Ischemic Mitral Regurgitation on the Threshold of a Solution

From Paradoxes to Unifying Concepts

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“More than once in history the discovery of paradox has been the occasion for major reconstruction at the foundations of thought.”

W.V. Quine, The Ways

One thing is certain: Ischemic mitral regurgitation (MR) conveys adverse prognosis, doubling mortality after myocardial infarction (MI), in chronic heart failure, and after surgical or catheter revascularization. It is common and increases mortality even when mild, with a graded relationship between severity and reduced survival (Figure 1A). In many other respects, however, ischemic MR has been a study in controversy and paradox. Its diagnosis is notoriously elusive, both by auscultation and intraoperatively. It may paradoxically decrease as driving pressure increases. Still commonly referred to as “papillary muscle dysfunction,” it cannot generally be produced by direct papillary muscle damage and may actually decrease with papillary muscle ischemia. Although leaflet motion is typically restricted, it may also be excessive, or both. Treatment benefit is hotly debated and will be difficult to resolve so long as existing therapies are incompletely effective in permanently abolishing MR. New therapeutic opportunities are perplexing in their diversity. By exploring such areas of confusion, we aim to clarify fundamental principles and achieve more effective solutions.

Ischemic MR is convenient shorthand for MR caused by changes in ventricular structure and function related ultimately to ischemia; it is predominantly postinfarction MR. Active ischemia can contribute, for example, creating intermittent “flash” pulmonary edema, although MR from brief single-vessel occlusion is usually mild, without preexisting ventricular abnormality. “Functional MR” broadly denotes abnormal function of normal leaflets in the context of impaired ventricular function; it typically occurs in globally dilated and hypokinetic ventricles or with segmental damage that affects valve closure (Figure 2). It occurs in roughly 20% to 25% of patients followed up after MI and 50% of those with congestive heart failure. It differs from the dramatic presentation of ruptured papillary muscle (PM), a surgical emergency.

Mechanisms

Burch, De Pasquale, and Phillips initially ascribed ischemic MR to PM dysfunction. Normally, as the left ventricle (LV) shortens, PM contraction maintains the distance between the PM tips and mitral annulus to prevent prolapse. PM damage could then produce prolapse, consistent with its frequently late-systolic murmur. Experimental damage to the PMs themselves, however, fails to produce MR acutely without damage to the underlying myocardial wall as well.

Burch et al alternatively postulated restricted leaflet motion. The PMs, normally parallel to the LV long axis and perpendicular to the leaflets, efficiently balance forces generated by ventricular pressure on the leaflet surface. Ischemia or heart failure causes the myocardial segments underlying the PMs to bulge posteriorly and outward, displacing the PMs, so that they pull the leaflets nonperpendicularly, away from their normal coaptation (Figure 3). The distance between the PM tips and the annulus also increases, drawing the leaflets into the ventricle and restricting their motion toward closure, as proposed by Paul Dudley White, Levy and Edwards, Silverman and Hurst, and Perloff and Roberts.

Two-dimensional echocardiography first demonstrated apically restricted leaflet motion, termed “incomplete mitral leaflet closure” (IMLC; Figure 2). Godley, Weyman, et al associated IMLC with inferior dyskinesis, postulating increased leaflet tethering. On the basis of myocardial injection studies, Alain Carpentier has succinctly renamed PM dysfunction “PM wall dysfunction,” namely, tethering caused by displacement of the leaflet attachments.

Kaul et al elegantly confirmed that reducing PM perfusion produced neither prolapse nor MR. In contrast, global hypoperfusion with LV dilatation, despite continued PM perfusion and thickening, caused MR with IMLC in direct correlation with LV dysfunction. In those studies, however, akinisia of the PMs and their underlying wall also failed to produce MR acutely. This led to the postulate that MR results from global LV
dysfunction, decreasing the leaflet closing force,\(^2\) as opposed to PM wall tethering. Conceivably, however, the acute PM wall displacement in that study was insufficient to produce MR, and as the authors acknowledged, LV dilatation paralleled global dysfunction, precluding separation of dysfunction from dilatation as primary cause of MR.

This distinction has practical implications: LV contractile dysfunction would demand inotropic therapy, revascularization, or transplantation, whereas tethering might respond to modifying LV wall or PM geometry. New models were therefore required to dissect the effects of dysfunction and dilatation.

He, Yoganthan, et al\(^{23}\) reproduced MR in excised mitral valves by displacing the PMs apically, posteriorly, and outward, as in patients. In vivo, Schwammenthal, Otsuji, et al\(^{24}\) created global LV dysfunction pharmacologically but limited LV expansion through pericardial restraint and decreased preload. Contractile dysfunction (ejection fraction <20%) without dilatation produced only trace MR; LV dilatation was a prerequisite for IMLC and MR.\(^{24}\) To quantify tethering geometry, Mark Handschumacher\(^{11}\) used 3D echocardiographic data to standardize the tethering length from the PM tips to the anterior mitral annulus (Figure 4A). In global dysfunction, Otsuji et al\(^{24}\) found that tethering length was the only independent predictor of MR, not LV ejection fraction or dP/dt. MR also correlated with LV sphericity, consistent with the key observation of Kono, Sabbah, et al\(^{25–27}\) that MR relates not to LV dilatation per se but to increased sphericity that could potentially displace the PMs posterolaterally, as verified by 3D echocardiography.\(^{24}\)

The centrality of geometric change was confirmed in acute segmental inferior ischemia, studied with and without external constraint,\(^{28}\) and in the chronic sheep model of Gorman and Edmunds, in which MR, initially absent, evolves in parallel with LV remodeling and PM displacement.\(^{28–31}\) In patients, Yiu, Enriquez-Sarano, et al\(^{32}\) strongly related PM tethering, leaflet tenting, and MR, which is frequently due to localized remodeling of the posterior PM-bearing walls, without the global remodeling required for MR with anterior infarctions.\(^{11}\) By 3D echocardiography, the medial mitral valve is most tented in ischemic cardiomyopathy, because the inferomedial PM is most displaced;\(^{33}\) this asymmetry might augment MR through asymmetrical coaptation between posterior leaflet scallops.\(^{34}\) Although the annulus is dilated in global dysfunction,\(^{35}\) isolated annular dilatation without increased tethering length in atrial fibrillation is not associated with important MR.\(^{36}\) Finally, Otsuji and colleagues\(^{37}\) recognized restricted diastolic as well as systolic leaflet excursion, an echocardiographic clue that tethering is increased.

The simple story, however, is often incomplete. First, although PM damage does not produce MR acutely, MR does occur in the chronic phase of ethanol injection, with PM scarring and retraction.\(^{11}\) Second, occasional patients with MI actually do have prolapse with PM elongation.\(^{38}\) These observations, rather than disproving tethering, actually confirm that tethering distance is the final common pathway determining the level of leaflet coaptation. The change in tethering distance is the resultant of 2 vectors: Displacement of the PM-bearing wall is modulated by changes in PM length. As Frater et al\(^{39}\) have shown, MR increases bipherically with too long or too short a tethering length.

We can therefore understand how PM contractile dysfunction can paradoxically diminish MR. Messas et al\(^{40}\) created a limited inferobasal MI with wall bulging and MR; making the adjacent PM acutely ischemic caused it to elongate in response to ventricular forces and reduced tethering distance and MR. Preserved PM shortening increases tethering and MR,\(^{41}\) which confirms the central role of tethering length and the concept of PM-ventricular wall complex expressed by Komeda, Miller, et al.\(^{42}\)

Tethering is one facet of a unifying principle of mitral valve function: that leaflet motion is determined by the 3D geometry of the leaflets and their attachments, relative to the surrounding flow field. Another example is the relation between systolic anterior mitral valve motion and anterior PM displacement combined with leaflet elongation, the converse of posterior PM displacement and leaflet restriction in ischemic MR.

The dichotomy between tethering versus closing forces is also a simplification: Both are involved. The equilibrium position of the mitral leaflets is determined by the balance of forces acting on them, including annular and PM tethering forces and LV-generated closing forces (Figure 3). Normally, little force is required to close the thin leaflets, so MR is not produced by global dysfunction without tethering.\(^{24}\) However, once tethering is increased, leaflet closure is further
impaired when less force is available to oppose tethering. This balance of competing forces creates a unique dynamic pattern, recognized by Schamntenthal et al,43 with flow and orifice area greatest in early and late systole and often paradoxically decreased in mid systole, when peak LV pressure maximizes leaflet closure (Figure 5A). Tethering sets the stage for MR; transmitral pressure modulates its variation throughout the cardiac cycle.23,44 We therefore understand the early systolic leaflet “loitering” described by Glasson, Miller, et al45 and late-systolic MR and murmurs in patients with inferior MIs, in whom tethering increases as the inferior wall is “left behind” the contracting ventricle.46

**The Dynamic Lesion**

A dramatic example of this dynamic behavior is the case of the vanishing intraoperative MR. A patient undergoing coronary revascularization is reported to have moderate ischemic MR by transthoracic echocardiography. After anesthetic induction, transesophageal echocardiography shows only minor MR, so the mitral valve is not approached, and after successful revascularization, transthoracic echocardiography 1 month later again shows moderate MR. This frequent scenario has led to recognition that anesthetic induction and inotropic agents can substantially reduce MR, confounding decisions regarding repair.47–49 Phenylephrine can restore representative driving pressures but may fail to reproduce volume-dependent tethering, so intravenous volume loading has also been advocated, titrated to ventricular diameter, mean blood pressure H11350 90 mm Hg, and wedge pressure of 12 mm Hg.47 Practically, some surgeons advocate decisions based on the appearance of restricted leaflet closure and prior MR assessment under routine loading conditions.
Ischemic MR also responds dynamically to exercise. Lancellotti, Pierard, et al. recently quantified MR during semisupine bicycle exercise in patients with LV dysfunction, at least mild MR, and no evidence of inducible ischemia. In most, exercise increased MR, with orifice area rising by >20 mm² (enough to change clinical grade) in nearly 30%, but without extended wall-motion abnormalities. Increased MR correlated best with increased tethering and PM displacement. MR decreased only in patients with recruitable contraction of the inferior wall. Exercise-increased MR also correlated with increased pulmonary artery pressure and adverse prognosis. Lapu-Bula, Vanoverschelde, et al. likewise have shown that exercise-induced MR limits stroke volume and exercise capacity in chronic congestive heart failure.

Pierard and Lancellotti have studied patients with established LV dysfunction admitted with acute pulmonary edema but without evident acute ischemia. When they exercised, these patients, unlike control subjects, doubled their regurgitant volume from mild to moderate-to-severe, with increased pulmonary pressures and limiting dyspnea; they appear sensitive to the volume load imposed by exercise and increased MR.

There are several practical messages: (1) We can now expand the differential of acute pulmonary edema to include acute exacerbation of ischemic MR without obvious acute coronary ischemia. When they exercised, these patients, unlike control subjects, doubled their regurgitant volume from mild to moderate-to-severe, with increased pulmonary pressures and limiting dyspnea; they appear sensitive to the volume load imposed by exercise and increased MR. (2) Exercise can unmask the severity of what might otherwise be considered mild MR. This may help explain the clinical puzzle of patients with exertional dyspnea out of proportion to their resting systolic dysfunction or MR (assuming no intermittent ischemia or diastolic dysfunction). This may also be a reason that apparently mild ischemic MR worsens prognosis.

Given the dynamic interplay of tethering and closing forces, why not reduce MR by raising LV pressure? That approach is limited, because increasing afterload dilates compromised ventricles and increases tethering. Therapy must therefore focus on reducing the geometric culprits.

**Therapy**

Prompt in-hospital revascularization of acute coronary occlusion can reverse ischemic MR. Leor et al. and Tenenbaum and colleagues showed that early thrombolysis of first inferior MIs reduces localized LV remodeling and MR. This would support revascularization of MIs that, although localized, can cause important MR. Delayed reperfusion may yield less benefit.

In acute MI with shock, MR conveys considerable excess mortality for any level of global LV function (Figure 1B), and as Picard, Hochman, and colleagues have shown, early revascularization increases survival across the board. Acute PM rupture may present with acute pulmonary edema despite relatively limited areas of damage, and experience supports aggressive repair.

In contrast to the clear therapeutic opportunity provided by rapid reperfusion, MR relief by revascularization alone in chronic coronary artery disease is problematic. Aklog et al. for example, recently found persistent moderate or severe MR in 77% of revascularized patients, without established means to predict improvement.

Standard surgical therapy includes annular ring reduction, which aims to improve leaflet apposition by correcting
posterior annular dilatation. Although often effective initially, long-term failures are increasingly recognized. Experienced centers consistently report important persistent and recurrent MR, often months after surgery, in 30% or more of patients, casting doubt on whether satisfactory early results represent success.58–61 Disappointing benefits, combined with the added risks of prolonged bypass and ischemic time, with reported mortalities of ≥6% to 12%,62–64 often deter surgeons from performing this procedure.

Intraoperative MR underestimation contributes to the impression of recurrence but is only part of the problem. The mitral valve is caught in a tug-of-war between the dilated annulus and the displaced PMs. Reducing annular size alone leaves persistent tethering to the displaced LV wall. Steven Bolling and Bach65 and others indicate that ischemic MR is a ventricular, not a valvular, problem. Calafiore et al58 have shown that annuloplasty failure is predicted by greater preoperative leaflet tethering. Most importantly, the ventricle is a moving target and often continues to remodel and dilate, which renders initial repair ineffective, as quantitatively confirmed by Hung, Duran, and colleagues60 (Figure 6) and Qin, Shiota, Thomas, et al.66

Bolling introduced the increasingly common practice of implanting rings 1 or 2 sizes smaller than predicted by measuring the fibrous intertrigonal annulus.65 However, as Carlos Duran59 has put it, this attempts to compensate for the fundamental problem, not correct it. Recently, McGee, Gillinov, et al61 reported high-grade recurrent MR in 35% of patients 6 months after surgery, highest for pericardial annuloplasty but still 25% for Cosgrove and complete Carpentier rings, with no significant difference between large and small rings. Rings also shift the posterior annulus anteriorly, but the posterior leaflet remains tethered posteriorly, so its anterior excursion is markedly restricted; nearly rigid, it coapts poorly.60,67
Modified approaches include asymmetrical annuloplasty, first introduced by Tirone David, to reduce the largest leaflet gap, located medially because the inferomedial PM is most affected; apical displacement of the medial annulus to restore its more normal 3D saddle shape, bringing the vulnerable commissural point closer to the PM to relieve tethering, as shown by He, Yoganathan, and colleagues in a preliminary study; and predominant anteroposterior (septal-lateral) annular reduction to bring the leaflets together most effectively. Percutaneous annular reduction by coronary sinus compression may increase applicability but may be limited in reducing the anteroposterior dimension, because the coronary sinus is posterior. Nevertheless, all these approaches share the limitation that if the remodeling ventricle is not addressed, MR may persist or recur.

Subvalvular tethering can be relieved by modifying ventricular, leaflet, or chordal structures (Figure 7). Early approaches involved scar resection with PM reimplantation. The partial ventriculectomy stress-reduction experience reminded surgeons that decreasing inter-PM separation could cause variable tethering, prolapse, and severe MR unless prevented by an edge-to-edge (Alfieri) stitch. More recent ventricular reconstruction approaches championed by investigators such as Gerald Buckberg and Lynda Mickleborough, as in the STICH trial (Surgical Treatments for Ischemic Heart Failure), restore a less spherical ventricle to optimize contraction and reduce MR. Dor’s excision and patching of large dysfunctional areas reduces MR, but tethering and MR may recur. Tethering can be reduced by infarct plication to reduce bulging, reported by Liel-Cohen et al (Figure 8). Plication was inspired by the observation of J. Luis Guerrero, an experienced physiological surgeon, that manually repositioning the PM-bearing wall inward and anteriorly reduces tethering and MR; plication prolongs this benefit. Kron et al brought displaced PMs closer to the annulus using sutures, in conjunction with annular reduction (Figure 4B). Others use internal slings or surgically buckle displaced PMs anteriorly.

To realign the PM simply, Hung, Levine, et al have applied a localized patch that contains an epicardial balloon over inferior infarcts (Figure 9). In the beating heart, the injection of saline into the buttressed balloon under echocardiographic guidance repositions the underlying wall and PM anteriorly, which reverses leaflet tenting and MR. Effective in both acute and chronic remodeled MIs, this maneuver does not increase LV end-diastolic pressure, decrease LV contractility, or significantly increase stiffness. Initial experience shows efficacy over 2 months; despite instances of continued global remodeling, the patch maintains the critical PM-valve alignment that prevents MR. Thus, a relatively simple external device can reverse tethering and MR under echocardiographic guidance in the beating heart. Moainie, Gorman, et al have used a Marlex mesh patch that reduces but does not always eliminate MR in the absence of a PM-realigning balloon; external bands can also reposition the PMs. McCarthy’s Coapsys device spans the LV with a reinforced suture that hoists a small pad at the posterior base anteriorly toward the right ventricular free wall. The localized LV compression and need for anterior attachment

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**Figure 7.** Therapeutic targets. Ao indicates aorta.

**Figure 8.** Infarct plication to bring displaced PM tip back toward anterior mitral annulus, reducing MR. AO indicates aorta. Modified and used with permission from Liel-Cohen et al. Copyright 2000, American Heart Association, Inc.

**Figure 9.** Patch placement and balloon inflation over infarct region (highlighted) to reposition displaced PM toward anterior annulus and relieve tethering and MR under ultrasound guidance in beating heart. LA indicates left atrium; AO, aorta. Modified and used with permission from Hung et al. Copyright 2002, American Heart Association, Inc.
without coronary or right ventricular compromise merit exploration.

External constraint can also limit ventricular remodeling and parallels development of global constraint devices for congestive heart failure that do not appear to cause constriction. Potential for minimally invasive port-access implantation has particular value in advanced heart failure. Alternatively, repopulating damaged myocardium with cells derived from autologous skeletal myoblasts or from embryonic stem cells could reduce MR mechanically if increased wall thickness decreases bulging and reduces wall stress; in a preliminary report, autologous skeletal myoblast engraftment into a large, scarred sheep infarct blunted the progression of ischemic MR and leaflet reduction. Kunzelman et al. have shown by elegant finite element modeling that tethering stresses alter collagen deposition and increase leaflet stiffness, but the body appears unable to compensate sufficiently by increasing leaflet area. Leaflet elongation can reduce MR but is seldom attempted, perhaps because of concerns regarding durability, calcification, and complexity. Suturing leaflet edges together (Alfieri), possibly percutaneously, can improve coaptation in flail or prolapse but may increase tension on tethered leaflets, unless unstressed, perhaps by annuloplasty. A steadily increasing frequency of moderate and severe ischemic MR has been reported after this maneuver; it may ideally address asymmetrical coaptation or prolapse that persists after relief of tethering (see below).

An alternative approach involves modifying the chordal tethering mechanism directly, in ways suggested by valve anatomy and clinical observations of valve shape. Fine marginal chordae position the leaflet tips and prevent prolapse; thicker intermediate (basal or strut) chordae insert closer to the leaflet bases. With increased tethering, the basal anterior leaflet near the annulus becomes nearly rigid and tented apically by these basal chordae (Figures 2 and 10). The more distal leaflet pivots around the “knee” where these chordae attach, but only its tip can then approach the posterior leaflet, which decreases the coaptational surface that normally seals the orifice.

Messas, Levine, and colleagues therefore proposed that cutting a limited number of these critically positioned basal chordae can reduce ischemic MR; eliminating the anterior leaflet bend can make the leaflets less taut and improve coaptation (Figure 10). The intact marginal chordae should continue to prevent prolapse. As an initial approach, the 2 most central basal chordae to the anterior leaflet were cut at their valvular insertions, because they are most stretched by PM displacement away from the LV center.

Relief of MR without prolapse has been confirmed in several settings. In porcine valves studied in vitro at Georgia Tech, chordal cutting decreases leaflet tension for the same tethering length. (2) In sheep with acute inferobasal infarction, LV ejection fraction, pressure, and dP/dt are unchanged as MR decreases. With greater inferobasal remodeling 2 months after MI, LV ejection fraction is not decreased by chordal cutting. (4) With chordal cutting at the onset of inferobasal infarcts known to produce progressive MR, after a mean follow-up of 33 weeks (up to 43 weeks), no MR or post-MI LV ejection fraction decline occurs. Goetz, Duran, et al. have confirmed that chordal cutting increases leaflet mobility, which could benefit the tethered valve. Alternatively, expanded polytetrafluoroethylene chordal elongation is feasible.

Does chordal cutting affect ventricular function? Complete chordal transsection can reduce function, particularly in chronically volume-overloaded ventricles, leading to the current practice of chordal-sparing valve replacement. In isolated hearts, even severing all basal chordae only slightly decreased shortening of a single myocardial segment. To reduce tethering, however, only 2 chords are cut, and although they individually bear more stress, Kunzelman and Cochran have suggested “it may be possible surgically to remove basal chordae without seriously compromising mitral valve function.” Furthermore, reducing MR may predominantly decompress the ventricle and reduce wall stress, thereby increasing contractile function.

A recent series of reports on chordal cutting is perplexing. In the first study, severing these 2 basal chordae in sheep without MI (to explore potential use in prolapse) did not alter LV size or function. The second study reported mild localized changes (including those in derived value subject to wide scatter), but global systolic function was unchanged, including LV dp/dt, elastance (contractility), and preload-recruitable stroke work. The third study, in contrast, suggested a decrease in 2 preload-independent measures of global systolic function. Ingeniously, the chords were cut by radiofrequency ablation in the beating heart using preattached wires to compare hemodynamics before and after cutting without altering load. Importantly, there were no changes in load-dependent measures, including LV volumes, pressures, and dp/dt, and there were no changes in loading conditions to limit applicability of these measures. The authors noted that perhaps the electrocautery and traction on the chords subtly affected function. Similar pilot studies using noninvasive Doppler strains have shown no acute decreases in global or...
regional function. Although that group could not consistently prevent MR by chordal cutting after 1 minute of circumflex occlusion, the MR generated was mainly trace to mild.

Basal chordae have been disconnected in routine repair of rheumatic and myxomatous valves for decades without adverse effect.97 Several surgical groups have begun cutting chords to increase leaflet mobility and coaptation after annuloplasty; it appears to eliminate the need to overcompensate for tethering by undersizing the ring, which may further stress the valve and occasionally causes stenosis. Wakiyama, Okada, et al98 have applied it in global LV dysfunction; Tirone David, MD, and Michael Borger MD, PhD (Toronto General Hospital/University of Toronto, Toronto, Canada; personal communication, 2005) have cut the medial chords to both leaflets in patients with inferior MIs, and preliminary communications to date do not indicate any decrease in LV function. Chordal elongation can obviate concerns about disconnection. Minimally invasive transcatheter approaches are conceivable, because chordae are immobile relative to the heart,99 separated from the marginal chordae, easily visualized by ultrasound, and accessible directly below the LV outflow tract.

To summarize, the tethering mechanism provides both annular and subvalvular targets for therapy, including reversing LV geometric changes and leaflet or chordal modification. As in the case of prolapse, the likelihood of repair will be enhanced by having a versatile “tool kit” of options, obviating the need for valve replacement. Detailed mapping of geometric substrates should allow us to tailor the ideal combination of annular, ventricular, and chordal approaches to achieve the best result in each patient.

An informal survey of surgical leaders and publications reveals consensus that ischemic MR is a ventricular disease, distinct from structural leaflet changes. Alain Carpentier, MD, PhD (Hôpital European Georges Pompidou, Paris, France; personal communication) notes similar mechanisms increase preexisting MR in coronary artery disease. Treatment requires a combined annular and subvalvular approach to address long-term mechanisms (Gus Vlahakes, MD, Massachusetts General Hospital, Boston, Mass; personal communication) and prevent subsequent PM displacement by external pressure, sutures, or a containment device (Cohn et al100,101). Duran predicts a continuum of therapies, with high LV sphericity indicating the need for PM repositioning procedures; increased tethering may require stay (basal) chordal intervention. Craig Miller indicates that, “no matter how small we make the mitral annulus, [annuloplasty] cannot recreate competent leaflet coaptation if one or both leaflets are extensively apically tethered because of PM displacement.”101 and subvalvular repair may be key102 to realign PM geometry, for example, by external LV plication or buttressing.103

Gorman et al propose that a partial LV wrap can resist development of both MR and ventricular expansion in this “large group of difficult patients.”104 Kron’s PM realignment technique27 and the LV reconstruction approaches of Mickleborough73 and Buckberg72 aim for this ventricular solution. Even Bolling, the leading proponent of undersized annuloplasty, has developed a nonplanar ring designed to modify subvalvular LV wall geometry. Finally, the dynamics of ischemic MR indicate the need for continuing intensive heart failure therapy.

Medical Therapy and Cardiac Resynchronization

The literature regarding medical therapy is comparatively sparse. Surprisingly, post-MI and heart failure patients commonly present with moderate MR despite the use of diuretics, ACE inhibitors, and β-adrenergic antagonists. Two questions arise: (1) Can medical therapy reduce regurgitation of a tethered valve? And (2) can it attenuate or reverse the underlying ventricular remodeling?

To summarize, the dynamic balance of tethering and closing forces that determines ischemic MR.23,43,104 Transmitral pressure, which drives regurgitant flow, also promotes valve closure.105 Therefore, it would appear that increased systemic blood pressure could reduce MR by increasing closing force. However, noninotropic vasopressors will increase afterload and LV volume, and therefore tethering and MR (Table). Inotropic agents, in contrast, can raise LV pressure without increasing tethering, so MR will decrease, as with dobutamine infusion104,106; however, this is not a viable outpatient option. Transmitral pressure can also be increased by decreasing atrial pressure, so diuretics and nitrates can reduce regurgitant orifice area and flow,107–111 Preload reduction and the initial decrease in MR can decrease ventricular size and further reduce tethering, creating a beneficial cycle. In severe heart failure, Stevenson and colleagues108,109 have shown that vasodilators and diuretics can partially reduce MR (from moderate to mild-to-moderate); Levine et al111 have uptitrated ACE inhibitors and nitrates to reduce MR partially. However, if afterload reduction is not accompanied by decreased PM tethering (for example, with fixed inferior wall scarring or a dilated, hypokinetic ventricle), regurgitant orifice area may paradoxically increase as closing force decreases, as illustrated by Kizilbash, Grayburn, et al112 with nitroprusside.

Regarding the second question, acute LV decompression by vasodilators and diuretics is not the same as true reversal of the complex molecular, cellular, and interstitial remodeling process. Unfortunately, there are no strong data about ACE inhibitors and ischemic MR. In the SAVE (Survival And Ventricular Enlargement) study, Lamas et al1 found comparable cardiovascular mortality in patients with MR receiving captopril versus placebo; post-MI LV remodeling could only be partially attenuated by early ACE inhibition, but not reversed or completely prevented.113,114 Ventricular dilatation and distortion may continue to progress beyond 1 year of therapy, and even those who do not initially dilate may

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### Potential Effects of Medical Therapy on the Forces Determining MR Orifice Size

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<tr>
<th>Therapy Type</th>
<th>Closing Force (LV—Left Atrial Pressure)</th>
<th>Tethering Force (PM Displacement)</th>
<th>Net Effect (Regurgitant Orifice Area)</th>
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"escape" later. In SOLVD (Studies Of Left Ventricular Dysfunction), ACE inhibitors could arrest progressive LV dilation,115 and might even reverse it,116 but there are no published data from large trials regarding whether attenuation of remodeling by ACE inhibitors or receptor blockers decreases the post-MI incidence of ischemic MR. MR appears to remain common despite use of these drugs and significantly increases morbidity and mortality.

Carabello and colleagues117,118 have firmly established that β-adrenergic receptor blockade can reverse the contractile and structural abnormalities caused by chronic nonischemic MR. Accordingly, in patients with chronic heart failure, β-blockade with carvedilol, when added to ACE inhibitors, can significantly decrease functional MR by reducing LV dilation.119,120 The CARMEN study (Carvedilol and ACE-Inhibitor Remodelling Mild Heart Failure Evaluation Trial), with mainly ischemic cardiomyopathy, demonstrated synergistic reverse remodeling by carvedilol and enalapril in mild heart failure,121 and CAPRICORN (Carvedilol Post-Infarct Survival Controlled Evaluation) has recently shown incremental benefit of carvedilol over ACE inhibitors on ventricular remodeling after MI122; the effects on MR, however, are unreported. Tei et al123 have demonstrated reduced LV volume and MR in congestive heart failure with vasodilation after warm bath and sauna, but chronic benefits require study.

Limiting ventricular remodeling will ultimately be most effective early in its evolution. It remains to be seen whether vigorous combinations of vasodilator, β-blocking, and diuretic therapy, including spironolactone and other inhibitors of fibrosis and extracellular matrix degradation,124 can limit the development of ischemic MR. Presently, such agents are not routinely administered to patients with inferior MI, whose localized remodeling may generate considerable MR. Practically, we must deal with the many patients with existing MR and the incomplete effectiveness of current medical therapy.

A more favorable balance of forces on the valve can also be restored by electrical therapy in patients with heart failure. St. John Sutton, Abraham, and colleagues125 have reported significantly decreased MR in the Multicenter InSync Randomized Controlled Clinical Evaluation. Biventricular pacing, with more effective LV contraction, can reduce end-systolic volume and therefore tachycardia. In heart failure, delayed lateral wall activation produces disorganized PM contraction, malalignment of leaflet scallops, and MR; Kanzaki, Goresan, et al126 have shown that eliminating such delays by LV pacing reduces MR. Resynchronization also increases the leaflet closing force throughout systole, as shown by Breithardt, Sinha, Schwammenthal, et al127 in patients with left bundle-branch block (Figure 5B); pacing can increase the rate of rise of LV pressure, thereby prolonging the time during systole when high LV and transmitral pressures oppose tethering to reduce regurgitant orifice area,127 in direct correlation with dP/dt. Electrical therapy will therefore be most useful in those patients with cardiomyopathy whose dP/dt rises and lateral wall conduction delay falls with pacing; its benefit extends to exercise, but with no evidence of benefit with preserved LV synchronicity or inferior MI.

**Remaining Questions**

**Can We Predict in Whom Revascularization Alone Will Reduce MR?**
To date, only limited studies with low-dose dobutamine or positron emission tomography (PET) have explored preoperative viability, particularly in PM-bearing segments, to predict improvement; higher-dose dobutamine may nonspecifically decrease LV volume and MR without predicting improvement after revascularization.104,106 Exercise testing may possibly help predict benefit if exercise-improved inferobasal motion reduces MR.50

**Do Patients With MR Who Will Be Having Bypass Surgery Benefit From Mitral Valve Repair?**
Conclusions vary widely, with some describing decreased symptoms, reduced mortality, and prolonged survival,62–64,128 and others suggesting comparable results with and without annuloplasty.129 MR severity and LV dysfunction vary widely in these studies, and whether MR actually decreases is frequently unknown. How can we reasonably evaluate the benefit of eliminating MR when it frequently persists or recurs with standard therapies? We must therefore first develop the most effective therapy for MR that is least disruptive to the patient before assessing the impact of therapy on outcome.

**Does Eliminating Ischemic MR Reduce Ventricular Remodeling?**
MR, caused by altered LV geometry and function after MI, can itself initiate remodeling. MR considerably alters LV loading130; it increases diastolic wall stress, which can induce eccentric hypertrophy with LV dilation and failure,131 and also increases end-systolic wall stress in patients with chronic MR because of induced LV remodeling, with decreased contractility and increased end-systolic volume.132,133 Increased wall stress can aggravate remodeling by activating metalloproteinases that degrade extracellular matrix134 and by increasing neurohumoral and cytokine promoters of remodeling, driving a vicious circle in which MR begets more MR.

External constraint, even when localized, can by itself limit global remodeling.82,134 In experimental inferior MIs with MR, Moanie et al46 showed that infarct patching blunts but does not eliminate progressive LV remodeling, although MR was only partially reduced, which left a potential remodeling stimulus. Subsequently, Guy et al83 reported greater attenuation of remodeling by external infarct constraint; however, because ventricular dilation continued unabated over 8 weeks with ring annuloplasty, despite apparent reduction of MR, they concluded that ischemic MR does not cause post-MI remodeling.

That study confirms that local infarct constraint limits both global remodeling and MR. On the other hand, the conclusion that ischemic MR does not promote remodeling is challenging, given clinical and experimental evidence. Carabello, Zile, Spinale, and colleagues117,118,131 conclusively established that important MR (in that case, nonischemic) causes progressive deterioration of ventricular contractile function at a cellular and molecular level, with a downward spiral of dilation, increased wall stress, and decreased contractile function that can be reversed by correcting the MR.
Guy et al.83 rather reflects the double-edged effect of ring remodeling in the nonischemic heart, and ischemia can further drive that process. Perhaps, therefore, the study by Bolling’s pioneering work in patients with dilated cardiomyopathy further proves that reducing MR can reverse LV remodeling at the whole-heart, cellular, and molecular level.65 To summarize, dilatation and dysfunction, as well as the associated, often controllable, standardized MR-type flow. Preliminary findings indicate this volume-overload lesion reversibly promotes which an apical MI, which by itself does not cause MR, is implanted: Annuloplasty, forced on a posteriorly infarcted ventricle, may actually stretch the posterobasal segments between the posteriorly displaced papillary muscles and the mitral annulus, which has been displaced anteriorly by the surgery. This stretch could mechanically promote remodeling despite acute elimination of MR.

Beeri, Hajjar, and Levine134a have developed a model in which an apical MI, which by itself does not cause MR, is combined with a Rankin LV-to-left atrial shunt to create controllable, standardized MR-type flow. Preliminary findings indicate this volume-overload lesion reversibly promotes remodeling at the whole-heart, cellular, and molecular level. Bolling’s pioneering work in patients with dilated cardiomyopathies further proves that reducing MR can reverse LV dilatation and dysfunction, as well as the associated, often counterproductive neurohumoral cascade.65 To summarize, external constraint, both local and global, powerfully combats remodeling, but the balance of evidence suggests that the MR stimulus should also be removed.

How Can We Repair Combined Restricted and Excessive Leaflet Motion?

In some patients, although both leaflets are apically tethered, one prolapses superiorly relative to the other (leaflet overshoot), which creates more severe malcoaptation and MR, with eccentric jets (Figure 11).136,137 This may occur in patients with inferior MIs. As Agricola et al.136 have recently postulated, asymmetrical displacement of the posterior PM angulates the posterior leaflet toward that muscle; the anterior leaflet slides superiorly along the posterior leaflet, imitating prolapse by coapting asymmetrically.136,137 This is frequent after annuloplasty, when the posterior leaflet becomes nearly rigid and the anterior leaflet tip meets it end-to-side. This phenomenon, however, is not limited to inferior MIs and may be caused by uneven elongation or shrinkage of chordae and PM portions, including chordal rupture. Short of flail, though, reducing tethering—the primary problem—should decrease MR; complete MR reduction, however, may require precise leaflet realignment with an Alfieri edge-to-edge stitch.

Diagnosis

Ischemic MR murmurs are frequently faint or inaudible, which may reflect the midystolic decrease in flow rate (Figure 5A),43 as well as decreased LV-to-left atrial pressure gradients and limited transmission. Jet area may overestimate severity as the jet expands into a dilated atrium. Calculating flow rate from velocity\times area proximal to the orifice (Figure 2B) will underestimate true values if the velocity surface is assumed hemispherical: It is generally hemielliptical, paralleling a slitlike orifice.138 The vena contracta dimension in a long-axis view is extremely useful, because the regurgitant orifice scales up or down with the vena contracta dimension perpendicular to the coaptation line.139 Dynamic MR variation indicates the need to integrate flow throughout systole.82 Evaluation at rest may underrepresent the burden on the active patient,50 and intraoperative evaluation is heavily influenced by changes in load and tethering.47–49

Summary and Perspectives

The exploration of paradoxes has clarified unifying concepts and fundamental mechanisms. The midystolic decrease in flow rate, for example, demonstrates the underlying balance of forces relevant to dynamics in the operating room, with exercise, and with medications. Paradoxical decreases in MR with acute ischemic PM elongation sharpen our understanding of tethering length and the therapeutic opportunities it provides.

In a broader perspective, ischemic MR is a substantial remaining frontier in the move toward valve repair as opposed to replacement and a growing opportunity for minimally invasive therapeutics. It highlights the value of exercise testing in valve disease and parallels new initiatives in heart failure therapy, including external constraint, resynchronization, and cell repopulation.

Understanding mechanisms has led to improved therapies targeted to primary causes. New therapeutic options have the potential to provide a more flexible approach, adaptable to patients with diverse ventricular and valvular changes. The guiding principle is to achieve a comprehensive repair that addresses tethering at both ends of the leaflets. Looking ahead to the next few years, we can envision that evaluation of annular and ventricular dimensions will direct therapies tailored to the individual patient. Ischemic MR, therefore, is on the threshold of a solution.

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Disclosure
Dr Levine is an inventor on 2 approved US patents: (1) No. 6,544,181, “Method and apparatus for measuring volume flow and area for a dynamic orifice,” held by Massachusetts General Hospital and Philips Medical Systems, which deals with an improved method for quantifying MR; and (2) No. 6,695,768, “Adjustable periventricular ring/ring-like device/method for control of ischemic mitral regurgitation and congestive heart disease,” which deals with a new device (not described in the text) for repair of ischemic MR by externally repositioning the papillary muscle attachments. No commercial products are derived from these patents, but commercial development is possible. He is also an inventor on 3 pending patent applications dealing with MR repair. He had a sponsored research agreement (now closed for >1 year) with Guidant.

References


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