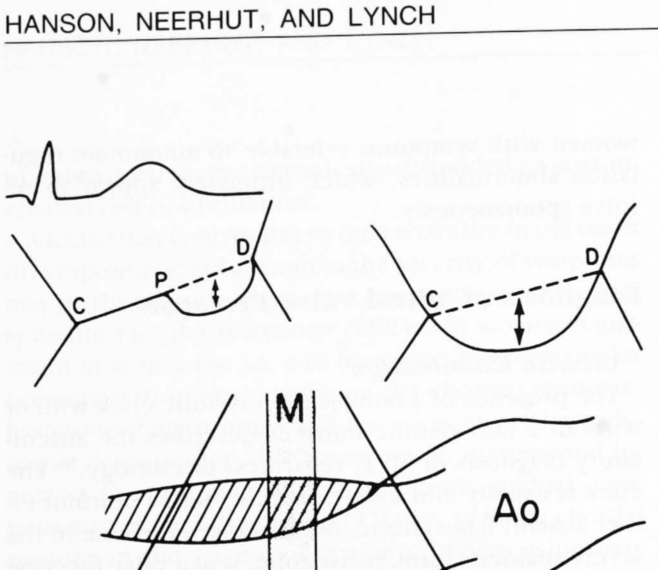

Fig. 1. Schematic diagram of currently accepted echocardiographic criteria for diagnosis of mitral valve prolapse. *Top.* Two-dimensionally targeted M-mode recordings of continuous mitral leaflet interfaces show (*top left*) late systolic prolapse, with prolapse beginning in mid-systole (*P*) and characterized by at least a 2-mm posterior displacement of leaflets behind the valve's C-D line and confirmed by demonstration of leaflet billowing in the two-dimensional parasternal long-axis view. *Bottom.* Two-dimensional, parasternal long-axis view showing systolic billowing of mitral leaflets (*arrows*) into the left atrium (*LA*), a motion the posterior component of which may be detected by the vertically oriented M-mode beam (*M*). Hatched areas indicate muscular walls of left ventricular myocardium, and dotted lines show normal position of mitral leaflets and annulus. Ao = aorta; LV = left ventricle. Reprinted with permission from R. B. Devereux *et al.*: Mitral valve prolapse: Causes, clinical manifestations and management. Ann Intern Med 1989; 111:305–17.

signs of MVP.[53–55] The explanation for this apparent inconsistency appears to lie in the shape of the MV annulus, which is not planar but "saddle shaped" (fig. 2).[56] As a result, the annulus is farthest from the LV apex in its anterior and posterior portions, seen on the parasternal long-axis view. In contrast, the apical four-chamber image passes through the annulus at its medial and lateral limits, where the annulus is closest to the LV apex. Viewed from this plane, the mitral leaflets may appear to be displaced toward the LA chamber, beyond a line connecting the points of annular attachment, consistent with the criteria for MVP. Based on this understanding, a diagnosis of MVP should be made using two-dimensional TTE only when there is evidence of systolic billowing of leaflets in the parasternal long-axis view.

In addition to the MV bulging into the LA, common echocardiographic features of MVP are increased leaflet thickening, elongated leaflets, and larger annular diameters compared with findings in healthy patients.[57]

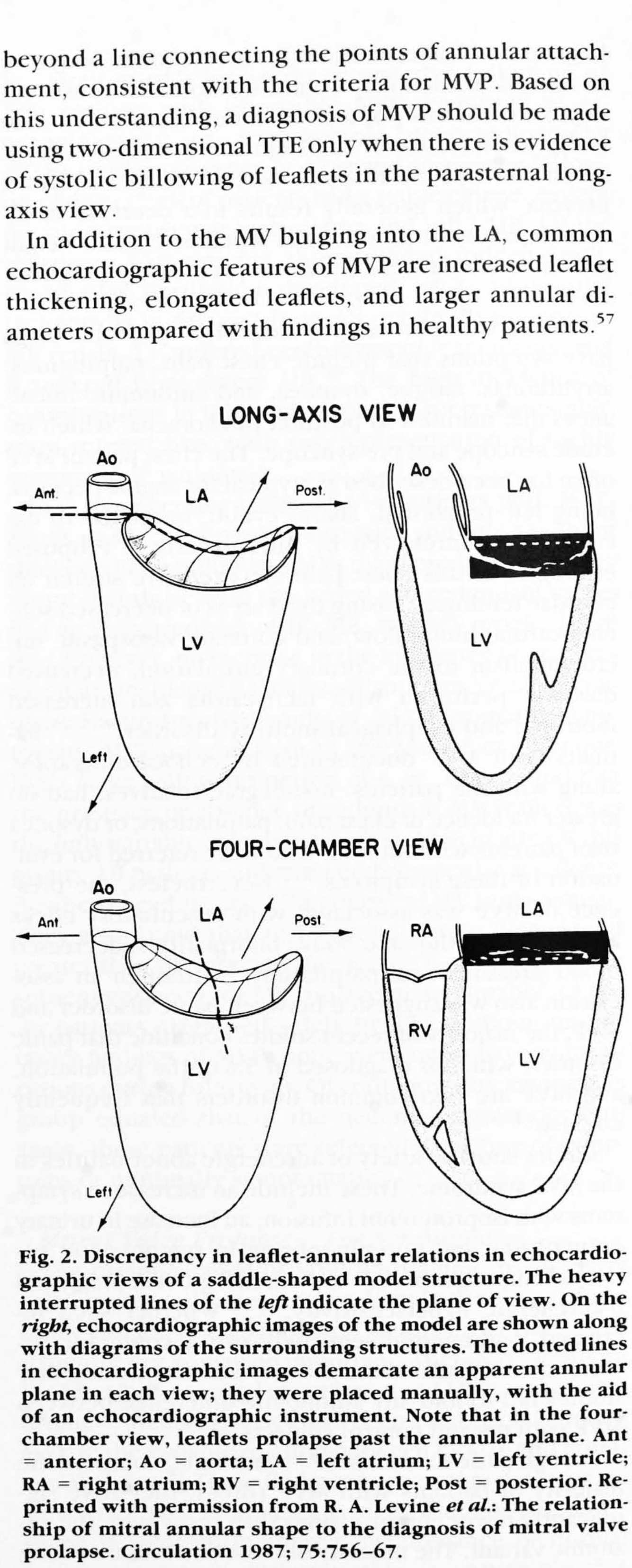

Fig. 2. Discrepancy in leaflet-annular relations in echocardiographic views of a saddle-shaped model structure. The heavy interrupted lines of the *left* indicate the plane of view. On the *right*, echocardiographic images of the model are shown along with diagrams of the surrounding structures. The dotted lines in echocardiographic images demarcate an apparent annular plane in each view; they were placed manually, with the aid of an echocardiographic instrument. Note that in the four-chamber view, leaflets prolapse past the annular plane. Ant = anterior; Ao = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; Post = posterior. Reprinted with permission from R. A. Levine *et al.*: The relationship of mitral annular shape to the diagnosis of mitral valve prolapse. Circulation 1987; 75:756–67.

In patients with severe MVP whose disease has progressed to include significant MR, there is greater lengthening of the posterior leaflet, more abnormal leaflet motion, greater annular dilation, and thicker mitral leaflets compared with MVP patients without MR.[57] The presence of leaflet thickening could not be used to differentiate these groups. The presence of ruptured chordae tendinae that results in leaflet flail is a frequent finding in patients whose MVP has progressed to the point of requiring surgical correction.[9]

Regurgitant flow through the incompetent MV can be envisioned readily using Doppler color flow analysis available on most echocardiography instruments. Whereas the area of the color jet has been shown to be proportional to the regurgitant volume determined angiographically,[58] the image is extremely sensitive to instrumentation settings and to the transvalvular pressure gradient,[59] orifice size, and compliance of the receiving chamber.[59–61] When a portion or all of the edge of a single mitral leaflet is flail, as is typical in MVP, the resulting systolic flow jet is directed to the opposite side of the atrium in 93% of cases.[62] Such eccentric flow jets may course along the atrial wall, and although their estimated image area is useful to characterize the nature of the regurgitation, they may underestimate the volume of regurgitant flow.[63] Because so many factors affect the Doppler color flow jet area, it may be a relatively unreliable indicator of the severity of MR, although under equivalent hemodynamic conditions in the same patient, it may provide an accurate assessment of changes in regurgitant flow. Two additional color Doppler flow measurements were developed to improve estimation of MR severity. Acceleration of systolic blood flow from the LV through the regurgitant orifice may provide a relatively independent measure of flow.[64] Pulmonary venous flow during systole, which may actually reverse during severe MR, also may prove extremely useful in judging severity,[65–68] although care is required to examine flow in the right and left pulmonary veins.[69]

Severe prolapse, redundancy, and thickening of the MV can make diagnosis of flail segments difficult, from the transthoracic approach. The close proximity of the esophagus to the posterior wall of the LA provides an excellent image of the MV apparatus by transesophageal echocardiography (TEE), whereas TTE images may not be of equivalent quality in this area because of the attenuation of echo signals by calcified mitral leaflets or annular components. Regardless of the quality of the TTE study, TEE can provide superior images of MVP with ruptured chordae tendinae, which permits more detailed definition and color flow Doppler analysis of central or eccentric regurgitant jets.[70] Jets of regurgitant flow imaged by TEE generally are larger than those seen with TTE, which may lead to an inappropriate overestimation of the severity of a regurgitant lesion.[71] Transesophageal echocardiography findings associated with more severe MVP/MR are listed in table 3.[72]

Mitral Valve Prolapse-related Complications

Mitral Valve Prolapse and Embolism

In 1976, Barnett *et al.*[73,74] described an abnormal prevalence of MVP in patients younger than age 45 yr with focal or generalized neurologic deficits, and later reconfirmed this association. Fibrin-platelet emboli formation present on roughened MV leaflet surfaces was suggested as the culprit.[12] Although MVP is clearly a relative risk factor for embolic events in younger age groups with no other risk for cerebrovascular disease, evidence for other age groups is equivocal.[75] The presence of atrial fibrillation is a separate risk factor that

Table 3. Transesophageal Echocardiography Findings in Severe Mitral Regurgitation

- Color flow detection
  - Jet area wide
  - Jet hugs LA wall
  - Jet enters LA appendage
  - Jet enters pulmonary veins
  - Jet circles LA
  - Proximal acceleration signals
  - Large jet crossing MV defect
- Pulsed and continuous wave Doppler
  - Systolic reversal in pulmonary venous pulsed Doppler flow
  - Increased pulsed Doppler signal of mitral inflow
  - Left ventricular outflow and transaortic flow velocities are decreased
  - Density of continuous wave Doppler jet is increased
  - V-wave cut-off of MR jet
- Two-dimensional ECHO
  - LA dilated
  - Exaggerated systolic expansion of LA
  - Interatrial septum bulges L → R
  - LV spherical enlargement
  - Hyperdynamic LV contraction
  - No spontaneous contrast in LA
  - Spontaneous contrast in aorta
  - Ruptured papillary muscle, chordae or flail leaflets on MV
  - RV enlargment

Summarized from Schiller *et al.*[72]

definitely increases the risk of thromboembolism[76] and, as noted previously, frequently occurs in those with MVP-related MR.

Infective Endocarditis and Antibiotic Prophylaxis

Mitral valve prolapse is reported to be the most common cause of IE in this country, responsible for 11–29% of all cases. Infective endocarditis begins on the surface of the cusps in myxomatous valves, an area of abnormal friction and fibrin deposition.[5] Risk factors for IE are the presence of MR, a systolic murmur, valvular redundancy, male gender, and age greater than 45 yr.[15,30,77,78]

The issue of prevention of IE is the subject of a recent review.[79] The most recent American Heart Association recommendations attempt to clarify issues that concern the use of antimicrobial prophylaxis in patients with MVP, clearly stating that antibiotics should be used *only* in the presence of a systolic murmur. Consequently, patients with a history of only MVP syndrome or a midsystolic click without echocardiographic evidence of MVP are at low risk for endocarditis and should not receive prophylactic antibiotic therapy. The risk of death from an anaphylactic reaction to parenteral antibiotics is probably greater than any risk of endocarditis in patients with isolated MVP.[80] These recommendations, however, fail to provide guidance in situations where patients have intermittent or end-systolic murmurs or in those cases where MR is only an echocardiographic diagnosis. Whereas conservative therapy would suggest prophylactic antibiotic administration to any patient who has a murmur at the time of examination when warranted by the surgical procedure, the potential risk and cost of such therapy and the lack of clearly demonstrable efficacy are noteworthy.

The American Heart Association guidelines of indications and regimens for endocarditis prophylaxis highlight several important points.[81] First, prophylaxis continues to be aimed primarily at α-hemolytic streptococci (viridans) in dental and airway procedures, and at group D streptococci (enterococcus) in genitourinary and gastrointestinal procedures. Although it is sufficient to use oral antibiotics as prophylaxis during dental and airway procedures, gastrointestinal and genitourinary procedures still warrant *two intravenous antibiotics* in most situations. Antibiotic prophylaxis is not necessary for oral endotracheal intubation or fiberoptic bronchoscopy, but is probably indicated for nasal endotracheal intubation. Similarly, the failure to reproducibly observe bacteremia during TEE suggests that antibiotic administration is unnecessary, if that is the sole indication.[82,83] Finally, differences exist between the use of antibiotics in routine *versus* complicated vaginal delivery, recognizing that one cannot predict which pregnancies will become "complicated."

Mitral Valve Prolapse and Arrhythmias

Arrhythmias most commonly associated with MVP are nonspecific, the origin being both supraventricular (sinus tachycardia, atrial fibrillation and flutter, and junctional tachycardia) and ventricular (premature ventricular beats [PVC] or nonsustained or sustained ventricular tachycardia). The resting electrocardiogram (ECG) shows repolarization abnormalities (particularly T-wave inversion in the inferior leads) in many subjects.[84–86] However, in the Framingham study, ST-T wave changes and QT changes were found to be no more common on 12-lead ECGs in the MVP group than in the general population.[41] The observed increase in ventricular arrhythmias on 24-h ambulatory ECG in MVP patients has not been reproduced in other studies,[87] and an increased incidence of inducible arrhythmias does not appear to be a consistent finding.[84,88,89] Complex ventricular arrhythmias monitored by 24-h ambulatory ECG recording were reported in 45% of middle-aged patients with MVP (average age: 47 yr), being more frequent in older patients who had posterior MV displacement and LA and LV chamber enlargement.[90] Consequently, in those older patients with MVP, MR, and ECG abnormalities, the incidence of life-threatening arrhythmias may be greater.[84,91] Multiple etiologies were postulated to explain the reported increase in arrhythmias in MVP. In 14 autopsies of patients with MVP who suffered sudden death, Chesler *et al.* found 11 of 14 hearts to have endocardial lesions, which presumably indicated electrically irritable foci. Microemboli from the posterior cusp recess that proceeded into the coronary circulation also were implicated.[92] The traction applied to papillary muscles as the MV stretches abnormally into the LA also was proposed as a mechanism for repolarization abnormalities and arrhythmias.[93] In addition to arrhythmias, conduction abnormalities are not uncommon in patients with MVP. In comparison with a similarly symptomatic control group (syncope and documented sustained arrhythmias), MVP patients have a greater proportion of dual AV nodal pathways and functional (rate-dependent) bundle branch block, as well as tachycardia-bradycardia syndrome.[94]

Certain risk factors for sudden death were delineated in MVP patients. Hemodynamically significant MR with MVP increases the risk of sudden cardiac death 50–100 times. A history of syncope, abnormal ECG, family history of sudden death, and a markedly myxomatous valve also are clear risk factors, though all are less important than significant MR.[5,95] Sudden death in MVP is most likely in those patients with hemodynamically significant MR, and it is likely that this risk is more strongly related to the hemodynamic and arrhythmic consequences of MR than to MVP itself.[96]

Mitral Valve Prolapse in Obstetric and Pediatric Populations

Obstetric

Though limited information exists about MVP during pregnancy, based on available data, the auscultatory findings and hemodynamic manifestations of MVP tend to dissipate with the onset of the second trimester. The likely mechanism of this is an increase in the intravascular volume in the parturient. This results in an increase in the relative dimensions of the LV to the MV annulus, decreasing the degree of prolapse into the LA, despite the decreased SVR associated with pregnancy.[97] Physical examination findings also may be masked by the systolic ejection murmur commonly found during pregnancy.[98]

Pediatric

Mitral valve prolapse is the most common cardiac disease in childhood; however, its prevalence may be overestimated by single plane echocardiography.[53,99] The clinical course is benign, at least during childhood and adolescence.[99,100] Bisset *et al.*,[99] in their follow-up of 119 children with MVP diagnosed by physical examination (mean follow-up of 6.9 yr), found no progression of mitral insufficiency, no sudden deaths, and one case each of cerebrovascular accident. Interestingly, they found that 63% of the children's ECGs were abnormal (many PVCs), with 48% of all ECGs showing T-wave inversion in the inferior leads.

Anesthetic Management

Preoperative evaluation of patients with MVP should focus on identification of those patients with purely functional disease *versus* those with significant degeneration of a myxomatous valve and associated hemodynamically significant MR. In addition to a previous diagnosis of MVP, historical features of note include the presence of a murmur at any time in the past, symptoms of dyspnea on exertion, fatigability, chest pain, palpitations, stroke, and a history of IE. Functional MVP most often will be present in younger (aged <45 yr), typically female patients with a history of palpitations and atypical chest pain, who on examination have a systolic click with or without a late systolic murmur. This group may be taking β-adrenergic blocking medications to control palpitations, agents that should be maintained through the perioperative period. The presence of MVP uncomplicated by other symptoms is probably not sufficient reason to obtain a preoperative ECG or chest roentgenogram. Although the ECG may frequently show PVCs or repolarization abnormalities, there is no evidence that these findings will predict intraoperative problems. Multiple case reports suggest an association between MVP and intraoperative arrhythmias[101,102]; however, no clear mechanistic pathway has been established, and outcome has not been altered consistently. Prudence would suggest optimization of preoperative serum electrolytes to reduce the risk of intraoperative arrhythmias.[87] Likewise, in the absence of a prior history of MVP, finding an isolated systolic click in the absence of other symptoms probably does not warrant cardiologic evaluation.

Those with the anatomic variant of MVP will usually be older, predominantly male patients, who may be in varied states of health depending on the progression of the disease. Although disease may only be evident on auscultation, many of these patients may have symptoms varying from mild to severe congestive heart failure, including exercise intolerance, orthopnea, and dyspnea on exertion. Such patients may require treatment with a host of medications, which include diuretics, digoxin, and angiotensin-converting enzyme inhibitors. Physical examination reveals a mid-to-holosystolic murmur and possibly an S3 gallop with signs of pulmonary congestion, and echocardiographic study reveals a myxomatous, regurgitant MV. Whereas the patient with MVP syndrome or one early in the course of anatomic MVP will often be seen preoperatively for a variety of procedures without evidence of overt disease, those with longstanding anatomic MVP usually will be readily identifiable, as when they arrive for MV surgery. Premedication in both isolated MVP and anatomic variant MVP should produce anxiolysis without causing excessive tachycardia, which may reduce ventricular volume and possibly worsen valve prolapse and regurgitation.

Mitral Valve Prolapse Syndrome

Symptoms referable to MVP syndrome frequently occur in the setting of decreased left ventricular filling; a moderate fluid challenge was shown to reverse echocardiographic evidence of MVP.[103,104] Likewise, "light" anesthesia with associated vasoconstriction decreases LV emptying and increases LV volume, which will reduce disproportion between MV annulus and LV size and ideally reduce prolapse. However, increased sympathetic tone and catecholamine release will increase contractility, which itself can worsen prolapse and aggravate arrhythmias. Modest doses of opioids and β-adrenergic blockers may be used to minimize these undesirable effects.[105] For treatment of perioperative arrhythmias, intravenous magnesium sulfate also may be useful.[106] Digoxin is not an appropriate choice for MVP-related arrhythmias, and may contribute to malignant ventricular arrhythmias.[107]

Although in Doppler echocardiographic studies, a minority of patients with MVP had mild diastolic filling impairment, the majority have normal LV function.[108,109] Patients with isolated MVP (lacking MR and coronary artery disease) and dyspnea or chest pain also were found to have normal LV hemodynamics.[110] Consequently, the volatile anesthetics should be well tolerated by these patients. In addition, the myocardial depressant properties of these agents may be advantageous, offsetting their mild to moderate vasodilating properties, which would decrease LV volume (and increase MVP). In particular, halothane may reduce myocardial contractility while causing modest arterial vasodilation, but these possibly beneficial effects must be weighed against the potential for increased cardiac arrhythmias in these patients with a possible increase in sympathetic tone.[111] There is no clinical evidence to contraindicate the use of neuraxial blockade in the patient with MVP syndrome. Although the loss of sympathetic tone to the myocardium may be beneficial, the decreased SVR may still lead to excessive ventricular emptying, greater leaflet prolapse, and possible regurgitation. This latter effect should be overcome by appropriate repletion of intravascular volume beforehand. Unfortunately, no clinical studies have been performed to document altered perioperative course or outcome depending on the management of this group.

Anatomic Mitral Valve Prolapse and Mitral Regurgitation

Intraoperative management of patients with anatomic MVP associated with significant MR will contrast sharply with that of patients with MVP syndrome in terms of anesthetic, pharmacologic, and volume management. In addition, anesthetic management depends largely on the patient's degree of MR. The historical and physical examination findings noted earlier in this section and the echocardiographic and hemodynamic characteristics listed in tables 3 and 4 provide criteria to determine the severity of disease.[72,112] Factors that determine regurgitant flow in MR are the systolic pressure gradient between the LV and LA, the size of the mitral orifice, and the duration of ventricular systole; hence, the classic advice of "faster, fuller, vasodilated" when describing management.[113] Vasodilator therapy with a variety of agents improves forward output in those patients with severe MR.[114–117] However, because patients with MR generally find symptoms of pulmonary congestion more objectionable than those of decreased systemic perfusion, they typically have undergone vigorous diuretic therapy that results in an intravascular volume deficit[118] that becomes manifest when vasodilators and anesthetics are superimposed.[119] Therefore, like patients with MVP syndrome, those with the anatomic MVP variant may benefit from an initial fluid challenge, administered with caution because of the risk of pulmonary congestion and ventricular over-distention.[115]

Vasoconstriction, as would be associated with "light" anesthesia, augments MR in anatomic MVP and can profoundly worsen hemodynamics.[119–121] Unfortu-

Table 4. Hemodynamic and Angiographic Indicators of Severe Mitral Regurgitaton

V-waves > twice the mean LA or PCWP (absence of prominent V-waves does not rule out severe MR) (V-waves significantly affected by SVR)
Failure to increase CO in response to exercise (*i.e.*, ≤80% predicted CO)
PCWP or LAP increases with exercise (≥35 mmHg)
Profound opacification (4+) of the LA during angiography
Regurgitant fraction >60% (RF <20% is mild)
Poor left ventricular function
LVEDP which is 8–10 mmHg lower than LAP or PCWP

PCWP = pulmonary capillary wedge pressure; MR = mitral regurgitation; LAP = left atrial pressure; LVEDP = left ventricular end diastolic pressure; CO = cardiac output; LA = left atrium; Regurgitant fraction = (total stroke volume − forward stroke volume)/total stroke volume; SVR = systemic vascular resistance.

Summarized from Grossman.[112]

nately, when modest to severe depression of LV function accompanies significant MR, deep levels of anesthesia may not be tolerated. Given the myocardial depressant effects of barbiturates,[122–126] their use for anesthetic induction may be contraindicated in this setting. Propofol appears to have more modest intrinsic myocardial depressant actions at clinical concentrations.[124,126–128] Although propofol causes a decrease in SVR,[124,129] which may maintain or improve forward LV ejection, its potential for decreasing preload[123] and depression in sympathetic outflow[130] may cause a depression in cardiac output. In this case, opioid anesthesia has proven valuable in providing adequate analgesia without significant myocardial depression. Fentanyl, sufentanil, and alfentanil all have been used with modest doses of various volatile agents with similar efficacy.[131,132] In addition, these agents can be used for induction of anesthesia. The combination of opioids and benzodiazepines was noted to cause profound decreases in blood pressure. Although this effect appears strictly to be due to loss of sympathetic tone,[133] it may result in profound myocardial depression in patients whose hearts receive substantial sympathetic stimulation. Etomidate causes minimal cardiac depression,[126,134] hemodynamic change,[124] or alteration in sympathetic tone,[130] and may be the best alternative in the face of severe dysfunction.[135] The use of ketamine traditionally has been discouraged in MVP because of its sympathomimetic actions increasing vascular resistance and worsening regurgitant flow. In the catecholamine-depleted patient with severe cardiac dysfunction and MVP/MR, ketamine occasionally may induce hemodynamic collapse.[136,137]

For the patient with hemodynamically significant MR, higher levels of volatile agent (especially enflurane and halothane) are not likely to be well tolerated because of clear depression of myocardial function during systole and early diastole.[111,138–140] Though smaller concentrations (~0.5 minimum alveolar concentration) of isoflurane, desflurane, or sevoflurane may decrease the regurgitant fraction because of their vasodilatory properties and minimal cardiac depression, this effect cannot be relied on. Potent vasodilators such as sodium nitroprusside, hydralazine, and nitroglycerin may be titrated carefully to maximize forward cardiac output.[114,116,141–143]

In the presence of adequate hydration, vasodilators have the added benefit of reducing left ventricular end-diastolic volume and pressure and decreasing cardiac oxygen demand, all of which become important considerations in the setting of coronary artery disease.[114] In patients with chronic MR who have elevated PA pressure and pulmonary vascular resistance, nitrous oxide may cause a further increase in pulmonary vascular resistance and thereby reduce right ventricular ejection.[144] Table 5 is a summary of the predicted effects of many commonly used anesthetic agents in the presence of MV disease. In the presence of isolated MVP, there are no clinical data to support the use of one neuromuscular blocking agent over another,[145] although the more profound hemodynamic alterations caused by a vagolytic/sympathomimetic agent (gallamine or pancuronium) or histamine-releasing agent warrant consideration.

In a patient with significant anatomic MVP, the hemodynamic consequences of neuraxial blockade depends on the degree to which sympathetic tone augments myocardial contractile performance and compensates for cardiac dysfunction. When preliminary loading of the vascular volume is adequate, loss of sympathetic tone may be well tolerated in cases of modest to moderate dysfunction, because the decrease in SVR will maintain cardiac output despite decreased myocardial contractility.

Preoperative evaluation should also distinguish between acute and chronic MR. Acute MR as a result of primary chordal rupture occurs most commonly in the setting of anatomic MVP.[9,10] When acute or subacute onset of massive MR occurs in the presence of a noncompliant LA, significant increases in pulmonary capillary occlusion pressure and PA pressure occur.[146] Such acute MR leads to sudden LV dilation, with an initial increase in stroke volume, and increases in the rate and extent of early diastolic filling secondary to an increase in the transmitral pressure gradient.[147,148] Symptoms of pulmonary congestion generally arise in this setting from excessive LA and pulmonary venous pressures, not from LV failure. This group of patients will benefit most from interventions to decrease afterload until surgical repair is possible, and, from an anesthetic standpoint, they should be considered as having severe MR.

For intraoperative monitoring of patients with hemodynamically significant MR who are undergoing major surgery, a PA catheter typically is used. Particular attention is paid to the presence of a ventricular wave (V wave) when the PA catheter is wedged, reflecting regurgitant flow into the LA and pulmonary veins. However, the V wave will be of most value in patients with acute MR, in which the LA has not had a sustained period to enlarge and increase its compliance. A sub-

Table 5. Predicted Effects of Commonly Used Anesthetic Agents in the Presence of Varying Degrees of Mitral Valve Prolapse

	Predominant Cardiovascular Effects	MVP Syndrome	Anatomic MVP with Mild MR	Anatomic MVP with Severe MR
Barbiturates	Significant myocardial depression; increased HR; venodilation	Slight ↓ LV size; may augment prolapse	Variable response; titrate carefully	Poorly tolerated in the presence of LV dysfunction
Propofol	Modest intrinsic myocardial depression; ↓ SVR; ↓ preload; ↓ sympathetic outflow	Slight ↓ LV size; may augment prolapse	↓ SVR may enhance FF	↓ SVR may enhance FF; ↓ sympathetic tone and cardiac depression may cause severe hypotension
Narcotics	Sympatholysis at higher doses	Minimal change	Minimal change	Sympatholysis with higher doses may ↓ cardiac output
Benzodiazepines	Modest ↓ SVR and sympathetic tone	Minimal change	Minimal change	Sympatholysis with high doses may ↓ cardiac output
Etomidate	Minimal change in sympathetic tone	Lack of sympatholysis may aggravate prolapse if ↑ HR and contractility	Minimal change	Usually well tolerated
Ketamine	Sympathomimetic effects; ↑ SVR; ↑ PAP; rare hemodynamic collapse	May aggravate prolapse with ↑ HR, contractility; somewhat offset by an ↑ in SVR	May ↑ RF due to ↑ SVR	May cause decompensation with ↑ RF; ↑ PVR and PAP may aggravate RV dysfunction
Isoflurane/desflurane/sevoflurane	↓↓ SVR; ↑ HR; modest myocardial depression	May worsen prolapse by increasing LV emptying and/or transient increase in sympathetic tone	Low concentrations may ↑ FF and are well tolerated	Low concentrations may ↑ FF; titrate carefully in the presence of LV dysfunction
Enflurane	↓ SVR; moderate myocardial depression	May worsen prolapse by increasing LV emptying	Lower concentrations well tolerated	Even lower concentrations may be poorly tolerated
Halothane	Modest change in SVR; significant myocardial depression; aggravation of arrhythmias	May reduce prolapse; may precipitate arrhythmias with ↑ sympathetic tone	Lower concentrations generally tolerated; may precipitate arrhythmias	Even lower concentrations may be poorly tolerated
Nitrous oxide	Mild sympathetic activation counterbalances myocardial depression; ± ↑ in PVR;	Minimal change	Minimal change	May not be well tolerated in severe LV dysfunction; may aggravate ↑ PAP and RV failure in some patients

MVP = mitral valve prolapse; HR = heart rate; SVR = systemic vascular resistance; CV = cardiovascular; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; LV = left ventricle; FF = forward fraction of left ventricular output; RF = regurgitant fraction of left ventricular output.

stantial body of evidence now supports the superiority of TEE over PA pressure monitoring to assess the degree of MR,[149–152] although PA catheters may still play an important role in the presence of varying degrees of MR to determine cardiac output and calculate hemodynamic variables. Pulmonary artery catheter measurements may be correlated with TEE changes to establish trends that may be followed postoperatively when the PA catheter remains after removal of the TEE probe. In the absence of associated hemodynamic compromise, monitoring of PA pressures for isolated MVP with modest MR is not justified.

Mitral Valve Surgery

In industrialized nations, anatomic MVP is the leading cause of MR that requires surgical intervention. Correction of MV disease historically has been associated with the highest postoperative mortality of surgically repaired, left-side heart lesions.[153] Predicting the small group of patients who spiral inexorably into low cardiac output heart failure in the postoperative period has been difficult.[154,155] In one study of a group of 214 patients undergoing MV surgery, increasing severity of heart failure, increased age, and the presence of coronary artery disease were important individual predictors of postoperative low cardiac output and increased postoperative mortality.[156] Although LV ejection fraction has been used widely as an estimate of preoperative LV function, Mudge[157] pointed out that it is falsely elevated in the setting of MR. Because blood is being ejected into the low-impedance LA, an LV undergoing progressive dysfunction can still appear to have adequate function.[18,153] After MV replacement or repair, the dilated LV is suddenly exposed to an increase in

Table 6. Hemodynamic and Cineangiographic Data in Patients before and after Mitral Valve Reconstruction or Replacement for Chronic Mitral Regurgitation

	Control Subjects (n = 10)	Patients with MV Reconstruction (n = 8)		Patients with MV Replacement (n = 6)	
		Before	After	Before	After
Heart rate (beats/min)	74 ± 13	64 ± 11	66 ± 12	77 ± 15	74 ± 17
Peak systolic pressure (mmHg)	128 ± 13	125 ± 11	143 ± 22	107 ± 13	124 ± 10
End-diastolic pressure (mmHg)	11 ± 4	22 ± 4*	12 ± 5‡	18 ± 3†	10 ± 4‡
PCWP (mmHg)	6 ± 2	17 ± 7*	10 ± 4	16 ± 6†	10 ± 7
Ejection fraction (%)	65 ± 13	64 ± 5	61 ± 16	60 ± 10	48 ± 10*·§·¶
Cardiac index (l/min/m²)	4.3 ± 0.7	3.0 ± 0.7*	3.4 ± 0.7	2.6 ± 0.4*	3.2 ± 0.4†
Regurgitant fraction (%)	—	60 ± 11*	5 ± 10§	67 ± 11*	6 ± 7§

Data are mean values ± standard deviation. Patients with mitral stenosis, aortic valve disease, coronary disease, or intraventricular conduction delay were excluded from the study. Regurgitant fraction is that proportion of blood ejected from the LV into the LA instead of into the aorta.

MV = mitral valve; PCWP = mean pulmonary capillary wedge pressure.

Data from Corin *et al.*[164]

* $P < 0.01$ *versus* control subjects' value.

† $P < 0.05$ *versus* control subjects' value.

‡ $P < 0.05$, *versus* value before surgery.

§ $P < 0.01$ *versus* value before surgery.

¶ $P < 0.01$ *versus* reconstruction.

afterload when the low-resistance LA "pop off" is removed. Most patients recover uneventfully, but in patients with marked deterioration of LV function, the loss of ejection into the highly compliant LA is thought to contribute to postoperative cardiac failure after MV surgery. Mudge[157] concludes that an LV end-systolic diameter of ≥4.5 cm and left ventricular end-diastolic volume of ≥55 ml/m² are the best predictors of poor postoperative LV function.

Although the degree of LV dysfunction can influence the postoperative course, it is now clear that *type* of surgical intervention dramatically effects outcome.[155,158,159] Previous valve replacement procedures destroyed the subvalvular apparatus and continuity of the papillary muscles, causing distorted LV contractile geometry. When the papillary muscles can no longer contribute to shortening of the LV long axis, circumferential shortening occurs prematurely, decreasing effective ejection in later systole.[155] Instead of excision, preservation of the mitral apparatus is associated with a decrease in ventricular stress relative to controls (MV replacement without preserved mitral apparatus), likely as a result of a decrease in LV size and a reduction in the radius-to-thickness ratio of the LV.[160] In both clinical and experimental studies in which MV surgery was evaluated, the importance of preserving papillary muscle insertions was emphasized, because this technique preserves normal systolic and diastolic LV function.[158,161–164] In a retrospective comparison of MV repair (or reconstruction) *versus* replacement, the latter resulted in a decrease in LV ejection fraction not seen with repair (table 6).[164]

The group led by Carpentier[165] and Duran *et al.*[166] were the first to demonstrate the long-term durability of MV repair in cases of the myxomatous MV. Approximately two thirds of cases of MR secondary to MVP are a result of prolapse of the mid-scallop of the posterior leaflet. This valve can be repaired by simple excision of the central portion of the leaflet with or, less frequently, without application of a ring to ensure a decrease in the annular circumference.[158] In one third of cases, MR is secondary to prolapse of the anterior leaflet or both leaflets. Anterior leaflet prolapse can be corrected by triangular resection of the prolapsing segment, chordal shortening, chordal transfer, or chordal replacement using polytetrafluoroethylene sutures.[167–169] Reflecting the success of earlier studies, Cohn *et al.* reported retrospectively on 219 patients who underwent MV repair, 77% of whom had severe cardiac dysfunction as reflected by New York Heart Association class III or IV status. After an operative mortality rate of 2.3%, freedom from cardiac morbidity (thromboembolism, endocarditis, reoperation, or New York Heart Association class III or IV status) was 90% at 1 year and 74% at 5 years.[162] Mitral valve repair for myxomatous valves is not without its disadvantages, however. Left ventricular outflow tract obstruction caused by abnormal systolic anterior motion of the anterior leaflet complicates 4.5–10% of cases postoperatively,[170–172] usually occurring in a setting in which localized plication of the MV annulus has been performed after removal of excessive tissue from the posterior leaflet.[173] Carpentier also devised the sliding leaflet plasty for the posterior leaflet to remove excess (myxomatous) tissue from the posterior leaflet and preserve LV geometry.[173] In addition to preservation of LV function, repair instead of replacement eliminates the need for long-term anticoagulation associated with a mechanical prosthetic valve.

To evaluate the functional results of such repairs, use of TEE during MV surgery has become valuable.[149,151,174] Despite the noted limitations, intraoperative TEE color flow Doppler imaging provides an accurate assessment of the adequacy of repair or replacement after separation from cardiopulmonary bypass,[149] permitting evaluation of residual MR and the need for further repair before surgical closure. Biplane or multiplane TEE can correctly predict adequate repair in 80–90% of cases. However, care must be taken to control hemodynamic variations that can markedly alter regurgitant flow.[121] After MV repair, use of the V wave on a PA catheter as a reflection of residual MR is fraught with inaccuracy, because the amplitude of the V wave is also related to LA and pulmonary venous compliance.[152]

With the increased success of MV repair, there is a trend toward earlier intervention to prevent deterioration in LV function and to decrease the risk of atrial fibrillation.[157] Because atrial fibrillation is by itself sufficient to justify anticoagulation, a case can be made for operating on patients in whom atrial fibrillation develops but who have no hemodynamic decompensation. Because sinus rhythm may be restored by early surgical intervention and MV repair,[175] the need for chronic anticoagulation can be avoided. In certain instances, MV repair may be combined with the Maze procedure to interfere surgically with atrial fibrillation.[176]

In summary, although MVP is the most common valvular cardiac disease encountered by the anesthesiologist, the majority of patients have a benign prognosis. Recent literature has allowed us to predictably determine certain characteristics of benign *versus* clinically significant MVP. Younger women with an isolated click, atypical chest pain, and supraventricular tachycardia are unlikely to have hemodynamic sequelae or complications, even during pregnancy. Likewise, those with MVP evident only on echocardiographic evaluation share a benign course. The older, more frequently male, patients with myxomatous valves and redundant leaflets are likely to progress to increasingly severe MR, eventually requiring MV surgery. The long-term prognosis of patients with MVP as part of a heritable connective tissue disorder is likely to depend on the course of the underlying disease. Careful clinical evaluation, including echocardiographic studies when indicated, will permit accurate definition of the type and severity of MVP present in any patient. Knowledge of the pathophysiologic features can then direct appropriate perioperative care, anesthetic management, and antibiotic prophylaxis. In more severe cases, incorporation of continuous TEE monitoring provides immediate visualization of the pathophysiologic process. Fortunately, MV repair of MVP-related MR is decreasing the postoperative morbidity of those who require such surgery.

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