COUNTERPOINT: Efficacy of adding mitral valve restrictive annuloplasty to coronary artery bypass grafting in patients with moderate ischemic mitral valve regurgitation

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Dr Fattouch and colleagues present the first prospective randomized trial on the very controversial group of patients with chronic moderate ischemic mitral regurgitation (MR) undergoing coronary artery bypass (CAB). They randomized 100 patients with 2+ ischemic MR to CAB alone and combined CAB plus restrictive mitral annuloplasty. All patients had a prior myocardial infarction (MI) and decreased ventricular function (ejection fraction [EF], 42%), New York Heart Association (NYHA) class was 2.3, left ventricular end-diastolic diameter (LVEDD) was 59 mm, and pulmonary artery pressure was 40 mm Hg. The 5-year survival was 88.8% in the CAB-only group and 93.7% in the combined group. The combined group showed reverse remodeling with resolution of MR at 5 years (mean MR grade, 0.08 ± 0.2 ; LVEDD, 52 mm; left ventricular [LV] EF, 48%; pulmonary artery pressure, 26 mm Hg; and mean NYHA class, 0.6). The CAB-only group showed an insignificant improvement in functional parameters and worsening of MR in 35%. Exercise echocardiographic analysis was basically normal in the combined group but significantly impaired in the CAB-only group. These results are impressive.

RETROSPECTIVE STUDIES

Previous publications have been retrospective studies that have important limitations even when statistical analysis of propensity-matched groups was used to compensate for the bias related to patient selection (Table 1).¹⁻⁶ One such study was published in the past year by the Cleveland Clinic group.¹ Mihaljevic and colleagues¹ reviewed 390 patients from 1991 to 2003 with 3+ or 4+ ischemic MR. Of these, 290 underwent CAB plus mitral valve (MV) annuloplasty, and 100 underwent CAB alone. Groups were propensity matched by using demographics, extent of coronary artery disease, regional wall motion, and quantitative echocardiographic analysis. The 1-, 5-, and 10-year survivals were

88%, 75%, and 47% after CAB alone and 92%, 74%, and 39% after CAB plus mitral annuloplasty. NYHA class improved substantially in both groups and remained improved at 5 years. Their conclusion was that MV annuloplasty reduces postoperative MR and improves early symptoms compared with CAB alone but does not improve long-term functional status or survival in patients with severe functional ischemic MR (Table 1).

We published a study of similar series² of patients with severe chronic ischemic MR (355 patients) who underwent revascularization alone ($n = 168$) and revascularization combined with MV repair ($n = 187$). The combined surgical group had a greater reduction in MR grade (2/4 vs 0.2). Both groups had similar operative mortality (11% in the combined group vs 4.7% in the revascularization-only group, $P = .11$) and actuarial survival at 5 years (44% vs 41%, $P = .53$). Independent predictors of long-term mortality were older age, fewer bypass grafts, and lower EF. After adjusting for these variables, there was only a trend ($P = .08$) toward higher survival with the combined surgical procedure (Table 1). These retrospective studies also indicate that there is a significant recurrence of MR after annuloplasty (Table 1).³ The issue is complicated by the fact that the retrospective reviews encompass patients who underwent surgical treatment over a long period of time and that the surgical techniques for mitral repair and the type of mitral rings have changed over time, making comparisons more difficult.

RECURRENCE OF ISCHEMIC MR

A more recent study by Braun and colleagues⁴ was presented at the Society of Thoracic Surgeons meeting in 2007. It was a prospective follow-up of 100 consecutive patients with severe ischemic MR undergoing restrictive mitral annuloplasty and coronary revascularization. The surgical technique was uniform, stringent downsizing by 2 ring sizes (median size, 26 mm) with the Carpentier-Edwards Physio Ring in all patients. The preoperative EF was 27%. The 5-year survival was a remarkable 71%, and it was 80% for patients with a preoperative LVEDD of 65 mm or less. There was a significant reduction of MR from 3.2+ to 0.8+, and at late follow-up, of the 75 survivors, only 1 patient had 3+ MR, 11 patients had 2+ MR, and 63 patients had 1+ or no MR. Their conclusion was that for patients with a preoperative LVEDD of 65 mm or less, restrictive mitral annuloplasty with revascularization provides a cure for ischemic

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MR and heart failure. This review is remarkable in that it shows complete success by means of restrictive mitral annuloplasty in patients with advanced ischemic MR (MR grade, 3.2+; EF, 28%; Table 1). We all experience in our practice a recurrence of MR in patients with severe type III-B MR, specifically when eccentric jets are directed posteriorly at the level of P3. A restrictive annuloplasty in these patients often is unsuccessful. Several techniques have been tried with variable success, including cutting of the secondary chordae, Alfieri edge-to-edge repair, infarct plication, surgical relocation of the papillary muscles, and posterior MV restoration. Braun and associates⁴ did not report the problem of recurrence with restrictive annuloplasty alone. A reasonable inference for patients with severe chronic ischemic MR undergoing coronary revascularization is that they should have an MV repair that would include a restrictive annuloplasty and some other repair technique for the eccentric MR yet at the level of P3. In many patients, however, MV annuloplasty alone will not improve long-term outcome because the ventricular pathology is not addressed with the MV repair. For moderate chronic ischemic MR, this is a very aggressive approach for which there is no general consensus.

We recently identified 83 patients who underwent revascularization between 1991 and 2004 (data previously unpublished). They all had reduced LV function and moderate 3+ MR. Twenty-eight patients underwent CAB and MV repair, and 55 underwent CAB alone. Preoperative clinical characteristics of these patients were comparable. We compared the changes in MR grade, functional class, and LVEF in both groups. We also compared 23 propensity-matched pairs of patients. The 1-year survival was 96% in both groups, and the 5-year survival was 87% in the CAB plus MV repair group and 81% in the CAB-only group. This was not statistically significant ($P = .13$). There was a significant reduction in MR grade at 1 year in the combined group versus the CAB-only group. There was only a trend at 5 years. This lack of sustained significance might be due to a relatively small number of patients at longer follow-up. We found a significant improvement in postoperative NYHA class in both groups the first year after surgical intervention, which persisted at the 5-year follow-up. There was no statistically significant difference between the 2 groups ($P = .10$), and the propensity analysis did not alter our results. Our analysis was a small retrospective review with significant limitations.

CLINICAL SIGNIFICANCE OF MODERATE ISCHEMIC MR

A better way to look at the issue of moderate ischemic MR was used by Di Mauro and colleagues,⁵ who compared, using propensity scores, a group of 70 patients who underwent CAB alone in the presence of 2+ ischemic MR and LV dysfunction with a group of 70 patients who underwent CAB

TABLE 1. Literature conclusion summary

Author	Conclusions
Mihaljevic and coworkers ¹	Although coronary artery bypass grafting plus mitral valve annuloplasty reduces postoperative mitral regurgitation and improves early symptoms compared with coronary artery bypass grafting alone, it does not improve long-term functional status or survival in patients with severe functional ischemic mitral regurgitation. The mitral valve annuloplasty in this setting, without addressing fundamental ventricular pathology, is insufficient to improve long-term clinical outcomes.
Kim and coworkers ²	In patients with ischemic mitral regurgitation, combined mitral valve repair and revascularization resulted in less postoperative mitral regurgitation and similar 5-year survival when compared with revascularization alone.
McGee and coworkers ³	Although initial mitral valve replacement would eliminate the risk of postoperative mitral regurgitation, this strategy has been associated with reduced survival.
Braun and coworkers ⁴	At 4.3 years' follow-up, intermediate-term cutoff values for left ventricular reverse remodeling proved to be predictors for late mortality. For patients with a preoperative left ventricular end-diastolic diameter of 65 mm or less, restrictive mitral annuloplasty with revascularization provides a cure for ischemic mitral regurgitation and heart failure. However, when the left ventricular end-diastolic diameter exceeds 65 mm, outcome is poor, and a ventricular approach should be considered.
Di Mauro and coworkers ⁵	This study confirms that moderate ischemic mitral regurgitation has an important negative effect on survival and quality of life of patients with severely impaired left ventricular function treated by means of coronary artery bypass grafting alone.
Lam and coworkers ⁶	Moderate ischemic mitral regurgitation does not reliably resolve with coronary artery bypass grafting surgery alone and is associated with reduced survival. Therefore a mitral valve procedure might be warranted for such patients presenting for coronary artery bypass grafting.

but did not have MR. The presence of moderate MR had a significantly negative effect on survival and NYHA functional class (Table 1). The same results were published by the Cleveland Clinic group.⁶ The presence of moderate ischemic MR showed a negative effect on survival among propensity-matched patients who underwent CAB (210

matched pairs, Table 1). These studies (by inference), as well as the present work of Dr Fattouch and colleagues, seem to indicate that restrictive annuloplasty in patients with moderate ischemic MR and LV dysfunction improves long-term survival and functional status and prevents the remodeling process.

STATISTICAL PITFALLS

The results of this first prospective randomized study are compelling, and intuitively, I tend to agree with their conclusions. There are, however, several statistical pitfalls in their study that significantly downgrade its scientific value.

The title of the paper refers to a "Prospective, randomized, double blinded study." I agree that the study is prospective and randomized, but it cannot be double blind. It is very difficult to perform a double-blind study when a surgical procedure is involved. The surgeon was not blinded because he knew whether the patient was going to have a ring. The cardiologist who did the echocardiographic follow-up knew which patient had a ring and which did not because he could see the mitral ring in the echocardiogram. Finally, the patients were not blinded because they needed to be told whether they had a prosthetic device in their heart.

Second, why did the author pick 50 patients in each group? Did they do a power analysis? A randomized trial with 50 patients per group is underpowered for overall survival at a 5-year period.

Finally, the use of the *t* test for comparison at follow-up on the grades of MR by means of echocardiographic analysis and on NYHA class is inappropriate because of comparison of different grades of MR (I+ to 4+) and different NYHA

classes. A Wilcoxon rank sum test would have been more appropriate. There are other statistical issues related to the small number of patients in each group. It would have also been interesting to check the basic natriuretic peptide levels and correlate them with the clinical status of the patients.

Despite these statistical pitfalls, the results of the study are compelling: patients with moderate chronic MR and LV dysfunction treated with revascularization and restrictive mitral annuloplasty have a reverse remodeling process with excellent 5-year survival, elimination of MR, near normalization of LV function, normalization of pulmonary artery pressures, and normalization of functional class with normal exercise tolerance. Confirmation of these findings in future studies is necessary to validate this potentially landmark work.

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