Mitral regurgitation

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Mitral regurgitation affects more than 2 million people in the USA. The main causes are classified as degenerative (with valve prolapse) and ischaemic (ie, due to consequences of coronary disease) in developed countries, or rheumatic (in developing countries). This disorder generally progresses insidiously, because the heart compensates for increasing regurgitant volume by left-atrial enlargement, causes left-ventricular overload and dysfunction, and yields poor outcome when it becomes severe. Doppler-echocardiographic methods can be used to quantify the severity of mitral regurgitation. Yearly mortality rates with medical treatment in patients aged 50 years or older are about 3% for moderate organic regurgitation and about 6% for severe organic regurgitation. Surgery is the only treatment proven to improve symptoms and prevent heart failure. Valve repair improves outcome compared with valve replacement and reduces mortality of patient with severe organic mitral regurgitation by about 70%. The best short-term and long-term results are obtained in asymptomatic patients operated on in advanced repair centres with low operative mortality (<1%) and high repair rates (≥80–90%). These results emphasise the importance of early detection and assessment of mitral regurgitation.

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Introduction

Mitral regurgitation is defined as systolic retrograde flow from the left ventricle into the left atrium. Although a trivial form of this valve disease is often seen in healthy people,[1] epidemiological data show that moderate or severe regurgitation is the most frequent valve disease in the USA[2] and is the second most common form of valvular heart disease needing surgery in Europe.[3] Despite substantial reduction in the incidence of rheumatic heart disease, mitral regurgitation is a growing public health problem.[2] Moderate or severe regurgitation is frequent, its prevalence increases with age, and it was estimated to affect 2·0–2·5 million people in the USA in 2000—a number expected to almost double by 2030 because of population ageing and growth.[2] Although no large epidemiological studies are available, mitral regurgitation is prevalent in young adults in countries with endemic rheumatic fever.[4] Substantial progress has been achieved to improve its diagnosis, quantification,[5] and surgical treatment. Improved knowledge of clinical outcome of patients with mitral regurgitation resulted in refined surgical indications.[6,7] Hence, mitral regurgitation is a disease in which restoration of life expectancy can often be achieved,[8,9] an encouraging outcome that emphasises the importance of early detection, assessment, and prompt consideration for treatment of patients with this condition.[6,7] Challenges in management of patients with mitral regurgitation remain—elderly patients and those with disease due to ischaemic heart disease are often not offered surgery; valve repair—the preferred surgical method—is insufficiently done;[3] new interventional techniques—minimally invasive or percutaneous—are under investigation.[10] However, the general absence of clinical trials means evidence to guide treatment is weak.

Causes and mechanisms

All lesions that cause mitral regurgitation do so by reduction or elimination of the normal systolic coaptation between anterior and posterior mitral leaflets, which normally ensures mitral competence. Consistent anatomical and functional descriptors of mitral lesions are essential to assess surgical reparability but overlapping and poorly defined terminology has caused confusion. Causes and mechanisms are not synonymous and a particular cause might produce regurgitation by different mechanisms (table 1). Surgical correction of this valve disease is dependent on both cause and mechanism, which affect reparability.[11] Causes are generally classified as ischaemic (mitral regurgitation due to consequences of coronary disease, not fortuitous association of both) and non-ischaemic (all other causes). Mechanisms are grossly classified as functional (mitral valve is structurally normal and disease results from valve deformation caused by ventricular remodelling) or organic (intrinsic valve lesions). They can be subclassified by leaflet movement (Carpentier's classification[11])—type I (normal valve movement, such as annular dilatation or leaflet perforation); type II (excessive movement); and type III (restrictive movement: IIIa—diastolic restriction such as rheumatic disease; IIIb—systolic restriction as in functional disease). Carpentier also proposed a simple lesion localisation classification (figure 1).

Major causes of surgical mitral regurgitation in western countries are degenerative (primary myxomatous disease, primary flail leaflets, annular calcification), representing 60–70% of cases, followed by ischaemic mitral regurgitation (20%), endocarditis (2–5%), rheumatic (2–5%), and miscellaneous causes (cardiomyopathies, inflammatory diseases, drug-induced,

Search strategy and selection criteria

We searched PubMed, Medline, and Embase with the terms "mitral regurgitation", "mitral valve", and "heart valve surgery" for papers up to 2007. There were no language restirictions. We also searched the reference lists in articles identified by this strategy. Reviews were included as references if they represented practice guidelines or provided a comprehensive overview of specific topics.

	Organic			Functional
	Type I*	Type II†	Type IIIa‡	Type I*/Type IIIb‡
Non-ischaemic	Endocarditis (perforation); degenerative (annular calcification); congenital (cleft leaflet)	Degenerative (billowing/flail leaflets); endocarditis (ruptured chordae); traumatic (ruptured Chord/PM); rheumatic (acute RF)	Rheumatic (chronic RF); iatrogenic (radiation/drug); inflammatory (lupus/anticardiolipin, eosinophilic endocardial disease, endomyocardial fibrosis)	Cardiomyopathy; myocarditis; left-ventricular; dysfunction (any cause)
Ischaemic	..	Ruptured PM	..	Functional ischaemic

MR=mitral regurgitation. PM=papillary muscle. RF=rheumatic fever. *Mechanism involves normal leaflet movement. †Mechanism involves excessive valve movement. ‡Restricted valve movement, IIIa in diastole, IIIb in systole.

Table 1: **Causes and mechanisms of mitral regurgitation**

traumatic, congenital).[12–14] Ischaemic disease probably represents a large proportion of the non-surgical disease burden.[15] Nomenclature and mechanisms of major causes are summarised below.

Degenerative mitral regurgitation is usually related to mitral-valve prolapse (figure 2) and rarely to isolated mitral annular calcification.[16,17] Mitral-valve prolapse is an abnormal systolic valve movement into the left atrium (≥2 mm beyond saddle-shaped annular level).[18] This excessive movement can be seen with other causes such as endocarditis. Prolapse might be of moderate magnitude (leaflet tips remain in the left ventricle—ie, billowing mitral valve) or can be severe (eversion of leaflet tip into left atrium—ie, flail leaflet—usually caused by ruptured chordae). The main phenotypes of mitral prolapse[19] are diffuse myxomatous degeneration (mitral-valve prolapse syndrome or Barlow's disease,[20] sometimes with posterior annular translocation into left atrium) or primary flail leaflets with ruptured chordae affecting the posterior leaflet in 70% of cases, and accompanied by myxomatous degeneration localised to the flail segment and generally normal valve morphology elsewhere.[21] Myxomatous degeneration remodels valve tissue by increasing the spongiosa layer and valve water content and thickness, with mucopolysaccharide and matrix changes,[22] as a functional manifestation of metalloproteinase alterations. These mitral tissue changes and prolapse might be genetically transmitted[23] and X-chromosome linked.[24] Degenerative mitral regurgitation is the most reparable form, warranting early and careful assessment.

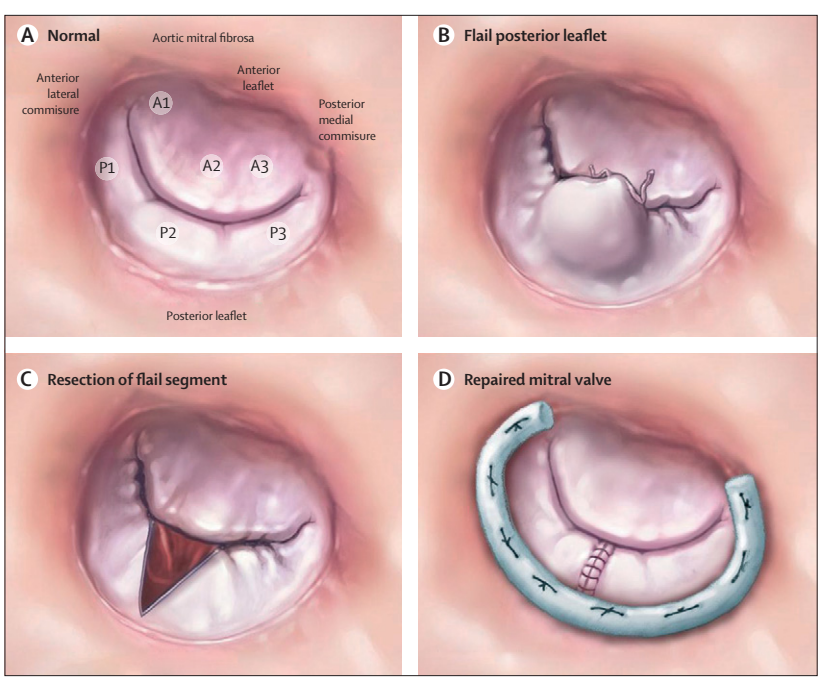

Figure 1: **Schematic anatomical mitral-valve presentation**
(A) Atrial view of a healthy mitral valve. Posterior leaflet has a shorter length but occupies a longer circumference than the anterior leaflet. Mitral annulus around the leaflet is part of the aortic-mitral fibrosa superiorly, is asymmetric, and short in its anteroposterior dimension. Leaflet segmentation starts with A1–P1 close to the anterolateral commissure, with A2–P2 centrally, and A3–P3 close to the posteromedial commissure. The normally apposing leaflets make up the mitral smile. (B) Example of a flail posterior leaflet affecting the P2 segment with ruptured chordae. Note the bulge and excess tissue of the flail segment and the annular enlargement mostly along the posterior part of its circumference. (C) Initial step of surgical valve repair. Resection of the flail segment can be triangular (as shown) or quadrangular and leaves the healthy P1 and P3 segments available for reattachment and repair. (D) Posterior leaflet has been restored by approximation of the remaining segment after resection of the flail segment and the mitral annular dimensions have been restored by an annuloplasty ring. In this example an incomplete ring has been used with its extremities sutured to the trigonal regions of the aortic-mitral fibrosa. The mitral smile and competence have been restored.

The ischaemic form of this disease rarely results from an organic mechanism (papillary-muscle rupture)[25] and is rarely acute. Frequently, it is functional (structurally normal leaflets) and chronic, epitomising left-ventricular disease that causes valvular dysfunction. Papillary-muscle dysfunction plays little part in the generation of functional mitral regurgitation, which is mostly caused by apical and inferior-papillary-muscle displacement due to ischaemic left-ventricular remodelling.[26] Because chordae are non-extensible, papillary-muscle displacement exerts traction on leaflets through strut chordae implanted on the body of leaflets,[27,28] resulting in tethered and apically displaced leaflets (tenting, figure 2).[26,29] Coupled with annular flattening, enlargement, and decreased contraction, mitral valve tenting results in coaptation loss that yields functional mitral regurgitation.[26] Asymmetric tenting due to regional scarring (inferior infarction) might explain commissural jets of ischaemic disease.[30]

Rheumatic mitral regurgitation—past the acute phase[31]—causes chordal and leaflet retraction,[32] which, amplified by annular dilatation, results in coaptation

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loss. Postinflammatory[33] and postradiation[34] mitral regurgitations have similar mechanisms. Retraction of tissue is a major limitation to successful valve repair.

Endocarditic mitral regurgitation might be caused by ruptured chordae or perforations. In all causes, annular enlargement is common, is located mostly or exclusively on the posterior part of the annular circumference, and surgical repair almost always requires annuloplasty.

Pathophysiology and progression

The degree of mitral regurgitation is defined by lesion severity (measured as effective regurgitant orifice [ERO] area)[35] and the yielding volume overload (measured as regurgitant volume[RVol]), but it is also affected by the driving force (left-ventricular systolic pressure) and left-atrial compliance.[5] Thus, in acute disease, the large regurgitant orifice converts ventricular energy mostly into potential energy (left-atrial pressure V-wave) due to non-compliant left atrium.[36] In chronic regurgitation, the enlarged left atrium is compliant, the V-wave is often small, and ventricular energy is converted mostly into kinetic energy (large RVol). This process of atrial enlargement and increased compliance probably explains atrial pressure reduction and clinical improvement after initial heart failure caused by acute mitral regurgitation.

The ERO area is not necessarily fixed and can be dynamic.[37] Increased loading or contractility can cause the ERO area to increase or decrease slightly.[38] With valve prolapse, the area is very dynamic, increasing progressively during systole, and is sometimes purely end-systolic.[39,40] In functional mitral regurgitation, ERO area is dynamic during systole, with large area during short isovolumic contraction and relaxation phases caused by lesser ventricular pressure apposing leaflets.[40] This type of regurgitation is also dynamic with decreased loading[41] or inotrope administration, and might disappear with these interventions, whereas exercise most often results in augmentation of ERO area.[42] Long-term progression of organic disease is about 5–7 mL per year for RVol and is determined by ERO area progression caused by new lesions or annular enlargement.[43] Thus, mitral regurgitation is self-sustained, causing atrial and annular enlargement, which in turn leads to increased ERO area.

The ventricular and atrial consequences of organic mitral regurgitation are initiated by volume overload with increased preload and left-ventricular and left-atrial enlargement. Impedance to ejection is reduced despite normal or increased vascular resistances, whereas myocardial afterload (end-systolic wall stress) is normal with an end-systolic volume that is normal to slightly increased.[44] Thus, in organic disease, altered left-ventricular function might coexist with normal or high ejection fraction.[45] Borderline normal ejection fraction, between 50–60%, already implies overt left-ventricular dysfunction.[46,47] Ventricular dysfunction should be suspected when end-systolic dimensions are large[48,49] but is often masked by a large ejection volume and is revealed after surgical elimination of mitral regurgitation, with a postoperative average immediate ejection fraction drop of about 10%.[47,50] Diastolic ventricular dysfunction is difficult to characterise, but seems to reduce exercise capacity.[51]

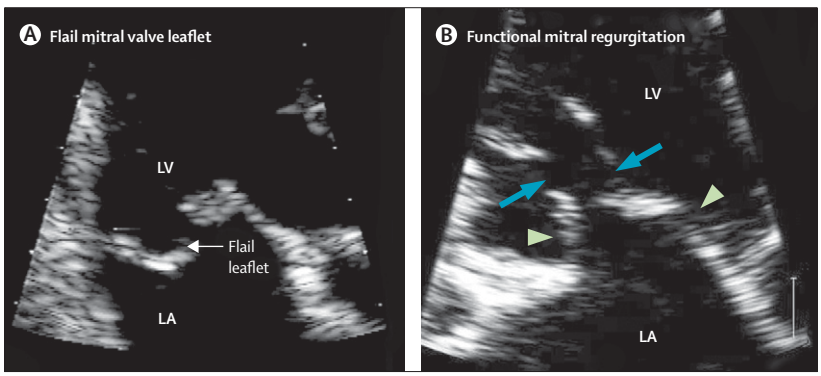

Figure 2: **Echocardiographic appearance of the two main anatomical types of mitral regurgitation from apical views centred on the mitral valve**
(A) An example of a flail posterior leaflet with the tip of the leaflet floating in the left atrium. Note the otherwise grossly normal anterior leaflet. (B) An example of functional mitral regurgitation. Strut chordae (long arrows) to the anterior and posterior leaflets exert an abnormal traction on the body of the leaflets, which displaces (arrowheads) the leaflets towards the ventricular apex, creating an area of tenting above the mitral annulus and an incomplete coaptation. LA=left atrium. LV=left ventricle.

Physiology of functional mitral regurgitation is even more complex than that of organic mitral regurgitation since ventricular dysfunction predates the regurgitation. Nevertheless, functional mitral regurgitation further increases atrial pressure, which leads to pulmonary hypertension[52] and heart failure.[53,54] With increased atrial pressure and low driving force, functional regurgitation often has low RVol[26] and can be silent.[55] Whether functional regurgitation affects remodelling and dysfunction is uncertain but is suspected because of the high mortality associated with increased severity of mitral regurgitation.[55–57] Progression or recurrence after annuloplasty is weakly related to annular enlargement but strongly to increased mitral tenting caused by ventricular remodelling, papillary-muscle displacement,[58] and increased chordal traction;[59] however, rates of progression are unknown.

Assessment

Initial clinical assessment looks for symptoms, signs of heart failure, and physical signs of severe mitral regurgitation—ie, displaced apical impulse, systolic thrill, loud systolic murmur, S3, early diastolic rumble, and cardiomegaly with left-atrial enlargement on chest radiography and atrial fibrillation. These signs are important but not specific enough to rely solely on them to suggest surgery.[6]

Doppler echocardiography is the main method for assessment of patients with mitral regurgitation. Transthoracic[14] or transoesophageal echocardiography[13] provides functional anatomical information that is crucial

	Mild	Moderate	Severe
Specific signs	Small central jet <4 cm² or <10% of LA, vena contracta width <0·3 cm, no or minimum flow convergence	MR more than mild, without any criteria for severe MR	Vena contracta width ≥0·7 cm with large central MR jet (area >40% of LA) or with a wall-impinging jet of any size; large flow convergence; systolic reversal in pulmonary veins; prominent flail leaflet or ruptured papillary muscle
Supportive signs	Systolic dominant flow in pulmonary veins; A-wave dominant mitral inflow; low-density doppler MR signal; normal LV size	MR more than mild, but no criteria for severe MR	Dense, triangular doppler MR signal; E-wave dominant mitral inflow (>1·2 m/s); enlarged LV and LA, (particularly with normal LV function)
Quantitative variables			
RVol (mL per beat)	<30	30–44; 45–59	≥60
RF	<30%	30–39%; 40–49%	≥50%
ERO area (cm²)	<0·20	0·20–0·29; 0·30–0·39	≥0·40

Modified from Zoghbi and colleagues.[5] ERO=effective regurgitant orifice area. LA=left atrium. LV=left ventricle. MR=mitral regurgitation. RF=regurgitant fraction. RVol=regurgitant volume.

***Table 2*: Gradation of mitral regurgitation by doppler echocardiography**

for assessment of reparability by defining cause, mechanism, presence of calcification, and localisation of lesions. Transoesophageal echocardiography provides better imaging quality than transthoracic echocardiography but its ability to detect details such as ruptured chordae rarely changes management.[13,14] Transoesophageal echocardiography essentially provides incremental clinically meaningful information (such as reparability) when transthoracic echocardiography is of poor quality or when complex, calcified, or endocarditic lesions are suspected.[13] Thus, transoesophageal echocardiography is rarely used on an outpatient basis and is mostly used intraoperatively for lesion verification and to monitor surgical results.[60] Real-time three-dimensional echocardiography has at present insufficient image resolution but pilot data suggest that it allows quantitative assessment of structures that are not easily measurable by two-dimensional echocardiography, such as mitral annulus. Although emerging technologies such as transoesophageal echocardiography three-dimensional imaging have great potential, they need to be rigorously tested.

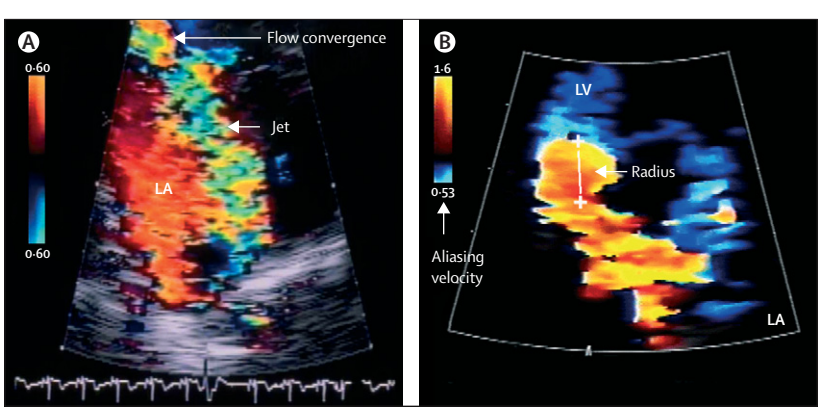

***Figure 3*: Use of colour-flow imaging for assessment of mitral regurgitation**
(A) Jet imaging in left atrium. The jet is eccentric and is displayed with mosaic colours, whereas the normal flow is of uniform colour. It fills only part of the left atrium and might underestimate the regurgitation. The observation of a large flow convergence should lead to suspicion of severe regurgitation. (B) Measurement of the flow convergence with colour-flow imaging. The baseline of the colour scale has been brought down to decrease the aliasing velocity to 53 cm/s (velocity at the blue-yellow border), which allows the flow convergence (yellow) to be seen. The radius (r) of the flow convergence is used in the formula for calculation of the instantaneous regurgitant flow (258 mL/s). Flow=$6{\cdot}28\times V_{aliasing}\times r^2=6{\cdot}28\times 53\times 0{\cdot}88^2=258$ mL/s. Division of this value by the jet velocity allows calculation of the effective regurgitant orifice of mitral regurgitation. LA=left atrium. LV=left ventricle.

Doppler echocardiography provides crucial information about mitral regurgitation severity (table 2).[5] Comprehensive integration of colour-flow imaging and pulsed and continuous wave doppler echocardiography is necessary because jet-based assessment has major limitations (figure 3).[61] Quantitative assessment of regurgitation is feasible by three methods—quantitative doppler echocardiography based on mitral and aortic stroke volumes,[62] quantitative two-dimensional echocardiography based on left-ventricular volumes, and flow-convergence analysis measuring flow with colour-flow imaging proximal to the regurgitant orifice (proximal isovelocity surface area method; figure 3).[63,64] These methods allow measurement of ERO area and RVol and have important prognostic value.[9] Severe mitral regurgitation is diagnosed with an ERO area of at least 40 mm² and RVol of at least 60 mL per beat; and moderate regurgitation with ERO area 20–39 mm² and RVol 30–59 mL per beat.[5,65] Outcome data suggest that a smaller volume mitral regurgitation and smaller ERO area (≥30 mL and ≥20 mm², respectively) are associated with severe outcome in patients with ischaemic disease;[54,57,66] therefore, thresholds for severe disease are cause-dependent. Consistency in all measures of mitral regurgitation severity is essential to appropriately grade disease severity (table 2). Haemodynamic assessment is completed with doppler measurement of cardiac index and pulmonary pressure.

Doppler echocardiography also measures left-ventricular and left-atrial consequences of mitral regurgitation. End-diastolic left-ventricular diameter and volume indicate volume overload whereas end-systolic dimension shows volume overload and ventricular function.[9] Patients with left-ventricular ejection fraction less than 60% or

end-systolic diameter of at least 40–45 mm are regarded as having overt left-ventricular dysfunction.[6] Left-atrial diameter indicates volume overload but also conveys important prognostic information.[67] Left-atrial volume was recommended as the preferred measure of atrial overload,[68] (at least 40 mL/m² for severe dilatation) and predicts the occurrence of atrial fibrillation.

Exercise tests are used to define functional capacity. One in five asymptomatic patients shows severe functional limitations during cardiopulmonary exercise.[51] Peak oxygen consumption compared with that expected for age, sex, and weight objectively measures functional limitations versus normal reference values.[51] Other exercise modalities, such as supine-bike exercise, examine changes in severity of mitral regurgitation with activity,[66] especially seen in ischaemic and functional disease and might reveal poor prognosis when ERO area increases. Standard postexercise echocardiography was used to detect exertional ventricular volume increase as a predictor of postoperative left-ventricular dysfunction,[69] but difficulties in measurement of monoplane ventricular volumes hinder this approach. Other stress tests are rarely used. Dobutamine echocardiography reduces mitral regurgitation universally,[70] but in selected patients with ischaemic disease it might reveal viability and ischaemia.

MRI shows mitral regurgitation jets, with limitations similar to those of colour-flow imaging; quantitative measurements are possible but validation studies are few.[71] This imaging method is unique in revealing ventricular scars and in assessment of viability in ischaemic disease and is useful in measurement of ventricular volumes[72] but its incremental diagnostic role remains unknown.

Detection of hormonal activation is important in many cardiac diseases. Atrial natriuretic peptide has little specificity for mitral regurgitation and is strongly activated by arrhythmias, irrespective of mitral regurgitation severity.[73] B-type natriuretic peptide is of greater value than atrial natriuretic peptide in patients with regurgitation.[74] Its activation in organic disease is determined by the consequences—mostly left-atrial enlargement, symptoms,[75] rhythm, and left-ventricular function[74]—rather than the severity of regurgitation. Importantly, its activation is associated with poor outcome and should alert clinicians.[74] Strong B-type natriuretic peptide activation is noted in functional mitral regurgitation linked to the severity of end-systolic ventricular changes and of mitral regurgitation. Subtle sympathetic activation and altered β receptors[76] in organic disease might indicate left-ventricular dysfunction[77,78] but are usually less prominent than in functional disease.

Cardiac catheterisation is not consistently used by institutions and might be overused in some.[3] In academic centres, it is rarely used to define haemodynamics, which are usually provided by doppler echocardiography. Left ventriculography and right-heart catheterisation are rarely needed for assessment of mitral regurgitation.[13] Conversely, in most patients aged 45 years or older, coronary angiography is routinely done preoperatively.[79]

Natural history and clinical outcome

Although a few prospective studies are available,[9,80,81] most data for mitral regurgitation outcome are extracted from observational series. Clinical outcome under medical management and after surgery is different in organic and functional disease.

Natural history of organic regurgitation has been poorly defined, largely because of limitations in severity assessment. Old studies, before echocardiography, showed a wide range in 5-year survival rates from 27% to 97%, probably related to variations in severity.[82] Most data (table 3) were from studies of patients diagnosed with mitral regurgitation due to flail leaflets,[84] most of whom had severe regurgitation. Such patients have ventricular enlargement causing the notable volume overload and incur excess mortality overall;[84] mortality was especially high in patients with class III–IV symptoms but also notable in those with no or minimum symptoms.[84] A sudden death rate of 1·8% per year overall varied from as high as 12·0% per year in patients with class III–IV symptoms who had not undergone surgery to 0·8% per year in asymptomatic patients with normal ejection fraction and sinus rhythm.[85,86] Patients in some mitral regurgitation subsets have low mortality,[81] such as young patients (<50 years) even with severe mitral regurgitation[83] or those of all ages with initially a moderate disorder.[9] Conversely, in a prospective study of asymptomatic patients with long-term follow-up, those with severe regurgitation proven by quantitative measurements showed increased mortality under medical management.[9] Thus, older patients (≥50 years) with severe (defined as ERO area ≥40 mm²) organic mitral regurgitation are at increased risk of mortality (yearly rates of about 3% for moderate regurgitation *vs* 6% for the severe organic form). For morbid complications, all studies substantiated the adverse effect of severe regurgitation.[81] Patients with flail leaflet[84] and in general those with severe mitral regurgitation[9,80] had, under medical management, yearly cardiac event rates of 10–12%—including about 9% for heart failure and 5% for atrial fibrillation.[67] Within 10 years of diagnosis, cardiac events arise in most patients with severe mitral regurgitation, and death occurs or cardiac surgery is needed in at least 90%, making surgery an almost unavoidable consideration in such patients.[84] The risk of stroke is low, but in excess of that expected in old patients[87] and is strongly linked to occurrence of atrial fibrillation, and thus to left-atrial size.[87] Predictors of reduced survival under medical management are symptoms (class III or IV), even if transient,[84,85] reduced ejection fraction,[83–85] severe mitral regurgitation with ERO area of 40 mm² or more,[9] and hormonal activation, although not as well substantiated.[74] Predictors of cardiac events are atrial fibrillation,[83] left-atrial enlargement of at

	Number of patients	Symptoms	MR cause	MR severity	Age (years)	LV diameter (mm)	Study specifics	Yearly mortality	Yearly cardiac events	Relative risk (95% CI) with surgery
Enriquez-Sarano, et al[9]*†	129	0	Organic	Moderate (ERO area 20–39 mm²)	65	56	Quantitative; prospective	3%‡	8%	..
Rosenhek, et al[81]*	132	0	Degenerative	Moderate to severe	55	56	Referral centre; prospective	1%	6%	..
Avierinos, et al[83]*	153	0	MVP	Moderate to severe	60	58	Community based	6%	14%	..
Ling, et al[84]§	229	19%	Flail leaflets	Severe	66	64	Cause specific	6·3% overall; 4·1% without symptoms	10–11%	0·29 (0·15–0·56)
Grigioni, et al[67]§	360	19%	Degenerative in SR	Severe	65	60	Cause specific	6%	10–11%	..
Rosen, et al[80]§	31	0	Organic	Severe	52	65	Prospective with exercise	..	10%	..
Enriquez-Sarano, et al[9]§†	198	0	Organic	Severe (ERO area ≥40 mm²)	61	61	Quantitative; prospective	9%	15%	0·28 (0·14–0·55)

ERO=effective regurgitant orifice. LV=left ventricle. MR=mitral regurgitation. MVP=mitral valve prolapse. SR=sinus rhythm. *Data for patients with exclusively or mostly moderate MR (as shown by slight ventricular enlargement or quantitative measures), showing average yearly mortality of about 3%. †Mortality computed during the first 3 years of follow-up. ‡Part of the same study of 456 asymptomatic patients with quantified MR. §Data for patients with exclusively or mostly severe mitral regurgitation (as shown by substantial ventricular enlargement or quantitative measures), showing average yearly mortality of about 6%. Outcome after surgery was markedly improved, mortality decreased by about 70%.

Table 3: **Clinical outcome of organic mitral regurgitation under medical management**

least 40–50 mm diameter,[67,83,87] flail leaflet[83] or large ERO area[5,9]—all markers of severe mitral regurgitation—and, during exercise, reduced peak oxygen consumption[51] and possibly reduced right ventricular function.[88]

Clinical outcome after surgery depends on patient-specific, disease-related, and surgery-related factors. Early postoperative mortality is largely affected by age, but improvement of surgical results reduced the risk to about 1% for patients younger than 65 years, 2% for those aged 65–75 years, and 4–5% for older than 75 years.[89,90] Increased surgical risk is also linked to preoperative severe symptoms[8] or heart failure whereas ejection fraction has less effect.[46] Surgery-related determinants of operative risk are governed by mitral reparability, which ensures reduced risk,[91,92] whereas risk is increased with concomitant coronary artery bypass grafting.[79] Other associated procedures, such as tricuspid repair or replacement, or those aimed at treatment or prevention of atrial fibrillation need a longer bypass time, which can increase risk. Long-term, patient-related factors continue to affect outcome, particularly coronary disease[79] or reduced renal function.[46] Age determines mortality but restoration of life expectancy is similar in young and old patients.[89] After surgery, patients with severe symptoms before surgery continue to have increased mortality despite symptom relief, whereas in those with no or few symptoms, restoration of life expectancy can be achieved.[8,93] Similarly, patients with overt preoperative ventricular dysfunction have increased postoperative mortality, especially with ejection fraction less than 50%.[46,50] Generally, a 10% early postoperative reduction in ejection fraction happens after elimination of volume overload, whereas end-systolic characteristics (volume, wall stress) are unchanged.[50] This reduction is lowest after valve repair[91] and is minimised by preservation of subvalvular apparatus during valve replacement.[94,95] Nevertheless, 25–30% of patients with mitral regurgitation present with postoperative left-ventricular dysfunction, especially those with preoperative ejection fraction of less than 60% or end-systolic diameter at least of 40–45 mm.[47–49] Occasional unexpected ventricular dysfunctions arise in patients with ejection fraction greater than 60% and no perfect predictor has been identified. Hence, in some centres, prevention of postoperative left-ventricular dysfunction relies on performance of early surgery when no sign of left-ventricular alteration is present.[96] Coronary disease (even in the absence of angina) increases the risk of left-ventricular dysfunction despite the performance of coronary artery bypass grafting.[79] Although no clinical trial has compared outcomes of patients randomised to repair versus replacement, observational evidence suggests that the major surgical determinant of improved long-term outcome is valve repair,[92,97] which allows restoration of life expectancy[9] and reduces the risk of heart failure after surgery.[91,97,98] Although mitral regurgitation can recur after repair,[99] reoperation rates do not differ after repair compared with replacement.[92,97] Thus, mitral valve repair is widely regarded as the preferred mode of correction of organic mitral regurgitation, especially degenerative.[92,100]

For ischaemic mitral regurgitation, the natural history of the functional form is incompletely defined[101] whereas that of papillary-muscle rupture is known to be rapidly fatal.[25] Whether functional regurgitation intrinsically causes poor outcome, or whether it indicates left-ventricular alterations, is still disputed. However, association of severe ischaemic mitral regurgitation with severe outcomes, independent of ejection fraction, age, and presentation, suggests that the regurgitation is indeed causal of the poor outcome. This prognostic role

of mitral regurgitation is now substantiated by results from studies of patients with acute[56,102,103] or chronic myocardial infarction,[55,57,66] by clinical trials[56] and by population studies.[55] Another important concept is that even modest regurgitation is associated with substantially increased mortality,[56] a fact proved by quantitative data.[57] ERO area of ischaemic mitral regurgitation independently predicts excess mortality.[57] Patients with an area larger than 20 mm² incur about a two-fold increase in mortality risk and about a four-fold increase in the risk of heart failure compared with those with a similar ischaemic left-ventricular dysfunction but no mitral regurgitation.[15,54] The better predictive value of ERO area than that of RVol is explained by the strong link between ERO area and filling pressure.[52] Increase in ERO area with exercise might additionally affect clinical outcome, survival,[66] and heart failure.[53] Nevertheless, a clinical trial is needed to determine whether surgical correction of the valvular consequence (ischaemic mitral regurgitation) improves mortality and heart failure in this mainly ventricular disease.[104–107] Clinical outcome of functional disease caused by cardiomyopathy is not well defined but few data suggest that mitral regurgitation yields poor outcomes.

Outcomes after surgery for functional disease remain suboptimum. Operative mortality is still high despite definite surgical improvements.[108] Long-term mortality and heart failure rates[98] are high, although not unexpected in patients with coronary disease, previous myocardial infarction, reduced ventricular function, and vascular comorbidity. These suboptimum outcomes explain uncertainties in surgical indications. The value of mitral repair compared with replacement is also debated[109] because mitral regurgitation often recurs after repair as a consequence of continued ventricular remodelling, which results in recurrent valve tenting.[58,59,110] Determinants of postoperative outcome are myocardial viability, preserved mitral competence, and absence of sustained or advanced ventricular remodelling.[111] Postoperative outcome of functional mitral regurgitation due to cardiomyopathy is mediocre and whether it is improved compared with outcome under medical management is doubtful.[112] However, with low operative mortality, postoperative heart failure and symptomatic improvements are possible.[113]

Treatment

The natural history of untreated organic and functional mitral regurgitation emphasises the importance of treatment of patients with severe regurgitation. Because the effects of various treatments on survival have not been tested in randomised clinical trials, the value of any approach is estimated on the basis of outcome studies.[6,7]

Medical treatment aims to prevent progression of organic disease. Prevention of endocarditis is directed at forestalling catastrophic infectious complications and sudden mitral regurgitation progression associated with endocarditis.[6] Diuretics often reduce or eliminate symptoms of disease but such improvement should not unduly reassure physicians. Patients who had transiently severe symptoms and improved with treatment continue to be at high risk and should be promptly assessed for surgery.[84] Treatment of organic mitral regurgitation with vasodilators has been advocated on the basis of experimental studies showing reductions in acute RVol and even ERO area with blood pressure reduction.[38] Acutely ill patients with mitral regurgitation benefit from vasodilator treatment. However, despite some encouraging data,[114] translation to chronic treatment of organic disease is unresolved because reported series were small, rarely randomised, and contradictory in conclusions.[115] Activation of the tissue (not systemic) renin-angiotensin myocardial system was shown in organic mitral regurgitation. Consistent pilot studies suggest potential of drugs blocking tissue renin-angiotensin system to stabilise organic disease severity and consequences.[116–118] The effect of such treatments on clinical outcome remains to be shown. β blockade in organic mitral regurgitation has only been tested in animal models and remains conjectural.[119] Conversely, in functional disease, medical treatment has been better studied than in organic disease. Maximum medical treatment of patients with heart failure and left-ventricular dysfunction reduces functional mitral regurgitation.[120] Specifically β blockade—with carvedilol[121,122] or long-acting metoprolol[123]—and inhibition of angiotensin-converting enzyme[124] reduce functional mitral regurgitation severity. These therapies are recommended for treatment of left-ventricular dysfunction. Thus, non-urgent surgical indications should be reviewed after maximum medical treatment has taken effect.

Interventional treatment is not yet approved for clinical use and remains investigational. Percutaneous revascularisation of patients with ischaemic regurgitation is possible but patients are often left with residual regurgitation that affects prognosis so that more effective treatment is necessary.[104] Resynchronisation treatment in left-ventricular dysfunction with delayed conduction might improve functional mitral regurgitation.[125,126] Two specific interventional approaches to treatment are discussed here.

Valvular edge-to-edge attachment mimics the surgical procedure proposed by Alfieri and colleagues,[127] creating a tissue bridge between anterior and posterior leaflets. Percutaneously, this technique uses a clip or sutures deployed through trans-septal catheterisation. Experimental studies have shown success and reliable clip or suture placement through the trans-septal approach (figure 4). Early trials also suggest safety and feasibility with close echocardiographic guidance in centres with much experience of interventional valvular procedures. Data for how well this intervention works are preliminary but encouraging,[128] suggesting that more than 80% of patients can be discharged from hospital with a clip, and

mild or little mitral regurgitation. A randomised trial comparing percutaneous clip and surgery is in progress. The edge-to-edge technique has important limitations. First, the application of this technique is restricted to localised prolapse of the central segment of the anterior and posterior leaflets. Second, annular dilatation is not addressed by the procedure and might cause residual regurgitation.

Annuloplasty aimed at reduction of annular dilatation is under investigation (figure 4), mostly with coronary sinus cinching. Technically, stabilisation of material with sufficient constraining force to obtain more than 20% diameter reduction is a challenge. Most devices are composed of anchoring devices placed in the distal and proximal coronary sinus and an intermediate tensioning or supporting element. Experimentally, reduction of mitral regurgitation is achievable,[129] but clinical results are preliminary.[130] Feasibility through a jugular approach and safety seem to be acceptable. Potential limitations are those of annuloplasty (incomplete valve tenting correction) and those of coronary sinus approach that might reduce only part of the annular circumference with an effectiveness limited by the 1–2 cm sinus-annular distance. Because of safety concerns related to proximity of the coronary sinus and circumflex artery with potential artery compression, non-coronary sinus approaches to annuloplasty and percutaneous ventricular remodelling-constraint devices are being investigated.

On the basis of the success of balloon valvuloplasty for mitral stenosis, percutaneous treatment of mitral regurgitation is expected to be successful but this success will necessitate complex development that needs strong cardiologist–engineer collaboration and rigorous assessment.

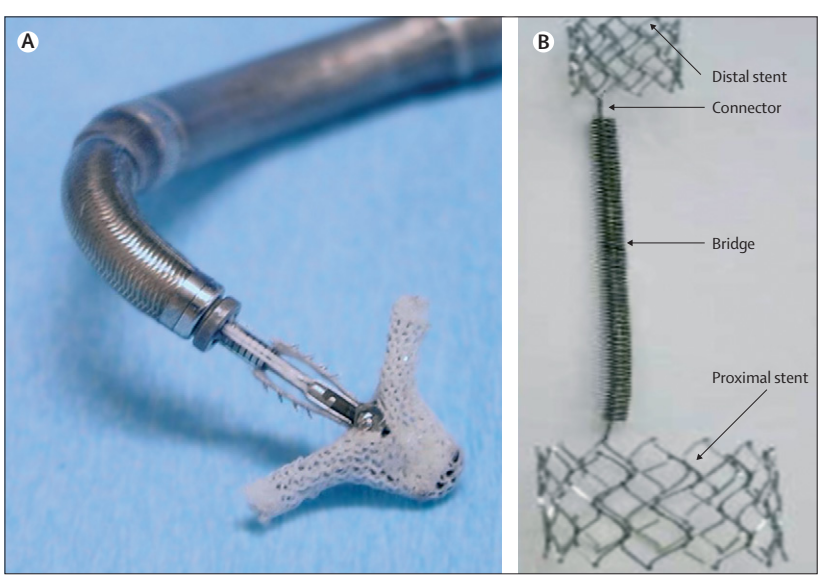

Figure 4: **Percutaneous devices used for treatment of mitral regurgitation**
(A) Percutaneous clip introduced by venous and trans-septal approach into the left atrium and through the mitral orifice. The clip then grabs both leaflets, resuspending them with prolapse. (B) Percutaneous coronary sinus cinching device introduced through the jugular vein into the coronary sinus. The distal stent (smallest) then the proximal stent are deployed. With time the bridge shrinks and cinches the annulus.

Surgical treatment of mitral regurgitation is the only approach with defined clinical success, providing sustained relief of symptoms or heart failure.[6] However, no randomised trial has been done to prove mortality or cardiac event reduction. The standard surgical approach is a median sternotomy, but sometimes only partial sternotomy or minimally invasive surgery through thoracoscopic approach can be used.[131,132]

Valve repair includes an array of valvular, subvalvular, and annular procedures aimed at restoration of leaflet coaptation (ie, valvular normal function) and elimination of mitral regurgitation. These surgical techniques are more successful with redundant than with retracted or calcified leaflets.[11,133–136] For valve prolapse, typical repair (figure 1) is resection (triangular or quadrangular) of the prolapsed posterior leaflet segment whereas the anterior leaflet is rarely resected. Subvalvular support can be obtained by chordal transfer[137] or artificial chords rather than chordal shortening.[138] Annuloplasty is routinely used with annular bands or flexible or rigid rings.[11,139] Many additional technical procedures might be used at the surgeon's discretion to restore coaptation and valve competence. Conversely, in functional mitral regurgitation, valve repair is rather uniform with restrictive annuloplasty substantially reducing the anteroposterior annular diameter.[111] New rings aimed at annular reshaping, specific to each cause of functional regurgitation (ischaemic disease or cardiomyopathy) are now available but their incremental value (compared with traditional rings) is not defined. Valve repair is done in about half of patients who undergo surgery for mitral regurgitation in the USA and Europe.[3] In centres with surgeons proficient in valve repair, more than 80–90% repair rates are achieved.[97] A failed repair is caused rarely by systolic anterior motion of the mitral valve due to excessively redundant tissue or by stenosis, but more often by insufficient correction of a prolapse, recurrence of ruptured chords, and excessive tissue retraction or resection. Overall, reoperation after 10 years is necessary in 5% of patients with repaired posterior leaflet prolapse and 10% of those with anterior leaflet interventions.[97,140] 20–30% of patients with repaired functional mitral regurgitation are estimated to have recurrent regurgitation.[110] Reoperation rate is not greater after valve repair than after replacement[97,140] and because of the morbidity and mortality advantages, valve repair is the preferred method of surgical correction of mitral regurgitation.[91,92,97]

Valve replacement involves insertion of a biological or mechanical prosthesis. Bioprosthetic valve replacement is associated with low embolic risk but shorter durability, whereas mechanical valve replacement is associated with high risk of embolism and haemorrhagic complications (due to intensive warfarin treatment) but

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has potential for long-lasting durability.[6,7] Results of randomised trials showed that within 10 years of surgery these risks are balanced.[141,142] Older age determines the probability that bioprosthetic durability will be longer than life expectancy, and is the main bioprosthesis insertion indication (usually >65 years of age).[6] Ability to achieve high-quality anticoagulation and patient's desire also affect the choice of prosthesis. Irrespective of the prosthesis selected, conservation of subvalvular apparatus is essential for preservation of ventricular function. The risk of prosthetic complications makes surgical indications more restrictive when valve replacement is likely.[6]

Controversies and guidelines for treatment

In view of the experimental nature of medical and interventional treatments for mitral regurgitation, surgery is the only treatment recommended by management guidelines.[6,7] Because surgery is associated with small but definite risks, those patients with a higher risk of spontaneous complications than of surgery-related complications are selected. Guidelines should, in our opinion, be interpreted as a minimum to be applied by all physicians but should not deter centres with better results than those of other centres from providing advanced care to patients with mitral regurgitation. Furthermore, the absence of clinical trials and few prospective studies create ample controversy, which should be addressed in future studies.

The natural history of mitral regurgitation has been described in individual centre studies, which have provided discordant data,[9,81,84] most of which is explained by differences in age, disease severity, and referral biases. Thus, multicentre data are essential to reconcile these discordant results. Assessment of the severity of mitral regurgitation is not uniform between centres, especially with use of qualitative assessment. The generalisability of quantitative assessment should be assessed in a multicentre study to provide benchmarks for the American Society of Echocardiography guidelines.[5] Moderate regurgitation represents a wide range of clinical situations.[9] Selection of patients who need treatment and the potential role of medical and percutaneous interventional treatments should be assessed prospectively. Improved characterisation of functional mitral-regurgitation grading and the effect on outcome is needed.[15] Specifically, the effect of surgical correction on outcome remains disputed.[143] The benefit of early surgery (ie, valve repair in asymptomatic patients) versus a watchful wait was suggested in observational studies[96] but is controversial.[81] To resolve these issues, clinical trials of surgery for mitral regurgitation will be necessary.

Although approaches to surgical indications are detailed in clinical guidelines,[6,7] they are summarised here. Rescue surgical indications—class I by guidelines—are compulsory. Patients with organic mitral regurgitation who have developed severe symptoms (class III or IV), heart failure, or signs of overt left-ventricular dysfunction (ejection fraction <60% or end-systolic dimension ≥40–45 mm) have an immediate high risk and therefore prompt surgery—repair (preferable) or replacement—is indicated.[6,7] Even with advanced heart failure or ventricular dysfunction, contraindications to surgery are rare as long as mitral regurgitation remains severe,[7] emphasising the importance of quantitative assessment of disease.[5] Such rescue surgery is indispensable, but is not the preferred timing for surgery in organic disease. Indeed, patients who need to be operated on at such a late stage of their disease have increased mortality after surgery. This outcome emphasises the importance of early detection and assessment of mitral regurgitation. In functional regurgitation, rescue surgery is the most frequent surgical indication, but consideration should be given to surgery in symptomatic patients before heart failure becomes intractable.

Restorative surgical indications—class II by guidelines—are optional. Patients with no or minimum symptoms at baseline cannot expect substantial symptomatic improvement. Those with functional mitral regurgitation are rarely candidates for restorative surgery while asymptomatic but might be suitable for valve repair if coronary artery bypass grafting is necessary independently of the mitral regurgitation. In organic regurgitation, postoperative outcome studies in patients with no or minimum symptoms before surgery show restoration of life expectancy,[8] emphasising the importance of this approach. Patients who are asymptomatic but had either reduced functional capacity by objective exercise testing, hormonal activation, or paroxysmal atrial fibrillation are specific but not exclusive candidates for restorative surgery. To ensure success of such restorative surgery, important requirements form the basis of advanced mitral-valve-repair centres.[133] First, surgical risk should be very low, below 1% in asymptomatic patients. Second, high-quality non-invasive mitral-regurgitation assessment should be available with complete description of causes, mechanisms, localisation of lesions, and quantitative assessment of regurgitation. Third, high repair rates of at least 80% of patients with mitral regurgitation are essential to qualify as an advanced repair centre.[144] Last, high quality intraoperative assessment of disease and of surgical results is essential to avoid residual disease. In such centres, many indications for surgery in asymptomatic patients are supported by most guidelines.[6]

Contributors

All authors contributed to the conceptualisation of the Review; acquisition, analysis, and interpretation of the data; drafting of the Review; and critical revision of the Review for important intellectual content.

Conflicts of interest

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