Predictors of Improvement of Unrepaired Moderate Ischemic Mitral Regurgitation in Patients Undergoing Elective Isolated Coronary Artery Bypass Graft Surgery

Martin Penicka, MD, PhD; Hana Linkova, MD; Otto Lang, MD, PhD; Richard Fojt, MD; Viktor Kocka, MD; Marc Vanderheyden, MD; Jozef Bartunek, MD, PhD

Background—The persistence of moderate ischemic mitral regurgitation (IMR) after isolated coronary artery bypass graft surgery is an important independent predictor of long-term mortality. The aim of the present study was to identify predictors of postoperative improvement in moderate IMR in patients with ischemic heart disease undergoing elective isolated coronary artery bypass graft surgery.

Methods and Results—The study population consisted of 135 patients with ischemic heart disease (age, 65±9 years; 81% male) and moderate IMR undergoing isolated coronary artery bypass graft surgery. Fourteen patients died before the 12-month follow-up echocardiography and were excluded. At the 12-month follow-up, 57 patients showed no or mild IMR (improvement group), whereas 64 patients failed to improve (failure group). Before coronary artery bypass graft surgery, the improvement group had significantly more viable myocardium and less dyssynchrony between papillary muscles than the failure group (P<0.001). All other preoperative parameters were similar in both groups. Large extent (>5 segments) of viable myocardium (odds ratio, 1.45; 95% confidence interval, 1.22 to 1.89; P<0.001) and absence (<60 ms) of dyssynchrony (odds ratio, 1.49; 95% confidence interval, 1.29 to 1.72; P<0.001) were independently associated with improvement in IMR. The majority (93%) of patients with viable myocardium and an absence of dyssynchrony showed an improvement in IMR. In contrast, only 34% and 18% of patients with dyssynchrony and nonviable myocardium, respectively, showed an improvement in IMR, whereas 32% and 49%, respectively, of these patients showed worsening of IMR (P<0.001).

Conclusion—Reliable improvement in moderate IMR by isolated coronary artery bypass graft surgery was observed only in patients with concomitant presence of viable myocardium and absence of dyssynchrony between papillary muscles. (Circulation. 2009;120:1474-1481.)

Key Words: cardiopulmonary bypass ■ hibernation ■ mitral valve ■ regurgitation ■ remodeling

Persistent moderate ischemic mitral regurgitation (IMR) after isolated coronary artery bypass graft (CABG) surgery is associated with poor prognosis.1 However, optimal interventional management is still under discussion. Randomized data on the benefit of restrictive annuloplasty at the time of CABG are lacking, and results of observational studies on the survival benefit are not consistent.2-6 Nevertheless, restrictive mitral valve annuloplasty at the time of CABG has become the recommended approach for the surgical management of patients presenting with severe preoperative IMR.7,8 Whether the same recommendation should be applied in patients with moderate perioperative IMR is controversial. The ambiguity relates to the higher perioperative mortality compared with isolated CABG.2 On the other hand, IMR may improve by CABG alone,2,9 and no reliable predictors of IMR improvement after isolated CABG have been identified. Accordingly, the aim of the present study was to identify preoperative predictors of unrepaired moderate IMR improvement in patients with ischemic heart disease undergoing elective CABG as the sole surgical procedure.

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Methods

Patients
Between February 2002 and June 2003, 1412 patients underwent CABG in 2 participating institutions. Overall indications for CABG were as follows. All patients with angina were considered eligible for surgery. In case of heart failure symptoms or in asymptomatic patients, the decision to perform CABG surgery was guided by the

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extent of coronary artery disease. All patients with left main or proximal 3-vessel disease were considered eligible for myocardial revascularization regardless of viability status. The study population consisted of 135 consecutive patients (age, 65±9 years; 81% male) with ischemic heart disease and moderate IMR referred electively for isolated CABG who met the following criteria: stable left ventricular (LV) dysfunction with an LV ejection fraction ≤45% for at least 3 months and stable moderate (vena contracta width, 0.3 to 0.7 cm; ratio of jet area to left atrial [LA] area, 20% to 40%) IMR on 2 different examinations performed at least 1 month apart during stable conditions. In the presence of qualifying LV dysfunction, an additional 2 criteria were required to diagnose IMR: the presence of apical displacement of mitral leaflets and the absence of organic leaflet lesions. Assessment of myocardial viability was not used for patient selection.

Patients with unstable clinical conditions, overt heart failure during the 30-day period before CABG, acute coronary syndrome in the previous 3 months, concomitant organic mitral valve lesions, or significant aortic valvular disease were excluded from the study. All patients included in the study had CABG as the sole procedure. No patients underwent concomitant LV remodeling, aneurysctomy, mitral valve repair, or the Maze procedure. The study was approved by the ethics committee of each institution. All patients gave written informed consent before participation in the study.

Study Protocol
Preoperative clinical characteristics were collected prospectively before CABG. In the week leading up to CABG, each patient underwent echocardiography, including tissue Doppler imaging (TDI), to assess mitral regurgitation, LV volumes, LV ejection fraction, and dyssynchrony between papillary muscles. Additionally, single-photon emission computed tomography (SPECT) was used to access myocardial perfusion (technetium-99m tetrofosmin) and glucose uptake (F18-fluorodeoxyglucose). At 12 months after surgery, echocardiography was repeated. Thereafter, patients were followed up clinically.

Echocardiography and TDI
All studies were performed with a commercially available system equipped with TDI. LV volumes and ejection fractions were assessed in apical 4-chamber and 2-chamber views with the biplane Simpson’s method. TDI was performed in pulsed-wave mode.14 In brief, in 3 apical views (4-, 3-, and 2-chamber views), longitudinal myocardial velocities were recorded in the 4 mid-LV segments (lateral, posterior, anterior, and inferior). The segments adjacent to the papillary muscles were noted. The sample volume was placed in the region of insertion of the papillary muscle within the midventricular segment. Gain and filters were adjusted to obtain an optimal tissue signal. Myocardial velocities were recorded at end expiration at a sweep speed of 100 mm/s. All studies were stored in digital format for offline analysis. The mean from at least 3 consecutive beats was taken for each measurement.

Assessment of IMR and Mitral Valve Deformation
All measurements were performed in the apical 4-chamber view. At baseline, IMR was evaluated by measuring the width of the vena contracta and the ratio of the IMR color flow jet area to the LA area. At 12 months after surgery, the assessment of the IMR jet area to LA area was repeated to evaluate the IMR change from baseline. The severity of IMR was graded as mild (ratio of jet area to LA area <20%), moderate (ratio of jet area to LA area, 20% to 40%), or severe (ratio of jet area to LA area >40%).8,12 Intraobserver and interobserver variabilities relative to assessment of ratio of jet area to LA area were 9.3% (2.7% units) and 10.8% (3.1% units), respectively.

The mitral valve tenting area was measured at midsystole as the area enclosed between the annular plane and mitral leaflets.13 Displacement of mitral coaptation (coaptation height) toward the LV apex was measured as the distance between leaflet coaptation and the mitral annulus plane.13 The posterior leaflet angle was calculated according to the previously described formula:13 PLA = sin⁻¹(CD/PLL), where PLA is the posterior leaflet angle, CD is the coaptation distance, and PLL is the posterior leaflet length. Mitral annulus diameter was measured at end diastole. LA area was measured with 2-dimensional planimetry.

Assessment of Dyssynchrony Between the Papillary Muscles by TDI
To assess dyssynchrony between papillary muscles, the time delay between the onset of the QRS complex on the surface ECG and the onset of the systolic velocity wave on the TDI recording was assessed in the lateral, posterior, anterior, and inferior mid-LV segments (Figure 1). The segments adjacent to the papillary muscles were used for assessment of dysynchrony; the lateral (71%) or anterior (29%) segment was used for the anterior papillary muscle, and the inferior (82%) or posterior (18%) segment was used for the posterior papillary muscle. Dyssynchrony was calculated as the difference between the time delay in the 2 segments adjacent to the papillary muscles.14,15

Assessment of Viability by SPECT
In brief,11 technetium-99m tetrofosmin (600 MBq) was injected intravenously to evaluate resting perfusion. After a light meal and administration of acipimox, F18-fluorodeoxyglucose (185 MBq) was injected intravenously to assess myocardial glucose uptake. Dual-isotope simultaneous image acquisition was performed 45 minutes after F18-fluorodeoxyglucose injection with high-energy 511-keV collimators. The images were displayed as polar maps, which were normalized to maximum activity (set at 100%). To assess myocardial viability, polar maps were divided into 16 segments. Segments showing normal perfusion of technetium-99m tetrofosmin and segments with perfusion defects but preserved or increased F18-fluorodeoxyglucose (perfusion-metabolism mismatch) were considered viable. Segments with concordantly reduced perfusion and metabolism were considered nonviable.

Statistical Analysis
Data are presented as mean±SD or median and interquartile range. The 2-sided paired and unpaired Student t test or Pearson correlation coefficient was used as appropriate. The Fisher exact test was used to compare categorical variables in 2×2 contingency tables. In cases when the contingency table had ≥2 rows or 2 columns, the χ² test was used. Multiple stepwise regression analysis was used to define independent predictors of IMR improvement. IMR improvement was defined by a decrease in IMR to trace or mild at the 12-month follow-up. This multiple analysis comprised the preoperative clinical, echocardiographic, and SPECT parameters listed in Tables 1 and 2. Of these variables, only the dysynchrony between papillary muscles and the number of dysfunctional viable segments were independent predictors of IMR improvement. Sensitivity, specificity, and positive and negative predictive values were calculated for these important predictors only. Cumulative survival curves for the composite of death resulting from any cause and hospitalization for worsening heart failure were derived according to the Kaplan–Meier method, and differences between curves were analyzed by log-rank statistics. For all tests, values of P<0.05 were considered significant. All analyses were conducted with SPSS software (version 13).

Results
Six patients (4.4%) died perioperatively of pump failure leading to low-output syndrome, multiorgan failure (n=5), or sepsis (n=1). An additional 8 patients (6.2%) died during the 12 months after CABG. The causes of deaths were cardiovascular in all patients (3 sudden cardiac and 5 pump failure deaths). The remaining 121 patients underwent 12-month follow-up echocardiography and were included in the analysis. At the 12-month follow-up, 57 patients showed either no or mild IMR (improvement group). In contrast, 64 patients...
failed to improve in degree of IMR (failure group). The failure group consisted of 30 patients who showed no change and 34 patients who showed deterioration in their IMR degree. All preoperative clinical characteristics were similar between groups (Table 1). Complete revascularization of all stenosed lesions of major coronary arteries (left main, left anterior descending, left circumflex, and right coronary arteries) was achieved in 83% of patients.

Table 2 shows preoperative and 12-month follow-up SPECT and echocardiographic data for both groups. Blood pressure and heart rate were similar at baseline and the 12-month follow-up echocardiography. At baseline, patients with postoperatively improved IMR had significantly more viable myocardium and less dyssynchrony between papillary muscles than patients without postoperative IMR improvement ($P<0.001$). All other parameters, including degree of LV remodeling and indexes of mitral valve deformation, were similar in both groups. At the 12-month follow-up, the improvement group showed significant reverse LV remodeling with a concomitant decrease in mitral valve deformation. In contrast, in the failure group, no significant reverse LV remodeling was observed, and mitral valve deformation indexes remained elevated at preoperative levels. At the 12-month follow-up, dyssynchrony between papillary muscles was 3.4 times higher in the failure than in the improvement group.

### Predictors of Improvement in IMR

The number of dysfunctional viable segments and the preoperative dyssynchrony between papillary muscles were the most accurate in identifying patients with improved IMR (Figure 2). Preoperative dyssynchrony between papillary muscles <60 ms showed the best ability to identify IMR improvement, with a positive predictive value of 89% and a negative predictive value of 85% (Figures 2 and 3). The number of dysfunctional viable segments with a cutoff value of ≥5 segments showed a lower accuracy.

Table 3 shows patients divided into 3 groups according to the presence (≥5 segments) or absence (<5 segments) of significant myocardial viability and the presence (≥60 ms) or absence (<60 ms) of significant dyssynchrony between papillary muscles before CABG. Table 3 also describes the myocardial viability status in segments adjacent to both papillary muscles.
Discussion

In the present study, we sought to investigate preoperative predictors of moderate IMR improvement after isolated
CABG. The major findings can be summarized as follows. First, before CABG, the large amount of viable myocardium and the absence of dyssynchrony between the papillary muscles are main independent predictors of long-term IMR improvement after isolated CABG (reduction in IMR was related to reverse LV remodeling with a concomitant decrease in mitral valve deformation indexes). Second, the behavior of moderate IMR after CABG alone may be accurately predicted from the assessment of myocardial viability and dyssynchrony between papillary muscles before CABG. Third, improvement in IMR was associated with improved long-term prognosis, whereas persistence or deteriorating IMR suggests a poor prognosis. Thus, assessment of myocardial viability and dyssynchrony provides a basis for clinical decision making as to whether mitral valve repair should be performed at the time of surgical revascularization in patients with moderate IMR referred for elective CABG.

**Surgical Management of IMR**

IMR is highly prevalent in patients undergoing CABG, and its presence is associated with worse long-term survival independently of other baseline characteristics and degree of LV dysfunction.1,5,7,8,16 Because severe IMR is not usually improved by revascularization alone,17–19 current expert consensus7,8 recommends concomitant restrictive annuloplasty at the time of CABG. On the other hand, in patients with moderate IMR undergoing CABG, the indication for concomitant mitral valve repair is highly controversial. Patients with unrepaired moderate IMR have greater early and long-term mortality than similar patients without IMR.1,20 Likewise, many patients show progression of IMR during follow-up despite revascularization.20 Our study corroborated these findings; persistent IMR after CABG was associated with poor long-term outcomes, and 28.1% of patients had deterioration of their unrepaired IMR during follow-up. Hence, one

**Table 3. Relationship Between Myocardial Viability, Dyssynchrony Between Papillary Muscles, and Degree of IMR at the 12-Month Follow-Up**

<table>
<thead>
<tr>
<th>Improvement Group</th>
<th>Failure Group</th>
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<tbody>
<tr>
<td></td>
<td>No or Mild IMR at Follow-Up (n=57), n (%)</td>
</tr>
<tr>
<td>≥5 Viable segments and APM-PPM dyssynchrony &lt;60 ms (n=41)</td>
<td>38 (93)</td>
</tr>
<tr>
<td>Viability in segments adjacent to papillary muscles</td>
<td></td>
</tr>
<tr>
<td>Both PM/1 PM/0 PM</td>
<td>19 (50)/13 (34)/19 (16)</td>
</tr>
<tr>
<td>≥5 Viable segments and APM-PPM dyssynchrony ≥60 ms (n=29)</td>
<td>10 (34)</td>
</tr>
<tr>
<td>Viability in segment adjacent to papillary muscles</td>
<td></td>
</tr>
<tr>
<td>Both PM/1 PM/0 PM</td>
<td>6 (60)/2 (20)/2 (20)</td>
</tr>
<tr>
<td>&lt;5 Viable segments (n=51)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Viability in segment adjacent to papillary muscles</td>
<td></td>
</tr>
<tr>
<td>Both PM/1 PM/0 PM</td>
<td>6 (67)/2 (22)/1 (11)*</td>
</tr>
</tbody>
</table>

PM indicates papillary muscle.

*P<0.001 improvement vs failure group (χ² test).
might presume that, in patients with moderate IMR, mitral valve repair combined with CABG will improve the patient’s prognosis. However, in these patients, several recent studies have failed to demonstrate a long-term survival benefit of the combined procedure compared with CABG alone.2,3,5,17,21 These surprising findings may be attributed partly to the high recurrence rate of IMR despite initially successful repair and higher perioperative mortality of the combined procedures compared with CABG alone.2,3,13,17,19,22–24 Furthermore, some studies have shown significant improvement in moderate IMR with CABG alone.2,9 This suggests that, in selected patients with moderate IMR, CABG alone may be sufficient to improve IMR and patient outcomes without adding significant perioperative risk associated with concomitant mitral valve repair.

Myocardial Viability and Dyssynchrony in Patients Undergoing CABG

Several studies have demonstrated that the presence of significant myocardial viability is closely related to the recovery of LV contractile function and favorable long-term outcomes after CABG.25,26 Campwala et al27 observed a close association between regression of IMR after CABG and reverse LV remodeling, suggesting an essential role of myocardial viability. In the present study, reduced IMR was paralleled by reverse LV remodeling with associated improvement in mitral valve geometry. This suggests that LV functional recovery of viable myocardium is necessary to restore mitral valve function. Previous articles28–32 demonstrated that local LV remodeling with apical and posterior displacement of papillary muscles is one of the major determinants of the degree of IMR independently of global LV remodeling. Corroborating these findings, this study showed that the presence of viability in the segments adjacent to papillary muscles is very important for reducing IMR. The likely explanation is local reverse LV remodeling with amelioration of the displacement of papillary muscles and reduction in mitral valve tenting area.

Onset of LV dyssynchrony is a marker of advanced cardiac dysfunction and carries an unfavorable prognosis for patients with heart failure.33 Resynchronization of LV contractions by revascularization or by biventricular pacing is associated with improved survival paralleled by reverse LV remodeling and a reduction in mitral regurgitation.11,14,34–36 Several studies demonstrated that reverse LV remodeling and resynchroniza-

<table>
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<tr>
<th>Table 4. Clinical Outcome in Patients Who Survived the First 12 Months After CABG and Underwent Follow-Up Echocardiography</th>
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<tr>
<td>NYHA class</td>
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<tr>
<td>NYHA class</td>
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<tr>
<td>Improved by CABG, n (%)</td>
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<tr>
<td>Late all-cause mortality, n (%)</td>
</tr>
<tr>
<td>Heart failure hospitalization, n (%)</td>
</tr>
<tr>
<td>Composite of all-cause mortality and heart failure hospitalization, n (%)</td>
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</table>

NYHA indicates New York Heart Association. *P<0.05, †P<0.01, ‡P<0.001 versus improvement group.

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The mild IMR at the 12-month follow-up was considered the optimal result. A recent study by Lancellotti et al38 evaluated. Hence, the methodology used to assess IMR is not likely to hamper the interpretation of results significantly.

Limitations

The accuracy of IMR assessment could be increased by assessment of the effective regurgitant orifice area with the proximal isovelocity surface area method. However, in the present study, IMR was assessed by an experienced echocardiographer using 2 alternative methods. Blood pressure and heart rate during both the pre-CABG and 12-month follow-up examinations were similar. The variability of measurement of applied indexes was low. Moreover, the change in degree of IMR rather than absolute value of regurgitant volume was evaluated. Hence, the methodology used to assess IMR is not likely to hamper the interpretation of results significantly.

The mild IMR at the 12-month follow-up was considered the optimal result. A recent study by Lancellotti et al38...
demonstrated that a significant exercise-induced increase in IMR is associated with poor outcome. One may assume that, in patients with moderate IMR, performing an exercise test may help determine the optimal therapeutic strategy.

Magne et al. demonstrated that severe restriction of posterior leaflet (posterior leaflet angle $\geq 45^\circ$) was associated with persistent IMR after repair. In the present study, this parameter failed to predict IMR behavior after isolated CABG. Of note, our patients showed a smaller average value of the posterior leaflet angle than patients with persistent IMR in the study of Magne et al. ($41^\circ$ vs $52^\circ$). This finding suggests that patients with the most distorted mitral valve configuration were not included in the present study. Hence, patients with severe restriction of the posterior leaflet may be considered candidates for concomitant mitral valve repair regardless of their viability and dyssynchrony status.

Conclusions

IMR is caused by disease of the left ventricle with secondary distortion of mitral valve geometry. Hence, causal therapy to manage IMR should primarily address the underlying mechanism leading to the disease of the left ventricle as opposed to systemic placement of a mitral annular ring in the dilated left ventricle. In the present study, reliable improvement in moderate IMR by CABG alone was observed only in patients with concomitant presence of viable myocardium and absence of dyssynchrony between papillary muscles. This finding suggests that recovery of LV function by revascularization of viable myocardium or resynchronization of contractions between the papillary muscles through biventricular pacing may be the optimal therapy for addressing the mechanism underlying IMR (ie, disease of the left ventricle). Thus, pre-CABG assessment of myocardial viability and dyssynchrony may be useful in identifying patients who stand to benefit from isolated CABG in terms of both improved IMR and long-term outcome.

Source of Funding

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Disclosures

None.

References

In this study, we sought to investigate preoperative predictors of moderate ischemic mitral regurgitation (IMR) improvement after elective isolated coronary artery bypass graft (CABG) surgery. The persistence of moderate IMR after isolated CABG surgery is an important independent predictor of long-term mortality. However, mitral valve repair at the time of CABG surgery does not appear to improve survival. In contrast, concomitant mitral valve repair is associated with increased perioperative risks compared with CABG alone. Hence, the optimal surgical management of patients with moderate IMR undergoing CABG surgery is unclear. In the present study, the presence of significant myocardial viability and the absence of dyssynchrony between papillary muscles were major independent predictors of long-term IMR improvement after isolated CABG surgery. Moreover, patients with IMR improvement also showed improved survival compared with patients who failed to improve. IMR is caused by disease of the left ventricle with a secondary distortion of mitral valve geometry. This suggests that recovery of left ventricular function by revascularization of viable myocardium or resynchronization of contractions between the papillary muscles through biventricular pacing may be the optimal therapy addressing the underlying IMR mechanism, ie, disease of the left ventricle. Thus, assessment of myocardial viability and dyssynchrony may provide a basis for clinical decision making as to whether to perform mitral valve repair at the time of surgical revascularization in patients with moderate IMR referred for elective CABG surgery.

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