Progress in the Treatment of Severe Mitral Regurgitation

Héctor I. Michelena,[a] Valentina M. Bichara,[a] Edit Margaryan,[a] Inga Forde,[a] Yan Topilsky,[a] Rakesh Suri,[b] and Maurice Enríquez-Sarano[a]

[a]División de Enfermedades Cardiovasculares, Clínica Mayo, Rochester, Minnesota, United States
[b]División de Cirugía Cardiovascular, Clínica Mayo, Rochester, Minnesota, United States

Organic mitral regurgitation (MR) is prevalent in the general population. Disease progression, involving potentially irreversible left ventricular dysfunction, implies a poor prognosis for patients who do not receive appropriate treatment. Immediate rescue surgery is indicated in those with severe MR in whom subclinical left ventricular dysfunction is suggested by echocardiographic measurements or the presence of symptoms, however minor. Patients whose symptomatology is unclear should be evaluated by exercise testing. Not all forms of severe organic MR are the same: the presence of risk factors in patients with severe asymptomatic MR and preserved ventricular function indicates a suboptimal prognosis over the medium-to-long term and should prompt early mitral repair if there is a low surgical risk and the probability of a successful repair is >90–95%. The patient should be referred to a specialized surgical center if necessary. Appropriate training of surgeons in mitral repair is essential. Ischemic MR carries a worse prognosis and the risk of surgery is higher. Consequently, treatment decisions must be patient-specific and take into account the possibility of repair, the risk of surgery, and the need for concomitant surgical revascularization. New percutaneous approaches to mitral repair are being developed for selected patient groups.

Key words: *Regurgitation. Mitral valve. Treatment.*

Avances en el tratamiento de la insuficiencia mitral grave

La insuficiencia mitral (IM) orgánica es prevalente en la población. Su progresión, con deterioro potencialmente irreversible de la función ventricular izquierda, pone de manifiesto el grave pronóstico de los pacientes que no reciben tratamiento oportunamente. La detección de disfunción subclínica del ventrículo izquierdo a través de parámetros ecocardiográficos o la presencia de síntomas, así sean mínimos, indican cirugía de rescate inmediata en la IM grave. Los pacientes con sintomatología incierta deben ser evaluados con prueba de esfuerzo.

No todas las IM orgánicas graves son iguales: la presencia de factores de riesgo en la IM grave asintomática con función ventricular normal indica peor pronóstico a medio y largo plazo, lo cual debe estimular la cirugía temprana con reparación si el riesgo quirúrgico es bajo y la posibilidad de reparación es > 90-95%. Si es necesario, se debe referir al paciente a centros especializados. El entrenamiento adecuado de cirujanos en la reparación mitral es crítico. La IM isquémica acarrea un peor pronóstico, con mayor riesgo quirúrgico, y las decisiones sobre el tratamiento deben ser específicas para cada paciente, teniendo en cuenta la posibilidad de reparación, el riesgo quirúrgico y la necesidad de revascularización quirúrgica concomitante. Se está estudiando nuevos procedimientos percutáneos para pacientes seleccionados.

Palabras clave: *Insuficiencia. Válvula mitral. Tratamiento.*

INTRODUCTION

Mitral regurgitation (MR) is characterized by flow reversal in systole from the left ventricle (LV) into the left atrium. The etiology of MR is predominantly primary or organic (intrinsic alteration of the leaflets), and in developed countries is most commonly degenerative. In less developed countries, the etiology is most frequently rheumatic. Functional MR (normal leaflets with annular dilation or apical displacement of the point of apposition of the leaflets -tenting- secondary to dilated cardiomyopathy or LV ischemia) continues to increase due to the global epidemic of heart disease. Chronic organic MR is the most common valvular disease in the United States, with a prevalence of moderate or severe MR of 1.7% in the general population, 6.4% of individuals between 65 and 74 years, and 9.3% in those aged >75 years.[1] Doppler echocardiography has proved to be the ultimate non-invasive method for diagnosis and treatment decision-making. This review aims to

ABBREVIATIONS

CABG: coronary artery bypass graft
EF: ejection fraction
ERO: effective regurgitant orifice
ESD: end systolic diameter
LV: left ventricle
MR: mitral regurgitation
RVol: regurgitant volume

discuss current thinking on the natural history, progression, consequences, and treatment of severe MR. We propose an algorithm that emphasizes the importance of a comprehensive echocardiographic assessment of MR as a starting point, followed by consideration of multiple clinical factors which should be applied on an individual basis to obtain the best treatment plan for each patient.

TREATMENT OF ACUTE MITRAL REGURGITATION

Acute IM constitutes a surgical emergency. It has a mortality rate of 15%-20% at 30 days.[2] Common causes are chordal rupture, bacterial endocarditis, ischemic rupture of the papillary muscle, acute rheumatic carditis, acute cardiomyopathy, and acute prosthetic dysfunction. The affected patient presents dyspnea, hemodynamic instability, and symptoms of shock. However, some patients may have dyspnea without clinical hemodynamic deterioration. These patients may be misdiagnosed with another process, because physical examination may not provide clear evidence of a slight systolic murmur. This makes the physician's clinical suspicion essential. The transthoracic echocardiogram shows a normal-sized hyperdynamic LV and an MR jet that may be inconspicuous, due to the predominance of the jet's potential energy (giant V-wave pressure) as opposed to its kinetic energy (speed). The transesophageal echocardiogram in this case is crucial, because it reveals the mechanism underlying the MR and provides a clearer picture of its severity. Medical therapy with vasodilators, vasopressors, and aortic balloon are used to stabilize the patient in preparation for immediate surgery, but should not delay surgery. Up to 7% of patients with ischemic cardiogenic shock (acute) have severe MR, and mortality is higher than in those without MR. Mortality is reduced with immediate revascularization so that, where surgical revascularization is indicated, the presence of severe MR should be a motive for even quicker implementation.[2]

NATURAL HISTORY OF SEVERE CHRONIC MITRAL REGURGITATION

Mitral regurgitation is a progressive disease, with average annual increases of 5-8 mL in regurgitant volume (RVol) and 4-6 mm^2 in the effective regurgitant orifice (ERO). Anatomical changes are determinants of progression, which is faster in patients with mitral valve prolapse, especially in those with ruptured chordae (up to 20 mL per year), and in patients with mitral annular dilatation. The progression of MR can lead to adverse LV remodeling, and development of ventricular dysfunction.[3] In these cases, ejection fraction (EF) may initially be "normal" (>50%) and symptoms may not be present, though prognosis is worse than in the unaffected population. Published estimates on long-term survival in patients with MR vary considerably.[4,5] At the Mayo Clinic, we analyzed the natural history of MR caused by ruptured chordae tendineae[6] and found significant mortality in MR (6.3% annually) compared with expected survival in the general population. There was also substantial morbidity at 10 years, with incidences of atrial fibrillation (AF) and heart failure of 30% and 63%, respectively. At 10 years, 90% of patients had died or undergone surgery, making the operation almost inevitable in this population. Patients who were even temporarily in New York Heart Association (NYHA) functional class III-IV showed high mortality (34% annually) if they were not operated on, but mortality was high (4.1% annually) even among those in functional class I-II. Patients with EF <60% also showed excess mortality compared to those with EF >60% on medical treatment. So waiting for a reduction in EF to <60%, or for the appearance of NYHA functional class II symptoms does not seem appropriate, as prognosis with treatment will be worse.

Sudden death is a cataclysmic event in severe MR with rupture of chordae tendineae and causes about 25% of deaths of patients on medical treatment.[7] Overall, the sudden death rate is 1.8% annually and even in patients without other risk factors (severe symptoms, LV dysfunction, and HF) is 0.8% per year. These data highlight the poor prognosis implied by severe organic MR, especially when ruptured chordae are involved. This is likely due to their being associated with massive MR (RVol >100 mL per beat and ERO >0.5 cm^2) in 85% of cases.

LEFT VENTRICULAR DYSFUNCTION: ECHOCARDIOGRAPHIC PARAMETERS

During ventricular systole, the RVol of MR heads to the left atrium with decreased ejection impedance, and afterload remains normal. A normal afterload

coupled with volume overload can maintain a normal or supranormal EF for a considerable time, and irreversible LV dysfunction can coexist with normal EF.

The EF and end-systolic diameter (ESD) of the LV are the most practical parameters for evaluating the LV as they are easy to quantify using an echocardiograph and because of their predictive power (they represent an approximation to intrinsic LV contractility). Left ventricular dysfunction (EF <60%) indicates poor prognosis with conservative treatment[6] and even postoperatively[8] regardless of the type of surgical correction used (Figure 1). Although advances in anesthesia and myocardial protection have meant that perioperative death is rare, LV dysfunction is still the most common cause of late postoperative death.[8] Thus, despite an improvement in symptoms, LV dysfunction occurs in about one third of patients with organic MR who are operated on successfully. Such dysfunction is associated with poor survival[3,9] and a high incidence of heart failure,[10] which must be prevented.
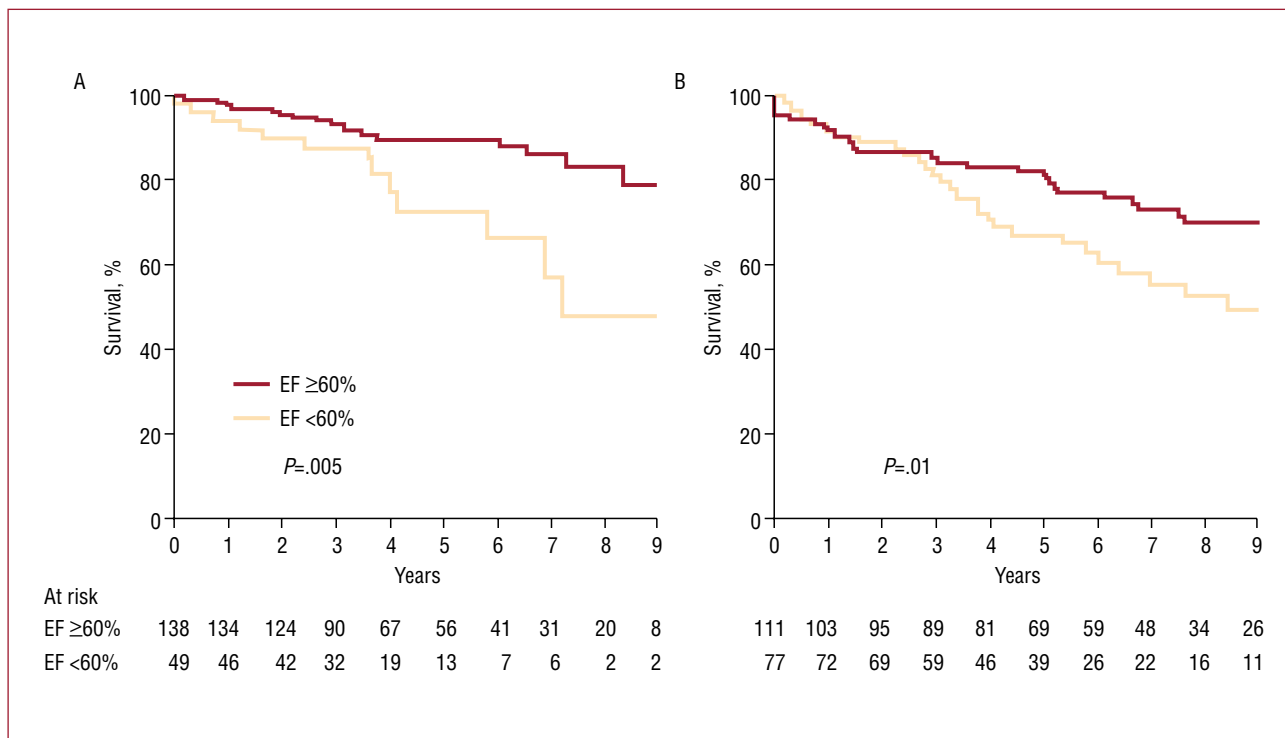
The ESD is also essential in predicting the reduction in postoperative EF[3] and survival. It has recently been shown that waiting for the ESD to reach ≥40 mm is independently associated with poorer postoperative survival in the medium and long term in severe MR (Figure 2).[11]

Subjects with EF <60% and / or ESD ≥40 mm should be considered as patients with manifest LV dysfunction even if they are asymptomatic, and, where it is not contraindicated, they should receive salvage surgery[12] (Table 1). This implies a discrepancy between current recommendations (Table 1) and those of the current authors (see below), but using EF <60% and ESD ≥40 mm as indicators for surgery may involve too long a delay and will lead to poorer medium and long term survival (Figures 1 and 2).

MITRAL SURGERY: RECENT ADVANCES

Mitral regurgitation is the result of a mechanical dysfunction of the mitral valve and definitive correction is also mechanical (surgical). The mitral valve is not an isolated entity; it is closely related to the LV and ensures the latter's geometry and function via the connection through the chordae tendineae. For that reason, mitral repair with preservation of the subvalvular apparatus forms the basis of current surgical treatment. In patients with organic MR, operative mortality has decreased considerably,[13] especially with mitral repair (Figure 3). In the Mayo Clinic in Rochester, operative mortality is around

At risk										
EF ≥60%	138	134	124	90	67	56	41	31	20	8
EF <60%	49	46	42	32	19	13	7	6	2	2

|										
	111	103	95	89	81	69	59	48	34	26
	77	72	69	59	46	39	26	22	16	11

Figure 1. Kaplan-Meier curves showing postoperative survival in severe mitral regurgitation, based on ejection fraction and surgical technique. A: although mitral repair is carried out, postoperative survival decreases if preoperative ejection fraction is <60%. B: the same result is obtained with mitral replacement. Reprinted from Enriquez-Sarano et al,[8] with permission from the American Heart Association. EF indicates ejection fraction.

TABLE 1. Summary of Indications for Mitral Surgery in Severe Mitral Regurgitation

Type of Indication	Specific Clinical Situation in Severe Mitral Regurgitation
Class I	Mitral repair should be recommended in the majority of patients referred for surgery
	Symptomatic acute MR
	Symptomatic chronic MR
	Asymptomatic chronic MR with EF <60% and/or LV ESD ≥40 mm
Class II	**Class IIa**
	Asymptomatic chronic MR with EF >60% and/or LV ESD <40 mm in a specialized center offering >90% probability of repair and low surgical mortality
	Asymptomatic chronic MR (EF >60%, LV ESD <40 mm) with new atrial fibrillation or pulmonary hypertension >50 mmHg resting or >60 mmHg when active
	Chronic MR with EF <30% or LV ESD >55 mm where repair is highly feasible
	Class IIb
	Chronic secondary MR (ischemic) with EF <30% and functional class (NYHA) III-IV in spite of maximal medical treatment, including resynchronization, only if the valve can be repaired

ESD indicates end systolic diameter; EF, ejection fraction, MR: mitral regurgitation, NYHA, New York Heart Association; LV, left ventricle; RVol, regurgitant volume.
Current indications for mitral surgery at the American College of Cardiology and American Heart Association.[11] These indications refer to severe mitral regurgitation with RVol ≥60 mL/beat and ERO ≥0.4 cm² and are aimed at organic and primary mitral disease, except where indicated in ischemic etiology.
Class I are indications whose effectiveness is established and accepted.
Class II are indications whose efficacy is less well established and there are divergent views (IIa is favored and IIb is in debate).
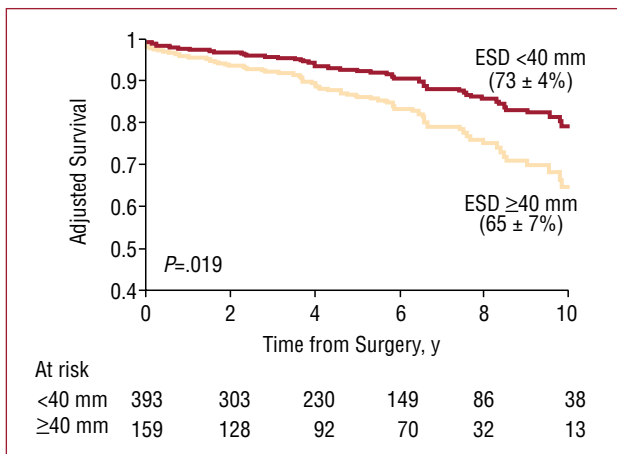
Figure 2. Kaplan-Meier postoperative survival curves in severe mitral regurgitation by end systolic diameter (ESD). Survival is significantly reduced in patients with ESD ≥40 mm, independently of whether symptoms are present. Reproduced from Tribouilloy et al,[11] with permission from Elsevier.

1% in patients under 75 years in cases of mitral valve repair or replacement,[8] and <1% in isolated repair. By contrast, operative mortality in patients over 75 years is approximately 5% in our institution. However, surgery in patients over 75 years leads to survival which approximates life expectancy in these patients to that of the general population.[14] Surgery in organic disease (usually fibroelastic deficiency in this age group) should therefore be considered in these patients to prevent LV dysfunction and restore normal survival.

Previous studies indicate lower perioperative mortality and greater long-term survival after valve repair.[15,16] In our experience, after adjusting for clinical differences among patients receiving repair versus replacement, valve repair per se is an independent predictor of better outcomes after surgery for MR.[10] The experience of the surgical center is essential to achieving optimal results. Hospitals performing over 140 repairs per year achieve surgical mortality rates of close to 1%, compared to 3% in hospitals performing fewer than 140 repairs per year.[17] Intraoperative transesophageal echocardiography is an essential component in successful valve repair and should be performed by experienced clinicians. They should supervise the procedure and assist in intraoperative decision-making.[18]

Currently, success rates in mitral repair are around 90%-95%. This high rate of success is possible once the surgeon's initial learning curve is completed and by using special techniques such as chordal transposition or insertion of artificial chordae, in particular to repair ruptured chordae tendineae in the anterior leaflet.[19,20]

Unfortunately, mitral repair in rheumatic lesions is not as successful.[21] However, mitral repair in rheumatic MR should be performed when anatomically and functionally possible, because it is associated with longer survival than valve replacement. Mitral replacement decreases the need for re-intervention in rheumatic MR, but limits survival and increases the risk of embolic complications.[22]

TIMING OF SURGERY

There are 2 strands in current thinking as to when surgery should be performed in severe MR.
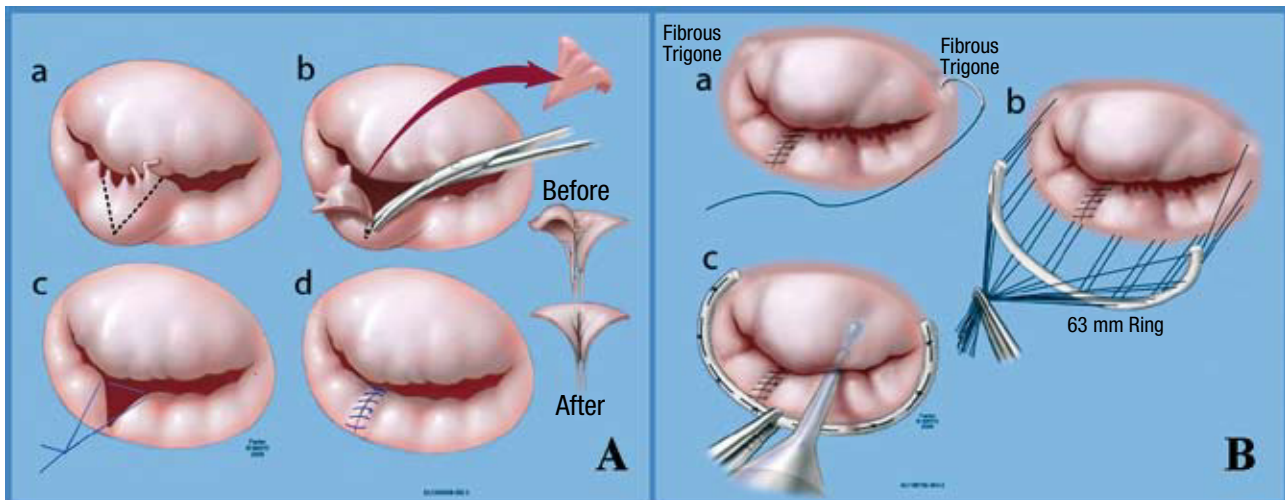
Figure 3. Mitral repair. Basic surgical concepts. A: a, P2 segment of the posterior leaflet without support due to chord rupture; outline of triangular resection (dotted line); b, triangular resection of P2; c and d, apposition and suturing of free edges. B: suturing of a 63 mm band (standard at the Mayo Clinic) to the fibrous trigones of the mitral ring (a and b), followed by integrity test with saline solution (c).

One of these recommends "watchful waiting" until the onset of symptoms or indicators of subclinical dysfunction in asymptomatic patients (eg, EF <60%, ESD LV>40 mm), with echocardiographic evaluation of the patient every 6 or 12 months. The other approach recommends considering "early mitral repair," ie, intervening before symptoms or indicators of subclinical LV dysfunction are present. This approach stresses the need for sufficient evidence of MR severity, obtained by appropriate echocardiographic quantification (with information on the values of RVol and ERO), and a likelihood of successful repair of >95%, with operative mortality of 1% or less. These conditions require a cardiologist who is able to quantify the MR and critically evaluate the patient, a surgeon with experience in mitral repair, and an experienced postoperative team. Estimation of MR severity should include quantitative methods and indicators or existing support (Table 2).[23] The most widely used quantitative techniques are Doppler quantification and the PISA (proximal isovelocity surface area) method. Both are based on the analysis of proximal flow convergence in the ERO region[24,25] and allow for the calculation of RVol and ERO.[26,27]

However, we believe that the two strands of thought mentioned are not mutually exclusive but are complementary, and indicate the spectrum of severity and risk in severe MR. In other words, patients with severe MR are not all the same. In the Mayo Clinic, 198 asymptomatic patients with severe MR (mean age, 63 years; mean RVol, 66 mL/beat; mean ERO, 0.4 cm^2) were studied prospectively. Mean LV and diastolic ESDs were 37 mm and 61 mm,

respectively.[28] We found that an ERO >0.4 cm^2 in asymptomatic patients was independently associated with decreased survival at 5 years (58% compared to 78%, P=.03) while surgical repair was associated with better outcome. We therefore recommend consideration of early surgery in asymptomatic patients with severe MR. The incidence of clinical events in these patients was 10%-15% per year. By contrast, Rosenhek et al[29] prospectively evaluated 132 asymptomatic patients with severe organic MR, and found that survival at 8 years was similar to that in the general population when "watchful waiting" to the onset of symptoms or echocardiographic indicators was employed. They concluded that this strategy was therefore appropriate. However, the average age of these patients was 55 years, LV and diastolic ESD were 34 mm and 56 mm (severe MR), and MR was not quantified using quantitative Doppler or PISA techniques. The incidence of total medical events was also much lower than in the previous study. The latter study therefore treated younger patients with likely moderate-severe MR, while ours included patients with more severe MR. A third group of researchers, Kang et al[30] studied 447 consecutive patients with severe organic MR (mean age, 50 years; mean ERO, 0.8 cm^2) managed using "early mitral repair" or "watchful waiting." A propensity matching subgroup of 127 pairs of patients was used to control for basic clinical features, and a high percentage (44%-46%) had ruptured chordae tendinaea; mean LV and diastolic ESD were 36 mm and 59 mm, respectively. Early elective surgical repair was associated with no mortality at 7 years, compared to 5% at 7 years for "watchful

TABLE 2. Echocardiographic Estimation of Deverity in Mitral Regurgitation

	Mild	Moderate	Severe	
Specific signs	Central jet <4 cm^2 or <20% of atrial area	Intermediate signs	Central jet >40% of atrial area or with Coanda effect	
	Vena contracta <30%		Vena contracta >0.7 cm	
	Small convergence zone		Large convergence zone	
			Systolic reversal in pulmonary veins	
			Rupture of chordae tendinosae or papillary muscle	
Support signs	Systolic flow dominant in the pulmonary veins	Intermediate signs	Continuous wave Doppler signal with dense triangular jet	
	A wave dominant in transmitral pulsed-wave Doppler		E wave dominant (>1.2 m/s) in transmitral pulsed-wave Doppler	
	Continuous wave Doppler signal with gentle, parabolic jet		Dilatation of LV and atrium	
	Normal size LV			
Quantitative parameters				
RVol, mL/beat	<30	30-44	45-59	≥60
RF, %	<30	30-39	40-49	≥50
ERO, cm^2	<0.2	0.2-0.29	0.3-0.39	≥0.4

ERO indicates effective regurgitant orifice; LV, left ventricle; RF, regurgitant fraction, RVol, regurgitant volume.
Adapted from Zoghbi et al,[23] with permission from Elsevier.

waiting." This third study was similar to ours in terms of echocardiographic severity and degree of LV dilation, although patients were younger. Thus, none of the studies were wrong, they just included different patients with different degrees of severity within an overall severe MR.

NOT ALL SEVERE ORGANIC MITRAL REGURGITATIONS ARE EQUAL: RISK FACTORS

From the previous discussion it follows that there are different levels and risk factors in severe MR (Table 3). The first risk factor is age. Studies agree that patients >55 years are at greater risk of complications, probably because of decreased contractile reserve associated with age. However, it is difficult to establish a cut-off age above which risk increases significantly. Chordal rupture and / or massive MR (RVol >100 mL and ERO >0.5 cm^2) are risk factors within the spectrum of severe MR. The annual incidence of AF is 5% in patients with significant organic MR, and its appearance is associated with decreased survival.[31] Even after valve repair, the presence of AF prior to the repair is associated with decreased survival at 5 years compared to normal sinus rhythm before repair (87% compared to 96%, P=.002).[32] Increased levels of brain natriuretic peptide (BNP) represent another risk factor, which was assessed in a prospective study of 124 patients with organic MR. Raised BNP levels are related to the consequences of regurgitation (eg, LV and left atrium volume, AF, and symptoms) and is an independent predictor of mortality and heart failure, regardless of whether symptoms are present or not.[33] This concept has been reassessed and validated prospectively in 269 consecutive patients, and it has been shown that a BNP value of ≥105 pg/mL is associated with 4.6 times greater risk of heart failure, decreased EF and death in asymptomatic patients with severe organic MR.[34]

The presence of pulmonary hypertension observed using echocardiography is another risk factor predicting a worse prognosis.[12] Recent analysis using data from the MIDA registry showed that risk of death is 2.5 times higher in patients with severe organic MR and pulmonary hypertension (unpublished data). Finally, whether or not the patient recognizes symptoms may be influenced by idiosyncratic differences in perception, fear of surgery, or because he / she performs little physical activity or has adapted levels of physical activity to accommodate the limitations imposed by mild symptoms. In 134 patients with severe organic MR and normal EF who self-classified as asymptomatic, we found that 1 in every 4-5 had a significant reduction in peak oxygen consumption (<85% of predicted values by age and sex) with evidence of limitation in exercise cardiac output and low functional capacity. These "asymptomatic" patients turned out to have greater number of adverse events or surgery within 3 years of follow-up.[35] It is therefore essential to stress test patients when there is any degree of uncertainty about symptoms. These risk factors should be taken into account when deciding the appropriate time for surgery for each patient (Figure 4).
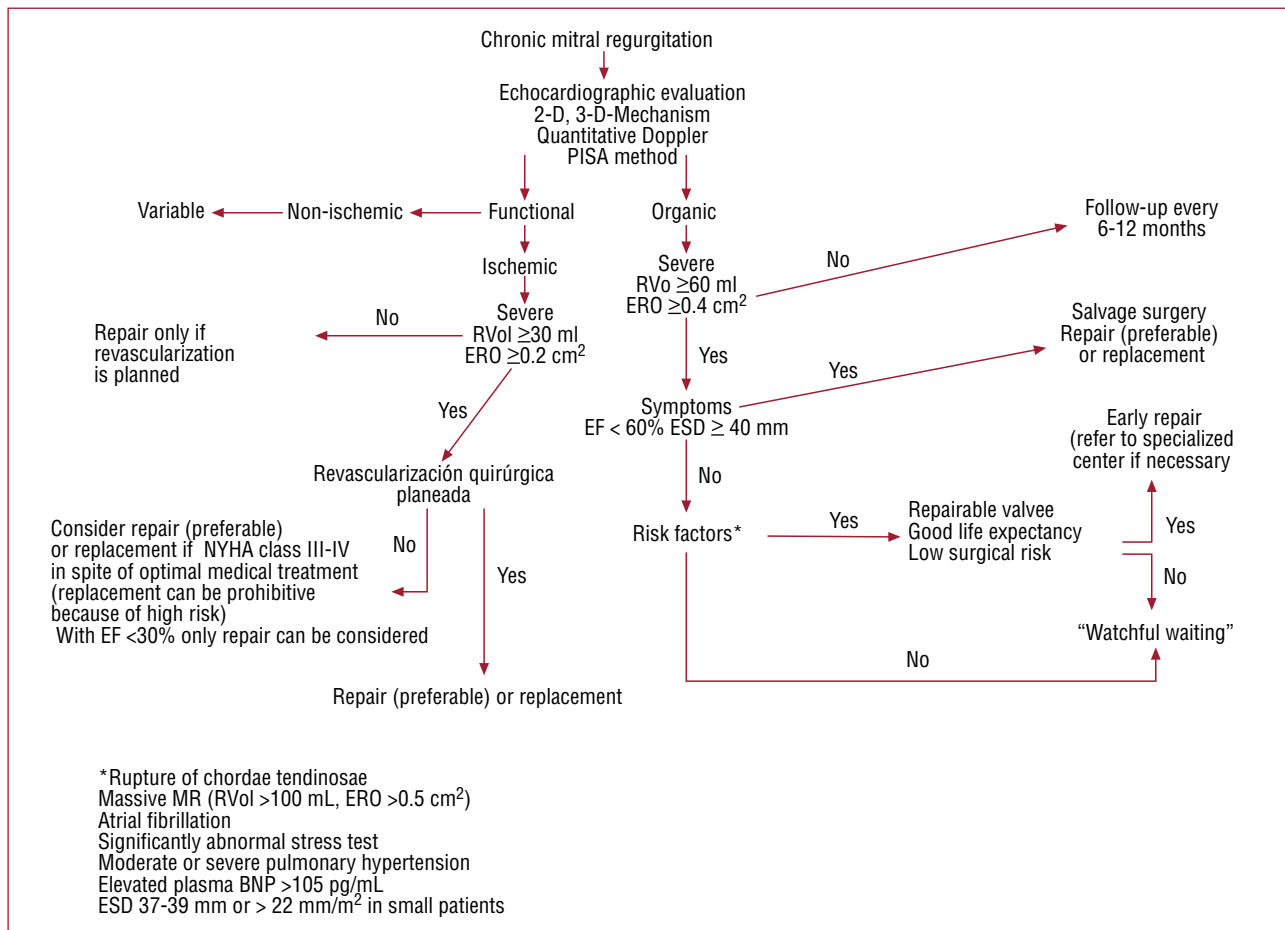
Figure 4. Algorithm for treatment of mitral regurgitation. BNP indiates brain natriuretic peptide; ESD, end systolic diameter; EF, ejection fraction; ERO, effective regurgitant orifice; MR, mitral regurgitation, NYHA, New York Heart Association; RVol, regurgitant volume.

MODERN TREATMENT OF SEVERE CHRONIC ORGANIC MITRAL REGURGITATION

Figure 4 provides a simple algorithm which tries to summarize the complexity of current management of severe MR. When referring a patient with MR, the etiology / mechanism of regurgitation should be determined. There are three basic mechanisms based on the mobility of the leaflets (Figure 5). The first is normal mobility with poor coaptation due to annular dilation or perforation of a leaflet. The second involves excessive mobility (prolapse or ruptured chordae) and the third, decreased mobility (shrinkage due to inflammatory or ischemic disease) (Figure 5). Organic MR may be due to a type 1 (eg, cleft mitral valve), type 2 (eg, MR arising from Barlow's disease) or type 3 (eg, rheumatic mitral valve) dysfunction. Functional MR is usually due to a combination of dysfunction 1 and 3.

Mitral regurgitation mediated by the second mechanism is the most susceptible to repair, especially when the posterior leaflet is involved and the ring does not show severe calcification. However, repair in the case of Barlow's disease with severe bileaflet prolapse or prolapse isolated from the anterior leaflet is also now as feasible as in isolated prolapse of the posterior leaflet. Repair is therefore possible in the vast majority of cases of mitral prolapse, when it is performed by experts.[21] Once the organic mechanism has been established, it is necessary to definitively confirm that the MR is severe (Table 2). The presence of symptoms, EF <60% or LV ESD ≥40 mm means ventricular dysfunction is manifest and the patient must be referred for salvage surgery (Figure 4). The aim of such surgery is to repair the valve or replace it if repair is not possible. In the absence of manifest ventricular dysfunction, patient risk should be stratified by investigating the presence of risk factors (Figure 4). If risk factors
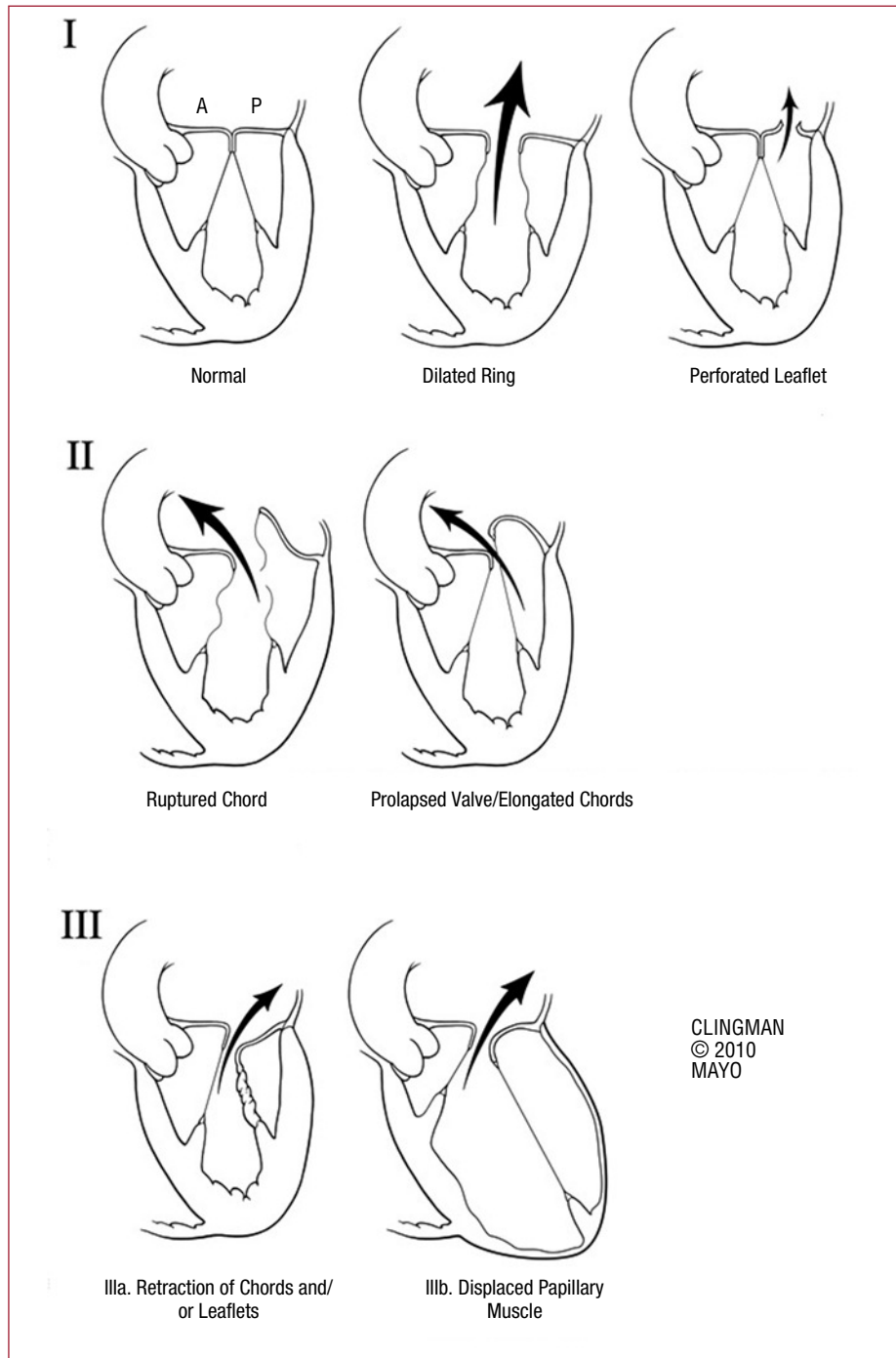
Figure 5. Mechanisms of mitral regurgitation. I: normal mobility of leaflets with annular dilation that causes a central jet or perforation of a leaflet (eg, cleft mitral valve). II: excessive mobility with ruptured chords or severe prolapse (eg, Barlow disease), causing a jet directed to the opposite side of the affected leaflet. III: restricted mobility due to shrinkage of the subvalvular apparatus (IIIa, eg, rheumatic disease) or displacement of the papillary muscle (ischemic remodeling) that causes apical displacement (tethering) of the leaflet (IIIb). Note that in both cases the jet is aimed at the same side of the affected valve.

are present (Table 3), the valve should be repaired early, but not before considering the patient's intrinsic factors and factors inherent to surgery: if the patient has a good life expectancy and the valve is repairable, the operation should be performed in a centre which can guarantee a high surgical success rate and low operative mortality (Figure 4). If necessary, the patient should be referred to a specialized center. If there are no such preconditions, "watchful waiting" (monitoring by a cardiologist with an echocardiogram every 6 months) can be implemented for signs echocardiographic and / or symptoms that indicate need for rescue, repair or replacement. If the patient has risk factors (Table 3), we recommend early repair, as there is a risk of short-term progression and prognosis is affected. There is thus a discrepancy between current guidelines and our recommendations, as we believe that finding

TABLE 3. Risk Factors in Ssymptomatic Severe Organic Mitral Regurgitation with EF >60% and LV ESD <40 mm

Rupture of chordae tendinosae
Massive MR (RVol >100 mL, ERO >0.5 cm^2)
Atrial fibrillation
Significantly abnormal stress test
Moderate or severe pulmonary hypertension
Elevated plasma BNP >105 pg/mL
ESD 37-39 mm or >22 mm/m^2 in small patients

BNP indicates brain natriuretic peptide; EF, ejection fraction; ERO, effective regurgitant orifice area; ESD, end systolic diameter; LV, left ventricle; MR, mitral regurgitation; RVol, regurgitant volume.

risk factors should be a type I indication for early repair. If there are no risk factors, 'watchful waiting' is safe and recommended.

ISCHEMIC MITRAL REGURGITATION: A HIGH RISK GROUP

The high risk implied by the ischemic rupture of a papillary muscle is well-known and requires immediate surgery. Operative mortality for papillary muscle rupture has decreased significantly (67% up to 1990 and 9% thereafter), reflecting the frequent use of revascularization and the surgical advances.[36] In addition, 5-year survival in patients who survive the initial rupture is identical to that of patients with myocardial infarction without papillary muscle rupture. This highlights the importance of early diagnosis and aggressive surgical treatment when this complication is present.

After myocardial infarction, MR can develop without papillary muscle rupture, as a result of LV remodeling due to apical and inferior displacement of the papillary muscles (Figure 5, IIIb). These then pull on the mitral leaflets causing tenting, with the resultant apical displacement of the coaptation point. The strong negative impact of this 'functional' post-ischemic MR after myocardial infarction has been demonstrated in two studies in which the mere presence of even mild ischemic MR was associated with low survival.[37,38] In patients with previous myocardial infarction, MR with an ERO ≥0.2 cm^2 is associated with 30% survival at 5 years, compared to 60% in patients without MR. We therefore believe that an ERO >0.2 cm^2 or RVol >30 mL in ischemic MR represents severe MR (Figure 4). Comprehensive echocardiographic quantification in these patients is essential to determine the severity of MR, as auscultation does not reveal a significant systolic murmur.[39]

The timing of surgery in ischemic MR is more complicated than in organic MR. Although repair is possible in most patients, the risk associated with surgery is greater in ischemic MR. Moreover, even if there is symptomatic improvement with surgical correction of dilated and ischemic MR (usually annuloplasty),[40] benefits in the long-term survival of these patients have not been observed with correction of MR. However, benefits may exist, especially with repair techniques specifically aimed at resolving the tenting and which are not limited to annuloplasty. Prospective studies with randomization of patients are still required, however.

It has not yet been clarified whether ischemic MR is a cause per se of poor prognosis or whether it is simply a marker of the severity of ischemic heart disease.[41] We believe that the degree of ischemic MR is a marker of the severity of heart disease (previous infarction), but also adds an additional volume overload for a weak ventricle. It seems likely that that both factors will give rise to a poor prognosis.

Prosthetic mitral ring annuloplasty can lead to mitral stenosis[42] and does not correct the basic problem of displacement of the papillary muscle which results in tenting of the leaflets. Therefore, the reduction of MR with mitral annuloplasty in ischemic MR, although sufficient in some cases of mild MR, is not lasting in many other cases and new techniques are being studied for mitral repair. The concept of repositioning the papillary muscles looks promising and is under development.[43]

When the mitral valve leaflets are subjected to stress due to tenting, are reactivated embryogenic processes are reactivated that result in cellular activation and transformation of endothelial cells in the interstices resulting in new cellular matrix. All this results in increased valve area and chordal thickening, which can lead to increased area of coaptation of the leaflets.[44] This is a breakthrough that promises opportunities in cell therapy for secondary MR. It has recently been shown that surgical extension of the posterior leaflet using bovine pericardium increases the area of coaptation and promises to be a therapeutic possibility with benefits in the short and medium term.[45]

In dilated cardiomyopathy, it is now possible to more accurately predict the possibility of repair by observing the mobility of the distal aspect of the anterior leaflet. If mobility is preserved, coaptation tends to remain even if the posterior leaflet is immobile after repair. Distal anterior leaflet mobility can be predicted via a simple measurement parameter in the preoperative echocardiogram.[46] Progress is therefore being made towards improved functional repair of the MR, with the process of repair being more complex and specific to each patient.

Currently, when surgical revascularization is planned and ischemic MR is mild or moderate (ERO <0.2 cm^2), the concomitant correction repair (simple annuloplasty) should be considered (Figure 4).

Patients with ERO>20 mm^2 should be offered repair (preferable) or mitral valve replacement (Figure 4). When CABG is not considered vital but is an option, the presence of viable myocardium and MR ERO >20 mm^2 should lead to combined mitral surgery (repair or replacement) with revascularization, especially if there are symptoms or a history of heart failure.

When bypass surgery is not possible or is not indicated and ischemic MR is ERO >0.2 cm^2, the indication for mitral surgery is more restrictive and should be considered only in patients with symptoms of functional class (NYHA) III-IV even with maximal medical therapy, including resynchronization. In these cases, replacement may involve a prohibitively high surgical risk, especially with EF <30% (Figure 4), so repair is essential. Alternatively, cardiac transplantation can be considered in selected patients and may provide optimal results.

PERCUTANEOUS APPROACHES TO MITRAL REGURGITATION

Percutaneous mitral annuloplasty based on implanting a device in the coronary sinus is currently under study. Although the coronary sinus is anatomically located on a superior plane to the mitral ring and there is a real possibility of compromising circumflex coronary flow, results from 48 patients with dilated cardiomyopathy showed that implantation of the device is safe in selected patients and results in increased functional capacity (NYHA).[47]

Another percutaneous approach to organic or functional MR that originates in the A2 and P2 area uses the E-valve/MitraClip. This is based on the Alfieri suture and creates a double mitral valve orifice. It has been studied in 107 selected patients; the procedure was successful in 74% and 66% of patients were still alive and without a need for mitral surgery at 12 months. MR was <2+.[48]

CONCLUSIONS

Mitral regurgitation is prevalent in the population as is its progression to impaired LV function due to adverse remodeling. This highlights the serious prognosis associated with the disease in patients who do not receive appropriate treatment.

The detection of subclinical LV dysfunction based on echocardiographic parameters (EF and ESD) should lead to consideration of immediate rescue mitral surgery. The parameters currently used (EF <60% and ESD ≥40 mm) for asymptomatic patients lead to late salvage surgery and should be modified. Similarly, the detection of even minimal symptoms should result in salvage surgery. Stress testing should be used to determine functional capacity in patients with uncertain symptoms.

Not all severe organic MRs are equal. The presence of risk factors in severe MR increases the likelihood of deterioration in cardiac function, development of symptoms, and worse prognosis in the long term, so it is necessary to consider each patient individually. In the absence of symptoms in patients with severe MR organic but no cardiac dysfunction (EF >60%, DTS <40 mm), the presence of risk factors implies treatment with early surgery to repair the valve, if the surgical risk is low and the possibility of repairing the valve is 90%-95%. If necessary, patients should be referred to a specialized center. Proper training of surgeons in mitral repair is essential in order to achieve the best possible survival for patients with severe organic MR and an indication for surgery. National and international collaboration in such training is essential.

Ischemic MR has a worse prognosis, with higher surgical risk. Treatment decisions should be specific to each patient and should take into account the possibility of repair, the surgical risk, and the need for concomitant surgical revascularization.

New percutaneous procedures are being studied which promise to be potentially useful for selected patients.

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enríquez Sarano M, et al. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368:1005-11.
2. Stout KK, Verrier ED. Acute valvular regurgitation. Circulation. 2009;119:3232-41.
3. Enríquez-Sarano M, Basmadjian A, Rossi A, Bailey KR, Seward JB, Tajik AJ, et al. Progression of mitral regurgitation: a prospective Doppler echocardiographic study. J Am Coll Cardiol. 1999;34:1137-44.
4. Delahaye J, Gare J, Viguier E, Delahaye F, De Gevigney G, Milon H, et al. Natural history of severe mitral regurgitation. Eur Heart J. 1991;12 Suppl B:5-9.
5. Horstkotte D, Loogen F, Kleikamp G, Schulte HD, Trampisch HJ, Bircks W. Effect of prosthetic heart valve replacement on the natural course of isolated mitral and aortic as well as multivalvular diseases. Clinical results in 783 patients up to 8 years following implantation of the Björk-Shiley tilting disc prosthesis. Z Kardiol. 1983;72:494-503.
6. Ling H, Enríquez-Sarano M, Seward J, Tajik AJ, Schaff HV, Bailey KR, et al. Clinical outcome of mitral regurgitation due to flail leaflets. N Engl J Med. 1996;335:1417-23.
7. Grigioni F, Enríquez-Sarano M, Ling L, Bailey KR, Seward JB, Tajik AJ, et al. Sudden death in mitral regurgitation due to flail leaflet. J Am Coll Cardiol. 1999;34:2078-85.
8. Enríquez-Sarano M, Tajik A, Schaff H, Orszulak TA, McGoon MD, Bailey KR, et al. Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. Circulation. 1994;90:830-7.
9. Crawford M, Souchek J, Oprian C, Miller DC, Rahimtoola S, Giacomini JC, et al. Determinants of survival and left ventricular performance after mitral valve replacement. Circulation. 1990;81:1173-81.

10. Enriquez-Sarano M, Schaff H, Orszulak T, Bailey KR, Tajik AJ, Frye RL, et al. Congestive heart failure after surgical correction of mitral regurgitation. A long-term study. Circulation. 1995;92:2496-503.

11. Tribouilloy C, Grigioni F, Avierinos JF, Barbieri A, Rusinaru D, Szymanski C, et al. Survival implication of left ventricular end- systolic diameter in mitral regurgitation due to flail leaflets. A long-term follow-up multicenter study. J Am Coll Cardiol. 2009;54:1961-8.

12. Bonow RO, Carabello BA, Chatterjje K, De Leon AC Jr, Faxon DP, Freed MD, et al. 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease: A report of the American College of Cradiology/American Heart Association Task Force on Practice Guidlines (Written Committe to Revise the 1998 Guidelines for the Managment of Patients With Valvular Heart Disease) endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52:e1-e142.

13. Cohn L, Couper G, Kinchla N, Collins JJ Jr. Decreased operative risk of surgical treatment of mitral regurgitation with or without coronary artery disease. J Am Coll Cardiol. 1990;16:1575-8.

14. Detaint D, Sundt TM, Nkomo VT, Scott CG, Tajik AJ, Schaff HV, et al. Surgical correction of mitral regurgitation in the elderly: outcomes and recent improvements. Circulation. 2006;114:265-72.

15. Cohn L, Kowalker W, Bhatia S, Disesa VJ, St John SM, Shenin R, et al. Comparative morbidity of mitral valve repair versus replacement for mitral regurgitation with and without coronary artery disease. Ann Thorac Surg. 1988;45:284-90.

16. Sand M, Naftel D, Blackstone E, Kirklin JW, Karp RB. A comparison of repair and replacement for mitral valve incompetence. J Thorac Cardiovasc Surg. 1987;94:208-19.

17. Gammie JS, O'Brien SM, Griffith BP, Ferguson TB, Peterson ED. Influence of hospital procedural volume on care process and mortality for patients undergoing elective surgery for mitral regurgitation. Circulation. 2007;115:881-7.

18. Freeman W, Schaff H, Khanderia B, Oh JK, Orzulak TA, Abel MD. Intraoperative evaluation of mitral valve regurgitation and repair by transesophageal echocardiography: incidence and significance of systolic anterior motion. J Am Coll Cardiol. 1992;20:599-609.

19. Frater R, Gabbay S, Shore D, Factor S, Strom J. Reproducible replacement of elongated or ruptured mitral valve chordae. Ann Thorac Surg. 1983;35:14-28.

20. Lessana A, Escorsin M, Romano M, Ades F, Vergoni W, Lorenzoni D, et al. Transposition of posterior leaflet for treatment of ruptured main chordae of the anterior mitral leaflet. J Thorac Cardiovasc Surg. 1985;89:804-6.

21. Gillinov A, Cosgrove D, Blackstone E, Diaz R, Arnold JH, Lytle BW, et al. Durability of mitral valve repair for degenerative disease. J Thorac Cardiovasc Surg. 1998;116: 734-43.

22. Yau TM, Farag EL, Ghoneimi YA, Armstrong S, Ivanov J, David TE. Mitral valve repair and replacement for rheumatic disease. J Thorac Cardiovasc Surg. 2000;119:53-61.

23. Zoghbi WA, Enríquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr. 2003;16:777-802.

24. Enríquez-Sarano M, Miller FJ, Hayes S, Bailey KR, Tajik JA, Seward JB. Effective mitral regurgitant orifice area: clinical use and pitfalls of the proximal isovelocity surface area method. J Am Coll Cardiol. 1995;25:703-9.

25. Vandervoort P, Rivera J, Mele D, Palacios IF, Disnmore RE, Weyman AE, et al. Application of color Doppler flow mapping to calculate effective regurgitant orifice area. An in vitro study and initial clinical observations. Circulation. 1993;88:1150-6.

26. Enríquez-Sarano M, Bailey K, Seward J, Tajik AJ, Khron MJ, Mays JM. Quantitative Doppler assessment of valvular regurgitation. Circulation. 1993;87:841-8.

27. Enríquez-Sarano M, Seward J, Bailey K, Tajik AJ. Effective regurgitant orifice area: a noninvasive Doppler development of an old hemodynamic concept. J Am Coll Cardiol. 1994;23: 443-51.

28. Enríquez-Sarano M, Avierinos JF, Messika-Zeitoun D, Detaint D, Capps M, Nkomo V, et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. N Engl J Med. 2005;352:875-83.

29. Rosenhek R, Rader F, Klaar U, Gabriel H, Krejc M, Kalbeck D, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. Circulation. 2006;113:2238-44.

30. Kang HD, Kim JH, Rim JH, Kim MJ, Yun SCh, Song JM, et al. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. Circulation. 2009;119:797-804.

31. Grigioni F, Avierinos JF, Ling LH, Scott CG, Bailey KR, Tajik AJ, et al. Atrial fibrillation complicating the course of degenerative mitral regurgitation: determinants and long-term outcome. J Am Coll Cardiol. 2002;40:84-92.

32. Eguchi K, Ohtaki E, Matsumura T, Tanaka K, Tohbaru T, Iguchi N, et al. Pre-operative atrial fibrillation as the key determinant of outcome of mitral valve repair for degenerative mitral regurgitation. Eur Heart J. 2005;26: 1866-72.

33. Detaint D, Messika-Zeitoun D, Avierinos JF, Scott C, Chen H, Burnett JC Jr, et al. B-type natriuretic peptide in organic mitral regurgitation: determinants and impact on outcome. Circulation. 2005;111:2391-7.

34. Pizarro R, Bazzino OO, Oberti P, Falconi M, Achilli F, Arias A, et al. Prospective validation of the prognostic usefulness of brain natriuretic peptide in asymptomatic patients with chronic severe mitral regurgitation. J Am Coll Cardiol. 2009;54:1099-106.

35. Messika-Zeitoun D, Johnson BD, Nkomo V, Avierinos JF, Allison TG, Scott C, et al. Cardiopulmonary exercise testing determination of functional capacity in mitral regurgitation: physiologic and outcome implications. J Am Coll Cardiol. 2006;47:2521-7.

36. Russo A, Suri RM, Grigioni F, Roger VL, Oh JK, Maghoney DW, et al. Clinical outcomes after surgical correction of mitral regurgitation due to papillary muscle rupture. Circulation. 2008;118:1528-34.

37. Lamas G, Mitchell G, Flaker G, Smith SC Jr, Gersh BJ, Basta L, et al. Clinical significance of mitral regurgitation after acute myocardial infarction. Circulation. 1997;96:827-33.

38. Grigioni F, Enríquez-Sarano M, Zehr K, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation. 2001;103:1759-64.

39. Desjardins V, Enríquez-Sarano M, Tajik A, Bailey KR, Seward JB. Intensity of murmurs correlates with severity of valvular regurgitation. Am J Med. 1996;100:149-56.

40. Bolling SF, Pagani FD, Deeb GM, Bach DS. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. J Thorac Cardiovasc Surg. 1998;115:381-6.

41. Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. J Am Coll Cardiol. 2005;45:381-7.

42. Magne J, Senecal M, Mathieu P, Dumesnil JG, Dagenais F, Pibarot P. Restrictive annuloplasty for ischemic mitral regurgitation may induce functional mitral stenosis. J Am Coll Cardiol. 2008;51:1692-701.

43. Hung J, Chaput M, Guerrero JL, Handschumacher MD, Papakostas L, Sullivan S, et al. Persistent reduction of ischemic mitral regurgitation by papillary muscle repositioning: structural stabilization of the papillary muscle-ventricular wall complex. Circulation. 2007;116 Suppl:I259-63.

44. Dal Bianco JP, Aikawa E, Bischoff J, Guerrero JL, Handschumacher MD, Sullivan S, et al. Active adaptation of the tethered mitral valve. Insights into a compensatory mechanism for functional mitral regurgitation. Circulation. 2009;120:334-42.

45. de Varennes B, Chaturvedi R, Sidhu S, Coté AV, Li Pi Shan W, Goyer C, et al. Initial results of posterior leaflet extension for severe type IIIb ischemic mitral regurgitation. Circulation. 2009;119:2837-43.

46. Wai Lee AP, Acker M, Kubo SH, Bolling SF, Park SW, Bruce CJ, et al. Mechanisms of recurrent functional mitral regurgitation after mitral valve repair in nonischemic dilated cardiomyopathy. Circulation. 2009;119:2606-14.

47. Schofer J, Siminiak T, Haude M, Herman JP, Vainer J, Wu JC, et al. Percutaneous mitral annuloplasty for functional mitral regurgitation. Results of the CARILLON Mitral Annuloplasty Device European Union Study. Circulation. 2009;120:326-33.

48. Feldman T, Kar S, Rinaldi M, Fail P, Hermiller J, Smalling R, et al. Percutaneous mitral repair with the MitraClip system. Safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge Repair Study) cohort. J Am Coll Cardiol. 2009;54:686-94.