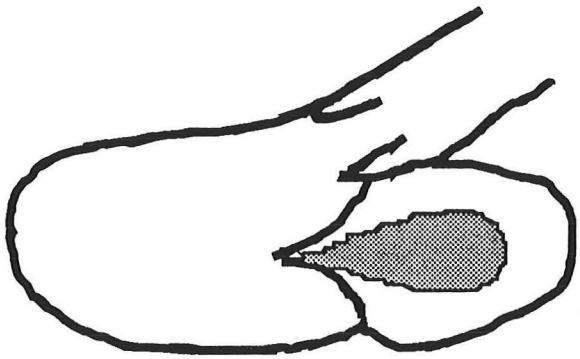
CHRONIC MITRAL REGURGITATION - ISSUES IN MANAGEMENT



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Medical Grand Rounds
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January 9, 1997

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Interests: I am the Medical Director of the Cardiovascular Laboratory at Parkland Memorial Hospital and I specialize in echocardiography. My primary interests center around the clinical uses of various echocardiographic modalities (including transesophageal and stress echocardiography). My major clinical interests include the assessment and management of valvular heart disease, intraoperative echocardiography, and congenital heart disease. My research interests include echocardiographic techniques for quantitation of regurgitation and uses of transesophageal echocardiography, particularly intraoperative echocardiography.

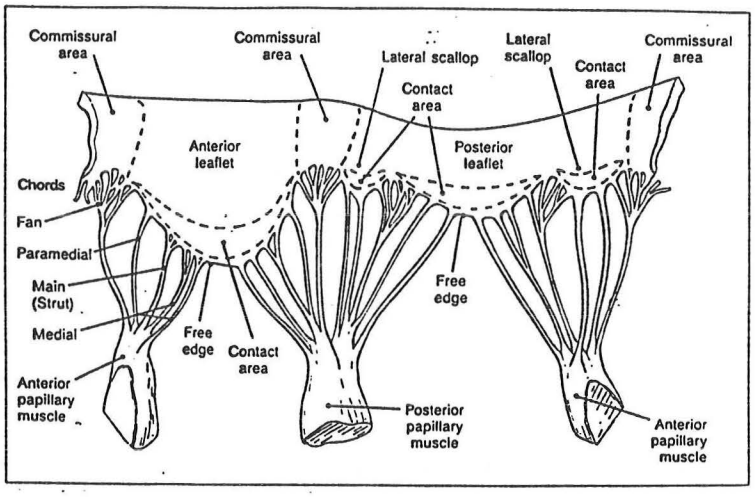
Mitral regurgitation is a common cardiac disorder that poses some particular difficulties in management. It is a progressive and insidious disease that is ultimately fatal if unrecognized and/or untreated. The major focus of this grand rounds will be on the etiology, pathophysiology, and management issues.

Definition of mitral regurgitation. Simply stated, mitral regurgitation is present when blood moves from the left ventricle to the left atrium. When there is a specific abnormality of the mitral apparatus that allows mitral regurgitation, this is known as "pathologic" mitral regurgitation. This is to be distinguished from "physiologic" mitral regurgitation. With the wide-spread application of echocardiographic techniques such as color Doppler, it is now known that mild degrees of valvular regurgitation can be seen in normal populations and are felt to be normal or "physiologic" [1]. In contrast to "physiologic" regurgitation which is clinically insignificant, "pathologic" mitral regurgitation can be sufficient to produce a volume load on the left ventricle. "Functional" mitral regurgitation is a term used to describe mitral regurgitation that occurs in the setting of a primary pathologic process involving the left ventricle, such as a dilated cardiomyopathy [2]. As the left ventricle dilates, the papillary muscles are pulled laterally, the ventricle assumes a more spherical shape, and the mitral annulus is dilated as well. Mitral regurgitation occurs as a secondary process or as a "function" of the primary left ventricular process. In a significant percentage of patients with primary left ventricular dilatation and dysfunction, mitral regurgitation will develop as a secondary process [3, 4].

prevalence of regurgitation by color Doppler in normal subjects

	age (yrs)		
	20-29	30-39	40-49
mitral regurgitation	43%	41%	38%
aortic regurgitation	0%	0%	0%
tricuspid regurgitation	64%	34%	15%
pulmonic regurgitation	68%	34%	28%

adapted from Yoshida, et al, Circ,1988.



Anatomy of the mitral valve apparatus. The mitral valve is a complex structure, composed of five different components: the mitral annulus, leaflets, chordae tendinae, papillary muscles, and the left ventricle [5-8]. The mitral annulus is a fibrous ring around the valve orifice that is soft and pliable. Its circumference constricts by about 25% in systole as the surrounding muscle tissue contracts, helping to bring the mitral leaflets into apposition. There are two mitral leaflets - an anterior leaflet and a posterior leaflet. The anterior leaflet has a longer base-to-margin length than the posterior leaflet, but the posterior leaflet has significantly greater attachment along the mitral annulus, leading to nearly identical surface area for the two leaflets. The posterior leaflet has three fairly well-defined scallops while the anterior leaflet is not segmented. Attached to the mitral leaflets are the chordae tendinae, avascular fibrous strands that serve to anchor the leaflet to the papillary muscles. Each papillary muscle provides chordae tendinae to each of the mitral leaflets and the chordae subdivide as they progress from papillary muscle to leaflet, with about five times as many chordae attached to the leaflets as to the papillary muscles. Some chordae tendinae arise directly from the posterior left ventricular wall, attaching to the posterior part of the mitral annulus. There are usually two papillary muscles, the anterolateral and posteromedial papillary muscles. The anterolateral papillary muscle has a dual blood supply from two coronary arteries while the posteromedial papillary muscle has a single source of blood supply, usually from the posterior descending branch of the right coronary artery. Therefore, the posteromedial papillary muscle is much more prone to complications of ischemia and infarction and is much more commonly involved in acute mitral regurgitation seen in the setting of acute myocardial infarction. The left ventricle itself is also an important component of the mitral apparatus. The contractile function of the ventricle and its shape play an important role in determining the geometry and orientation of the papillary muscles, thus influencing the closure of the mitral leaflets [2-4].

Etiologies of mitral regurgitation.

There are a number of different means of classifying causes of mitral regurgitation. Etiologies can be divided on a histologic basis into inflammatory, infectious, ischemic, infiltrative etiologies, etc. (Table I) [5] Alternatively, etiologies can be divided according to which component of the mitral apparatus is involved (table II) [9]. However, many of the pathologic processes that cause mitral regurgitation involve more than one component. From a practical standpoint, the most common causes of pure mitral regurgitation are listed in table III [10, 11].

Table I. Causes of chronic mitral regurgitation

Inflammatory
- Rheumatic heart disease
- Systemic lupus erythematosus
- Scleroderma

Degenerative
- Myxomatous degeneration of mitral valve leaflets
- Marfan syndrome
- Ehlers-Danlos sydnrome
- Pseudoxanthoma elasticum
- Calcification of mitral valve annulus

Infective
- Infective endocarditis affecting normal, abnormal, or prosthetic valves

Structural
- Ruptured chordae tendinae (spontaneou or secondary)
- Rupture or dysfunction of papillary muscle
- Dilatation of mitral annulus and left ventricular cavity
- Hypertrophic cardiomyopathy
- Paravalvular prosthetic leak

Congenital
- Mitral valve clefts or fenestrations
- Parachute mitral valve abnormality in association with:
  - endocardial cushion defects
  - endocardial fibroelastosis
  - transposition of great arteries
  - anomalous origin of the left coronary artery

from reference 5.

Table II. CAUSES OF MITRAL REGURGITATION

DISORDERS OF THE MITRAL LEAFLETS

Loss or contracture of valvular tissue
- Rheumatic fever
- Infection - bacterial, viral, fungal
- External and direct trauma
- Spontaneous rupture
- Systemic lupus erythematosus

Incomplete or abnormal valvular development
- Anterior leaflet clefts with AV cushion defect
- Isolated clefts or perforations
- Absence of leaflets
- Redundancy of leaflets (mitral valve prolapse)
- Anomalous leaflet attachment
- Ebstein's malformation with corrected transposition of great arteries

Proliferation, thickening or infiltration of leaflets
- Mitral valve prolapse syndrome
- Methysergide
- Carcinoid sydnrome
- Whipple's disease

Defects of connective tissue
- Ehlers-Danlos syndrome
- Hurler's syndrome
- Marfan's syndrome
- Pseudoxanthoma elasticum
- Osteogenesis imperfecta

Interference with leaflet coaptation

DISORDERS OF THE PAPILLARY MUSCLES

Dysfunction or rupture of papillary muscle
- Myocardial infarction, ischemia, fibrosis, rupture
- Bacterial abscess
- Trauma
- Anomalous coronary artery
- Periarteritis
- Aortic stenosis
- Syphilis
- Sarcoidosis
- Amyloidosis
- Cardiomyopathy
- Myocarditis
- Temporal disturbance of activation/contraction

Malalignment
- Endocardial fibroelastosis
- Left ventricular dilatation
- Hypertrophic cardiomyopathy
- Massive left atrial dilatation
- Left ventricular aneurysm

Congenital abnormality in development
- Absent papillary muscle
- Congenital mitral stenosis
- Anomalous mitral arcade

DISORDERS OF THE CHORDAE TENDINAE

Rupture of chordae tendinae
- Idiopathic
- Mitral valve prolapse syndrome
- Infective endocarditis
- Trauma
- Marfan's sydnrome
- Ehlers-Danlos syndrome
- Rheumatic fever
- Hypertrophic cardiomyopathy

Disorders associated with thickened or poorly defined chordae tendinae
- Congenital mitral stenosis
- Congenital mitral regurgitation
- AV cushion defect
- Hypoplastic left heart syndrome
- Parachute mitral valve complex
- Supraventricular ring of left atrium
- Cardinoid syndrome
- Hurler's syndrome
- Marfan's syndrome
- Ehlers-Danlos syndrome

Disorders associated with unusual location from which chordae originate
- AV cushion defect
- Corrected transposition of great vessels
- Congenital mitral regurgitation

DISORDERS OF THE MITRAL ANNULUS

Calcification
- Degenerative
- Associated with coronary artery disease, hypertension, rheumatic heart disease
- Marfan's syndrome
- Hurler's syndrome

Destruction of the annulus fibrosa
- Bacterial valve ring abscess
- Rheumatic fever
- Rheumatoid arthritis
- Left atrial myxoma

Dilatation of the annulus fibrosa
- Connective tissue disorders
- Mitral valve prolapse syndrome
- Left ventricular dilatation

Disruption of prosthetic valve ring

Adapted from reference 9 .

Table III.

most common mechanisms of pure mitral regurgitation

- mitral valve prolapse
- active or healed endocarditis
- papillary muscle dysfunction
- annular calcium
- idiopathic chordae tendinae rupture
- rheumatic
- dilated and hypertrophic cardiomyopathy
- Marfan's or similar disorders

Prior to the 1970s, rheumatic valvular disease was the most common cause of mitral regurgitation requiring surgical intervention. However, as data by Luxereau, et al demonstrate, there has been a significant change in etiology over the last three decades [12]. The most common etiology of pure mitral regurgitation requiring mitral valve surgery is now degenerative mitral valve disease, also known as mitral valve prolapse. Mitral valve prolapse is most commonly caused by myxomatous degeneration, although there are other causes [13]. The primary pathologic abnormality seen in myxomatous degeneration is an increase in the mucopolysaccharide content of the spongiosa (inner) layer of the mitral leaflets [10]. This results in stretching and weakening of the leaflets as well as causing stretching and weakening of the chordae tendinae. Over time, the strain placed on the leaflets and the chordae produces more and more mitral regurgitation. Mitral regurgitation due to mitral valve prolapse can also abruptly worsen when chordal rupture occurs, resulting in a flail or partially flail leaflet.

Etiology of surgically treated mitral regurgitation

	years			
	1970-74 (n=41)	1975-79 (n=84)	1980-84 (n=97)	1984-1989 (n=114)
rheumatic fever	46%	31%	33%	15%
prolapse	37%	52%	44%	60%
endocarditis	7%	10%	11%	11%
others	10%	7%	12%	14%

Luxereau, et al. European Heart J, 1991.

Active or healed endocarditis is another fairly common etiology for mitral regurgitation. This disease is primarily a leaflet disorder, with perforation of leaflets commonly responsible for causing regurgitation in acute endocarditis, while in healed endocarditis the abnormality is more commonly scarring and retraction of the leaflets leading to regurgitation.

Papillary muscle dysfunction can also cause mitral regurgitation. This commonly occurs due to underlying coronary artery disease but can be due to infiltrative diseases such as amyloidosis or sarcoidosis involving the papillary muscles. In patients with coronary artery disease, the posteromedial papillary muscle is most commonly involved (due to its single source of blood supply). It is interesting to note that in animal models isolated infarction of a papillary muscle (without involvement of the surrounding ventricular walls) does not result in significant mitral regurgitation [14, 15]. The development of mitral regurgitation requires involvement (either ischemia or infarction) of the adjacent left ventricular myocardium in order to result in mitral regurgitation. Transient left ventricular ischemia can result in mitral regurgitation that resolves with resolution of the ischemia (as can be demonstrated during coronary angioplasty) [16]. In addition, papillary muscles can become infarcted, becoming shortened and fibrotic which impairs normal mitral valve closure, causing mitral regurgitation. Papillary muscles can also rupture, either partially (resulting in acute pulmonary edema) or completely (resulting in cardiogenic shock and death). Such rupture is an important cause of acute mitral regurgitation.

Abnormalities of the mitral annulus can also contribute to mitral regurgitation. Annular dilatation can occurs in many cardiac conditions which cause left ventricular dilatation and the dilatation of the annulus may result in impaired coaptation of the leaflets, resulting in secondary or "functional" mitral regurgitation. Calcification of the mitral annulus is a degenerative process which involves predominantly the posterior portion of the mitral annulus. Mitral annular calcification usually does not result in clinically important valvular dysfunction. However, in some cases the calcification can begin to encroach on the leaflets themselves and can cause either mitral stenosis or mitral regurgitation by impairing leaflet mobility [6].

Another important cause of mitral regurgitation is chordal rupture. Chordae tendinae are avascular structures, therefore rupture does not occur as a consequence of infarction. Rupture can occur in the setting of mitral valve prolapse, may be secondary to trauma or endocarditis, and can occur without an obvious precipitating factor (idiopathic chordal rupture). Chordal rupture usually results in severe mitral regurgitation, with the severity being dependent on the number, type and location of the chordae involved.

Various types of cardiomyopathies are associated with mitral regurgitation, including dilated cardiomyopathies as well as hypertrophic cardiomyopathies. Other less common causes of mitral regurgitation include endocardial fibrosis, restrictive cardiomyopathies, and collagen vascular disorders such as systemic lupus erythematosus. While valvular

involvement with the so-called "Libmann-Sacks" endocarditis is fairly common in patients with systemic lupus erythematosus, significant valvular disease requiring valve surgery is relatively uncommon [17, 18]. Mitral regurgitation also occurs in patients with Marfans' syndrome or other connective tissue disorders. Marfans is commonly associated with mitral annular dilatation and/or mitral valve prolapse.

Clinical evaluation of the patient with chronic mitral regurgitation.

The natural history of chronic mitral regurgitation depends on a number of factors including the etiology of the regurgitation, the severity of regurgitation, and the presence of other associated cardiac disease. Frequently, the time period between the onset of pathologic mitral regurgitation and the onset of symptoms is quite long, often in the range of 15-20 years [19]. The prolonged nature of the disease with this long asymptomatic period accounts for some of the difficulty in managing patients with chronic mitral regurgitation. The onset of symptoms is often quite insidious, with fewer acute complications (pulmonary edema, systemic emboli, acute decompensation with the onset of atrial fibrillation) than is seen in mitral stenosis. Unfortunately, the "indolent course" may result in patients presenting at a very late stage of their disease when significant (and often irreversible) left ventricular dysfunction is present [5].

Patients with chronic mitral regurgitation usually develop symptoms of a low cardiac output state, such as chronic weakness and fatigue. Symptoms of pulmonary congestion (exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea) may also occur. Symptoms often are not prominent until late in the course of the disease. The onset of atrial fibrillation may abruptly precipitate or worsen symptoms. Palpitations due to atrial fibrillation are fairly common, as well. Angina pectoris is rare, unless there is coexistent coronary artery disease. The severity of regurgitation can abruptly worsen when "acute on chronic" regurgitation occurs, such as can be seen with chordal rupture (in the setting of chronic mitral regurgitation due to mitral valve prolapse) or with the development of endocarditis [5, 20]. Thus, a previously asymptomatic patient with severe mitral regurgitation may present with pulmonary edema and acute decompensation. Clues to the etiology of mitral regurgitation may be found in the history. A history of angina or documented myocardial infarction would be strong evidence for an ischemic etiology, for example. Other important issues to address in the history include evaluating for a history of rheumatic fever, endocarditis, or mitral valve prolapse.

In patients with chronic mitral regurgitation, the jugular venous pulse is usually normal unless pulmonary hypertension is present. The apical impulse is hyperdynamic and laterally displaced, reflecting the enlarged, volume-overloaded left ventricle. A right parasternal lift may be detected and can be due either to marked left atrial enlargement (with systolic expansion of the left atrium causing anterior displacement of the heart) or

due to right ventricular hypertrophy from pulmonary hypertension. The intensity of S1 will be decreased if the valve leaflets fail to coapt normally in systole. The second heart sound is usually widely split (due to decreased ejection time across the aortic valve, resulting in earlier closure of the aortic valve). The pulmonary component of S2 will be increased if there is significant pulmonary hypertension. An S3 is usually present, reflecting the increased diastolic flow across the mitral valve and is not a reliable marker of left ventricular dysfunction.

The murmur of chronic mitral regurgitation begins immediately after S1 and continues beyond A2 (as the left ventricle continues to eject blood into the left atrium after aortic valve closure). The classic murmur is described as a holosystolic, high-pitched, blowing murmur, loudest at the apex with radiation to the axilla. It is important to recognize that abnormalities of the posterior mitral leaflet can result in a mitral regurgitant jet that is directed anteriorly and thus the murmur may radiate to the sternum or the aortic area. The changes in the murmur with dynamic auscultation vary with the etiology of the regurgitation. For rheumatic mitral regurgitation, the murmur increases with handgrip or squatting and will decrease with standing or during the strain phase of the Valsalva maneuver. In patients with mitral valve prolapse, maneuvers which increase ventricular volume (such as squatting or the supine position) will decrease the murmur, while maneuvers which decrease ventricular volume (such as standing) will increase the intensity of the murmur. Murmurs due to ventricular dilatation will decrease with vasodilator therapy and other maneuvers to decrease left ventricular size [5]. While there is some correlation between the intensity of the murmur and the severity of regurgitation, , the correlation is weak, especially for ischemic or functional mitral regurgitation [21]. Also, clinically "silent" mitral regurgitation has been well described [22]. Thus, the physical exam is not sufficient to assess the severity of mitral regurgitation.

The electrocardiogram demonstrates left ventricular hypertrophy in approximately one-third of patients. Right ventricular hypertrophy is less common, seen in approximately 15%. Left atrial enlargement is quite common and atrial fibrillation is frequently seen. The chest x-ray in patients with chronic mitral regurgitation usually demonstrates left atrial and left ventricular enlargement. Findings of pulmonary congestion on chest x-ray are uncommon, except in acute decompensation or with end-stage disease. Mitral annular calcification may also be detected radiographically [5].

Assessment of the severity of mitral regurgitation

An "ideal" method for assessing the severity of regurgitant lesions would 1) provide an accurate assessment of the volume of regurgitation, 2) be easily reproducible, 3) be noninvasive (thus suitable for serial examinations), and 4) provide an accurate assessment of the effect of the regurgitant lesion on the myocardium. Unfortunately, no such "ideal" method exists. A full

discussion of quantitation of regurgitant lesions is beyond the scope of this discussion. A brief description of commonly used methods follows.

One common means of quantitating the severity of regurgitation is calculation of the regurgitant fraction.

Regurgitant volume = total stroke volume - forward stroke volume

$$\text{Regurgitant fraction (RF)} = \frac{\text{regurgitant volume}}{\text{total stroke volume}}$$

grading by regurgitant fraction

RF = 0-20%	insignificant
RF = 20-40%	mild
RF = 40-60%	moderate
RF = >60%	severe

Regurgitant volume and regurgitant fraction can be assessed by cardiac catheterization, echocardiography or magnetic resonance imaging. However, regurgitant volumes are known to be dependent on loading conditions of the ventricle. The size of the regurgitant orifice (regurgitant orifice area) can be calculated by either catheterization or, more commonly, echocardiographic techniques and may a provide a less load-dependent (and thus, potentially more accurate) assessment of the severity of regurgitation [23].

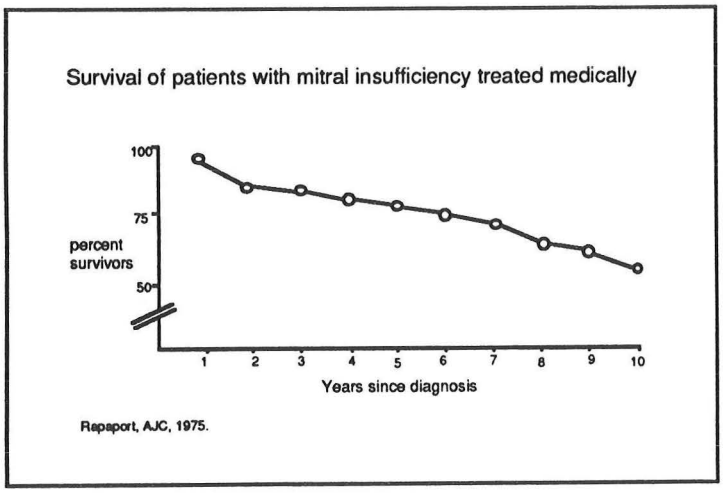
Echocardiography is quite useful in assessing mitral regurgitation and provides information regarding the severity of regurgitation (calculation of regurgitant fraction and regurgitant orifice area), assessment of ventricular function, and important information regarding the etiology of the regurgitation. Cardiac catheterization provides assessment of the severity of regurgitation (angiographic grade by left ventriculography, calculation of regurgitant volume and regurgitant fraction), assessment of left ventricular size and function, and assessment of coronary anatomy. Magnetic resonance imaging has been shown to be quite accurate in the assessment of ventricular volumes and measurement of regurgitant flow [24, 25]. This rapidly developing technique should have important applications in the assessment of chronic regurgitant lesions.

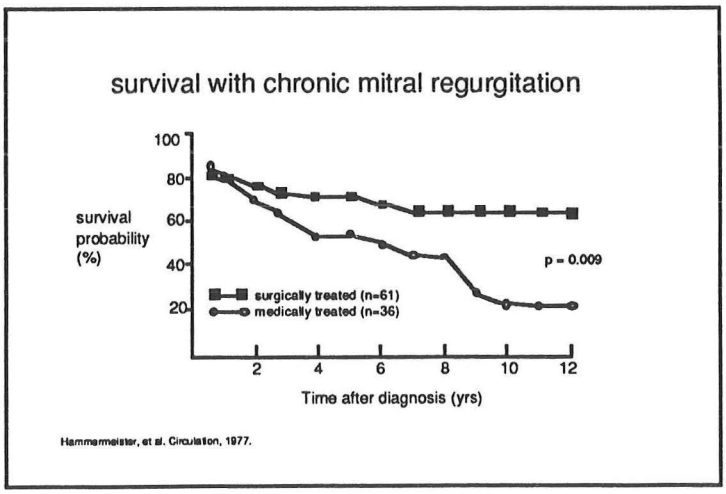
Currently, echocardiography is commonly used as the initial diagnostic tool to provide information regarding the severity of mitral regurgitation, determining its etiology, and assessing its hemodynamic consequences. Because of its noninvasive nature, it is suitable for serial examinations and is commonly used to follow the progression of disease. Cardiac catheterization is usually reserved for patients in whom surgery is being considered and may not be necessary in all cases (if coronary artery is not a consideration) [26, 27].

Natural history of chronic mitral regurgitation

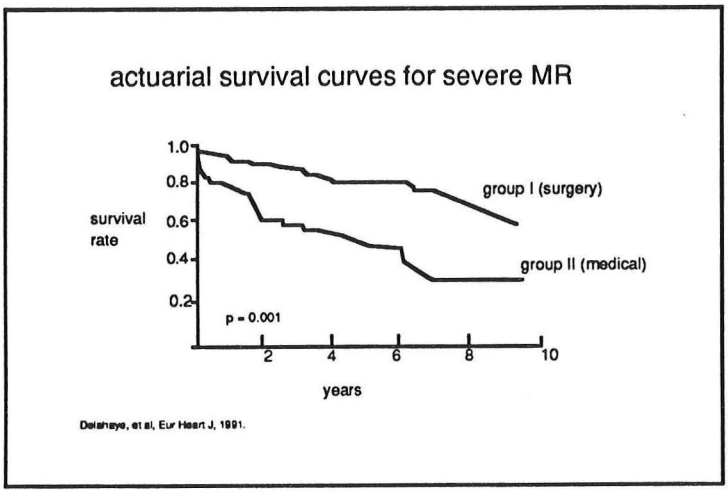
The natural history of this disease depends on multiple factors, including the severity of the regurgitant lesion, the etiology of regurgitation, and the function of the left ventricle. As discussed earlier, there is usually a long asymptomatic period. During this period, the left ventricular dysfunction begins to occur and becomes irreversible at some point.

Without surgical intervention, the long term prognosis of chronic mitral regurgitation is poor. Rapaport reported the long-term survival of patients with predominantly rheumatic mitral regurgitation who were treated medically [20]. The five year survival rate was 80% and the 10 year survival rate was 60%. From the same era, a retrospective review by Hammermeister compared the outcome of patients with chronic mitral regurgitation who were treated either surgically or with medical therapy. The operative mortality was quite high (12.4%) [28]. The survival curve for the medically treated patients demonstrates a dismal prognosis (with only a 20% survival rate at 10 years), while the survival rate for the surgically treated patients was significantly better.



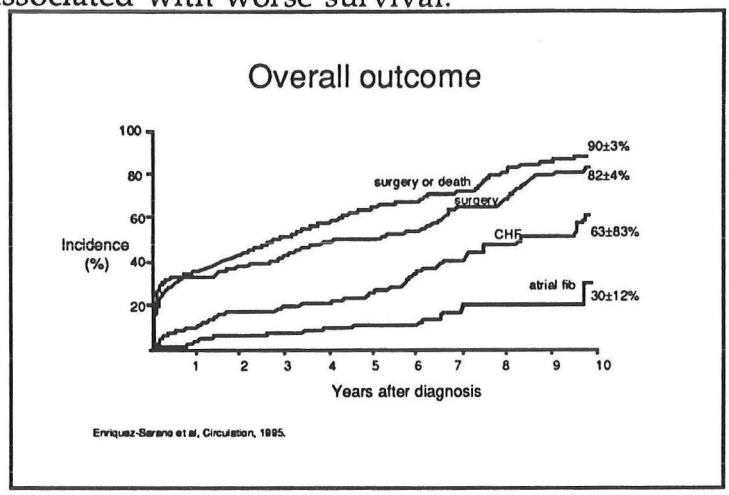


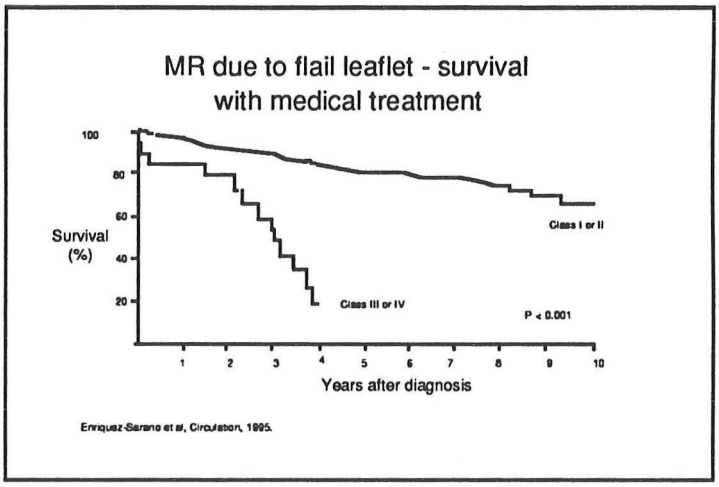
In a more recent era, Delahaye reported the survival rates for both surgically and medically treated patients [29]. This was a retrospective review of patients who were considered as possible surgical candidates, leading to an inevitable selection bias in the results. There was a statistically significant improvement in survival for patients who had surgical therapy, with a 10 year survival rate of 74±4.% versus 32±9% for the medically treated patients. It is interesting to look at the fate of the non-operated patients. In thirteen patients, surgery was felt to be contraindicated, either due to poor ventricular function (n=8) or to other significant associated disease (n=3). The mortality rate was 100% in this group of patients. Three patients refused surgery and two died during the follow-up period. Four patients were scheduled for surgery but died before surgery was performed. Most importantly, in the 32 patients in whom surgery was not felt to be necessary, eight patients (25%) died, mostly from cardiac causes.

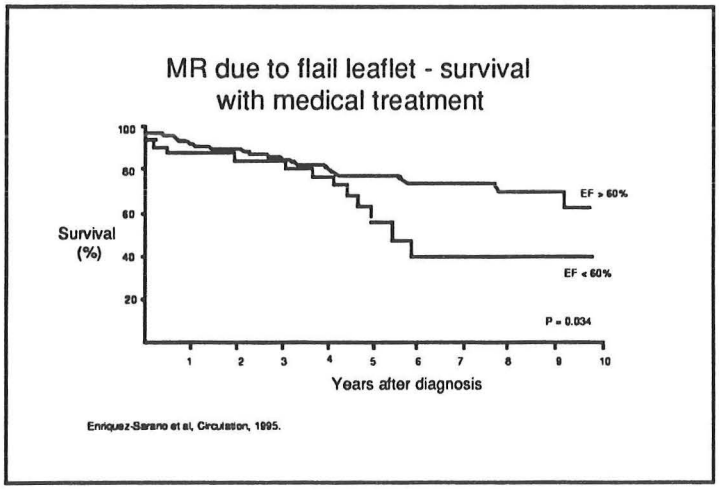


Recently, data was published on the clinical outcome of patients with flail mitral leaflets [30]. This study is interesting since it describes the outcome for patients with a single common etiology of regurgitation. A total of 229 patients were diagnosed a flail leaflet by echocardiography between 1980 and 1989. Follow-up was obtained in 1994 and 1995. Seventy percent of patients were male with a mean age of 65.5±13 at the time of presentation. Forty-eight percent were in NYHA class I, 23% in class II, 17% in class III, and 11 % in class IV. Twenty-four percent were in atrial fibrillation. The average ejection fraction was 65±9%. Long-term follow-up demonstrated significant morbidity and mortality in these patients. By 10 years, the incidence of surgery was 82±4%, the combined incidence of surgery or death was 90± 3%, the incidence of congestive heart failure was 63±8%, and the incidence of atrial fibrillation was 30±12%. Thus, death or the need for surgery occurred in nearly all patients by 10 years after the diagnosis. For patients treated medically, 20% died during the follow-up period and long-term survival was

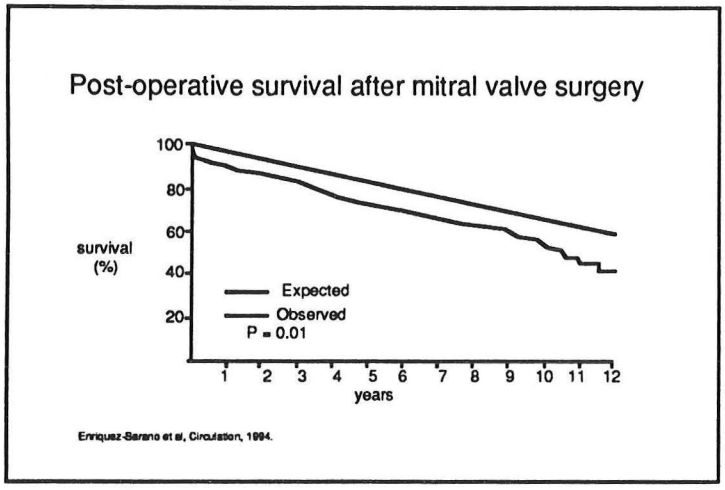
less than the expected survival. The baseline variables that were predictive of survival included age, NYHA class, and ejection fraction. For patients treated medically, survival was substantially worse for patients with NYHA class III or IV symptoms, with a 34% yearly mortality. Patients in NYHA class I or II had an annual mortality rate of 4.1%. An ejection fraction of < 60% was also associated with worse survival.

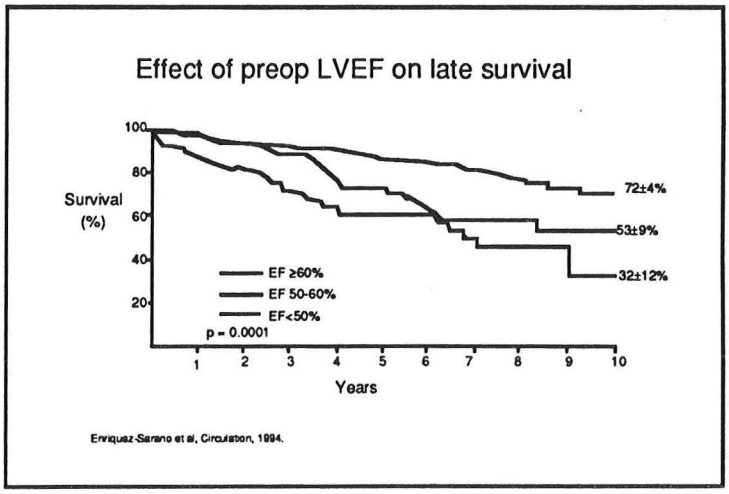




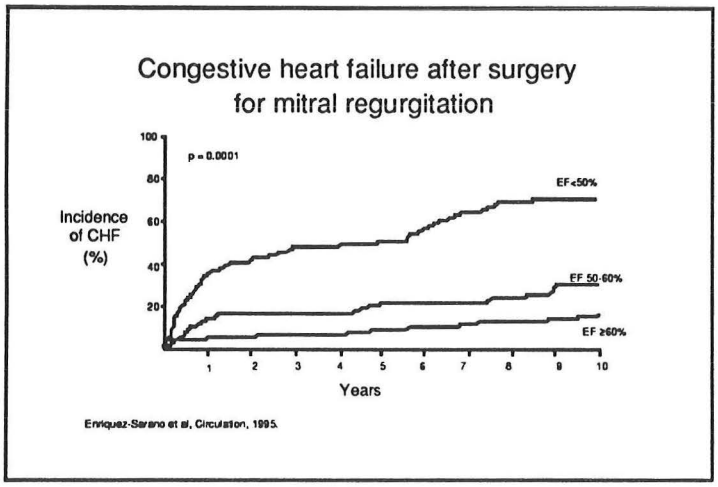


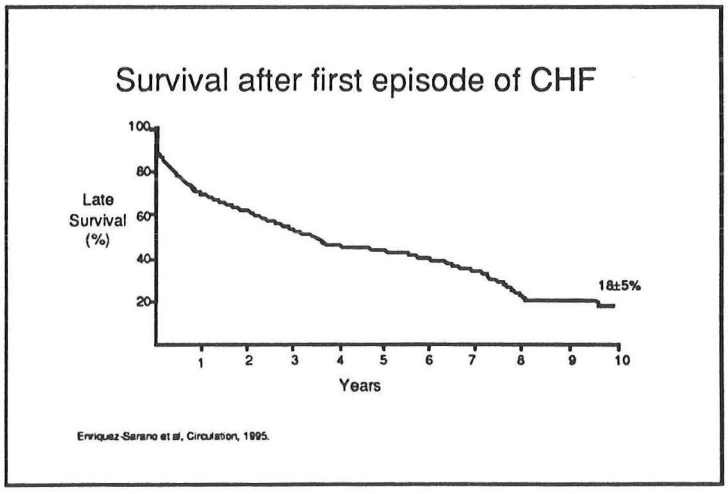
In the most recent large series of data available, Enriquez-Sarano described the survival rates after surgery for mitral regurgitation in a series of 409 patients operated on at the Mayo Clinic between 1980 and 1989 [31]. This retrospective analysis included patients undergoing a first mitral valve operation for "pure" mitral regurgitation (excluding patients with ischemic etiologies and "functional" mitral regurgitation). The data includes results for both valve replacement and valve repair surgery. The mean age of the patients was 64 years with 163 women and 246 men. Forty-seven percent of patients were in atrial fibrillation at the time of their surgery. Degenerative mitral valve disease (e.g. mitral valve prolapse) was the most common etiology (n=311), with rheumatic (n=42), endocarditis (n=40), and other miscellaneous etiologies (n=16) seen much less often. Most patients were symptomatic, with over two-thirds being in functional class III or IV at the time of their operation (NYHA class I, n = 11%, class II, n = 21%, class III, n = 52%, class IV, n = 16%). Long-term post-operative survival was seen be less than predicted, with 75% survival at five years, 58% at 10 years, and 44% at 12 years. The most important predictor of survival by multivariate analysis was the pre-operative ejection fraction. Thus, even in this more recent experience, the long-term survival after surgical intervention is disappointing.





In terms of morbidity, the results of surgical intervention have also been less than optimal. Enriquez-Sarano, et al also reported on the long-term incidence of congestive heart failure after surgery for mitral regurgitation. This retrospective study included many of the patients reported in the previous study, including patients undergoing a first mitral valve operation (either replacement or repair) for "pure" mitral regurgitation [32]. The cumulative incidence of congestive heart failure was 23±2% at 5 years, 33±3% at 10 years and 37±3% at 14 years. The pre-operative ejection fraction was highly predictive for the development of post-operative heart failure. Heart failure occurred in 70±6% of patients with pre-operative ejection fractions below 50 %, in 29±5% of patients with pre-operative ejection fractions between 50 and 60%, and in only 19±3% of patients with preoperative ejection fractions above 60%. The prognosis for patients who developed heart failure was very poor, with five-year survival after the first episode of congestive heart failure at 44±4%.

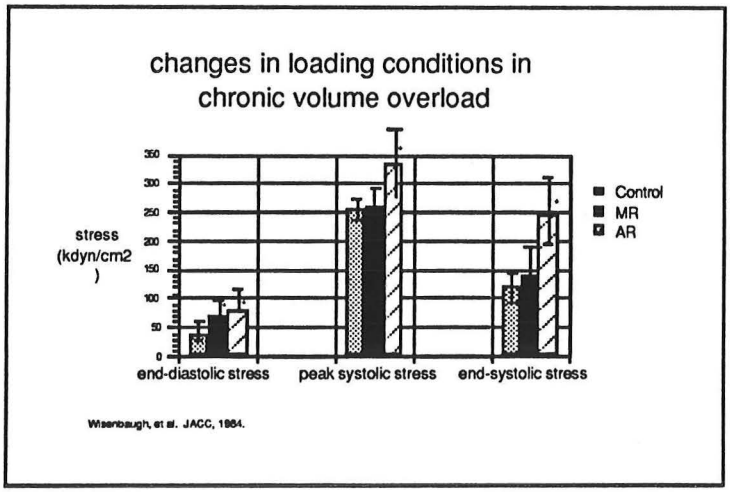




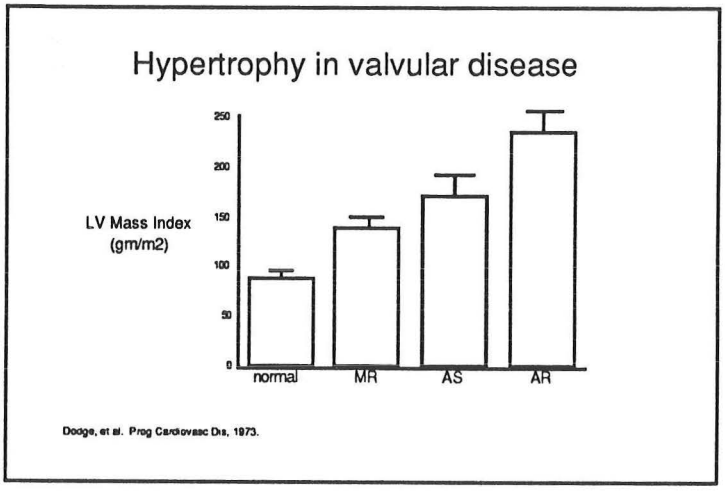
Pathophysiology of chronic mitral regurgitation.

In order to understand the natural history of mitral regurgitation (both with and without surgical intervention) it is important to understand the pathophysiology of the disease. Chronic mitral regurgitation is a disease of the myocardium itself which occurs as a consequence of the regurgitant load on the ventricle. Impairment of the contractile function of the left ventricle occurs early in the disease but, because of the favorable loading conditions placed on the ventricle by the mitral regurgitant lesion, this contractile dysfunction is "masked."

Because only a portion of the blood ejected by the ventricle actually is effectively ejected "forwards," the left ventricle is required to pump extra total volume in order to achieve a normal forward stroke volume. Because the left ventricle ejects excess volume into a relatively low pressure left atrium, the increased work of the ventricle is purely a volume overload [33]. In response to this volume load, the left ventricle dilates and increases its mass without substantially increasing the thickness of the ventricular wall (so-called eccentric hypertrophy) [34]. The increase in left ventricular end-diastolic dimension results in an increase in preload (the stretch on the myocardium prior to stimulation). While the left atrium does provide a low-impedance chamber for the left ventricle to eject into, afterload (the load the myocardium must bear to contract) is not decreased. The disproportionate increase in the radius of the left ventricle compared to the increase in wall thickness are unfavorable changes in left-ventricular geometry that result in normal to mildly increased wall stress (a measure of afterload). When frank left ventricular decompensation occurs, wall stress is actually increased [35]. These changes in loading conditions were demonstrated by Wisenbaugh, et al who studied loading conditions in patients with comparable degrees of chronic mitral and aortic regurgitation as compared to normal controls [36].



End-diastolic stress (as an estimate of preload) was increased in both aortic and mitral regurgitation as compared to normal controls. However, peak and end-systolic stress (measures of afterload) were increased in patients with aortic regurgitation but were normal in patients with mitral regurgitation. Since afterload is the most potent stimulus for myocardial hypertrophy, it is not surprising that the mitral regurgitation results in much less hypertrophy than is seen other valvular lesions associated with increased afterload [37]. Thus, while the valve lesion serves to "unload" the left ventricle, it produces changes in left ventricular geometry that place the left ventricle at a mechanical disadvantage [34].



Early in the course of chronic mitral regurgitation, contractile dysfunction occurs due to the increased work of the ventricle with an inadequate hypertrophic response. However, because of the favorable loading conditions, ejection performance (e.g. ejection fraction) is usually preserved until the late stages of the disease [38]. Surgical correction often unmasks this contractile dysfunction[39-42]. Closure of the low-impedance pathway for ejection into the left atrium causes systolic pressure to increase and afterload usually increases (especially if the chordae tendinae are not preserved), resulting in a decline in ejection performance [43].

Thus, ejection fraction cannot be used as an indicator of left ventricular contractile function in patients with chronic mitral regurgitation. Ejection fraction is dependent on loading conditions (preload and afterload), heart rate, and the contractile state of the ventricle. The favorable loading conditions seen in chronic mitral regurgitation result in a preservation of the ejection fraction despite impairment of left ventricular contractile function. This concept was elegantly demonstrated by Starling et al, who used a relatively load-independent measure of contractile function to assess patients with chronic mitral regurgitation [41]. Simultaneous left ventricular pressure and volume measurements were made throughout the cardiac cycle under

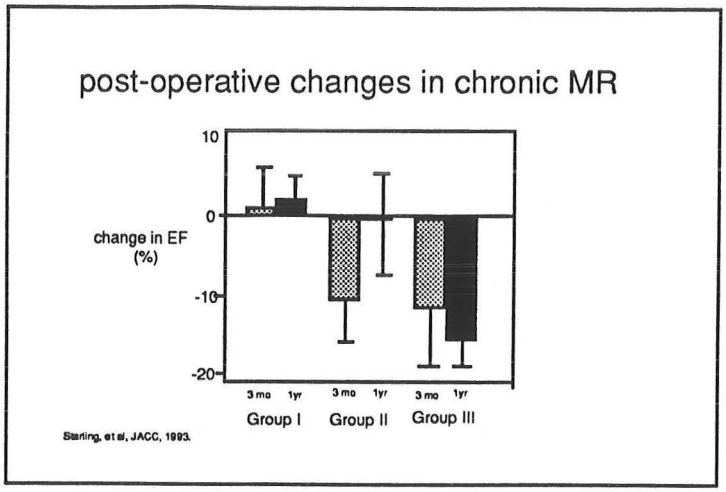
varying afterload conditions at a constant heart rate to generate a series of pressure volume loops. The slope of the pressure-volume relationship at end-systole was measured to yield myocardial elastance (Emax) as a measure of contractile function. Wall stress (as a measure of afterload) and ejection fraction were also calculated. A control group of 11 patients had normal wall stress, a normal ejection fraction and a normal value for myocardial elastance. Three groups of patients with chronic mitral regurgitation were studied. Groups I and II consisted of patients with normal wall stress and a normal ejection fraction. In Group I, myocardial elastance was preserved (statistically no different from control when corrected for cardiac size). In Group II, myocardial elastance was depressed, despite preservation of the ejection fraction. Group III consisted of patients with increased afterload and depressed ejection fraction. As expected, myocardial elastance was also significantly depressed in these patients.

These data were useful in predicting the post-operative response to valve surgery. In group I patients, post-operative ejection fraction did not fall. In patients in group II with impaired contractile function, post-operative ejection fraction fell at 3 months but had returned to baseline by one year. Those patients with the most severe contractile dysfunction, group III, also had a significant fall in ejection fraction post-operatively that persisted long-term. While this technique appears to provide very useful information regarding the state of left ventricular contractile function, it has significant limitations. The end-systolic pressure relationship is not completely linear and is dependent on left ventricular mass and volume. More importantly, calculation of myocardial elastance requires invasive techniques with manipulation of loading conditions which dramatically limits its clinical utility. For this reason, this technique is limited to experimental evaluation.

contractile function in chronic MR

group	wall stress (g/cm2)	EF (%)	Emax (mmHg/ml)
control (n=11)	189± 82	62±12	5.28±1.49
MR			
group I (n=11)	206±77	60±10	2.91±0.86
group II (n=13)	184±55	60±8	0.96±0.43
group III (n=4)	269=±108	41±6	0.64±0.36

Starling, et al. JACC, 1993.



Thus, detection of contractile dysfunction in patients with chronic mitral regurgitation is difficult since commonly used measures of left ventricular function, such as ejection fraction, do not provide an accurate assessment of the contractile state of the ventricle. A variety of methods have been developed which may be useful in assessing patients with chronic mitral regurgitation [26, 44]. The limitations of ejection phase indices such as ejection fraction and of the end-systolic pressure volume relationship techniques have already been discussed. End-systolic indices have been developed which involve assessment of end-systolic stress or end-systolic pressure in relationship to left ventricular size (e.g. end-systolic stress/end-systolic volume ratio). These techniques offers a preload-independent index of contractile function that is corrected for afterload. End-diastolic indices such as end-diastolic dimension and end-diastolic stress have also been used to assess left ventricular function. The utility and limitations of end-systolic pressure-volume relations (Emax or elastance) have already been discussed.

Given the importance of occult contractile dysfunction in this disease, the pathophysiology is more easily understood. When the regurgitant lesion first occurs, there is an acute increase in left atrial pressure as the regurgitant blood is ejected into a small, noncompliant chamber. Because changes in left ventricular geometry have not yet occurred, afterload is actually decreased in the acute setting. Since afterload is decreased and preload is increased, the ejection fraction increases to "supernormal" range. Over time, a series of adaptive and maladaptive changes occur. Progressive dilation of the left atrium occurs, resulting in a large, compliant chamber that is able to receive a large regurgitant volume with normal or only minimally elevated mean left atrial pressure. The left ventricle enlarges it volume and increases its mass, as described earlier. However, the increase in left ventricular size is predominantly by an increase in its radius, rather than its wall thickness (i.e. eccentric hypertrophy). Afterload returns to the normal range due to the

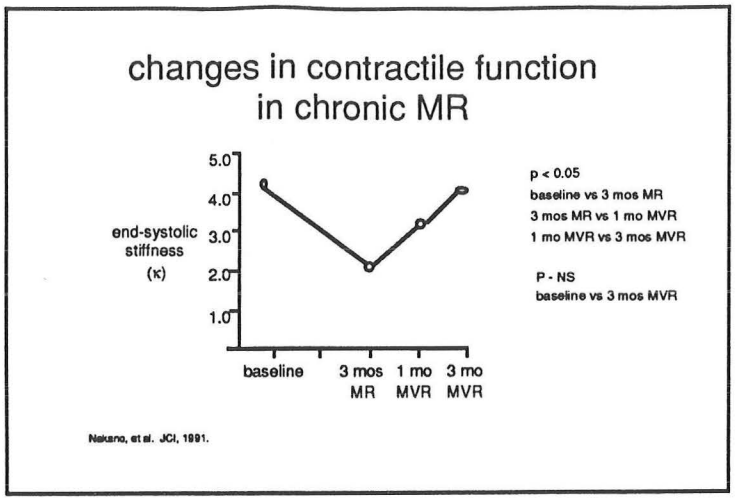
changes in left ventricular geometry. Ejection performance is enhanced by the changes in loading conditions and, thus, ejection fraction remains "normal." However, at some point progressive contractile dysfunction begins to occur. When the patient reaches a decompensated state, wall stress or afterload increases and ventricular emptying is impaired, leading to an increase in end-systolic volume and a decrease in ejection fraction. Left ventricular end-diastolic pressure also increases in this stage of the disease and this increase in filling pressures leads to symptoms of pulmonary congestion [5, 45, 46]. It is presumed that contractile dysfunction is reversible early on, but becomes irreversible with time. By the time ejection performance is impaired (i.e. ejection fraction is decreased) some degree of irreversible contractile dysfunction is present.

Animal models: A canine model of mitral regurgitation has been developed which provides useful insights regarding this disease. Mitral regurgitation can be created by using a grasping forceps inserted through the carotid artery to sever some of the chordae tendinae, resulting in a flail leaflet [47]. By three months, this produces a 50-100% increase in end-diastolic volume, a 30% increase in myocardial mass, and a decrease in all measured indices of contractile function. Frank congestive heart failure develops in some animals. At a structural level, there is an increase in myocyte cross-sectional area, predominantly due to an increase in myocyte length. There is also a loss of myofibril volume, indicating a loss of contractile proteins [48, 49]. The loss of contractile elements correlated directly with the degree of contractile dysfunction [49]. In these animal models, contractile dysfunction is reversible by correction of the regurgitation. Mitral valve replacement in these animals has been shown to result in an increase in myofibril volume and recovery of indices of contractile function towards or to normal [47, 48].

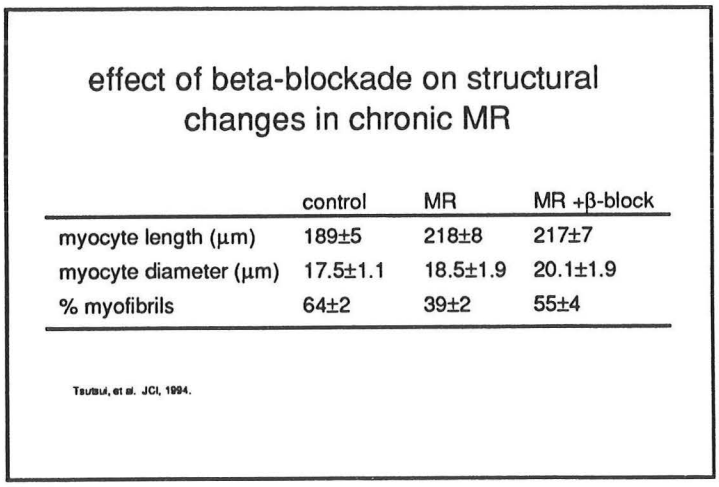
structural changes in chronic MR - animal model

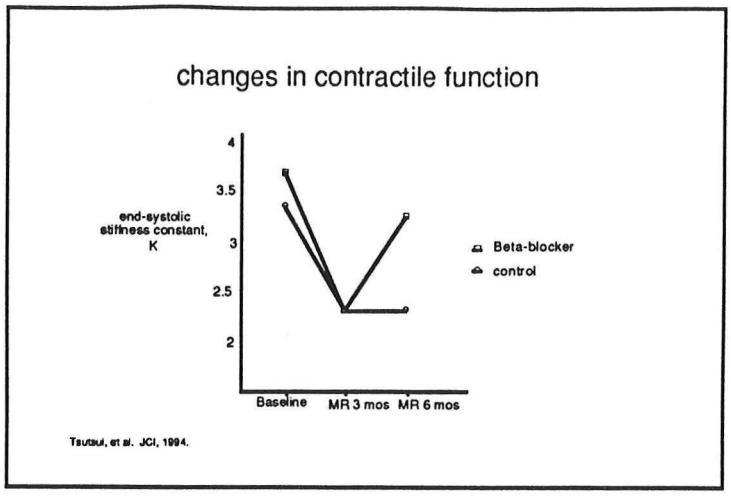
	control	MR	s/p MVR
myocyte length (μm)	194±4	218±8	231±7
myofibril volume (μm³)	22.2±0.7	14.8±1.5	27.1±1.1
mitochondrial volume(μm³)	8.6±0.4	8.6±1.2	10.3±0.5
nuclear DNA area(μm2)	1163±89	1430±122	2209±250

Spinale, et al. Circulation, 1992.



An interesting finding in the animal model has been the observation that chronic beta-adrenergic blockade can improve contractile function and is associated with restoration of contractile elements in dogs with chronic mitral regurgitation [50]. Beta-adrenergic stimulation of the myocardium in failing ventricles is now believed to have deleterious long-term effects and beta-blockade has been shown in human studies to improve ejection performance and survival in patients with systolic dysfunction[51-53]. In this animal model, two groups of dogs were studied after 3 months of mitral regurgitation and had similar degrees of left ventricular dysfunction. One group received gradual beta-blockade while the second group had no further intervention. Contractile function (as measured by assessment of the end-systolic stiffness constant, k) remained unchanged in the group that did not receive beta-blockers. However, in the beta-blocked animals, contractile function improved significantly (to the normal range). At a cellular level, myofibrillar density was much higher in the beta-blocked group, indicating more contractile elements in these animals. Since catecholamines have been shown to decrease protein synthesis in adult cardiac cells, it was postulated that beta-blockade permitted cardiac hypertrophy to occur by protecting the myocytes from catecholamine toxicity [50, 54].



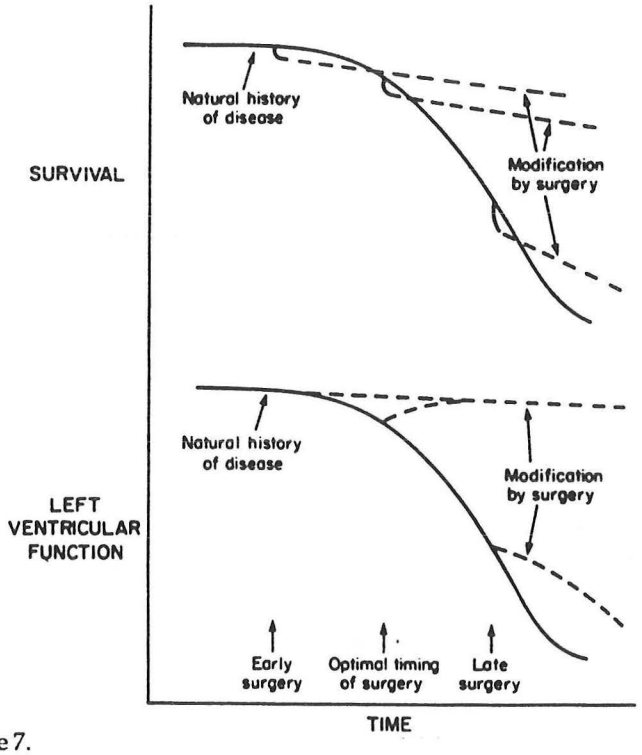


Treatment of chronic mitral regurgitation

The primary goal of treatment of chronic mitral regurgitation should be to preserve contractile function of the ventricle. Thus, it becomes critically important to be able to identify or recognize contractile dysfunction and to correct mitral regurgitation before irreversible dysfunction occurs. While contractile function appears to be reversible in the canine model of mitral regurgitation, the human disease may be different. In man, the disease is present for years rather than months [55]. Data by Starling, et al. suggests that contractile dysfunction may be reversible over a longer time period than in the animal model [41]. In those patients with normal ejection fractions but reduced myocardial elastance, although ejection fractions fell after surgery, ejection fraction had returned to baseline by 1 year post-op, suggesting that contractile function may have been restored over this longer time period. In a small study of 15 patients with chronic mitral regurgitation and normal ejection fractions who underwent mitral valve surgery, left ventricular contractile index (E_{es}) was measured both preoperatively and one year post-operatively [56]. The mean Ees increased from 0.95±0.66mmHg/ml preoperatively to 2.62±2.16mmHg/ml one year post-operatively, indicating that contractile dysfunction was reversible in many <u>but not all</u> of these patients.

In addition to the goal of preserving contractile function, our aim should also be to relieve symptoms and to reduce long-term morbidity and mortality [57]. Surgical correction of the regurgitant lesion will achieve all of these goals, provided that it is not performed too late in the course of the disease. The advantages of surgery include correction of the regurgitant lesion, preservation of contractile function, and relieve of symptoms. The disadvantages include the mortality associated with the operation itself and long term complications of the surgery, predominantly complications associated with prosthetic valves (thromboembolic complications, bleeding complications from anticoagulation, and endocarditis). Because of these

disadvantages, there is a strong reluctance to operate "too early" in the disease. However, surgery late in the course of the disease when contractile dysfunction has become irreversible is associated with impaired survival and a high risk of congestive heart failure [31, 32, 57, 58]. Thus, the proper timing of surgical intervention becomes critical.



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Multiple studies have been done in an attempt to identify predictors of post-operative outcome and a number of both clinical factors and hemodynamic predictors of poor post-operative outcome have been defined. Clinical factors associated with a worse post-operative outcome include increasing age [59, 60], severity heart failure symptoms [31, 32, 60, 61], presence of atrial fibrillation [31, 32, 60], and coexistent coronary artery disease [31, 32, 60]. Hemodynamic parameters associated with a worse post-operative outcome include an ejection fraction < 50-60% (depending on the study) [31, 32, 40], end-systolic volume index of greater than 50-60 ml/m^2 [38, 58, 62], cardiac index < 2 l/min/m^2 [61], mean pulmonary artery pressure > 20 mmHg [58], left ventricular end-diastolic dimension > 7.0 cm (by echocardiography) [40, 63], and a left ventricular end-systolic dimension > 4.5 - 5.0 cm [31, 64]. In the past, recommendations for consideration of surgical intervention have suggested that surgery be considered when a patient develops significant decompensation, as suggested by these predictors [57, 65]. However, since these are predictors of a poor post-operative outcome, it seems reasonable to

recommend that patients undergo surgery prior to developing these adverse predictors [56].

Gaasch has proposed a staging system for asymptomatic patients using these hemodynamic predictors [46]. Patients are divided into one of three categories: compensated, transitional, and decompensated. Patients in the decompensated stage have hemodynamic predictors for poor post-operative outcome, while patients in the compensated stage have hemodynamic predictors associated with good post-operative outcome. The transitional stage is the point in time at which he proposes that surgical intervention be undertaken. While interesting and potentially helpful, this approach has not been systematically used or studied.

Stages of chronic mitral regurgitation

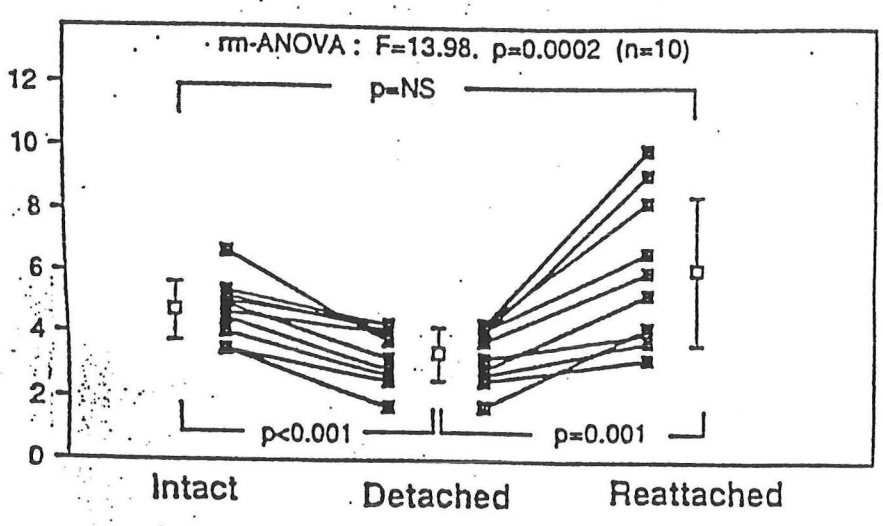
	compensated	transitional	decompensated
cardiac catheterization			
end-diastolic volume, ml/m2	<110	120-150	>160
end-systolic volume, ml/m2	<45	50-55	>60
ejection fraction, %	>60	53-57	<50
echocardiography			
end-diastolic dimension, mm	<63	65-68	>70
end-systolic dimension, mm	<42	44-45	>47

adapted from Gaasch, et al. Chest, 1995.

Evolution of surgical techniques:

Two critically important advances in mitral valve surgery have been made: an understanding of the importance of preserving the chordae tendinae during valve replacement and the evolution of techniques for mitral valve repair. Conventional mitral valve replacement in the past consisted of transection of the chordae tendinae and excision of all of the subvalvular apparatus. However, this approach nearly always results in a decline in post-operative left ventricular function, even in patients with normal pre-operative ejection fraction. In a canine model of mitral regurgitation, systolic performance was noted to drop after chordal detachment and return to baseline with reattachment of the chordae [66]. Studies in humans undergoing mitral valve replacement have compared patients with preservation of the chordae versus patients with chordal transection and have shown better preservation of ejection fraction in those patients in whom the chordae are preserved [67, 68] Operative mortality has been shown to be lower and overall survival better when the subvalvular apparatus is preserved during mitral valve replacement [69]. Preservation of

the chordae tendinae preserves papillary-annular continuity which preserves left ventricular geometry, resulting in smaller left ventricular volumes and lower end-systolic wall stress [70]. Thus, if mitral valve replacement is required, every attempt should be made to preserve the chordae tendinae.



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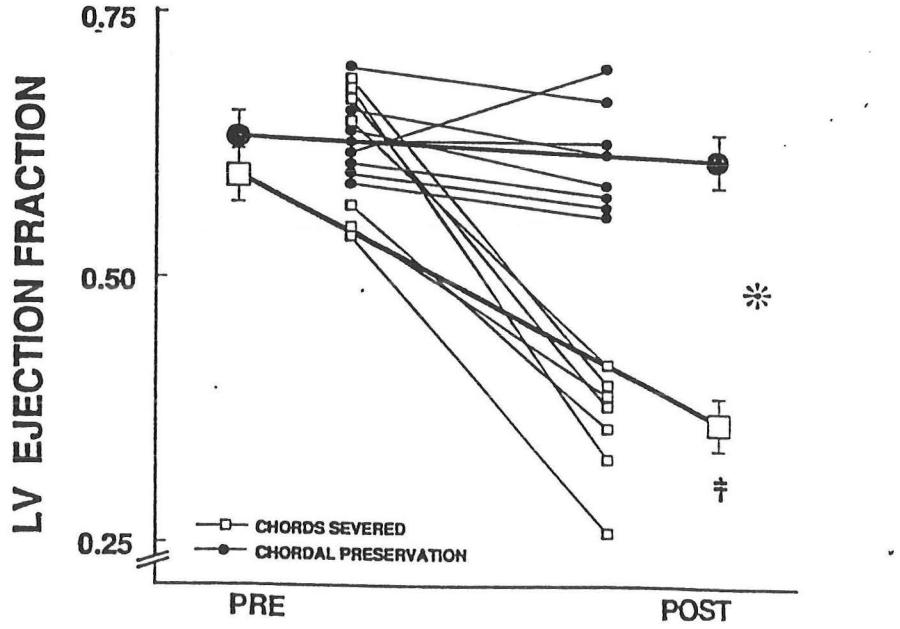

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Mitral valve repair or reconstruction (also known as mitral valvuloplasty) has been a major advance in the treatment of mitral regurgitation. Repair of the mitral valve has been attempted since the early days of cardiac surgery, but with the development of prosthetic heart valves, mitral valve replacement became the accepted procedure for many years [71]. Attempts to repair the mitral valve have continued and mitral valve repair has experienced a well-deserved surge in popularity recently with continuing improvement and refinement in surgical techniques. In contrast to mitral valve replacement, mitral valve repair has several advantages (Tables IV and V). Operative mortality is substantially lower with valve repair compared to valve replacement [60, 72-83], ejection fraction is better preserved [60, 72, 84-86], and long-term survival is improved compared to valve replacement [60, 73, 76]. Thromboembolic complications are significantly less common with mitral valve repair [87] and, since only a minority of patients on maintained on chronic anticoagulation, the incidence of hemorrhagic complications is also quite small [81, 87]. Likewise, the incidence of endocarditis is much less with valve repair versus replacement [72, 87]. One disadvantage to mitral valve repair is that there is a substantial learning curve for the various techniques as compared to valve replacement. Thus, post-operative results are even more highly dependent on the skill and experience of the operator.

Table IV. Pre-op and Post-op ejection fraction (%)

		repair		replacement with chordal transection		replacement with chordal preservation	
Author	year	preop	postop	preop	postop	preop	postop
Duran et al	1980	47	57	54	47		
David et al	1983	63	63	62	51	64	65
David et al	1984			55	48	53	52
Goldman et al	187	44	49	64	40		
Hennein et al	1990			46	31	50	54
Sakai et al	1992	65	68	64	57		
Rozich et al	1992			60	36	63	61
Enriquez-Sarano	1995	63	54	69	49		

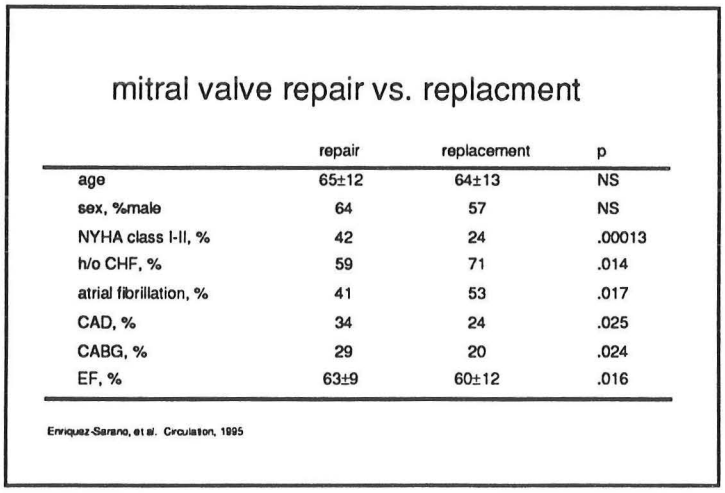
from reference 24.

Table V. Operative mortality

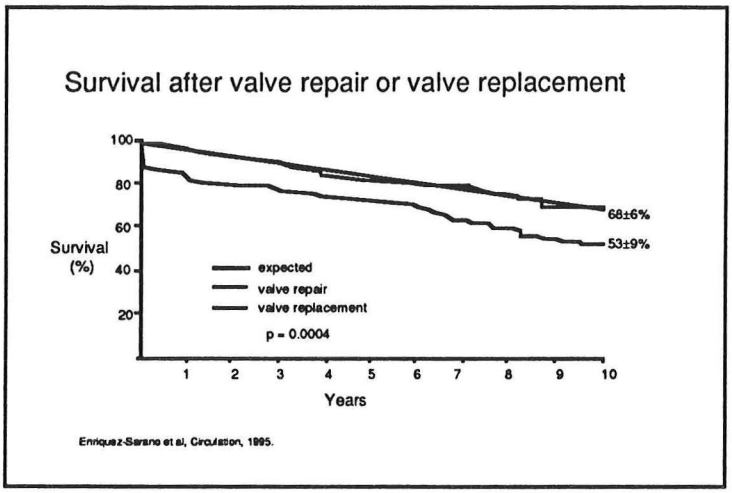
		repair		replacement	
study	year	#	%	#	%
Duran et al	1980	255	1.8	307	11.4
Yacoub et al	1981	86	3.1	46	7.0
Olivera et al	1983	82	4.9	101	5.0
Abedo and Ross	1984	21	0	144	11
Perier et al	1984	100	2	200	12
Orszulak et al	1985	131	6.1	106	7.5
Sand et al	1987	48	0	222	4.0
Angell et al	1987	112	5.4	72	18.1
Cohn et al	1988	75	4.0	63	3.0
Galloway et al	1989	280	2.0	1144	8.2
Carver et al	1990	65	1.5	65	4.6
Kawachi et al	1991	43	2.3	48	8.3
Enriquez-Sarano	1995	151	1.3	175	5.7
		44	6.8	39	30.8

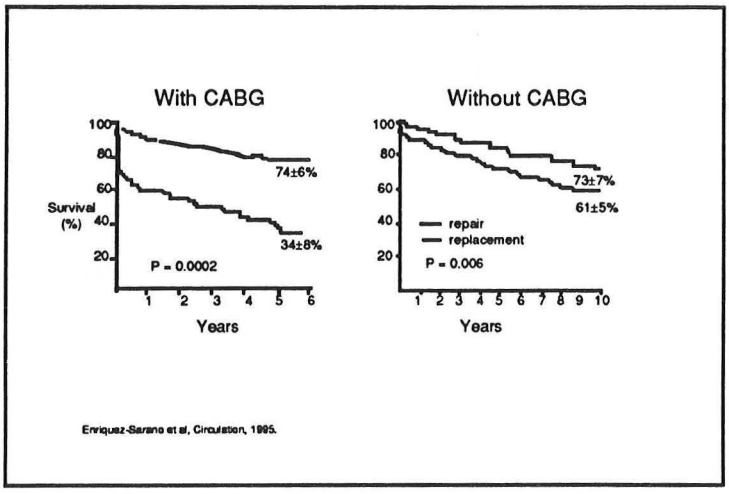
from reference 24.

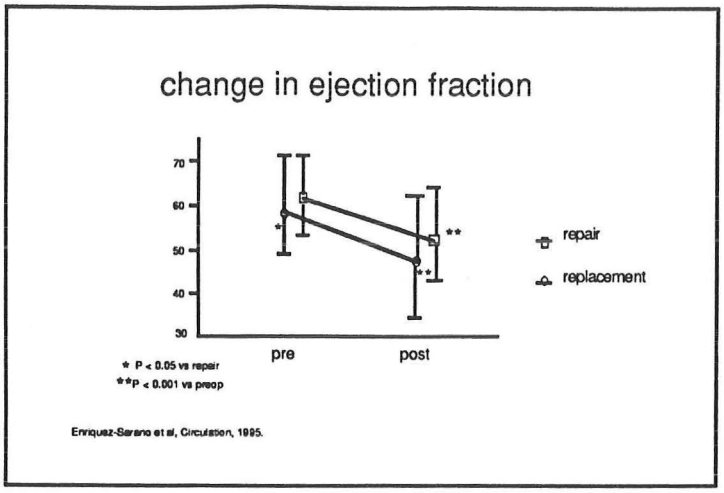
A retrospective comparison of mitral valve repair versus replacement in a large series of patients from the Mayo clinic was recently published[60]. This retrospective review involved patients with acquired organic mitral regurgitation undergoing a first mitral valve surgery between 1980 and 1989. The two patient groups were quite different, with the patients undergoing valve repair being less symptomatic, with less atrial fibrillation and a slightly higher ejection fraction. The prevalence of coronary artery disease and the need for concurrent coronary bypass surgery were not different between the two groups.

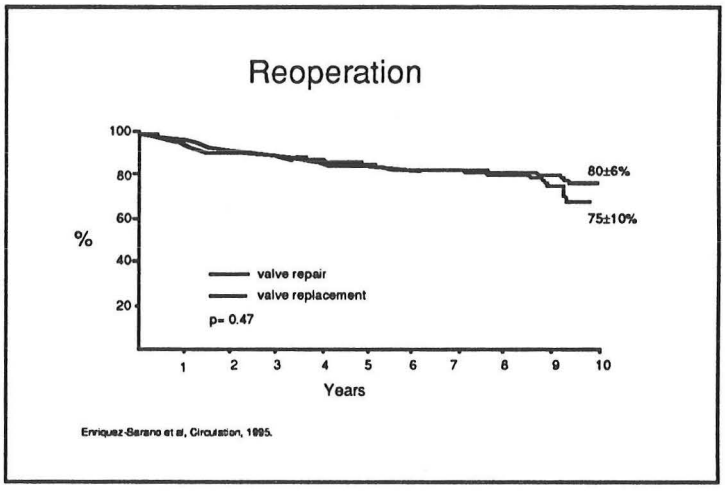


The operative mortality was lower for valve repair than for valve replacement (2.6% versus 10.3%, p = 0.002) and overall survival was better for patients undergoing valve repair with a 68±6% 10-year survival for the repair group compared to 53±9% for the replacement group (p=0.004). Valve repair appeared to be particularly advantageous for patients who underwent coronary artery bypass. Mean ejection fraction fell in both groups but was significantly higher after valve repair. Importantly, there was no difference in the need for reoperation between patients having repair versus replacement.









The mechanism of regurgitation plays a critical role in determining the likelihood of valve repair [71]. Valve repair is most likely to be successful in patients with degenerative disease. The most common abnormalities seen in degenerative disease are (in order of frequency) posterior chordal rupture, elongated chordae, dilated annulus, anterior chordal rupture, and combined anterior and posterior chordal rupture. The likelihood of repair is highest for posterior chordal rupture and elongated chordae. Patients with mitral regurgitation secondary to ischemic heart disease are often candidates for valve repair as well. Valve repair may be less feasible in patients with mitral regurgitation due to congenital defects, rheumatic valvular disease, and endocarditis, but should be considered.

Role of echocardiography in valve repair: Echocardiography plays an important role in assessing the feasibility of valve repair preoperatively and in assessing the immediate results of valve repair in the operating room.

From a functional standpoint, the surgeon needs to know whether leaflet motion is normal (type I), increased (type II, e.g. as in mitral valve prolapse), or restricted (type III) [88]. Mitral regurgitation with normal leaflet motion can be seen with leaflet perforations or with annular dilatation. Mitral regurgitation due to increased leaflet motion is seen prolapse of the leaflet tissue, chordal elongation or rupture, or papillary muscle elongation or rupture. Mitral regurgitation with restricted leaflet motion is commonly seen with rheumatic valvular disease. Both transthoracic and transesophageal echocardiography are useful preoperatively in assessing the mechanism of mitral regurgitation and to determine the likelihood of successful valve repair [89, 90]. Intraoperatively, either epicardial or (more commonly) transesophageal echocardiography are used to assess the adequacy of valve repair and to detect post-operative complications such as left ventricular outflow tract obstruction which can occur with some surgical techniques [71, 91].

Vasodilator therapy in chronic mitral regurgitation:

In patients with chronic mitral regurgitation, the short-term administration of vasodilators has been shown to have beneficial effects [92]. In general, regurgitant volume is decreased, forward stroke volume is increased and ejection fraction remains unchanged. In symptomatic patients, the administration of vasodilators improves symptoms. However, whether or not vasodilator therapy can delay the onset of symptoms in asymptomatic patients or can prevent or delay impairment of left ventricular function has never been proven. Two small studies have addressed this issue. Schoen, et al administered Quinapril to 12 patients with chronic mitral regurgitation in an open-label trial with no placebo arm [93]. Most patients were already on digoxin and diuretics and most were symptomatic (50% in class II, 25% in class III). At the end of one year of therapy, regurgitant fraction had decreased and left ventricular volumes had also decreased. There was no change in ejection fraction and more detailed assessment of contractile function was not performed. Wisenbaugh, et al studied 32 patients with predominantly rheumatic mitral regurgitation in a placebo-controlled study of fairly low-dose Captopril [94]. In contrast to the previous study, these patients were either asymptomatic or mildly symptomatic. Other vasodilator therapy and digoxin were not used in these patients, but diuretic therapy was permitted. There was no demonstrable change in left ventricular dimension or ejection fraction at six months. Thus, vasodilator therapy has no proven role in the management of patients with chronic mitral regurgitation and should not be used as a substitute for surgical therapy.

Quinapril in chronic mitral regurgitation - results

	baseline	1 yr	p
regurgitant fraction	.43±.10	.25±.08	.0001
LV end-diastolic volume index	146±26	109±24	.0001
LV end-systolic volume index	63±43	47±29	.001
ejection fraction	.59±.20	.59±.16	NS

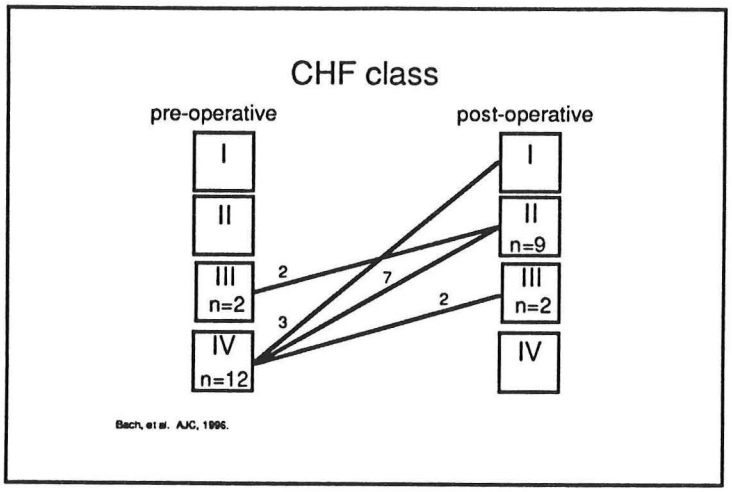
Schon, et al. J of Heart Valve Disease, 1994.

Mitral valve repair for patients with severe left ventricular dysfunction.

Mitral regurgitation often occurs in patients with left ventricular dysfunction (e.g. both ischemic or nonischemic cardiomyopathies) as a complication of dilatation of the mitral annulus and the left ventricle as well as alterations in left ventricular geometry [2-4]. Mitral regurgitation leads to further volume overload of the ventricle, leading to progressive dilatation of the annulus and the ventricle with worsening mitral regurgitation, thus creating a "vicious cycle."

Some intriguing work has been done by Bach, et al at the University of Michigan to assess the feasibility of attempting mitral valve repair in this situation [95]. They studied twenty patients with dilated cardiomyopathies and severe left ventricular dysfunction, severe mitral regurgitation and refractory congestive heart failure. The etiology of the cardiomyopathy was ischemic in 7 and nonischemic in 13. Ages ranged from 44 to 78 years old with a mean age of 64. The mean ejection fraction was 18±5% (range 10-25%). All patients were severely symptomatic with 85% in NYHA class IV and 15% in class III. Two patients were awaiting cardiac transplantation, while the remaining eighteen were ineligible for transplant. All patients underwent mitral valve reconstruction with a ring annuloplasty. Coronary artery bypass grafting was also performed in three patients and tricuspid annuloplasty was performed in three patients for concomitant tricuspid insufficiency. There were no operative deaths. Six patients (30%) died during follow-up, with their deaths occurring between 3 weeks and 8 months after surgery. All survivors reported an improvement in functional class following surgery. Two of the twelve survivors required post-operative admissions for congestive heart failure. Thirteen patients had both preoperative and postoperative echocardiograms. A significant decrease in left ventricular volumes was seen postoperatively (end-diastolic volume decreased from 276±78 ml to 215±80 ml, $p<0.001$ and end-systolic volume decreased from 222±72 ml to 163±78 ml, $p<0.001$) and ejection fraction increased (from 20±4%

to 26±7%, p=0.001). Thus, in this small, observational study, mitral valve reconstruction resulted in improved symptom status and had an acceptable 1 year mortality rate as compared to patients with similar degrees of severely symptomatic left ventricular dysfunction[96-98]. While this approach needs further study, it raises the intriguing possibility that consideration of mitral valve repair may be appropriate for patients with mitral regurgitation, even those with severe contractile dysfunction.



Recommendations for surgery:

Once severe mitral regurgitation has been identified, the timing of surgical intervention becomes the major issue to be addressed. Mitral valve surgery (preferably mitral valve repair) should be done for all symptomatic patients, regardless of ejection fraction unless their operative mortality is felt to be prohibitive [5, 26, 99]. Any symptoms of congestive heart failure (even transient) and/or decreased exercise tolerance are considered appropriate indications for referral for surgery [26, 30, 99]. Waiting for patients to develop class III or IV congestive heart failure symptoms places them in a category of patients with a higher risk of post-operative left ventricular dysfunction and persistent or worsening congestive heart failure [31]. Although patients with advanced contractile dysfunction as indicated by depressed ejection fractions have a poorer outcome, patient survival is better with surgical than medical therapy [57].

For asymptomatic patients, the risks and benefits of surgery need to be weighed on an individual basis. The risk of operative mortality needs to be considered but needs to be balanced by the risk of progressing to irreversible contractile dysfunction, resulting in poor long-term survival. If surgery is not felt to be indicated at the initial evaluation, patients should be followed closely for either the development of symptoms or signs of declining ejection fraction or increasing left ventricular dimensions [5, 26, 46, 99].

Some authorities consider the development of atrial fibrillation to be an indication for mitral valve surgery [100]. In a group of 685 patients undergoing a variety of valve replacement procedures (not limited to mitral valve replacement), atrial fibrillation was present in 148 of 589 survivors. Of these, 96 patients remained in or reverted to atrial fibrillation after cardioversion. The preoperative variables associated with persistent atrial fibrillation included left atrial enlargement (> 5.0cm) and preoperative atrial fibrillation for greater than 1 year [101]. In a study of 323 consecutive patients undergoing mitral valve repair for mitral regurgitation, 216 were in sinus rhythm, 11 were in atrial fibrillation of recent onset (less than 3 months) and the remaining 86 were in chronic atrial fibrillation [102]. There was no difference in operative mortality or late survival between those patients in sinus rhythm versus atrial fibrillation. However, at late follow-up, atrial fibrillation was present in 80% of patients with preoperative chronic atrial fibrillation, none of the patients with recent onset preoperative atrial fibrillation and in 5% of patient with preoperative sinus rhythm, suggesting that mitral valve repair before or shortly after the onset of atrial fibrillation maximizes the chance of maintaining postoperative sinus rhythm.

An algorithm for determining the timing of mitral valve surgery in asymptomatic patients has been proposed [26]. Patients are assigned points for clinical variables , left ventricular size and function, and the feasibility of mitral valve repair (based on the mechanism of regurgitation). Patients with ≥ 3 points are referred for surgery whereas surgery is delayed in patients with 0-1 point (but routine follow-up of clinical symptoms and left ventricular function is performed every 6-12 months). Patients with a point score of 2 are considered borderline and close follow-up is recommended within 6 months. In addition, additional predictors of adverse outcome can be evaluated to support the decision to delay or proceed with surgery. While this algorithm has not been prospectively evaluated , it does provide a reasonable guideline for managing the asymptomatic patient with severe mitral regurgitation.

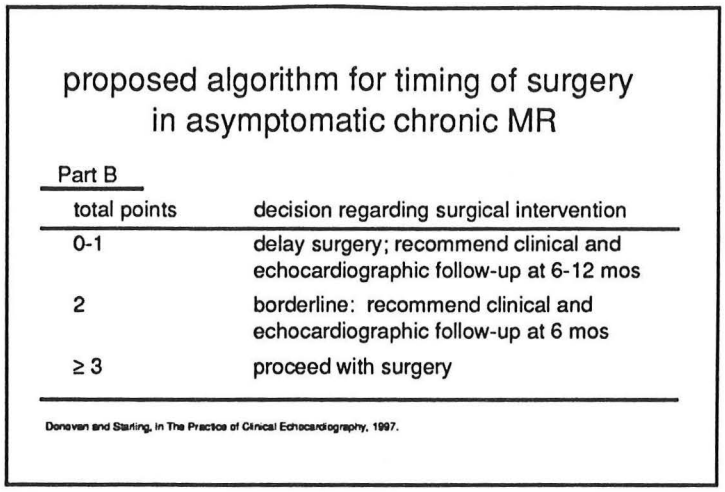
proposed algorithm for timing of surgery in asymptomatic chronic MR

Part A

points	clinical variables	EF (%)	ESD (mm)	feasibility of repair
0	none	> 65	< 40	none
1	1	60-65	40-45	possible
2	≥ 2	< 60	> 45	definite

*age > 60, mean pulmonary artery pressure > 20 mmHg, cardiac index ≤ 2 L/m/m2, end-diastolic pressure > 12mmHg, coronary artery disease, history of atrial arrhythmias

Donovan and Starling, In The Practice of Clinical Echocardiography, 1997.



Conclusions:

In summary, chronic mitral regurgitation places a volume load on the left ventricle that leads to unfavorable changes in left ventricular geometry and, over time, produces progressive contractile dysfunction. This contractile function appears to be reversible initially, but becomes irreversible at some point, resulting in progressive left ventricular dysfunction, congestive heart failure, and death. Patients with chronic mitral regurgitation are often asymptomatic until significant contractile dysfunction is present. Because of favorable loading conditions, ejection fraction may be preserved at a time when contractile function is impaired. Thus, ejection fraction cannot be used to assess contractile function. Surgical correction improves symptoms and long-term survival and results are best when surgery is performed in patients with normal left ventricular function or reversible contractile dysfunction. Therefore, patients must be followed closely and surgical intervention (preferably valve repair) should be undertaken as soon as contractile dysfunction is suspected.

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