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Another Multi-Disciplinary Look at Ischemic Mitral Regurgitation

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The mitral valve is a complex structure with dynamic physiology which relies on an intricate interplay of its individual components to achieve timely and efficient valve closure, sustain normal cardiac performance, and prevent mitral regurgitation (MR). This process requires well orchestrated coordination of the left ventricle, papillary muscles, mitral annulus, and left atrium to achieve competent valve closure. Failure of any one of these components, regardless of cause, can lead to mitral regurgitation requiring surgical correction. Ischemic mitral regurgitation (IMR) presents a particular challenge in that the mitral valve appears structurally normal yet substantial regurgitation exists¹. The causative mechanisms are in the annular and subvalvular domains rather than leaflet or chordal structure leading to such labels as “ischemic”, “functional”, “non-organic”, and “cardiomyopathy associated”. The traditional definition of IMR as mitral insufficiency caused by coronary disease and its consequences appears overly broad as the spectrum of coronary disease and left ventricular (LV) dysfunction varies tremendously in ischemic mitral regurgitation ranging from preserved LV function^{2,3} to moderate dysfunction^{4,5} to end-stage dilated ischemic cardiomyopathy with advanced congestive heart failure^{6–9}. Classification of ischemic mitral regurgitation into: 1.) Sudden onset insufficiency due to acute myocardial infarction and papillary muscle rupture and or LV wall dysfunction; 2.) MR associated with consequences of coronary disease with normal mitral leaflets; and, 3.) Mitral insufficiency associated with end-stage ischemic dilated cardiomyopathy, offers a more rational categorization which reflects the heterogeneity of the conditions seen clinically.¹⁰ The term “functional mitral regurgitation” (FMR) has been used synonymously in the literature to describe MR caused by ischemic cardiomyopathy; moreover, it has been used interchangeably to refer to mitral insufficiency associated with end-stage ischemic or idiopathic dilated cardiomyopathy^{11–13}. The mechanisms causing the valve to leak in these clinical situations, however, differ importantly^{12,14}. Descriptions such as “chronic functional ischemic mitral regurgitation”

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while referring to patients with IMR without cardiomyopathy^{15,16} further muddies the waters. Most authorities today limit the term “functional” to describe collectively mitral regurgitation related to severe LV systolic dysfunction with pronounced LV dilatation (usually defined by an ejection fraction less than 30%) regardless of etiology⁸. Ischemic mitral regurgitation, on the other hand, refers to mitral insufficiency due to the adverse consequences of coronary disease with more asymmetric ventricular remodeling, most often affecting the inferior and lateral left ventricular wall¹⁷. Naturally, these entities lie on a clinical continuum and cannot be precisely specified due to the heterogeneity of ischemic heart disease. It is therefore important to recognize the clinical continuum between IMR and FMR when considering the pathophysiology causing the mitral regurgitation and thereby determining which reparative approach would be best since the degree of LV dysfunction, chamber remodeling, and valvular complex perturbation differ.

Ischemic or functional MR: Same, different, or does it matter?

Left ventricular dilatation usually accompanies ischemic mitral regurgitation, yet the degree of LV chamber remodeling may be different. Echocardiographic studies in patients with dilated non-ischemic cardiomyopathy confirm enlarged LV diameter and sphericity to be major predictors of MR¹² in addition to the tenting or apical tethering of the chordae tendineae and valve leaflets, while sphericity also can accompany progression of MR in end-stage coronary disease¹⁸ and recurrent MR after LV reduction surgery¹⁹. Ischemic mitral regurgitation is, on the other hand, not so much dependent on global LV dilatation^{20–23} but rather on a more localized LV insult. IMR is more common after inferior rather than anterior myocardial infarction^{3, 24, 25}, yet equal incidence^{26,27}, or greater association with anterior MI has been reported^{28,29}. It is this heterogeneity of human disease that does not permit identification of clear boundaries in the pathogenesis of mitral insufficiency. In the literature, IMR associated with anterior infarction is usually accompanied by greater LV and mitral annular dilatation in the septal-lateral (S-L) (also known as “antero-posterior”) axis^{25,30,31}, more impressive annular flattening³², and lower ejection fraction³¹ relative to inferior MI. It appears that anterior infarction does not sufficiently affect critical annular-subvalvular spatial relationships that are perturbed by a smaller posterolateral infarct^{20,33}, yet with chronic remodeling and impairment of LV function, IMR does result. Thus, IMR associated with anterior MI may lie closer on the clinical spectrum to functional mitral regurgitation characterized by severely depressed LV function, global LV dilatation, and annular enlargement. On the other hand, an inferior MI is associated with less global LV dilatation and systolic dysfunction but more substantial perturbation of the mitral subvalvular apparatus. Surgical procedures used to correct chronic IMR in sheep models have not been associated with major changes in LV size^{34–37}; however, LV reverse remodeling after restrictive (under-sized) ring annuloplasty is more predictable in patients with smaller LV size (LVED dimension less than 65 mm) and survival is enhanced³⁸.

Mitral annular dilatation is found ubiquitously in patients with LV dysfunction and mitral regurgitation³⁹, but MR associated with pure annular dilatation is usually present in patients with more the depressed LV systolic function and more advanced left ventricular remodeling^{30,40} characteristic of FMR. Indeed, the degree of annular dilatation, especially in the septal-lateral dimension, correlates with the degree of LV systolic dysfunction in patients

with dilated cardiomyopathy⁴¹. In animal experiments, mitral regurgitation in a canine model of tachycardia-induced cardiomyopathy was predicted purely by annular dilation⁴². These studies support the notion that mitral insufficiency in end-stage dilated cardiomyopathy is chiefly related to substantial annular dilatation, particularly in the septal-lateral dimension. In an acute model of IMR provoked by a localized LV insult⁴³, annular dilatation was shown to be one component of the geometric perturbation leading to mitral insufficiency rather than the sole mechanism. Similar findings have been observed by other investigators in both acute⁴⁴ and chronic²⁰ experimental models of ovine IMR and corroborated by clinical studies which identified annular dilatation as a contributor to the development of mitral insufficiency with subvalvular deformations playing a central role^{14, 23}. Furthermore, in clinical echocardiographic studies, the pattern of annular dilation in IMR is more asymmetric (largest alterations in the posterior commissure side) compared to the annular dilation associated with FMR being symmetric⁴⁵. Such findings underscore subtle but important differences in the mechanisms responsible for ischemic and functional mitral insufficiency. The mitral annulus is a non-planar saddle-shaped structure with significant elevation of the mid-septal annulus (also known as the annular “saddle horn”)^{46,47} and dipped in the commissure sectors. The three dimensional shape of the annulus may be important for proper leaflet stress distribution and is conserved across mammalian species⁴⁸. The annulus becomes flatter with FMR and IMR in both clinical^{32,49–51} and experimental^{48,52} studies. Progressive and heterogeneous flattening of the annulus was well documented in a recent longitudinal study of ovine IMR⁵³. Although annular flattening may not be directly related to the pathogenesis of ischemic mitral insufficiency, altered annular shape may act to increase leaflet forces and lead to pathologic remodeling that in the chronic state could contribute to the evolution of mitral regurgitation. Naturally, abnormal annular geometry has surgical implications in terms of design and implantation of annular prostheses.

Inadequate leaflet coaptation during systole is the final common pathway of annular and subvalvular geometric perturbations that result in functional and ischemic mitral regurgitation. It is this coupling that translates the “ventricular” disease of FMR and IMR into a valvular problem. Multiple experimental^{34,54} and clinical^{7,12,14,18,23} studies have focused on leaflet coaptation depth - also referred to as coaptation height - and leaflet tenting area as representing the sum of geometric deformations leading to mitral insufficiency. These parameters are easily measured with echocardiography or MRI and lend themselves to quantification; however, ischemic mitral regurgitation can be associated with normal^{30,55}, tethered^{14,23}, or prolapsed^{56,57} leaflet motion with symmetric or asymmetric leaflet motion abnormalities^{14,31,58}. Therefore, larger tenting area may be due to apical leaflet tethering, annular dilatation, or both. In experimental FMR, leaflet motion was normal without restriction or tethering being present.⁵⁹ Therefore, the leaflet edges were simply displaced along the leaflet coaptation line perpendicular to the direction of annular enlargement, *viz.*, septal-lateral axis, and leaflet coaptation or occlusion area was exhausted with progressive annular dilation resulting in increased leaflet edge separation noted above. Similar findings were reported long ago by Boltwood⁵⁵ in human subjects with dilated cardiomyopathy: Using M-mode and 2-D echocardiography tenting area was larger in patients with FMR secondary to significant annular dilatation, yet coaptation depth also increased. This was

thought to be secondary to annular dilatation as papillary muscle tethering and chordal length did not change. Although annular dilatation may affect coaptation depth if subvalvular geometry remains constant, it is septal-lateral annular enlargement which exhausts mitral leaflet redundancy resulting in MR by decreasing leaflet coaptation length (*i.e.* the length of leaflet apposition at the coaptation line)⁵⁴. Similar observations were reported by Popovic and colleagues⁴² in their echocardiographic assessment of FMR in a canine model of tachycardia induced cardiomyopathy.

Tethering of both leaflets has also been observed echocardiographically in patients with IMR^{27,58}. Kwan and colleagues¹⁴ reported **symmetrical** leaflet deformation in patients with idiopathic dilated cardiomyopathy and **asymmetric** abnormal leaflet and annular geometry in those with ischemic cardiomyopathy and mitral regurgitation, yet all patients had increased coaptation depth indicative of apical tethering. Similarly, in patients with mitral insufficiency and prior anterior MI, the leaflets were markedly tethered while with inferior MI, the tethering was more localized and tenting volume was lower³¹. Indeed, leaflet deformation in patients with an anterior MI characterized by much more LV dysfunction and dilatation resembles that observed in patients with idiopathic dilated cardiomyopathy rather than after localized inferior infarction with preserved LV function. Another clinical study found patients with IMR to have increased coaptation depth indicative of apical tethering while MR associated with idiopathic dilated cardiomyopathy was related to global LV dilatation where gross annular dilation predominates¹². Valvular tenting and decreased annular contraction were also shown to be the two multivariate predictors of effective regurgitant orifice in a large clinical study²³ underscoring the combination of annular enlargement and leaflet tethering that leads to mitral insufficiency. This additive effect on leaflet coaptation was elegantly demonstrated by Tibayan and colleagues²² in a chronic sheep model of IMR. Additionally, mitral insufficiency in IMR may not only be a result of abnormal leaflet coaptation, but also due to posterior leaflet inter-scallop separation that is strongly associated with annular dilation⁶⁰. Clearly, ischemic mitral regurgitation embodies a diverse set of leaflet perturbations, and the literature corroborates the supposition that ischemic and functional mitral insufficiency may be associated with different types of leaflet deformations, with overlap. It is not surprising, therefore, that leaflet tenting, which represents the sum effect of annular and subvalvular geometric deformations on leaflet coaptation, is consistently found in patients with FMR⁵⁵ and IMR^{23, 31, 34, 61} to be the main predictor of MR severity, yet the challenge remaining is to dissect out the individual contributions of leaflet, annular, and subvalvular perturbations. The clinical continuum of ventricular, subvalvular, and leaflet geometric perturbations between ischemic and functional mitral regurgitation is summarized in Figure 1.

How “functional” is IMR?

The accepted pathophysiology of ischemic IMR focuses on the “ventricular” disease that leads to subvalvular remodeling and leaflet malcoaptation. The “functional” label is often applied as the valve structurally appears normal and the leaflets, as opposed to organic MR, are not grossly abnormal. Recent observations have exposed the fallacy of these oversimplified assumptions. Anatomical and biochemical studies of the mitral leaflets show that normal mitral valvular tissue is richly innervated⁶² and has a complex blood supply⁶³,

heterogeneous biochemical composition⁶⁴, and non-homogeneous deformation⁶⁵. These investigations suggest that mitral leaflets are not inert flaps strictly bound to the hemodynamic conditions, but rather active components of the valvular-ventricular complex capable of regulating valvular function in health and disease. Human studies reveal that both anterior and posterior mitral leaflets remodel in cardiomyopathy, suggesting that leaflet tissue is a contributor to the pathophysiology of FMR, and by virtue of such leaflet remodeling, may affect the severity of FMR.⁶⁶ Observations by Grande-Allen⁶⁶ and colleagues demonstrated that mitral leaflets from explanted recipient hearts with FMR have a much different biochemical profile than control leaflets, *e.g.*, significantly higher DNA content and collagen concentration with greatest deposition in the anterior leaflet free edge. Overall, leaflets from human subjects with heart failure were 28–41% longer than control values. Further mechanical analysis revealed that the leaflet tissue was 61% stiffer in the radial direction and 50% stiffer in the circumferential direction than normal leaflets. These findings suggest prominent biochemical and ultrastructural remodeling of leaflet tissue occurs, particularly in the region of the free edge. Such leaflet remodeling particularly near the free edge has also been reported in an experimental ovine model of FMR⁵⁹. Thus, “normal” appearing mitral leaflets that are visualized during surgical repair may only be normal to the naked eye and the definition of “functional” mitral regurgitation needs reconsideration. Tibayan⁶⁷ recently described leaflet shape in a chronic ovine ischemic MR model where the radii of curvature of both leaflets were significantly increased 7 weeks after posterolateral myocardial infarction. This was due to stretching of the leaflets from papillary muscle displacement leading to flattening of leaflet geometry. These data corroborate the altered leaflet geometry, including concave shape relative to the left atrium, in patients being a strong predictor of ischemic MR⁶⁸. Annular septal-lateral diameter dilatation and altered papillary muscle position were reported by Tibayan⁶⁷ to be independent predictors of anterior leaflet shape in sheep, while Grande-Allen⁶⁶ found that leaflet length correlated with annular diameter in human transplant recipient hearts. Annular dilatation along with subvalvular changes can be expected to stretch leaflet tissue across the valve orifice and alter loading conditions thus leading to leaflet remodeling as a compensatory mechanism that becomes exhausted as ventricular and annular pathologic changes progress. Such leaflet stretching coupled with annular flattening can be expected to increase stresses on the leaflet⁴⁸ and thus induce tissue remodeling as seen in the chronic model of ovine IMR⁶⁷. The possible effects of altered valvular mechanical forces, tissue properties, and biochemical composition associated with FMR and IMR on leaflet remodeling are summarized in Figure 2. A recent echocardiographic study in patients with reduced LV function and infarction found leaflet area enlargement to be present in patients both with and without mitral insufficiency, but severe MR was seen only in those with inadequate leaflet remodeling relative to the demands of subvalvular tethering geometry.⁶⁹ Furthermore, subvalvular tethering without associated mitral regurgitation is sufficient to induce geometric leaflet remodeling and altered gene expression⁷⁰. Therefore, heterogeneity of leaflet remodeling may partially contribute to the wide spectrum of mitral insufficiency that is seen clinically due to variable degrees of compensatory leaflet thickening and enlargement. It is conceivable that during the evolution of mitral insufficiency, leaflet motion changes from restriction to normal leaflet motion with progressive chamber dilatation and leaflet tissue remodeling, and IMR and FMR represent two points on a clinical continuum. The cellular

mechanisms and genomics of leaflet remodeling and their modulators, however, remain to be characterized.

Novel Surgical Interventions

The best surgical correction of IMR remains elusive as contemporary reparative techniques continue to provide suboptimal results.^{16,24} Currently, reduction annuloplasty with an undersized, disease-specific, custom-designed complete ring along with coronary revascularization represents the clinical standard for treating FMR and IMR, yet the predictors of success remain perplexing. Mitral annular reduction with an annuloplasty ring treats IMR by reducing the septal-lateral annular diameter⁷¹, the principal direction of annular dilatation, which augments leaflet coaptation.^{20,21} Newer disease-specific annuloplasty rings for patients with IMR incorporate selective septal-lateral diameter reduction in their design. As both the fibrous and muscular portions of the annulus dilate in IMR and FMR, a complete rigid ring is advisable. Annular flattening is also significant in both IMR and FMR and re-establishment of the 3-D shape of the annulus is optimal to normalize leaflet stress distribution. This concept is intrinsic to the Carpentier-Edwards Physio II ring and even more so in the GeoformTM annuloplasty ring (Edwards Lifesciences, Irvine, CATM) which includes a major amount of elevation in the mid-posterior annular region (Figure 3). Experimental annular reduction has been shown to reduce curvature of the LV chamber⁷² and therefore be expected to decrease LV wall stress and improve systolic LV function. This is the goal of an annular intervention to treat the subannular ventricular disease that is the real culprit in patients with IMR. As such, undersized annuloplasty ring in patients with FMR where symmetric annular dilation predominates may show more clinical benefit compared to those with IMR due to the dual salutary effects of abolishing mitral insufficiency and optimizing LV energetics. Indeed, if annular dilatation and global LV remodeling are the main problems, annular reduction with an undersized annuloplasty ring may provide satisfactory results⁷³. In patients with post-infarction IMR, however, recurrent MR can be expected in more 30% of patients even in the short term^{24, 74} after annuloplasty plus bypass grafting due to continued LV remodeling and associated papillary muscle displacement^{4,16}. Interestingly, most of these patients had only moderate LV dysfunction with preoperative ejection fraction greater than 40%^{4,16}. It appears therefore that for patients with preserved LV systolic function but localized geometric deformation leading to leaflet tethering, appropriate surgical intervention should directly correct both annular dilatation and the subvalvular tethering. Although annular undersizing does alter global LV shape⁷² and subvalvular geometry⁷⁵, this may be insufficient to address large local asymmetric displacements as seen in chronic IMR in ovine models²².

Failure of undersized annuloplasty to correct reliably ischemic mitral regurgitation has generated interest in novel surgical approaches derived from innovative experimental techniques. The surgical approaches to correct IMR and FMR can be classified as annular and subvalvular as elegantly summarized by Levine⁷⁶ in Figure 4. Increased inter-papillary muscle distance has been observed in association with experimental²¹ and clinical^{23, 7} IMR, but its contribution to the pathogenesis of IMR, beyond being a marker of LV chamber dilatation, is unclear. Experimental data from ovine studies suggests that repositioning of the posterior papillary muscle toward the mid-anterior septal annulus helps abolish IMR^{34,36}.

Thus, it may be that subvalvular interventions should be aimed more specifically at reducing this tethering distance by directly repositioning the posterior papillary muscle toward the septal annulus as successfully reported experimentally⁷⁸, and clinically⁷⁹. Repositioning of the posterior papillary muscle with an externally adjusted chord anchored at the fibrous trigone as an adjunct to ring annuloplasty was first described in an ovine model of acute IMR by Langer and colleagues.⁸⁰ This innovative technique has subsequently found clinical application⁸¹ (Figure 5). In 30 patients with severe IMR and high risk for recurrence with conventional repair, as evidenced by leaflet tenting height of greater than 10 mm, an impressive 94% freedom from grade 2 or more IMR was observed after 2 years along with salutary LV reverse remodeling. Papillary muscle imbrication which sews the papillary muscles together as an adjunct to undersized annuloplasty also reduces leaflet tenting height more effectively than annuloplasty alone in a recent small clinical series from Japan⁸². A sling of PTFE encircling the papillary muscles has been demonstrated by Hvaas et al. to correct IMR and induce reverse remodeling.⁸³

Cutting the secondary chordae tendineae to relieve leaflet apical tenting based on the experimental data of Messas³⁵ was introduced into clinical practice by Borger and colleagues at the Toronto General Hospital. Although not randomized, retrospective analysis of over 80 patients demonstrated that coronary bypass grafting plus chordal cutting and undersized annuloplasty ring were associated with significantly less recurrent IMR at 2 years *versus* annuloplasty alone⁸⁴. More recent ovine experiments using this technique suggest that chordal cutting decreases progression of LV remodeling in chronic IMR and effectively reduces the degree of valvular insufficiency⁸⁵. Cutting the secondary chordae, however, may adversely affect LV systolic function since valvular-ventricular continuity is interrupted⁸⁶. To ameliorate this concern, Arai and colleagues⁸⁷ have introduced a novel procedure consisting of anterior leaflet secondary chordae division and replacement with artificial chordae, repositioning of both papillary muscles toward the posterior annulus, and undersized ring annuloplasty. This technique represents the sum of current surgical approaches and has been successfully applied in three high risk patients, but its long term efficacy and wider application await a rigorous clinical trial. Relief of leaflet tethering may be achieved through subvalvular repair and also by direct leaflet approaches. Posterior leaflet extension with a pericardial patch in the middle and posteromedial scallops of the posterior mitral leaflet along with reduction annuloplasty resulted in 90% freedom from moderate or greater IMR at 2 years in a cohort of 44 patients with severe IMR⁸⁸. Although no control group was available, these results surpassed expectations based on current literature using undersized annuloplasty alone. All these interventions are aimed at ameliorating leaflet tethering, the final common pathway in the pathogenesis of IMR, that is incompletely corrected by ring annuloplasty alone.

Percutaneous approaches to ischemic mitral regurgitation deserve particular mention as these devices are on the clinical horizon. The MitraClip (Abbott Vascular, Abbott Park, IL) percutaneous leaflet-to-leaflet repair (Figure 6.), analogous to the Alfieri edge-to-edge mitral leaflet approximation suture, was shown to be safe in 23 patients with functional mitral regurgitation, but long term efficacy data were not reported⁸⁹. Although, percutaneous MitraClip repair may not provide comparable results to standard surgical repair in terms of

reduction of MR severity, patients at high surgical risk may be good candidates for this alternative interventional therapy. In 51 patients with FMR who had multiple severe comorbidities, Franzen⁹⁰ and colleagues demonstrated acute reduction of MR by two grades or more in 65% of patients, the majority of whom (69%) presented with symptomatic functional MR. Clinical improvement was observed in 90% of treated patients without procedure-related major adverse events or in-hospital mortality; unfortunately, no control group was available for analysis. These results were corroborated by a smaller Italian study of 31 high risk patients predominantly with functional MR.⁹¹ The results of the EVEREST II trial comparing MitraClip with open surgical mitral repair in patients with MR (mostly due to prolapse) revealed the MitraClip procedure was safe, but successful deployment could not be achieved in a sizeable minority of patients and its effectiveness in eliminating the MR was inferior to surgical repair. A future prospective randomized trial comparing MitraClip and maximal medical therapy in patients with FMR or IMR is planned, which holds great promise. Similarly, the Carillon percutaneous coronary sinus mitral cerclage device was shown to be safe and associated with clinical improvement, yet reduction in the severity of FMR was only modest⁹². Certainly, these techniques will continue to evolve as technology improves, but at this time do not represent a proven alternative to surgical repair. Theoretically, the combination of a percutaneous leaflet procedure plus interventional annular reduction would provide better results, or more exciting would be a procedure such as the Coapsys® device which directly reshapes the ventricle used concomitantly with percutaneous leaflet repair. A recent randomized trial in patients with IMR demonstrated that treatment with the Coapsys® device improved survival and decreased complications *versus* standard ring annuloplasty repair in patients with IMR undergoing concomitant coronary revascularization.⁹³ Interestingly, although reduction in MR was superior after ring annuloplasty, survival was better at 2 years with the Coapsys® device, probably due to much greater reduction of LV end-diastolic diameter which directly reshapes the ventricle. This study adds to the growing controversy whether the prognosis of patients with IMR and heart failure is determined more by abnormal ventricular geometry and LV dysfunction or by the degree of mitral regurgitation. Certainly, these interventional techniques will continue to evolve, and should be evaluated in prospective randomized trials, but at this time cannot be considered first line therapy.

Although surgical approaches represent the clinical standard for treating symptomatic patients with congestive heart failure who have functional mitral regurgitation, cardiac resynchronization therapy (CRT) has also shown promise.^{94,95} The pioneering MIRACLE randomized trial revealed that CRT not only improved ventricular function and induced reverse remodeling but also reduced the degree of ischemic MR.⁹⁶ This effect was sustained out to 12 months.⁹⁷ Subsequent studies have shown that reduction of LV dyssynchrony and improvement of LV function contribute to greater valve closing forces⁹⁸ while reverse LV remodeling results in more favorable subvalvular geometry and decreased leaflet tethering.⁹⁹ Correction of dyssynchrony in the region of posterior papillary muscle and the lateral LV wall may be particularly important for the therapeutic effect of CRT.¹⁰⁰ A recent report demonstrated that CRT decreases both early- and late-systolic MR in patients with functional mitral insufficiency, although the effect in the early ejection phase dominates.¹⁰¹ These data suggest that increased valve closing forces associated with CRT may be the most

important mechanism although ventricular reverse remodeling also contributes. Early efforts are currently underway to design novel percutaneous annuloplasty devices with built in CRT capabilities¹⁰² to capitalize on combining a mechanical and function treatment for IMR through a minimally invasive approach.

In addition to novel reparative techniques, recent research efforts have also concentrated on improving patient selection to identify more precisely which individuals will benefit from surgical intervention. There is considerable controversy whether valvular surgery beyond coronary artery bypass grafting (CABG) prolongs survival in patients with IMR^{5,103,104}. The debate is especially heated on whether moderate IMR should even be addressed at the time of myocardial revascularization.^{105–7} Patients with dilated cardiomyopathy, be it ischemic or idiopathic, and functional mitral regurgitation seem to derive benefit from mitral surgery in terms of morbidity, and symptomatology^{6,7,108} yet prolonged survival has not been demonstrated¹⁰⁹. Penicka and colleagues¹¹⁰ reported a series of 135 patients with moderate IMR treated with surgical revascularization alone. In 93% of patients with viable myocardium and absence of dyssynchrony between papillary muscles preoperatively, improvement in IMR grade was found at one year. Indeed, myocardial viability and absence of dyssynchrony were independent predictors of IMR improvement. Similarly, enhancement of inferior myocardial contractile function with dobutamine was associated with reduction of apical tenting and IMR severity in 51 patients with ischemic and non-ischemic cardiomyopathy¹¹¹. Conversely, patients with severe IMR and advanced scarring of the posterior papillary muscle region as assessed by MRI are at higher risk for recurrent mitral insufficiency after revascularization and standard annuloplasty repair¹¹². LV end-diastolic diameter greater than 65 mm³⁸ and coaptation depth of greater than 10 mm⁷ have been identified as predictors of suboptimal outcomes with the current clinical standard of coronary artery bypass grafting and undersized complete ring annuloplasty. Continuation of this line of investigation will hopefully permit clinicians to customize surgical treatment to encompass the wide range of clinical and pathoanatomic situations which accompany IMR. In partnership with the National Institute of Health, the Cardiothoracic Surgical Trials Network (CSTN) is currently enrolling patients in two randomized multi-center prospective studies which should shed more light on the optimal surgical treatment of IMR. One trial focuses on the treatment of moderate IMR at the time of surgical revascularization and whether concomitant mitral repair with or without CABG differ in their effects on LV size. The other trial examines the effects of mitral valve repair *versus* valve replacement plus CABG in patients with severe IMR, again using LV size and function as the primary end point at 24 months. These randomized trials should provide information which will guide our surgical treatments. Larger randomized trials using clinical end points will still be needed in the future to develop predictive models using preoperative characteristics of patients with IMR to optimize the choice and effectiveness of particular surgical interventions or more rationally guide medical treatment with or without CRT therapy alone.

Summary

Ischemic mitral regurgitation continues to represent a vexing clinical problem with major public health consequences that has challenged surgeons and cardiologists alike. The clinical universe of ischemic mitral regurgitation covers a very heterogeneous patient population that

ranges from moderate mitral insufficiency with preserved LV systolic function in patients undergoing CABG to end-stage dilated ischemic cardiomyopathy with severe MR and advanced heart failure. A “one size fits all” mentality has been the empiric surgical approach to these patients using an undersized annuloplasty ring and coronary revascularization. Mounting clinical and experimental literature is shedding light on the inadequacy of this strategy. Novel surgical techniques focused on the subvalvular changes which cause IMR are starting to show promise for more durable and predictable outcomes, and some directly reshape the failing, globular left ventricular cavity. Combined with efforts to stratify patients better within this heterogeneous clinical population, these new reparative techniques may ultimately provide better clinical outcomes for these very sick patients.

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IMR

FMR

Inferior MI	Anterior MI	End Stage CMP
Preserved EF	Ischemic CMP	Severe Reduced EF
Local LV remodeling	Increased LV size	Spherical LV
Leaflet tethering	Annular dilation	Very dilated annulus
Type IIIb leaflet motion		Type I leaflet motion

Figure 1.

Spectrum of left ventricular function, remodeling, and valvular dysfunction along a clinical continuum between ischemic and functional mitral regurgitation.

Figure 2.

Proposed mechanisms for valvular remodeling in IMR and FMR from altered mechanical loads, tissue properties, and biochemical composition of the mitral leaflets (Reproduced from Grande-Allen KJ, et al. *J Thorac Cardiovasc Surg.* 2005;130(3):783–790).

Figure 3. The Geoform™ mitral annuloplasty ring design for repair of ischemic mitral regurgitation. The prosthesis geometry aims to reduce markedly the septal-lateral annular diameter while hoisting the posteromedial papillary muscle up towards the annulus.

Potential Therapeutic Targets

Figure 4. Potential surgical targets for the therapy of IMR (Reproduced from Levine, RA. *Circulation*. 2005;112(5):745–758).

Figure 5.

A. Intraoperative photograph of the transventricular suture technique (STRING). A.) Pledgeted 4-0 PTFE (polytetrafluoroethylene) suture is anchored in the head of the posteromedial papillary muscle (*PPM*). The suture is then passed through the mid-septal annulus under direct vision and exteriorized through the aortic wall underneath the commissure between the non-coronary and left coronary aortic cusps. *APM*, Anterior papillary muscle. B.) Schematic representation of the transventricular suture technique (STRING). The suture is tied under echocardiographic guidance in the loaded beating heart to reposition the displaced posterior papillary muscle toward the septal annulus (Reproduced from Langer, F. *J Thorac Cardiovasc Surg.* 2007;133:247–249).

Figure 6.

The Abbott E-Valve MitraClip percutaneous mitral valve repair based on the Alfieri edge-to-edge leaflet approximation. A double orifice valve is created after approximation of mitral leaflets with the percutaneously delivered clip device. (Reproduced from St Goar, FG. *Circulation*. 2003;108:1990–1993).