Chapter 259: Mitral Regurgitation

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INTRODUCTION

The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in **Chaps. 38** and **234**; of electrocardiography (ECG) in **Chap. 235**; of echocardiography and other noninvasive imaging techniques in **Chap. 236**; and of cardiac catheterization and angiography in **Chap. 237**.

ETIOLOGY

Mitral regurgitation (MR) may result from an abnormality or disease process that affects any one or more of the five functional components of the mitral valve apparatus (leaflets, annulus, chordae tendineae, papillary muscles, and subjacent myocardium) **(Table 259-1)**. Acute MR can occur in the setting of acute myocardial infarction (MI) with papillary muscle rupture **(Chap. 269)**, following blunt chest wall trauma, or during the course of infective endocarditis (IE) owing to leaflet perforation or destruction. With acute MI, the posteromedial papillary muscle is involved much more frequently than the anterolateral papillary muscle because of its singular blood supply. Transient, acute MR can occur during periods of active ischemia and bouts of angina pectoris. Rupture of chordae tendineae can result in "acute-on-chronic MR" in patients with myxomatous degeneration of the valve apparatus.

TABLE 259-1

Major Causes of Mitral Regurgitation

Etiologies
Acute
IE
Papillary muscle rupture (post-MI)
Chordal rupture/leaflet flail (MVP, IE)
Blunt trauma
Chronic
Primary (affecting leaflets, chordae)
Myxomatous (MVP, Barlow's, forme fruste)
Rheumatic fever
IE (healed)
Congenital (cleft, AV canal)
Radiation
Secondary (leaflets, chordae are "innocent bystanders")
Ischemic cardiomyopathy
Dilated cardiomyopathy
HOCM (with SAM)
Chronic AF with LA enlargement and annular dilatation
Mitral annular calcification[a]

[a]Mitral annular calcification may include elements of both primary and secondary MR as the disease process may encroach on the leaflets, impair the normal sphincteric function of the annulus, or both.

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; IE, infective endocarditis; HOCM, hypertrophic obstructive cardiomyopathy; LA, left atrial; LV, left ventricular; MI, myocardial infarction; MVP, mitral valve prolapse; SAM, systolic anterior motion.

Chronic MR can result from several disease processes (Table 259-1). Distinction should be drawn between primary MR, in which the leaflets and/or chordae tendineae are primarily responsible for abnormal valve function, and secondary (functional) MR, in which the leaflets and chordae tendineae are usually normal but the regurgitation is caused by left ventricular (LV) remodeling with annular enlargement, papillary muscle displacement, leaflet

tethering, or their combination. Patient assessment, treatment approach, and long-term prognosis differ significantly between primary and secondary MR. Mitral valve prolapse (MVP) is discussed more extensively in **Chap. 260**. The rheumatic process produces rigidity, deformity, and retraction of the valve cusps and commissural fusion, as well as shortening, contraction, and fusion of the chordae tendineae. MR can persist after resolution of the acute phase of infection and inflammation. MR may occur as a congenital anomaly **(Chap. 264)**, most commonly as a defect of the endocardial cushions (atrioventricular cushion defects). A cleft anterior mitral valve leaflet accompanies ostium primum atrial septal defect. Radiation can result in leaflet thickening, retraction, and calcification, often in association with annular and chordal involvement. Chronic MR is frequently secondary to ischemia and may occur as a consequence of ventricular remodeling, papillary muscle displacement, and leaflet tethering, or with fibrosis of a papillary muscle, in patients with healed MI(s) and ischemic cardiomyopathy. Similar mechanisms of annular dilation and ventricular remodeling contribute to the MR that occurs among patients with nonischemic forms of dilated cardiomyopathy once the LV end-diastolic dimension reaches 6 cm. The MR associated with hypertrophic obstructive cardiomyopathy (HOCM) is usually dynamic in nature and dependent on systolic anterior motion of the anterior mitral valve leaflet into a narrowed LV outflow tract. Patients with long-standing, chronic atrial fibrillation (AF) develop atrial remodeling and annular dilatation that can result in MR. Annular calcification can result in MR when it encroaches on the leaflets or results in decreased sphincteric function and is especially prevalent among patients with advanced renal disease and is commonly observed in women >65 years of age with hypertension and diabetes. Irrespective of cause, chronic severe MR is often progressive, because enlargement of the left atrial (LA) places tension on the posterior mitral leaflet, pulling it away from the mitral orifice and thereby aggravating the valvular dysfunction. Similarly, LV dilation increases the regurgitation, which, in turn, enlarges the LA and LV further, resulting in a vicious circle; hence the aphorism, “MR begets MR.”

PATHOPHYSIOLOGY

The resistance to LV emptying (LV afterload) is reduced in patients with MR. As a consequence, the LV is decompressed into the LA during ejection, and with the reduction in LV size during systole, there is a rapid decline in LV tension. The initial compensation to MR is more complete LV emptying. However, LV volume increases progressively with time as the severity of the regurgitation increases and as LV contractile function deteriorates. This increase in LV volume is often accompanied by a reduced forward cardiac output (CO). LV compliance is often increased, and thus, LV diastolic pressure does not increase until late in the course. The regurgitant volume varies directly with the LV systolic pressure and the size of the regurgitant orifice; the latter, in turn, is influenced by the extent of LV and mitral annular dilation. Because ejection fraction (EF) rises in severe MR in the presence of normal LV function, even a modest reduction in this parameter (<60%) reflects significant contractile dysfunction.

During early diastole, as the distended LA empties, there is a particularly rapid *y* descent in the absence of accompanying MS. A brief, early diastolic LA-LV pressure gradient (often generating a rapid filling sound [S_3] and mid-diastolic murmur masquerading as MS) may occur in patients with pure, severe MR as a result of the very rapid flow of blood across a normal-sized mitral orifice.

Measurements of LV ejection fraction (LVEF), CO, pulmonary arterial (PA) systolic pressure, regurgitant volume, regurgitant fraction (RF), and the effective regurgitant orifice area can be obtained during a careful Doppler echocardiographic examination. These measurements can also be obtained accurately with cardiac magnetic resonance (CMR) imaging, although this technology is not widely available. Left and right heart catheterization with contrast ventriculography is used less frequently. Chronic, severe MR is defined by a regurgitant volume ≥60 mL/beat, RF ≥50%, and effective regurgitant orifice area ≥0.40 cm^2. In patients with secondary MR, in whom the severity of MR can be underappreciated, lesser degrees of regurgitation carry relatively greater prognostic weight.

LA Compliance

In acute severe MR, the regurgitant volume is delivered into a normal-sized LA having normal or reduced compliance. As a result, LA pressures rise markedly for any increase in LA volume. The *v* wave in the LA pressure pulse is usually prominent, LA and pulmonary venous pressures are markedly elevated, and pulmonary edema is common. Because of the rapid rise in LA pressures during ventricular systole, the murmur of acute MR is early in timing and decrescendo in configuration ending well before S_2, as a reflection of the progressive diminution in the LV-LA pressure gradient. LV systolic function in acute MR may be normal, hyperdynamic, or reduced, depending on the clinical context.

Patients with chronic severe MR, on the other hand, develop marked LA enlargement and *increased* LA compliance with little if any increase in LA and pulmonary venous pressures for any increase in LA volume. The LA *v* wave is relatively less prominent. The murmur of chronic MR is classically holosystolic in timing and plateau in configuration, as a reflection of the near-constant LV-LA pressure gradient. These patients usually complain of severe fatigue and exhaustion secondary to a low forward CO, whereas symptoms resulting from pulmonary congestion are less prominent initially; AF

is almost invariably present once the LA dilates significantly.

SYMPTOMS

Patients with chronic mild-to-moderate, isolated MR are usually asymptomatic. This form of LV volume overload is well tolerated. Fatigue, exertional dyspnea, and orthopnea are the most prominent complaints in patients with chronic severe MR. Palpitations are common and may signify the onset of AF. Right-sided heart failure, with painful hepatic congestion, ankle edema, distended neck veins, ascites, and secondary tricuspid regurgitation (TR), occurs in patients with MR who have associated pulmonary vascular disease and pulmonary hypertension. Acute pulmonary edema is common in patients with acute severe MR.

PHYSICAL FINDINGS

In patients with chronic severe MR, the arterial pressure is usually normal, although the carotid arterial pulse may show a sharp, low-volume upstroke owing to the reduced forward CO. A systolic thrill is often palpable at the cardiac apex, the LV is hyperdynamic with a brisk systolic impulse and a palpable rapid-filling wave (S_3), and the apex beat is often displaced laterally.

In patients with acute severe MR, the arterial pressure may be reduced with a narrow pulse pressure, the jugular venous pressure and waveforms may be normal or increased and exaggerated, the apical impulse is not displaced, and signs of pulmonary congestion are prominent.

Auscultation

S_1 is generally absent, soft, or buried in the holosystolic murmur of chronic, severe MR. In patients with severe MR, the aortic valve may close prematurely, resulting in wide but physiologic splitting of S_2. A low-pitched S_3 occurring 0.12–0.17 s after the aortic valve closure sound, i.e., at the completion of the rapid-filling phase of the LV, is believed to be caused by the sudden tensing of the papillary muscles, chordae tendineae, and valve leaflets. It may be followed by a short, rumbling, mid-diastolic murmur, even in the absence of structural MS. In patients with ischemic or dilated cardiomyopathy, however, a third sound (S_3) may also signify ventricular dysfunction. A fourth heart sound is often audible in patients with *acute* severe MR who are in sinus rhythm. A presystolic murmur is not ordinarily heard with isolated MR.

A systolic murmur of at least grade III/VI intensity is the most characteristic auscultatory finding in chronic severe MR. It is usually holosystolic **(see Fig. 234-5A)**, but as previously noted, it is decrescendo and ceases in mid-to-late systole in patients with acute severe MR. The systolic murmur of chronic MR is usually most prominent at the apex and radiates to the axilla. However, in patients with ruptured chordae tendineae or primary involvement of the posterior mitral leaflet with prolapse or flail, the regurgitant jet is eccentric, directed anteriorly, and strikes the LA wall adjacent to the aortic root. In this situation, the systolic murmur is transmitted to the base of the heart and, therefore, may be confused with the murmur of AS. In patients with ruptured chordae tendineae, the systolic murmur may have a cooing or “seagull” quality, whereas a flail leaflet may produce a murmur with a musical quality. The systolic murmur of chronic MR not due to MVP is intensified by isometric exercise (handgrip) but is reduced during the strain phase of the Valsalva maneuver because of the associated decrease in LV preload.

LABORATORY EXAMINATION

ECG

In patients with sinus rhythm, there is evidence of LA enlargement, but right atrial (RA) enlargement also may be present when pulmonary hypertension is significant and affects RV function and size. Chronic severe MR is frequently associated with AF. In many patients, there is no clear-cut ECG evidence of enlargement of either ventricle. In others, the signs of eccentric LV hypertrophy are present.

Echocardiogram

Transthoracic echocardiography (TTE) is indicated to assess the mechanism of the MR and its hemodynamic severity. LV function can be assessed from LV end-diastolic and end-systolic volumes and EF. Observations can be made regarding leaflet structure and function, chordal integrity, LA and LV size, annular calcification, and regional and global LV systolic function. Doppler imaging should demonstrate the width or area of the color flow MR jet

within the LA, the duration and intensity of the continuous wave Doppler signal, the pulmonary venous flow contour, the early peak mitral inflow velocity, and quantitative measures of regurgitant volume, RF, and effective regurgitant orifice area. In addition, the PA pressures (PAPs) can be estimated from the TR jet velocity. TTE is also indicated to follow the course of patients with chronic MR and to provide rapid assessment for any clinical change. Transesophageal echocardiography (TEE) provides greater anatomic detail than TTE **(see Fig. 236-5)**. Exercise testing with TTE can be useful to assess exercise capacity as well as any dynamic change in MR severity, PA systolic pressures, and biventricular function, for patients in whom there is a discrepancy between clinical findings and the results of other noninvasive testing.

Chest X-Ray

The LA and LV are the dominant chambers in chronic MR. Late in the course of the disease, the LA may be massively enlarged and forms the right border of the cardiac silhouette. Pulmonary venous congestion, interstitial edema, and Kerley B lines are sometimes noted. Marked calcification of the mitral leaflets occurs commonly in patients with long-standing, combined rheumatic MR and MS. Calcification of the mitral annulus may be visualized, particularly on the lateral view of the chest. Patients with acute severe MR may have asymmetric pulmonary edema if the regurgitant jet is directed predominantly to the orifice of an upper lobe pulmonary vein.

TREATMENT

TREATMENT

Mitral Regurgitation

MEDICAL TREATMENT

The management of chronic severe MR depends to some degree on its cause (**Fig. 259-1**). Anticoagulation with either warfarin or a direct oral agent (e.g., apixaban, rivaroxaban) should be provided if AF intervenes, as guided by the CHA2DS2-VASc risk score. The direct oral anticoagulants should not be used if rheumatic mitral stenosis is also present; they are also not approved for use in patients with mechanical prosthetic heart valves. Cardioversion should be considered depending on the clinical context, AF chronicity, LA size. In contrast to the acute setting, there are no large, long-term prospective studies to substantiate the use of vasodilators for the treatment of chronic, isolated severe MR with preserved LV systolic function *in the absence of systemic hypertension.* The severity of MR in the setting of an ischemic or dilated cardiomyopathy may diminish with aggressive guideline-directed treatment of heart failure including the use of diuretics, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, digitalis, and biventricular pacing (cardiac resynchronization therapy [CRT]) when otherwise indicated. Antibiotic prophylaxis for prevention of IE is indicated for MR patients with a prior history of IE. Asymptomatic patients with severe MR in sinus rhythm with normal LV size and systolic function should avoid isometric forms of exercise.

Patients with acute severe MR require urgent stabilization and preparation for surgery. Diuretics, intravenous vasodilators (particularly sodium nitroprusside), and even mechanical support may be needed for patients with post-MI papillary muscle rupture or other forms of acute severe MR.

SURGICAL TREATMENT

In the selection of patients with chronic, severe, primary MR for surgical treatment, the often slowly progressive nature of the condition must be balanced against the immediate and long-term risks associated with operation. These risks are significantly lower for primary valve repair than for valve replacement (**Table 259-2**). Repair usually consists of valve reconstruction using a variety of valvuloplasty techniques and insertion of an annuloplasty ring. Repair spares the patient the long-term adverse consequences of valve replacement, including thromboembolic and hemorrhagic complications in the case of mechanical prostheses and late valve failure necessitating repeat valve replacement in the case of bioprostheses. In addition, by preserving the integrity of the papillary muscles, subvalvular apparatus, and chordae tendineae, mitral repair and valvuloplasty maintain LV function to a relatively greater degree than does valve replacement.

Surgery for chronic severe primary MR is indicated once symptoms occur, especially if valve repair is feasible (Fig. 259-1). Surgery should also be recommended for asymptomatic patients with LV dysfunction characterized by an EF <60% or an LV end-systolic dimension (LV ESD) >40 mm. Other indications for early consideration of mitral valve repair in asymptomatic patients include (1) recent-onset AF (duration <3 months); (2) pulmonary hypertension (defined as a systolic PA pressure ≥50 mmHg at rest or ≥60 mmHg with exercise); and (3) a progressive decrease in LV EF or increase in LV ESD on serial imaging. These aggressive recommendations for surgery are predicated on the adverse long-term consequences of waiting for LV function to decline further as well as the outstanding results achievable with mitral valve repair by reference surgeons at high-volume centers.

Indeed, repair of myxomatous MR (e.g., prolapse, flail) in patients <75 years with normal LV systolic function and no coronary artery disease (CAD) can now be performed by experienced surgeons with <1% perioperative mortality risk. The risk of stroke, however, is also ~1%. Repair is feasible in up to 95% of patients with myxomatous disease operated on by a high-volume surgeon in a referral center of excellence. Repair techniques include chordal transfer, creation of neochords, limited leaflet resection, and insertion of an annuloplasty band. Long-term durability is excellent; the incidence of reoperative surgery for failed primary repair is ~1% per year for the first 10 years after surgery. For patients with AF, left or biatrial maze surgery, or radiofrequency isolation of the pulmonary veins is often performed to reduce the risk of recurrent postoperative AF.

The surgical management of patients with secondary MR is more complicated. Surgery for patients with ischemic MR most often involves simultaneous coronary artery revascularization. Current surgical practice includes annuloplasty repair with an undersized, rigid ring or chord-sparing valve replacement for patients with moderate or greater degrees of MR. Valve repair for ischemic MR is associated with lower perioperative mortality rates than valve replacement but significantly higher rates of recurrent MR over time. In patients with ischemic MR and significantly impaired LV systolic function (EF <30%), the risk of surgery is higher, recovery of LV performance is incomplete, and long-term survival is reduced. Referral for surgery must be individualized and made only after aggressive attempts to improve symptoms with guideline-directed medical therapy and CRT, when indicated. The routine performance of valve repair in patients with significant secondary MR due to a dilated cardiomyopathy has not been shown to improve long-term survival compared with optimal medical therapy. Patients with acute severe MR can often be stabilized temporarily with appropriate medical therapy, but surgical correction will be necessary emergently in the case of papillary muscle rupture and within days to weeks in most other settings.

When surgical treatment is contemplated, left and right heart catheterization and left ventriculography *may* be helpful in confirming the presence of severe MR in patients in whom there is a discrepancy between the clinical and TTE findings that cannot be resolved with TEE or CMR. Coronary angiography identifies patients who require concomitant coronary revascularization.

TRANSCATHETER MITRAL VALVE REPAIR AND REPLACEMENT

A transcatheter approach to the treatment of either primary or functional MR may be feasible in selected patients with appropriate anatomy. The proper role of currently available techniques remains under active investigation. One approach involves the deployment of a clip delivered via transseptal puncture that grasps the leading edges of the mitral leaflets in their mid-portion (anterior scallop to posterior scallop or A2-P2; **Fig. 259-2**). The length and width of the gap between these leading edges dictate patient eligibility. The device is commercially available. In the United States only for the treatment of prohibitive- or high-surgical risk, symptomatic patients with severe, primary (myxomatous) MR. The edge-to-edge clip technique is undergoing study in the United States for treatment of patients with symptomatic heart failure, reduced LVEF, and severe, secondary MR despite guideline-directed medical therapy. Other approaches include the deployment of a device within the coronary sinus that can be adjusted to reduce mitral annular circumference and the effective orifice area of the valve much like a surgically implanted ring. Variations in the anatomic relationship of the coronary sinus to the mitral annulus and circumflex coronary artery have limited the applicability of this technique. Attempts to reduce the septal-lateral dimension of a dilated annulus using adjustable cords placed across the LV in a subvalvular location have also been investigated. Construction of neochords to the mitral leaflets under TEE guidance using a system delivered via the cardiac apex is also under study. Investigational experience to date with transcatheter mitral valve replacement systems is in early clinical stages, although the field is evolving rapidly.

FIGURE 259-1

Management of mitral regurgitation. See legend for **Fig. 256-4** for explanation of treatment recommendations (class I, IIa, IIb) and disease stages (B, C1, C2, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. AF, atrial fibrillation; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; EF, ejection fraction; ERO, effective regurgitant orifice; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation, MV, mitral valve; MVR, mitral valve replacement; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; and Rx, therapy. *(Adapted from RA Nishimura et al: 2017 Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol. Available at www.onlinejacc.org/lookup/doi/10.1016/j.jacc.2017.03.011.)*

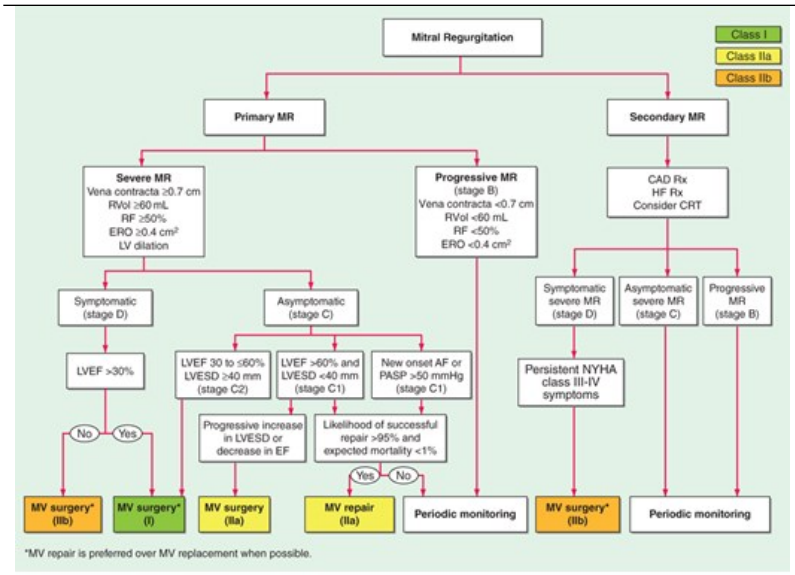

TABLE 259-2

Mortality Rates after Mitral Valve Surgery[a]

Operation	Number	Unadjusted Operative Mortality (%)
MVR (isolated)	3448	4.6
MVR + CAB	1321	10.0
MVRp	4284	1.2
MVRp + CAB	2051	4.8

[a]Data are for the first two quarters of calendar year 2015, during which 1013 sites reported a total of 141,225 procedures. Data are available from the Society of Thoracic Surgeons at *http://www.sts.org/sites/default/files/documents/2015Harvest3_ExecutiveSummary.pdf.*

Abbreviations: CAB, coronary artery bypass; MVR, mitral valve replacement; MVRp, mitral valve repair.

FIGURE 259-2

Clip used to grasp the free edges of the anterior and posterior leaflets in their midsections during transcatheter repair of selected patients with mitral regurgitation. *(Courtesy of Abbott Vascular. © 2014 Abbott Laboratories. All rights reserved.)*

FURTHER READING

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