

# Low-dose dobutamine stress echocardiography cannot predict mitral regurgitation reversibility after coronary artery bypass grafting

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**Background:** The ideal management of ischemic mitral regurgitation (MR) remains a clinical dilemma because of the suboptimal available therapeutic options. Recently, new concepts have emerged, pointing to the benefits of a patient selection approach when debating the management of moderate ischemic MR. We investigated the predictability of low-dose dobutamine stress echocardiography (DSE) in selecting candidates for CABG with moderate MR for valve repair.

**Methods:** From November 2002 to May 2010, 110 candidates for first-time CABG, who were admitted to the cardiac surgery department in Day General Hospital (Tehran, Iran), were enrolled in the present cross-sectional study. DSE was performed for each case before CABG. Those with positive findings underwent CABG alone and those with negative results underwent concomitant CABG and mitral valve repair. The patients were followed up for a minimum of 60 months.

**Results:** Of the 110 patients, 47 (42.72%) had positive test results and underwent CABG alone and 63 (57.28%) had negative DSE results and underwent concomitant CABG and mitral valve repair. The MR degree had decreased from  $2.8 \pm 0.3$  preoperatively to  $1.46 \pm 0.6$  early during the hospital stay and  $1.9 \pm 0.7$  during late follow-up in the CABG group. It had decreased from  $2.84 \pm 0.4$  preoperatively to  $0.93 \pm 0.65$  postoperatively but then increased to  $1.41 \pm 0.9$  during late follow-up, for a significant decrease in the combined group ( $P < .05$ ).

**Conclusions:** Despite its utility in selecting CABG patients with moderate ischemic MR for valve repair from a short-term perspective, the use of DSE cannot predict the long-term outcomes of these patients. (J Thorac Cardiovasc Surg 2014;148:1323-7)

Ischemic mitral regurgitation (IMR) occurs as a result of ischemia-induced mitral valve functional insufficiency.<sup>1,2</sup> Despite advances in the management of IMR, it has proved to be adversely associated with survival, even in mild to moderate severity.<sup>2-5</sup> In addition, the prevalence of IMR subsequent to myocardial infarction has been reported to be 20% to 40%.<sup>2,6,7</sup> With the large number of patients experiencing myocardial infarction, IMR has continued to impose a huge burden on the healthcare system.<sup>2,4,7,8</sup>

The ideal management of IMR remains a clinical dilemma because of the suboptimal available therapeutic options.<sup>9-13</sup> Because the long-term prognosis of uncorrected IMR has been documented to be poor,<sup>10,14</sup> some investigators have

proposed surgical correction of IMR, using either repair or replacement, concurrent with coronary artery bypass grafting (CABG).<sup>10,12,15-18</sup> However, the greater morbidity and mortality of a combined approach has kept surgeons from widely performing such a correction technique for moderate IMR.<sup>4,19-23</sup>

Recently, attention has been given to a selection approach in the management of simultaneous coronary artery diseases and moderate IMR.<sup>1,24,25</sup> The selective approach is used preoperatively to measure the probability of IMR reversibility after CABG.<sup>26,27</sup>

To determine which patient with moderate IMR will benefit from intervening on the mitral valve and which patient should undergo CABG alone, we previously reported on the valuable utility of low-dose dobutamine stress echocardiography (DSE) in selecting patients who would be undergoing CABG to receive concurrent mitral valve repair.<sup>26</sup> In a continuation of that study, we investigated the benefits of DSE in predicting the long-term outcomes.

## METHODS

### Study Population

From November 2002 to May 2010, 110 candidates for first-time CABG, who had been admitted to the cardiac surgery department in Day General Hospital (Tehran, Iran), were consecutively enrolled in the present cross-sectional study. The inclusion criteria were candidacy for CABG and

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### Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
DSE	= dobutamine stress echocardiography
EF	= ejection fraction
IMR	= ischemic mitral regurgitation
MR	= mitral regurgitation

the presence of grade 2 and 3 (referred to as moderate) functional MR on a scale of 1 to 4, using quantitative echocardiography, measured by 2 independent cardiologists, who were unaware of the study protocol. Patients with structural MR, including a ruptured chordae tendinea or papillary muscle, abnormal leaflet thickening, annular calcification, and ventricular aneurysms or other congenital or acquired valvular diseases, and those considered for other concomitant surgical procedures were excluded from the present study.

The institutional review board of Day General Hospital approved the study protocol on human subjects, and each patient provided informed consent before enrollment in the present study.

### Dobutamine Stress Echocardiography

Dobutamine was infused at doses of 2.5, 5.0, 7.5, and 10.0  $\mu\text{g}/\text{kg}/\text{min}$  after the echocardiogram at rest was finished. The patients were closely monitored by their physician during the dobutamine infusion for any symptoms of distress. The DSE findings were considered positive if echocardiographic MR had decreased in response to the dobutamine infusion and negative if the degree of MR had remained unchanged or had increased.

DSE-positive patients were assigned to the CABG-alone group, with no additional procedure on the valves. The DSE-negative patients underwent concomitant CABG and mitral valve repair.

### Preoperative Echocardiography

The patients underwent the echocardiographic assessment in a left lateral decubitus position with a multifrequency phased-array probe (VIVID 7, GE Medical Systems, Little Chalfont, UK; and iE33, Philips Medical Systems, Best, The Netherlands) before and after dobutamine infusion in an at rest and stress status, respectively, to assess the myocardial viability and severity of MR. The instrument settings were kept constant during all echocardiographic studies. The settings included the rate of pulse repetition, transducer frequencies, and optimal gain. The optimal gain for intracardiac blood flow imaging and the detection of the extension area related to the regurgitant signals was adjusted to the level at which the background noise began to faintly appear.

The digital recording of each echocardiography was analyzed for segmental wall motion abnormality using the American Society of Echocardiography 16-segment convention by 2 independent observers who were unaware of the purpose of the study. The ejection fraction (EF) was measured using the modified biplane Simpson method. MR was graded using a combination of quantitative and qualitative variables, including color Doppler jet characteristics, width and area of the jet, continuous wave Doppler intensity, shape of the spectral recording, mitral inflow and evaluation of pulmonary vein flow, using the proximal isovelocity surface area method, and calculation of the effective regurgitant orifice area, regurgitant volume, and regurgitant fraction. Two independent observers reached a consensus in the analysis of all the recordings.

### Operation Technique

The left internal mammary artery for the left anterior descending artery and a greater saphenous vein graft for other involved coronary arteries were harvested and distally anastomosed after a full midline sternotomy. The cardiopulmonary circulation was bypassed, along with preservation of

the myocardium by administration of iced saline to provide topical and systemic hypothermia to 28°C. According to the assigned treatment group, concomitant CABG and valve repair using complete ring annuloplasty was performed. The size of the mitral annuloplasty ring (Carpentier-Edwards Physio Ring; Edwards Life Sciences, Irving, Calif) was determined by a standard measurement of the intertrigonal distance and anterior leaflet height after downsizing was performed. Finally, intraoperative transesophageal echocardiography was performed to assess the severity of MR in the surgical patients.

### Postoperative Echocardiography

The echocardiographic study was repeatedly performed for all patients 4 to 7 days and 5 to 6 months postoperatively and then annually to assess the EF, wall motion, and MR severity.

### Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences, version 16 (SPSS, Chicago, Ill). The Student *t* test was applied for a comparison of the clinical outcomes between the 2 groups. One-way repeated measurement analysis of variance was also used for the measurement of the within-subject effects for EF, MR, and New York Heart Association function class.

## RESULTS

### Patients Characteristics

A total of 110 patients were enrolled in our study. Of these 110 patients, 47 (42.72%) had DSE-related MR improvement ( $1 \pm 0.62$ ) and underwent CABG alone and 63 patients (57.28%) did not have DSE-related MR improvement ( $0.14 \pm 0.2$ ) and underwent concomitant CABG and mitral valve repair. The mean  $\pm$  standard deviation duration of follow-up was  $81.5 \pm 17.7$  and  $77.5 \pm 19.2$  months in CABG and combined groups, respectively. The demographics and primary characteristics of the study patients are listed in Table 1. No significant difference was found between the 2 groups in terms of the primary characteristics ( $P > .05$ ).

### Echocardiographic Evaluation

Regarding the echocardiographic features for the patients undergoing CABG or concomitant CABG and valve repair, the size of the annulus was  $37.70 \pm 3.78$  mm in group 1 and  $37.30 \pm 3.97$  mm in group 2, which was not a statistically significant difference ( $P > .05$ ). The effective regurgitant orifice area had a mean  $\pm$  SD of  $28.83 \pm 5.57$   $\text{cm}^2$  in group 1 and  $28.90 \pm 5.83$   $\text{cm}^2$  in group 2, with no significant differences ( $P > .05$ ). The mean  $\pm$  SD coaptation depth was measured at  $7.77 \pm 1.02$  mm in group 1 and  $7.76 \pm 0.91$  mm in group 2, with no significant difference ( $P > .05$ ). In addition, the MR degree did not differ significantly ( $P > .05$ ) between groups 1 and 2 (mean  $\pm$  SD of  $2.87 \pm 0.33$  and  $2.84 \pm 0.36$ , respectively). The EF for the 110 patients was a mean  $\pm$  SD of  $39.04\% \pm 5.95\%$  in group 1 and  $40.95\% \pm 5.59\%$  in group 2. The difference was also not statistically significant ( $P > .05$ ). The left ventricular end-diastolic and end-systolic volume was  $140.72 \pm 33.37$  mL and  $90.23 \pm 21.05$  mL in group 1

**TABLE 1. Demographic and clinical patient characteristics**

Characteristic	CABG group (n = 48)	Combined group (n = 62)	P value
Age (y)	56.9 ± 10.1	58.4 ± 9.3	.45
Gender (n)			.15
Male	33	52	
Female	14	11	
Follow-up duration (mo)	81.5 ± 17.7	77.5 ± 19.2	.30
DM (%)	36.2	27	.35
HLP (%)	68.1	58.7	.20
HTN (%)	53.2	46.0	.50
NYHA functional class	2.87 ± 0.6	2.70 ± 0.5	.10
Graft vessel (n)	3.2 ± 1.2	3.3 ± 1.1	.70

CABG, Coronary artery bypass grafting; DM, diabetes mellitus; HLP, hyperlipidemia; HTN, hypertension; NYHA, New York Heart Association.

and 139.21 ± 29.62 mL and 90.29 ± 21.90 mL in group 2, respectively, with no significant differences. The echocardiographic features of the patients before surgery are listed in Table 2.

### Follow-up Reassessment

During the follow-up period, the patients were assessed at 3 intervals: preoperatively, early postoperatively, and later, at the end of the study period. At these intervals, the MR, EF, and function class were assessed.

### MR Severity

The MR severity decreased from 2.87 ± 0.3 preoperatively to 1.46 ± 0.62 at early postoperatively and 1.91 ± 0.70 at late follow-up for the patients in the CABG-alone group. The MR severity decreased from 2.84 ± 0.36 preoperatively to 0.93 ± 0.65 at early postoperatively and 1.41 ± 0.89 at late follow-up in combined group. The decrease in MR severity was significantly greater in group 2 (combined group) than in group 1 (CABG alone;  $P < .05$ ).

### EF Improvement

The EF was 39.04% ± 5.95% preoperatively, 42.91% ± 5.79% early postoperatively, and 43.93% ± 6.10% at late

**TABLE 2. Comparison of echocardiographic parameters between groups**

Variable	CABG group (n = 48)	Combined group (n = 62)	P value
Annulus size (mm)	37.7 ± 3.8	37.30 ± 3.9	.60
Effective regurgitant orifice area (cm <sup>2</sup> )	28.8 ± 5.6	28.90 ± 5.9	.95
Coaptation depth mm	7.77 ± 1	7.76 ± 0.9	.98
MR (mean)	2.87 ± 0.3	2.84 ± 0.4	.65
EF (%)	39.04 ± 5.9	40.95 ± 5.6	.10
LVEDV (mL)	140.72 ± 33.4	139.21 ± 29.6	.80
LVESV (mL)	90.23 ± 21	90.29 ± 21.9	.99
Dobutamine-induced MR improvement	0.14 ± 0.2	1 ± 0.62	<.01

Data presented as mean ± standard deviation. CABG, Coronary artery bypass grafting; MR, mitral regurgitation; EF, ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.

follow-up in group 1 and 40.95% ± 5.59% preoperatively, 45.74% ± 4.64% early postoperatively, and 48.10% ± 3.60% at late follow-up in group 2. The improvement was significantly better in group 1 than in group 2 ( $P < .05$ ).

### Improvement in Function Class

The functional class in the group 1 patients changed from 2.87 ± 0.61 preoperatively to 1.38 ± 0.49 at late follow-up compared with a change from 2.70 ± 0.55 preoperatively to 1.41 ± 0.53 at late follow-up for group 2. This difference was not statistically significant ( $P > .05$ ).

### DISCUSSION

It has been well described that the reversibility of IMR depends on the underlying mechanism that has evoked the functional insufficiency of the mitral valve.<sup>13,28-30</sup> If the disease has occurred because of rupture of a papillary muscle or chordae, the repair will result in improvement of valve function.<sup>12,16</sup> However, IMR develops more probably as a result of ventricular dysfunction affected by impairment in the coronary artery circulation.<sup>1</sup> By a similar rationale, it would be expected that IMR would resolve to some extent by improving the coronary artery perfusion to the ventricular myocardium.<sup>10</sup>

The surgical management of IMR comprises CABG alone for revascularization of the ischemic myocardium and mitral valve replacement or additional techniques of valve repair concomitant with CABG.<sup>1,21,23,24,31</sup> In contrast to severe IMR for which concomitant CABG and valve procedures have been strongly advised,<sup>32</sup> the optimal treatment of moderate IMR is still a source of debate.<sup>1,10,18,32,33</sup> Currently, evidence supports an individualized approach in deciding the best treatment modality for each patient with moderate IMR.<sup>32,34</sup> This selective approach mainly uses the extent of damage to the mitral valve due to ischemia.<sup>1,12,16</sup> Depending on the modality used to determine the extent of the damage, patients could be selected more efficiently for concomitant valve procedures.<sup>27,35</sup> Despite the utility of Doppler color flow imaging for patient selection of operative treatment of IMR, its long-term usefulness, especially in the case of moderate IMR, has not been documented.<sup>36,37</sup> However, using preoperative and intraoperative echocardiography, mitral valve regurgitation could be accurately monitored and MR reversibility could be more reliably determined.<sup>26,27,35-38</sup>

We had previously reported on the beneficial utility of DSE in the preoperative prediction of IMR reversibility.<sup>26</sup> In that study, we showed the predictability of IMR reversibility using DSE. However, the long-term survival and recurrence of MR in the patients with unrepaired moderate IMR who had undergone CABG alone without an additional valve procedure was unclear. In the present study, we continued monitoring our patients to determine whether

TABLE 3. Comparison of outcomes between 2 groups

Variable	CABG group (n = 48)	Combined group (n = 62)	P value
MR (mean)			<.0001
Preoperative	2.87 ± 0.3	2.84 ± 0.4	
Early follow-up	1.46 ± 0.6	0.93 ± 0.6	
Late follow-up	1.91 ± 0.7	1.41 ± 0.9	
EF (%)			<.0001
Preoperative	39.04 ± 5.9	40.95 ± 5.6	
Early follow-up	42.91 ± 5.8	45.74 ± 4.6	
Late follow-up	43.93 ± 6.1	48.10 ± 3.6	
NYHA functional class			.5
Preoperative	2.87 ± 0.6	2.70 ± 0.5	
Early follow-up	2.1 ± 0.5	1.9 ± 0.4	
Late follow-up	1.38 ± 0.5	1.41 ± 0.5	

Data presented as mean ± standard deviation. CABG, Coronary artery bypass grafting; MR, mitral regurgitation; EF, ejection fraction; NYHA, New York Heart Association.

DSE would remain predictive after a longer follow-up period.

According to the results from the present study, the severity of MR decreased more significantly in patients undergoing concomitant valve repair and CABG, although the improvement in EF was more remarkable among the patients undergoing CABG alone. However, the less desirable outcomes in both groups did not lead to readmission or reoperation for MR. Stratified by the DSE findings, the patients without MR improvement during the test (CABG group) were less likely to develop improvement in the EF and MR. However, their New York Heart Association score had resolved more significantly at the late follow-up assessment. In contrast, those patients who had undergone concomitant CABG and valve repair had better improvement in the EF and a more remarkable reversal of MR, although they showed less resolution of the New York Heart Association score at the late follow-up assessment. The differences between the 2 groups with respect to EF and MR severity were less substantial in the early follow-up period than in the late-term period (Table 3). Thus, despite the predictive value of DSE in the early postoperative period, as previously reported,<sup>26</sup> its utility in predicting later outcomes is not definite. One reason for this could be the minimal difference in the EF and MR severity between the 2 groups that in the long term do not represent useful determining and predictive parameters. The MR degree in the CABG group might have improved even more if mitral repair had also been performed. Therefore, our data might suggest that mitral valve repair should be considered even with a positive viability test result, because it is possible that the outcomes might be improved even further. Moreover, the similar symptomatic status of both groups at an average of 6 years of follow-up could be misleading and could deteriorate later in the CABG-alone group with the observed poorer hemodynamic conditions.

Considering the limitations of our study, we would suggest application of 3-dimensional echocardiography and more quantitative measurement when assessing the parameters of cardiac function. Also, additional studies are needed to consider the relation between the baseline risk profile of the patients and their final outcomes and account for such an important parameter when measuring patient survival.

## CONCLUSIONS

We have concluded that the reversibility of IMR is dependant on the reduction in the underlying ischemia. However, this is true for viable ischemic myocardium in which reversal of blood flow will result in improved ventricular function and wall motion. The status of viability and its effect on the early reversibility of moderate IMR, although it can be predicted by DSE, the long-term results could be misleading.

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