Ischemic mitral regurgitation redux—To repair or to replace?

D. Craig Miller, MD

See related articles on
 pages 1107 and 1125.

"Most often the entire valve appears normal; . . . There is little to fix, yet the valve leaks. . . . the valve is structurally normal; it need not be replaced, but currently we do not know how to fix it"

—L. Henry Edmunds, Jr, 1997¹

The pair of articles in this issue of the *Journal* by Gillinov,² Grossi,³ and their colleagues revisits an old and unanswered question: Is it better to repair or replace the leaking mitral valve in patients with coronary artery disease that has caused ischemic mitral regurgitation (IMR)? These two articles bring contemporary clarity to this dilemma and represent a major step forward, but they do not answer all our questions.

This controversy was reignited in 1995 by Lawrence Cohn and his colleagues⁴ from the Brigham, who reported that the outcome of patients with IMR undergoing mitral repair or mitral valve replacement (MVR) plus coronary artery bypass grafting (CABG) was not so much dependent on the choice of operative procedure per se, but more on the underlying pathophysiology of the IMR and the patient's clinical presentation. This enlightened certain surgeons who had already convinced themselves that repair was better, but also reminded us that the prognosis for these sick patients was markedly suboptimal. Patients with IMR have morphologically normal mitral leaflets and subvalvular apparatus, but the valve can leak badly. Previously, surgeons had not talked a lot about IMR, perhaps because none of our surgical results were particularly good. Subsequently, we learned conclusively in the multicenter SAVE (Survival and Ventricular Enlargement) trial that even a mild degree of mitral regurgitation (MR) portended a substantial excessive risk of cardiovascular mortality within 5 years after acute myocardial infarction,⁵ even in patients who did not have any overt signs of congestive heart failure at the time of study entry. These data reinforced the results of prior observational studies of patients with IMR, both those treated medically after a myocardial infarction and those undergoing CABG or percutaneous transluminal coronary angioplasty.

Earlier retrospective surgical studies included patients with many different types of mitral valve disease, including those with prolapse found to have incidental coronary artery disease, which only confounded the issue. One beauty of the two articles published in this issue of the *Journal* is that only patients with IMR caused by coronary artery disease were investigated; that is, these are "clean" studies. Second, these papers used strict pathophysiologic criteria to classify the patients with respect to the mechanism of IMR. Even though different descriptive terms were used, an important message is that we distinguish between "functional IMR," infarcted but not ruptured papillary muscle, and ruptured papillary muscle. The vast majority is represented by patients with functional IMR, which can be due to one

From the Department of Cardiovascular Surgery, Stanford University School of Medicine, Stanford, Calif.

Received for publication Aug 20, 2001; accepted for publication Sept 7, 2001.

Address for reprints: D. Craig Miller, MD, Department of Cardiovascular Surgery, Stanford University School of Medicine, Falk Cardiovascular Research Center, CV 243, 3000 Pasteur Dr, Stanford, CA 94305-5247.

J Thorac Cardiovasc Surg 2001;122:1059-62

Copyright © 2001 by The American Association for Thoracic Surgery

0022-5223/2001 \$35.00 + 0 12/1/120341

doi:10.1067/mtc.2001.120341

of the following reasons: (1) simple annular dilatation (secondary to left ventricular [LV] enlargement), which causes incomplete mitral leaflet coaptation associated with Carpentier type I (normal) leaflet motion; (2) local LV remodeling with papillary muscle displacement producing apical tethering or tenting of the leaflets (with Carpentier type III-b restricted systolic leaflet motion); or (3) both mechanisms. Importantly, exhaustive analyses from the Mayo Clinic echocardiography laboratory^{6,7} have provided a great amount of insight into the mechanisms of IMR and its clinical impact. Thanks to these investigators, we can now reliably measure leaflet tenting area and tenting height quantitatively from transthoracic echocardiograms in patients with LV dysfunction and IMR or functional MR, as well as estimate the effective regurgitant orifice.⁶ Larger effective regurgitant orifice, or more leak, was directly and independently predicted by excess leaflet tenting and loss of systolic annular contraction, but it was not related to the degree of LV dysfunction. Adverse prognostic consequences were also clearly documented, moreover, as medium-term survival for patients with IMR and LV dysfunction was strongly and independently related to calculated effective regurgitant orifice, even after statistical adjustment for all other variables.⁷ Recently, Otsuji and associates,⁸ working in Vlahakes' and Levine's laboratory at the Massachusetts General Hospital, experimenting with short-term canine and long-term sheep models and 3-dimensional echocardiographic imaging, also contributed new information concerning the mechanisms of IMR resulting from LV local remodeling.

Now that we better understand what we are talking about (and can actually measure it!), surgeons should be more aggressive and not ignore substantial degrees of IMR at the time of CABG. This policy should also apply to patients undergoing percutaneous coronary revascularization with percutaneous transluminal coronary angioplasty and stenting to optimize their prognosis, but such is unlikely since we do not live in a utopia and the interventional cardiologists have not figured out quite yet how to repair leaking mitral valves in the cardiac catheterization laboratory.

But, does one do a ring annuloplasty or a more reliable chordal-preserving MVR? As the authors of the two accompanying articles declare,^{2,3} the answer is not a simple one. Historically, we have been handicapped by comparing very different cohorts of patients in attempting to assess whether repair offers a better outcome than does MVR. The patients receiving these two procedures were very dissimilar and not directly comparable, truly an apples versus oranges situation. Fallacious conclusions resulted from such comparisons. In the absence of randomized trials, which are probably unrealistic, this handicap persists as demonstrated in both accompanying papers^{2,3}; but, new statistical tools are now available that can help neutralize the inherent

patient selection bias that plagues such retrospective studies. In the Gillinov analysis of 482 patients,² Blackstone used propensity score analysis and other sophisticated statistical methods to generate quintiles of patients undergoing either repair or MVR that were relatively well matched to answer the question whether one procedure is better than the other, and, if so, in which particular patient. This approach identified subsets of patients (unbalanced in numbers) that were reasonably well balanced in terms of risk factors. Bootstrap resampling (so-called "bagging") was also used to validate the results of the model and confirm that the results were generalizable. This important paper (together with the appendixes) deserves to be read carefully and repeatedly; it is remarkable for its clarity of prose (even though it is written in a tongue that I affectionately call "Gene-speak." A massive amount of effort was invested, including Gillinov reviewing all available original echocardiographic tapes to reclassify the patient population. About 70% of patients—but not the sickest patients—were believed to benefit from repair. The amount of relative benefit of repair in terms of survival was less or actually erased if a thoracic artery was not used for CABG, a lateral LV wall motion abnormality was present, or the IMR jet was "complex." The sickest patients did equally poorly with either procedure, and in certain cases MVR was in fact associated with better predicted survival. Overall 5-year survival was still disappointing, regardless of whether the valve was repaired or replaced.

Propensity score analysis was also explored by Grossi and associates,³ who evaluated 223 patients with IMR; but, the New York University statisticians concluded that the marked imbalance in numbers of patients undergoing one procedure or another within the quintiles was such that the propensity score models did not provide an adequate fit to the data. Therefore, propensity score adjustments were not used. Instead, the New York University group did multiple convoluted layers of multivariable analyses to adjust for the confounding effects of functional disability (New York Heart Association class), presence of angina, and particular operation performed, followed by separate Cox modeling within each of the two surgical groups. The nuances of this arcane statistical debate are best left to the professional biostatisticians, whom I invite to air their differences in public so as to educate the rest of us. Perhaps propensity score analysis worked in the Cleveland Clinic series because it comprised more than twice the number of patients as did the New York University series. Fortunately, several invited papers concerning these statistical topics will be forthcoming soon in the *Journal*. Suffice it to say, the patients who underwent mitral repair at New York University were not as sick as those who required MVR (as was also the case in the Gillinov report²); medium-term survival was suboptimal but roughly equivalent between the two types of procedures. Certain subsets of patients were identified who appeared to

do better if they could undergo repair. This lack of pronounced difference in survival between the repair and the MVR groups is similar to the conclusions just reported by Calafiore and colleagues⁹ in patients with functional MR and incomplete mitral leaflet coaptation due to dilated idiopathic cardiomyopathy (n = 12) or IMR due to ischemic cardiomyopathy (n = 7), but certain differences beg amplification. In the Italian experience,⁹ recurrence of MR was frequent after repair if what Calafiore called mitral valve coaptation depth (which is equivalent to the Mayo term “coaptation height”⁶ and indicative of apical leaflet tenting) was 11 mm or greater; this stands to reason as no matter how small one makes the mitral annulus, this maneuver cannot recreate competent leaflet coaptation if one or both leaflets are extensively apically tethered because of papillary muscle displacement. If one wants to save the valve in these cases, more radical repair procedures are required, such as external LV plication or buttressing,⁸ realignment of papillary muscle geometry inside the ventricle, leaflet patch extension as described by Dobre, Koul, and Rojer,¹⁰ or perhaps an Alfieri stitch. Second, the mitral reparative procedures performed in Calafiore’s series included pericardial strip annuloplasty or a modified De Vega-type or Paneth-type continuous suture annuloplasty, which have been abandoned by most surgeons. In the Cleveland Clinic² and the New York University³ articles, both of these techniques were much less effective than implantation of a synthetic mitral annuloplasty band or ring.

Despite my enthusiasm to see these two articles finally published and my appreciation of their clinical value, one must still be a little circumspect.

1. Neither study^{2,3} included a control group of patients that had comparable degrees of IMR but underwent CABG only; hence, what Donald Glower calls the “straw man hypothesis” exists, again.
2. Two other important end-points were not evaluated in either study: (a) the impact of mitral repair versus MVR on LV systolic function over time and (b) the adequacy of the repair as assessed by serial echocardiographic surveillance. Although the incidence of reoperation after repair was low, this could be misleading for two reasons: (I) many patients could have had recurrent IMR but been so sick they were not considered suitable candidates for reoperation and (II) the death rates were so high that relatively few patients remained at risk for structural valve deterioration of the repair beyond 2 to 3 years. These two essential end-points should be the focus of future investigations.
3. Finally, despite whatever procedure was performed, the 5-year survival was still not much better than 50%. This indicates that successful revascularization and correction of the IMR does relatively little in terms of ameliorating the ravages of previous LV infarction and ischemia.

The Bottom Line

Patients with IMR represent a heterogeneous group that has a soberingly dismal medium-term prognosis because of underlying LV systolic dysfunction. As Steven Bolling is wont to say: “IMR is a *ventricular* disease, not a *valvular* disease.” We now recognize that ignoring an important degree of IMR at the time of CABG is not prudent because it will only limit the potential functional benefit to be attained from operation and compound the patient’s poor life expectancy. One exception to this policy would be the uncommon situation where an inferior LV wall motion abnormality causing IMR is known preoperatively to be due to reversible ischemia involving viable myocardium, such that revascularization alone has a high likelihood of correcting the IMR.

Valve repair with an undersized annuloplasty ring works satisfactorily in most cases of functional IMR, but the surgeon needs to pay keen attention in interpreting the genesis and direction of the MR leak. If simple annular dilatation resulting in incomplete mitral leaflet coaptation and associated with Carpentier type I leaflet motion is the main culprit and the leak is centrally directed straight back into the atrium or slightly posteriorly directed (due to “pseudo-prolapse” of the anterior leaflet, which reflects restriction of the posterior leaflet), then it is likely that simple ring annuloplasty will work well and will be fairly durable; conversely, if the pattern of the IMR leak is complex, or substantial apical tenting of the leaflets is identified (Carpentier type III-b restricted systolic leaflet motion), or a lateral wall infarct is present, then simple ring annuloplasty may not be the most prudent course of action. The most important surgical goal in repairing the valve is to reduce and fix the mitral annular dimension in the anterior-posterior (or “septal-lateral” in anatomic terms) axis, not the commissure-commissure axis. Although both partial or complete and flexible or rigid rings perform satisfactorily,^{2,3} in theory this goal may best be accomplished in patients with IMR by using stiffer rings, for example, Carpentier-Edwards Classic (not Physio) (Edwards Lifesciences, Irvine, Calif), Carbomedics AnnuloFlo (Sulzer Carbomedics, Austin, Tex), or the newly approved Medtronic CG Future Band (a partial, semirigid ring, Medtronic Heart Valve Division, Minneapolis, Minn), developed by Colvin, Galloway, and Grossi. This is despite the fact that the first two types of ring completely abolish annular dynamic motion and in contrast to patients with mitral prolapse, in whom a flexible, partial (posterior only) band is preferred by me and many others.

Surgeons today frequently are taking a more aggressive approach and adding a mitral ring during coronary revascularization if substantial IMR is present. Does this mean that all patients undergoing CABG who have more than mild MR should receive concomitant mitral annuloplasty? Probably not. Such enhances the risk of air embolism and

prolongs cardiopulmonary bypass time, which is likely to increase the already high operative mortality risk because these patients invariably have poor LV systolic function.^{2,3,9,11} This judgment decision needs to be based on the severity and the mechanism of the IMR as assessed on the *preoperative* echocardiogram under stress or ambulatory hemodynamic conditions; assessment intraoperatively by transesophageal echocardiography is unreliable and often misleading because of the LV pressure and volume unloading effects of general anesthesia. Given our current excellent methods of myocardial protection, making an error of commission rather than one of omission with respect to ring annuloplasty is perhaps the most sensible course of action when one is uncertain; however, again, the nature and mechanism of the IMR leak needs to be fully appreciated.

Without a doubt, a role still remains for MVR, especially if all anterior and posterior leaflet chordae are preserved. This reasonable alternative may be preferable for surgeons who do not do many dozens of mitral repair procedures each year. Other circumstances in which a quick and dependable MVR may be the better side of valor when facing functional IMR include the very sickest patients, those with a complex MR leak or a lateral LV wall motion abnormality, and patients with considerable apical leaflet tenting. Additionally, individuals with an infarcted or ruptured papillary muscle and very ill patients presenting on an emergency basis after an acute myocardial infarction probably are best served by chordal-sparing MVR. Given the markedly limited life expectancy of patients with IMR, it does not make any sense to use a mechanical prosthesis for MVR, irrespective of the patient's age; a tissue valve is indicated because very few of these patients will actually live long enough to sustain structural deterioration of their bioprosthesis. Further, saving all the subvalvular apparatus is less technically demanding and fraught with fewer potential postoperative valve-related complications if a bioprosthesis is used.

I respect the cardiac surgeons at these two institutions, and I salute them and their statistical coworkers for their honesty and candor. Thanks to a huge amount of hard work on their part, our knowledge base concerning the surgical treatment of patients with IMR is more complete after publication of these two articles.

References

1. Edmunds LH Jr. Ischemic mitral regurgitation. In: Edmunds LH Jr, editor. Cardiac surgery in the adult. New York: McGraw-Hill: 1997. p. 657-76.
2. Gillinov AM, Wierup PN, Blackstone EH, Bishay ES, Cosgrove DM, White J, et al. Is repair preferable to replacement for ischemic mitral regurgitation? *J Thorac Cardiovasc Surg.* 2001;122:1125-41.
3. Grossi EA, Goldberg JD, LaPietra A, Ye X, Zakow P, Sussman M, et al. Ischemic mitral valve reconstruction and replacement: comparison of long-term survival and complications. *J Thorac Cardiovasc Surg.* 2001;122:1107-24.
4. Cohn LH, Rizzo RJ, Adams DH, Couper GS, Sullivan TE, Collins JJ Jr, et al. The effect of pathophysiology on the surgical treatment of ischemic mitral regurgitation: operative and late risks of repair versus replacement. *Eur J Cardiothorac Surg.* 1995;9:568-74.
5. Lamas GA, Mitchell GF, Flaker GC, Smith SC, Gersh BJ, Basta L, et al. Clinical significance of mitral regurgitation after acute myocardial infarction. *Circulation.* 1997;96:827-33.
6. Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. *Circulation.* 2000;102:1400-6.
7. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation.* 2001; 103:1759-64.
8. Otsuji Y, Handschumacher MD, Liel-Cohen N, Tanabe H, Jiang L, Schwammenthal E, et al. Mechanism of ischemic mitral regurgitation with segmental left ventricular dysfunction: three-dimensional echocardiographic studies in models of acute and chronic progressive regurgitation. *J Am Coll Cardiol.* 2001;37:641-8.
9. Calafiore AM, Gallina S, DiMauro M, Gaeta F, Iacò AL, D'Alessandro S, et al. Mitral valve procedure in dilated cardiomyopathy. *Ann Thorac Surg.* 2001;71:1146-53.
10. Dobre M, Koul B, Rojer A. Anatomic and physiologic correction of the restricted posterior mitral leaflet motion in chronic ischemic mitral regurgitation. *J Thorac Cardiovasc Surg.* 2000;120:409-11.
11. Edwards FH, Peterson ED, Coombs LP, DeLong ER, Jamieson WRE, Shroyer LW, et al. Prediction of operative mortality after valve replacement surgery. *J Am Coll Cardiol.* 2001;37:885-92.