

VALVULAR HEART DISEASE

The Pathophysiology of Ischemic Mitral Regurgitation: Implications for Surgical and Percutaneous Intervention

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Introduction

Mitral regurgitation (MR) resulting from prior myocardial infarction is now recognized as an important clinical sequel that directly impacts the long-term outcome of patients. The pathophysiology of this disease process is now well established, and much clinical interest is currently directed toward defining the optimal management strategy of patients with ischemic MR. This review will focus on current concepts relating to the pathophysiology and therapy of ischemic MR.

Defining Ischemic MR. Carpentier's pathophysiologic triad¹ defines the relationship between etiology, lesion(s) (pathological changes in the valve), and dysfunction (abnormalities of leaflet motion) that results in MR. Carpentier's classification of leaflet dysfunction is based on the motion of the margin of the leaflet in relation to the annular plane (Fig. 1). Often authors use an etiologic definition for ischemic MR such as "mitral regurgitation resulting from prior myocardial infarction associated with *normal* mitral valve leaflets and chordae."² Such etiologic definitions (based solely

on the history of myocardial infarction) are inadequate as they fail to take into account the lesions or dysfunction(s) that actually result in ischemic MR.³ Indeed MR in patients with prior history of infarction does not necessarily imply ischemic MR (degenerative disease, for example, may coexist with coronary artery disease) hence the need to also define ischemic MR based on lesions and dysfunction.

In terms of defining ischemic MR it is important to note that the majority of patients have an etiologic basis of prior myocardial infarction, not an acute myocardial infarction or papillary ischemic event. Resulting wall motion abnormalities and left ventricular remodeling leading to lateral and apical displacement of papillary muscles are the key pathophysiologic events. The predominant mitral valve lesion, therefore, is leaflet tethering, mainly of the posterior-medial scallop of the posterior leaflet (P-3) adjacent to the posterior commissure area, particularly in the setting of posterior infarction (Fig. 2). Mitral annular dilatation often accompanies leaflet tethering as an associated lesion. The leaflet dysfunction resulting in the most common form of ischemic MR is Type IIIb, with restricted motion of the margin of the leaflet(s) in systole. Therefore for the majority of patients ischemic MR is defined by the presence of the following (a) prior history of myocardial infarction (b) tethering of predominantly the posterior-medial scallop of the posterior leaflet, and (c) Type IIIb Carpentier dysfunction with restricted leaflet motion in systole.

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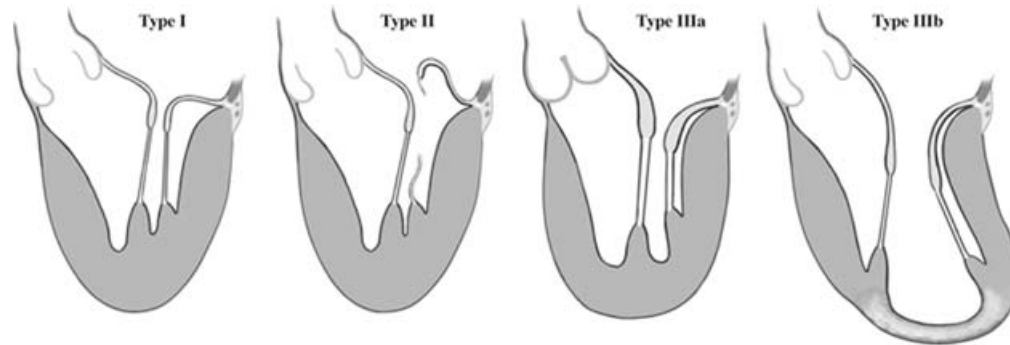


Figure 1. Carpentier's functional classification. Type I, normal leaflet motion; Type II, increased leaflet motion (leaflet prolapse); Type IIIa restricted leaflet motion during diastole and systole; Type IIIb restricted leaflet motion predominantly during systole (Modified from Carpentier A, Adams DH, Filsoufi F (in press). Carpentier's Techniques of Valve Reconstruction. Philadelphia: W.B. Saunders).³⁴

Other forms of ischemic MR are less common. Type I dysfunction without leaflet restriction (normal leaflet motion) and isolated annular dilatation can occur in the setting of isolated basilar myocardial infarction.

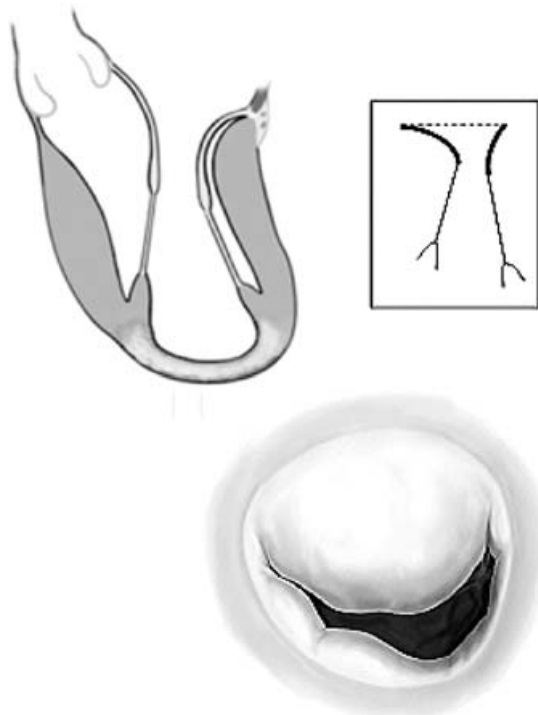


Figure 2. Leaflet restriction, mainly of the posterior-medial scallop of the posterior leaflet (P-3) in the setting of posterior infarction (Modified from Carpentier A, Adams DH, Filsoufi F (in press). Carpentier's Techniques of Valve Reconstruction. Philadelphia: W.B. Saunders).³⁴

Some patients with ischemic MR have Type II dysfunction (excess leaflet motion), resulting from either an acute (ruptured papillary muscle) or chronic (fibrotic and elongated papillary muscle) myocardial ischemic event. It should be emphasized that the prior concept of "acute ischemia with papillary muscle dysfunction" that would reverse with revascularization is now recognized to be valid in only a small percentage of patients with ischemic MR. This review will concentrate on ischemic MR with restricted leaflet motion that is most frequently seen in clinical practice.

Current Concepts in the Pathophysiology of Ischemic MR. Ischemic MR had originally been thought to be due to "papillary muscle dysfunction." The concept of an acutely ischemic papillary muscle causing MR was the basis for the teaching and practice (which held till the mid 1990s) that coronary artery revascularization alone should reverse ischemic MR. However, clinical observations in the 1990s showed that revascularization does not generally result in resolution of MR.⁴ Experimental and clinical imaging studies have confirmed that the main trigger for ischemic MR is not papillary muscle dysfunction, but lateral and apical displacement of the papillary muscle with resultant restricted leaflet motion.

Myocardial infarction of the segments underlying the papillary muscles (typically a lateral or inferior infarct) results in remodeling of that region of the ventricle. The papillary muscle is displaced resulting in leaflet tethering and MR due to restricted closure. Annular dilatation, predominantly of the septolateral dimension, is also usually present. The pathophysiological process then becomes self-perpetuating as resultant

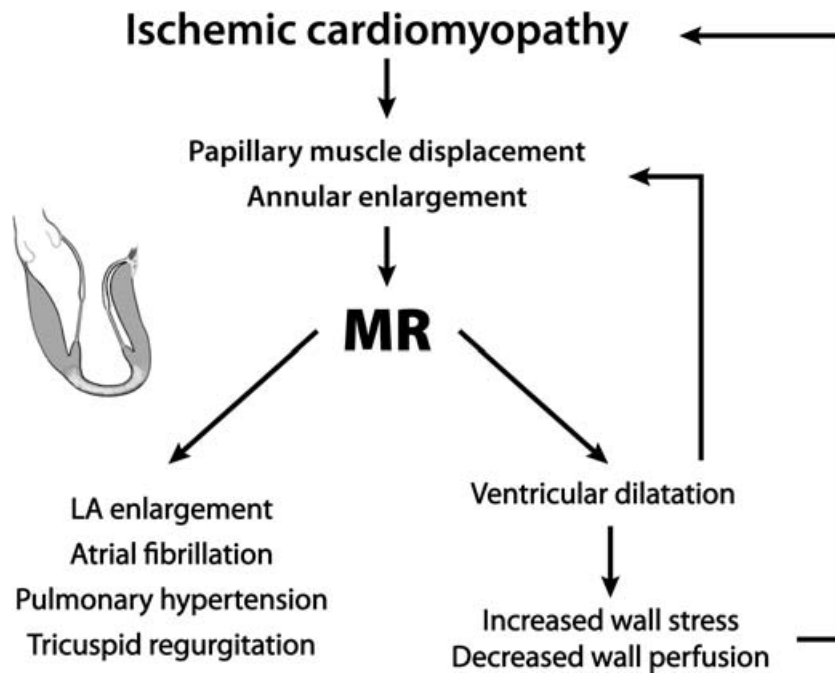


Figure 3. Pathophysiology of ischemic mitral regurgitation.

MR leads to ventricular dilatation which in turn leads to further papillary muscle displacement, annular enlargement, and then further MR (Fig. 3). Although correction of the MR by annuloplasty can halt this vicious cycle and produce reverse remodeling of the ventricle,⁵ several surgical series report that ventricular dilatation and papillary muscle displacement may continue in spite of annuloplasty resulting in recurrent regurgitation.⁵⁻⁸

Recent experimental and imaging studies have clarified some key pathophysiological concepts in ischemic MR crucial to understanding therapeutic approaches to this disease.

The *coaptation depth* refers to the distance between the annular plane and the plane of coaptation. This distance correlates with the presence and severity of ischemic MR. The coaptation depth is a measure of the degree of leaflet tethering.⁹ An objective of therapy for ischemic MR is to reduce the coaptation depth allowing coaptation closer to the annular plane.

Annular dilatation occurs primarily in the septo-lateral dimension due to dilatation of the posterior mitral annulus. Although most of the dilatation is in the posterior annulus, the fibrous (anterior) annulus also dilates.^{10,11} Kaji and colleagues¹² demon-

strated this using three-dimensional reconstructions, also showing that the annular dilatation is asymmetric and is more in the region of the posterior commissure (Fig. 4).

Leaflet changes. Although it is often stated that the valve leaflets are normal in IIIb restrictive disease, pathological studies have shown that these leaflets differ in structure and morphology when compared to autopsy controls.¹³ Leaflets are thinned out with altered collagen composition. Possible implications of these changes should be taken into account if therapeutic measures include interventions on the leaflets.

Anterior infarction. Ischemic MR has traditionally been associated with infarction in the posterior (infero-lateral) territories. Recently it has been recognized that anterior infarction is also a significant contributor in the pathophysiology of ischemic MR. In anterior infarction, leaflet tethering tends to be more symmetric, compared to posterior infarction. The areas of stress and tenting are also different (Fig. 5) with a more uniform distribution of stress and a greater area of tenting in anterior infarction compared to the concentration in the P3 region seen in classical ischemic MR.¹⁴

The ventricle. Postinfarction remodeling is the cause, rather than effect of ischemic MR. Experimentally, ischemic MR can be reduced by placing an external

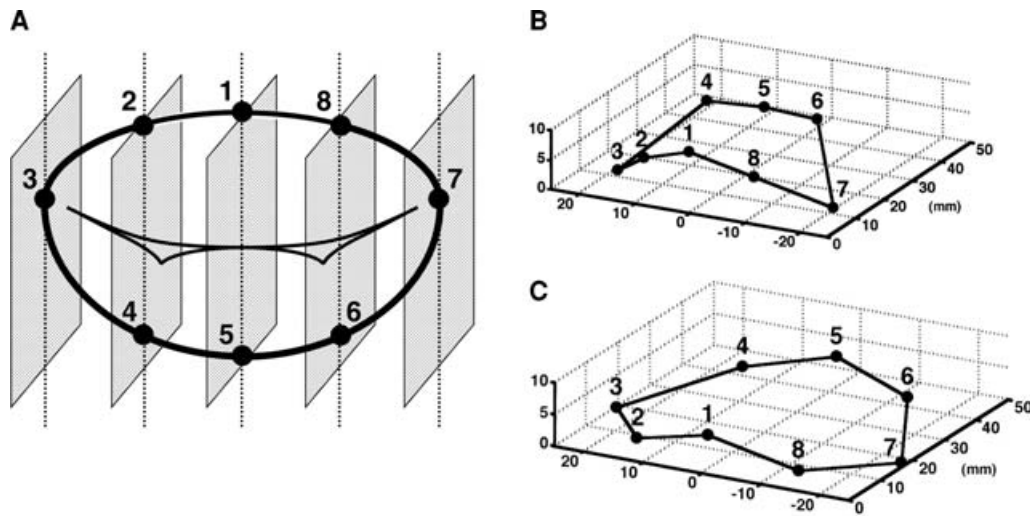


Figure 4. (A) Schematic representation of the mitral annular points. Points 2 and 8 correspond to the right and left trigones, respectively. Points 3 and 7 correspond to the posterior and anterior commissures, respectively (view is the reverse of the surgeon's view). (B) 3D reconstruction of the 8 mitral annular points without ischemic MR. (C) 3D reconstruction of the 8 mitral annular points (numbered) in a patient with severe ischemic MR (Modified from Kaji S, Nasu M, Yamamuro A, et al. Annular geometry in patients with chronic ischemic mitral regurgitation: Three-dimensional magnetic resonance imaging study. *Circulation* 2005;112:I409–I414).¹²

ventricular restraint (which prevents ventricular expansion); these restraints reduce adverse remodeling and MR. However, a prophylactic annuloplasty does not necessarily prevent ischemic MR as the ventricle will still remodel postinfarct causing MR.¹⁵ Pathophysiologically, therefore, the ventricle is another target for intervention in ischemic MR. Preventing postinfarction remodeling will prevent MR. Similarly, elimination of continued adverse remodeling after therapeutic intervention (such as annuloplasty) should theoretically prevent most recurrences of MR postrepair. Annuloplasty, the hallmark of current treatment strategies, is an effective therapy for ischemic MR but does not directly address the primary cause of ischemic MR. This may partly explain the mixed long-term results seen with surgical repair. In many patients halting the vicious cycle of ventricular remodeling (Fig. 3) by eliminating MR is adequate,⁵ while in others adjunctive novel ventricular therapy may be necessary to prevent further adverse ventricular remodeling.

Therapeutic Targets in Ischemic MR. Being essentially a ventricular disease with effects on the papillary muscle, chords, and consequently valve coaptation, ischemic mitral valve regurgitation lends itself to several therapeutic conceptual approaches.

Coronary Artery. Coronary artery revascularization, either surgically or percutaneously, of any critical lesions is performed to recruit any hibernating segments and thus improve ventricular function and limit future adverse remodeling secondary to continuing ischemia or new infarction. Revascularization alone cannot be relied on, however, as sole therapy for ischemic MR. From a pathophysiological basis, the cause of regurgitation is usually myocardial infarction leading to ventricular remodeling, which by definition should not improve significantly with revascularization. Coronary artery bypass surgery alone has been shown to leave a majority of patients with residual moderate ischemic MR.⁴ Revascularization by surgery¹⁶ or angioplasty¹⁷ has also been shown not to impact survival in patients with ischemic MR. Notably in the study by Ellis and colleagues,¹⁷ patients with moderate-to-severe MR and ejection fraction below 40% had a 50% mortality at 3 years despite successful percutaneous revascularization (Fig. 6). Other data from nonsurgical series also show that uncorrected regurgitation portends a poorer long-term prognosis.¹⁸ Although there are no randomized trials comparing coronary revascularization with adjunctive mitral repair to revascularization alone, extrapolation from observational studies suggests that

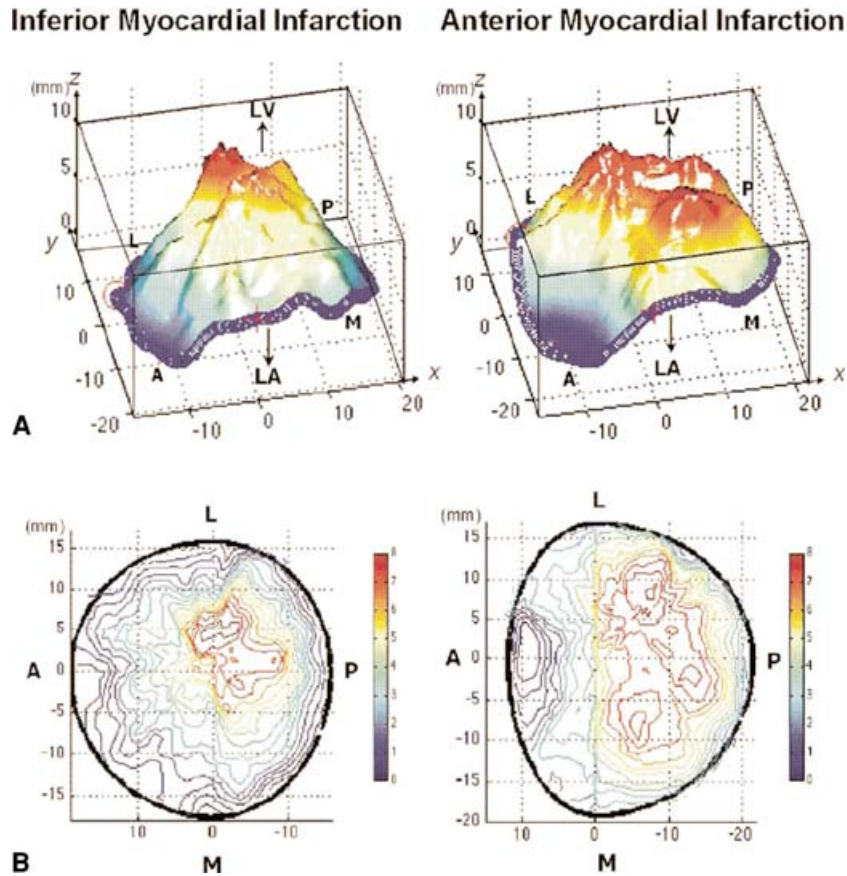


Figure 5. (A) Tenting of mitral leaflets, tethered into the left ventricle (LV), seen in patients with ischemic mitral regurgitation. For patients with anterior infarction, mitral valve leaflets are widely tethered and bulged toward LV, in contrast to patients with inferior infarction showing localized tenting of leaflet with less bulging. (B) Tethered leaflet area is smaller in inferior (left) than anterior (right) myocardial infarction. A = anterior; P = posterior; M = medial; L = lateral (Modified from Watanabe N, Ogasawara Y, Yamaura Y, et al. Geometric differences of the mitral valve tenting between anterior and inferior myocardial infarction with significant ischemic mitral regurgitation: Quantitation by novel software system with transthoracic real-time three-dimensional echocardiography. *J Am Soc Echocardiogr* 2006;19:71–75).¹⁴

isolated revascularization without direct therapy for MR is likely to result in poorer long-term outcomes. Revascularization should therefore be considered an adjunct, and not the primary therapy, for ischemic MR. The approach to revascularization is probably of little importance and in some settings a hybrid approach may be used with percutaneous revascularization and subsequent surgical mitral valve repair.

Mitral Annulus. The mitral annulus has been the prime focus for surgical repair techniques. A mitral annuloplasty corrects the annular dilatation. Undersizing this annuloplasty corrects the septolateral displacement, thus reducing IIIb restriction and restoring leaflet coaptation. Because the anterior annulus also dilates, a

complete remodeling ring is favored over incomplete bands. Novel asymmetric rings are increasingly utilized and help address the asymmetric tenting and restriction seen in this disease (Fig. 7).^{19,20} The inability to “overcorrect” the septolateral dimension, and to address anterior annular or asymmetric dilatation, makes current percutaneous approaches challenged to provide an optimal annuloplasty for ischemic MR (Fig. 8).

Increasing clarification of annular geometry with modern imaging techniques (such as 3D echocardiography and MRI), particularly in anterior infarction, should lead to exciting developments in mitral annuloplasty with development of annuloplasty techniques tailored to the individual patient. It is recognized that in

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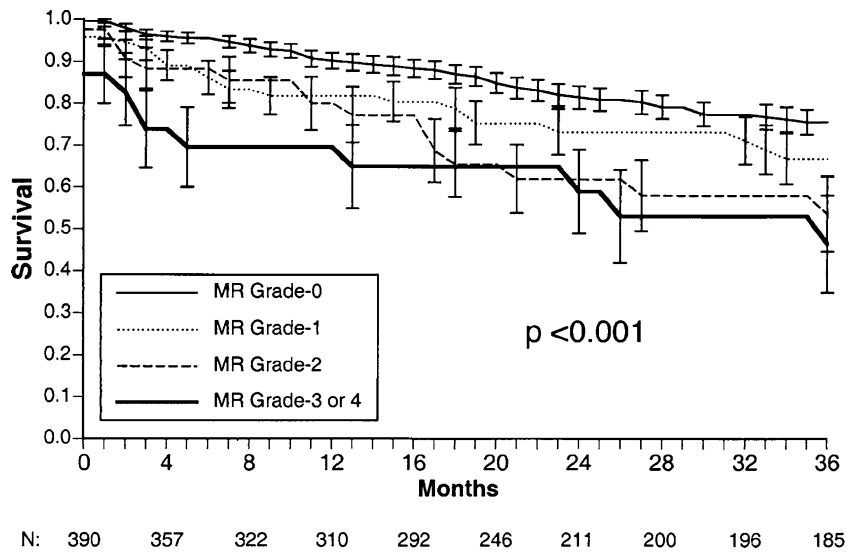


Figure 6. Kaplan-Meier survival curves for patients with left ventricular ejection fraction $\leq 40\%$ undergoing percutaneous balloon angioplasty stratified by degree of mitral regurgitation (Modified from Ellis SG, Whitlow PL, Raymond RE, et al. Impact of mitral regurgitation on long-term survival after percutaneous coronary intervention. *Am J Cardiol* 2002;89:315–318.

a substantial subgroup of patients adverse ventricular remodeling will continue despite annuloplasty with resultant ischemic MR—echocardiographic data are beginning to emerge that will help identify prospectively those patients in whom annuloplasty alone will not yield long-term resolution of MR such that alternative or adjunctive measures can be used.

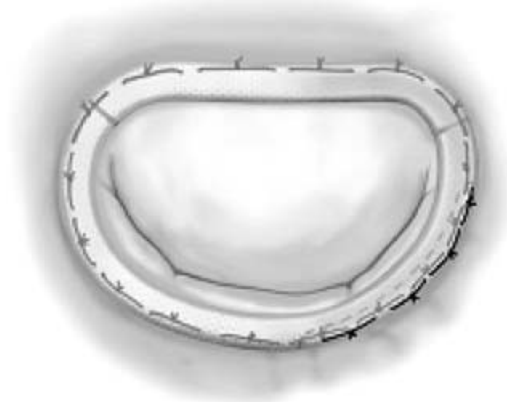


Figure 7. Remodeling annuloplasty using the asymmetrical Carpentier-McCarthy-Adams Etlogix IMR ring (undersized, 14% reduction in the posteromedial dimension) (Modified from Carpentier A, Adams DH, Filsoofi F (in press). *Carpentier’s Techniques of Valve Reconstruction*. Philadelphia: W.B. Saunders).³⁴

Subvalvar Apparatus. The subvalvar structures are currently only directly accessible by open surgical techniques. Subvalvar approaches aim to reduce leaflet tethering, and thus reduce coaptation depth, with resultant increase in the coaptation surface. Two broad approaches exist, (a) division of tethering chordae or (b) reduction of the distance between the papillary muscle heads and leaflet margin. Where a specific tethering chord is seen, this may be divided allowing greater leaflet mobility, either via atriotomy, aortotomy,²¹ or potentially percutaneously. Some workers even propose division of all basal chords at the time of mitral valve repair to allow greater leaflet mobility.²² Techniques have also been developed which relocate the papillary muscles such that they are closer to the annulus thereby reducing the leaflet tethering; currently this is done using sutures or by some form of resection and reimplantation of the papillary muscle,²³ but it is likely that internal or external prosthetic devices will be developed for this role.

Leaflets. Because the leaflets do not have any lesions that cause MR in the ischemic setting, there is a limited role for leaflet techniques in therapy for ischemic MR. The posterior leaflet can be augmented with a pericardial patch to improve mobility and available surface of coaptation; however, it is technically challenging to suture to what is often a thinned out leaflet.

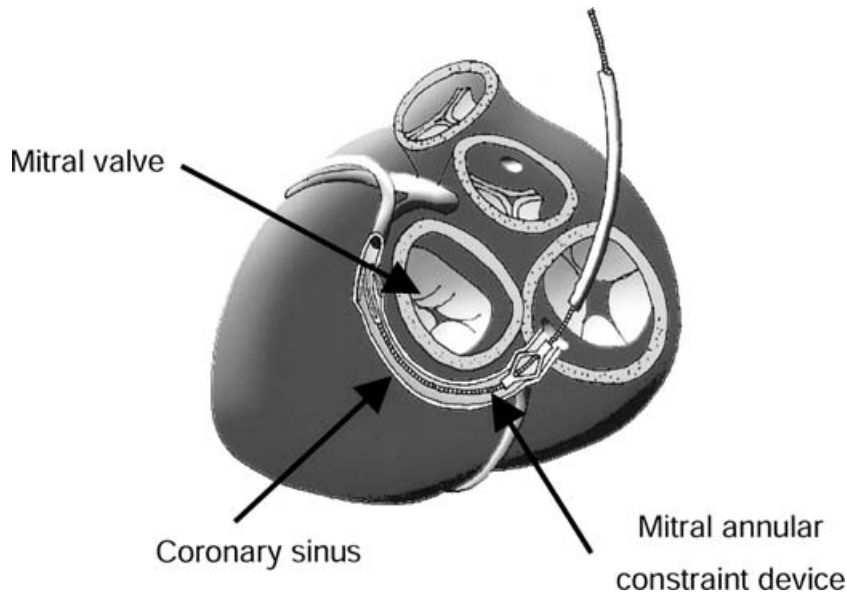


Figure 8. Percutaneous mitral valve annuloplasty; the position of the mitral annular constraint device in the coronary sinus and its relation to the posterior aspect of the mitral valve. Note a complete remodeling of the annulus is not possible via the coronary sinus (Modified from Kaye DM, Byrne M, Alferness C, et al. Feasibility and short-term efficacy of percutaneous mitral annular reduction for the therapy of heart failure-induced mitral regurgitation. *Circulation* 2003;108:1795–1797).³⁵

The edge-to-edge technique has been proposed, but from understanding of the pathophysiology, this approach, either surgically or percutaneously, will generally not be successful without a concomitant annuloplasty as it does not address the primary lesions causing the MR (leaflet tethering and annular dilatation). Experimental work in animal models highlights potential inadequacies of the edge-to-edge repair as sole therapy for ischemic MR, as it does prevent occurrence of ischemic MR or alter the annular, subvalvular, or leaflet geometrical alterations seen in the disease.²⁴ Surgical proponents of the edge-to-edge technique do not regard an isolated edge-to-edge repair as sufficient therapy for patients with MR where lesions include significant annular dilatation;²⁵ such that all surgical series on edge-to-edge repair in ischemic MR have included concurrent annuloplasty. The edge-to-edge is, however, used as an adjunct to a surgical annuloplasty and in this setting may result in a durable repair.²⁶ Current experience in percutaneous edge-to-edge repair in ischemic MR is limited.²⁷

Ventricle. Recognition in the last decade of ischemic MR as a ventricular, rather than a primary valve disease, and also the relatively high incidence of recurrent MR following isolated annuloplasty, has led to a

recent focus on ventricular approaches for treating ischemic MR. Indeed, it remains unclear if a successful mitral valve repair impacts long-term survival in patients with ischemic MR, and this most likely relates to the ventricular component of the disease.

Restoration of ventricular geometry, as in the Dor procedure and similar operations, can relieve papillary muscle displacement leading to reduction of MR. Localized plication of a lateral wall infarct may also result in reduced displacement of the posterior papillary muscle. Epicardial approaches are under investigation and will likely be applied more widely in the future. Hung and colleagues²⁸ have demonstrated that fixation of an external balloon in the region of the inferior infarct can elevate the posterior papillary muscle thus relieving tethering. This procedure is performed on a beating heart and thus the changing geometry and resolution of MR can be observed echocardiographically. Such balloon devices can potentially be deployed percutaneously. Other external devices that can help reposition the papillary muscles are also described.²⁹ External ventricular constraints wrapped around the ventricle at the time of mitral valve repair have been shown to reduce future ventricular dilatation and may prevent the adverse remodeling that produces recurrent MR

after conventional annuloplasty.³⁰ Injection of stem cells into infarcted tissue is another potentially beneficial approach that could be used surgically or percutaneously.

Future Directions. Treatment strategies in ischemic MR continue to evolve. Current surgical techniques can eliminate MR in a majority of patients, but ultimately rely on reverse ventricular remodeling and a low rate of recurrent MR, which often may not occur. At present, effective treatment based on pathophysiologic principles can only be achieved surgically. Percutaneous therapy is theoretically feasible, but will likely require a combination of modalities (for example, coronary sinus annuloplasty device and edge-to-edge leaflet fixation). Progress in surgical therapy includes development of new annuloplasty devices, subvalvular techniques, and novel operations to address the ventricular etiology of the disease. Recent recognition of the role of anterior infarction may lead to a dichotomy in therapy for anterior versus posterior infarction. The development of advanced imaging techniques for mapping valve geometry may allow a more directed approach where the surgeon and cardiologist can tailor the therapeutic strategy to each patient. Finally, the importance to emphasize the evidence for intervention in ischemic MR in terms of improving long-term survival remains unclear.^{31,32} Future studies will clarify the impact of correcting ischemic MR on survival as well as symptoms related to congestive heart failure.³³

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