Impact of Mitral Valve Regurgitation Evaluated by Intraoperative Transesophageal Echocardiography on Long-Term Outcomes After Coronary Artery Bypass Grafting

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***Background*—**It is unclear if mild or moderate mitral valve regurgitation (MR) should be repaired at the time of coronary artery bypass grafting (CABG). We sought to determine the long-term effect of uncorrected MR, measured by intraoperative transesophageal echocardiography (TEE), in CABG patients.

***Methods and Results*—**Between May 1999 and September 2003, data were gathered for 3264 consecutive patients who underwent isolated CABG and had MR graded by intraoperative TEE. MR was graded on the following 5 levels: none, trace, mild, moderate, and severe. Patients who had severe MR or who underwent mitral valve surgery were eliminated from the analysis. The remaining patients were combined into the following 3 groups: none or trace, mild, and moderate MR. Preoperative and follow-up data were 99% complete. The median length of follow-up was 3.0 years. Multivariable analysis controlling for important preoperative risk factors was performed to determine predictors of death and death/hospitalization for heart failure. Increasing MR was a risk factor for death [hazard ratio (HR), 1.44; $P<0.001$] and death/heart failure hospitalization (HR, 1.34; $P<0.01$). When patients with moderate MR were eliminated from the analysis, mild MR was a risk factor for death (HR, 1.34; $P=0.011$) and death/hospitalization for heart failure (HR, 1.34; $P<0.001$).

***Conclusions*—**Even mild MR, identified by intraoperative TEE, predicts worse outcomes after CABG. Revascularization alone did not eliminate the negative long-term effects of mild MR. CABG patients with uncorrected mild or moderate MR are at increased risk for death and heart-failure hospitalization; consideration for surgical repair or more aggressive medical management and follow-up is warranted. **(*Circulation*. 2005;112[suppl I]:I-293–I-298.)**

Key Words: CABG surgery ■ coronary artery disease ■ mitral regurgitation ■ transesophageal echocardiography

The presence of mitral regurgitation (MR) has been identified as an important independent predictor of long-term outcomes in patients with left ventricular dysfunction.[1,2] Additionally, the presence of severe MR has a negative impact on patients with ischemic heart disease. MR predicts poor long-term outcomes among patients who suffer myocardial infarction (MI) or who undergo percutaneous coronary interventions.[3–6] Trichon et al[7] suggest that, in patients with coronary artery disease, revascularization alone ameliorates some of the negative impact of MR. Despite these reports, little information is available concerning the long-term outcomes of patients with MR who undergo surgical revascularization. To address this question, we analyzed long-term outcomes of patients with uncorrected, mild, or moderate MR who underwent coronary artery bypass grafting (CABG).

The use of transesophageal echocardiography (TEE) to grade MR in all of the patients makes the current study unique. TEE has multiple advantages over other methods, such as ventriculography or transthoracic echocardiography (TTE). Despite the systemic effects of general anesthesia, intraoperative TEE can be performed with adjustment of afterload to better estimate MR severity.[8] The introduction of general anesthesia can reduce the risk of exacerbated ischemia, which can be encountered during cardiac catheterization. Additionally, during ventriculography, the catheter itself may induce artifactual MR. TTE may be compromised by poor sound transmission and limited windows. TEE provides the most precise assessment of MR.[9,10] For these reasons, TEE assessment of MR is becoming widely available in the operating room, and our institution and others have been

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.104.523472**

TABLE 1. Criteria Used for Grading of MR

MR Grade	Extent of RJ	RJA/LAA	VC Width
None/trace	Just into LA	<20%	0–1 mm
Mild	<1/3 length LA	20–40%	1–3 mm
Moderate	<2/3 length LA	20–40%	3–6 mm
Severe	>2/3 length LA	>40%	>6 mm

RJ indicates regurgitant jet; LA, left atrium; RJA, regurgitant jet area; LAA, left atrial area; VC, vena contracta.

routinely performing TEE for adult cardiac surgeries for the last several years. This report is unique in that MR is assessed in all of the patients by intraoperative TEE rather than less precise modalities.

In this study, 3264 consecutive CABG patients were followed for late outcome. All of the patients underwent intraoperative TEE, and 32.2% had mild or moderate MR. The impact of this uncorrected, mild, or moderate MR on death and the need for heart-failure hospitalization was determined using a multivariable analysis, Cox proportional hazard regression model.

Methods

Patient Selection

All of the data collection and analysis was performed with Institutional Review Board approval. Data were analyzed from 2 separate databases. The Duke Cardiovascular Databank provided prospectively collected data for patients who underwent CABG from May 1999 until September 2003.[11] If patients underwent >1 CABG during this time period, only the first operation was considered. Preoperative and follow-up data were 99% complete. Follow-up data from the Duke Cardiovascular Databank were obtained by self-administered questionnaires and telephone calls to nonresponders at 6 months after operation and yearly thereafter. If hospitalization was reported to have occurred, those records were obtained with patient consent, and the reason for the admission was ascertained. The second database consisted of intraoperative TEEs performed during CABG from May 1999 until September 2003. All of the TEEs were independently read by 1 of 2 experienced anesthesiologists certified in perioperative echocardiography. These 2 databases were merged. Patients who underwent surgical procedures in addition to CABG, such as combined CABG and mitral operations, were excluded. All of the patients that had any degree of mitral stenosis or severe MR were also excluded from the analysis.

Echocardiography

All of the intraoperative TEE examinations were performed according to prescribed guidelines.[12] Images were digitally acquired on a Philips Sonos 5500 or 7500 Ultrasound Imaging System (Philips Medical Systems) echocardiography machine and stored for offline analysis and database archiving. Only intraoperative TEEs performed before surgical revascularization were included in this study; postprocedure studies were not used. MR was graded on the following 5 levels: none, trace, mild, moderate, or severe. For the purposes of our analysis, none and trace were combined to form 1 category. The characteristics of the regurgitant jet were used to grade MR, and the specific criteria are shown in Table 1.[13] Vena contracta is defined as the narrowest portion of the regurgitant jet, seen at its origin. In all of the cases, it was assumed that the MR severity was downgraded by general anesthesia because of reduced afterload conditions. In cases where MR was determined to be trace, mild, or moderate, the afterload was manipulated by bolus injections of phenylephrine to approximate the preanesthesia, awake blood pressure. The final MR grade was assigned after this maneuver was completed. If conflicting results were observed for different criteria, the reviewing anesthesiologist made a judgment as to the final grade of MR.

Statistical Analysis

Multivariable Cox proportional hazards regression modeling was used to adjust for differences in demographic and clinical variables. Variables used in the model have been described previously and are shown in Table 2.[14–16] Comparisons among groups were made with the Mantel-Haenszel χ^2 for discrete variables and ANOVA with the Bonferroni method for continuous variables. MR was graded as none or trace (MR=0), mild (MR=1), or moderate (MR=2). Two different end points were selected for analysis: death and the composite end point of death or hospitalization for heart failure. Cox proportional hazards regression models were generated for 2 different patient cohorts (Tables 3 and 4). In the first, all of the patients who met study criteria were included; in the second, those patients with MR graded as moderate were excluded. Unadjusted survival curves were generated using the Kaplan-Meier method (Figure 1). Adjusted survival curves were generated from the Cox proportional hazards models (Figure 2). All of the analyses were performed with SAS version 8.2 (SAS Institute, Inc.).

Results

Our study cohort included 3264 consecutive patients who underwent CABG and met the study criteria. The median duration of follow-up was 3 years. Table 2 shows the demographic characteristics of each patient cohort. Of the included patients, 28.2% had mild MR, and 4.0% had moderate MR. When compared with patients with no or trace MR, those with mild or moderate MR were older, more likely to be female, and more likely to suffer from renal failure. Patients with MR had worse New York Heart Association (NYHA) functional class and lower left ventricular ejection fraction. In addition, they had a higher incidence of 3-vessel coronary artery disease and were more likely to have had a MI before surgery. Before surgery, patients with MR were more likely to have had an intraaortic balloon pump in place, and their CABG was more likely to have been done as an emergency status procedure. The 3 patient cohorts appear to have received equivalent treatments, with a similar percentage of patients undergoing off-pump CABG and all arterial grafting. Although the ratio of grafts performed to diseased vessels was statistically different when comparing the no/trace and moderate MR groups (1.18 versus 1.10, $P<0.05$, ANOVA with Bonferroni correction), the ratio was not significantly different between the no/trace and mild MR groups (1.18 versus 1.17; $P>0.05$).

These data suggest that patients with increasing degrees of MR have more comorbidities than patients without MR. Cox proportional hazards regression models were used to control for these differences in baseline characteristics. The results from these models are demonstrated in Tables 3 and 4. The most important independent predictors of death in both models (mild and moderate MR combined or mild MR alone) were renal failure, stroke, peripheral vascular disease, decreased ejection fraction, and worse NYHA functional class (Table 3). Similarly, decreased ejection fraction, renal failure, worse NYHA class, and peripheral vascular disease emerged as the most important independent predictors of the combined end points of death or the need for heart failure admission (Table 4).

TABLE 2. Demographic and Clinical Characteristics of Cohorts

Variable	All Patients (n=3264)	No/Trace MR (n=2212) (67.8%)	Mild MR (n=922) (28.2%)	Moderate MR (n=130) (4.0%)	P Value
Age (mean±SD)	63.1±10.9	61.9±10.9	65.4±10.9	66.9±11.2	<0.05
Cerebrovascular disease (%)	11.6	11.3	12.4	11.5	0.485
History of stroke (%)	8.6	8.41	9.44	6.15	0.890
Hypercholesterolemia (%)	57.1	58.5	58.9	50.8	0.018
Hypertension (%)	70.8	70.5	71.9	67.7	0.864
Diabetes (%)	34.9	35.1	34.8	32.3	0.606
Chronic obstructive pulmonary disease (%)	10.1	9.9	10.7	10.0	0.593
Smoker (%)	50.0	50.5	49.5	46.2	0.335
Peripheral vascular disease (%)	15.0	14.7	15.3	16.1	0.580
Renal failure (%)	4.3	3.6	6.1	4.6	0.009
NYHA class >II (%)	9.0	7.6	10.9	20.0	<0.0001
Ejection fraction <35% (%)	20.0	15.1	28.4	48.8	<0.0001
Re-do surgery (%)	1.8	1.6	2.2	2.3	0.235
Emergency status (%)	3.9	3.5	4.0	8.5	0.029
Preoperative IABP(%)	4.4	3.6	5.8	10	<0.0001
Gender (female) (%)	29.6	28.5	30.6	40.8	0.008
No. of diseased vessels					0.0002
One (%)	5.9	6.7	3.9	3.9	
Two (%)	17.5	18.3	16.2	10	
Three (%)	76.6	74.6	79.4	85.4	
Left main disease (%)	21.2	21.5	20.8	19.2	0.491
MI within 2 weeks (%)	20.3	17.3	25.2	37.7	<0.0001
MI, any age (%)	40.3	36.4	46.2	63.8	<0.0001
Off-Pump CABG	15.8	16.3	15.1	10	0.073
All arterial grafts	5.8	6.2	4.9	6.2	0.317
No. of grafts:No. of diseased vessels (ratio)	1.17±0.31	1.18±0.32	1.17±0.29	1.10±0.26	<0.05

IABP indicates intraaortic balloon pump.

In the first analysis, we combined mild and moderate MR as a single variable in the Cox proportional hazards regression model. When compared with patients with no or trace MR, the presence of mild or moderate MR was a significant independent predictor of death, with a hazard ratio (HR) of 1.44 (Table 3). Additionally, the presence of mild or moderate MR was also a significant predictor of worse event-free survival, as defined by either death or heart failure hospitalization, with a HR of 1.34 (Table 4).

TABLE 3. Independent Predictors of Death After CABG

	Mild/Moderate MR		Mild MR	
Variable	HR	Probability $>\chi^2$	HR	Probability $>\chi^2$
Increasing MR	1.44	<0.001	1.34	0.011
Age	1.04	<0.001	1.04	<0.001
Renal failure	2.46	<0.001	2.38	<0.001
NYHA class >II	1.63	<0.001	1.73	<0.001
Ejection fraction <35%	1.59	<0.001	1.67	<0.001
Diabetes	1.44	<0.001	1.46	<0.001
Gender	1.46	<0.001	1.41	0.003
Hypercholesterolemia	0.64	<0.001	0.66	<0.001
Stroke	3.50	0.007	3.92	0.009
Peripheral vascular disease	1.85	<0.001	1.82	<0.001
COPD	1.49	0.005	1.48	0.009

TABLE 4. Independent Predictors of Death/Hospitalization for Heart Failure After CABG

	Mild/Moderate MR		Mild MR	
Variable	HR	Probability $>\chi^2$	HR	Probability $>\chi^2$
Increasing MR	1.34	<0.001	1.34	<0.001
Age	1.03	<0.001	1.03	<0.001
Renal failure	1.90	<0.001	1.84	<0.001
NYHA class >II	1.82	<0.001	1.91	<0.001
Ejection fraction <35%	2.02	<0.001	2.07	<0.001
Diabetes	1.44	<0.001	1.45	<0.001
Gender	1.48	<0.001	1.41	0.003
Hypercholesterolemia	0.74	<0.001	0.77	0.002
Peripheral vascular disease	1.69	<0.001	1.82	<0.001
COPD	N/S	N/S	1.26	0.047

NS indicates not significant.

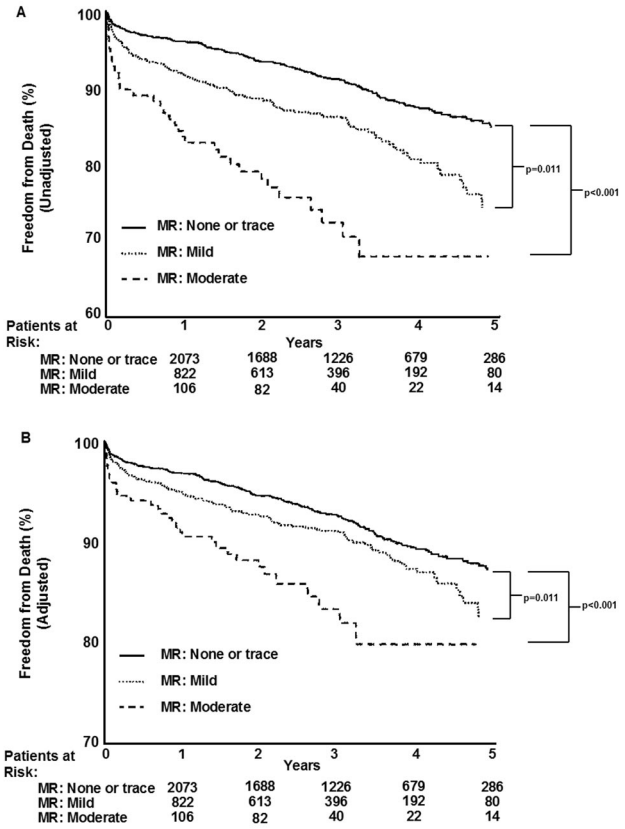

Figure 1. Unadjusted and adjusted survival estimates for the 3 patient cohorts: no/trace MR, mild MR, and moderate MR.

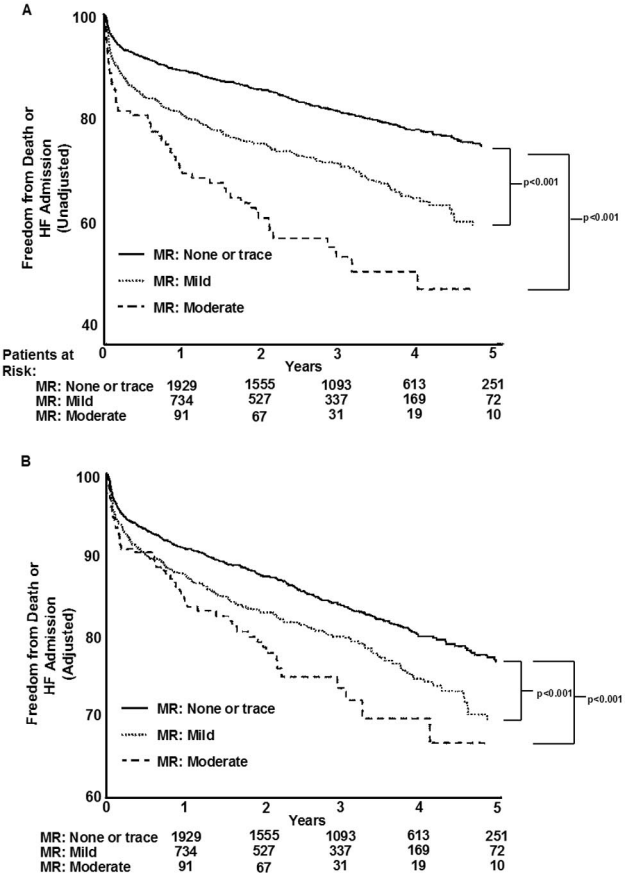

Figure 2. Unadjusted and adjusted event-free survival estimates for the 3 patient cohorts: no/trace MR, mild MR, and moderate MR.

In the second analysis, patients with moderate MR were excluded from analysis. In this model, mild MR was used as a single variable in the Cox proportional hazards regression model. When analyzed as an independent variable, mild MR predicted both death and worse event-free survival with HRs of 1.34 (Tables 3 and 4).

Although the purpose of this study was to investigate the long-term effects of any type of mild or moderate MR found by TEE at the time of CABG, we attempted to understand the effect of nonischemic, structural mitral abnormalities on the results. From the detailed echocardiographic examinations, the mitral valve leaflets were assessed. Patients with leaflet thickening, prolapse, or flail segments we identified. We identified 133 patients (6.0%) with no or trace MR, 132 patients (14.3%) with mild MR, and 36 patients (27.7%) with moderate MR with primary leaflet pathology ($P<0.001$, Mantzel-Haenszel χ^2 test). To correct for the possible effects of this identifiable leaflet pathology, we constructed a new multivariable Cox proportional hazard model in which these patients were eliminated. Interestingly, when all of the patients with identifiable leaflet pathology were eliminated from analysis, the presence of mild or moderate MR continued to be a risk factor for death (HR, 1.355; $P=0.002$) and death or heart failure hospitalization (HR, 1.258; $P=0.0013$). Additionally, when the patients with moderate MR were eliminated, mild MR alone was also a risk factor for death (HR, 1.301; $P=0.0371$) and death or heart failure hospitalization (HR, 1.292; $P=0.0048$).

Unadjusted and adjusted results for the 3 different levels of MR found in the study cohort are depicted graphically in Figures 1 and 2. Examination of the unadjusted Kaplan-Meier curves (Figures 1A and 2A) reveals a clear and significant divergence of the 3 patient cohorts; with increasing MR severity, patients are at increased risk for both death and heart failure hospitalization. Even after adjustment for other important clinical characteristics, patients with increasing MR severity had decreased survival and event-free survival. Mild MR continued to be a predictor of worse long-term outcome (Figures 1B and 2B).

Discussion

This study defines the long-term impact of uncorrected mild and moderate MR in patients undergoing CABG. When compared with the cohort of patients with no or trace MR, both mild and moderate MR were found to be independent predictors of poor outcome; patients with both mild and moderate MR had reduced survival, as well as greater admission for heart failure. Although moderate MR has been shown to be a risk factor for poor outcome, the negative impact of mild MR by TEE is surprising.[17,18] It has been shown that increasing severity of MR has a progressively negative impact on survival in patients treated with percuta-

neous and surgical revascularization.[6,19,20] However, in these prior studies, the most significant decrease in survival begins to emerge in the population with moderate MR.

Recently, Mallidi et al[21] reported a matched cohort study in which 163 CABG patients with uncorrected MR were compared with 326 control CABG patients. In addition to patient matching, Cox regression was used to assess the effects of MR on late survival and event-free survival. Although a small proportion of the patients underwent preoperative echocardiography, this study relied on ventriculography to determine the degree of MR. With a mean follow up of 3.4 years, their data reported that the presence of mild or moderate MR was not associated with worse survival, but did predict poorer event-free survival. Although not statistically significant, this previous study showed a trend toward worse event-free survival in patients with mild MR. By following a much larger cohort of patents with uncorrected MR, the current study adds to the work by Mallidi et al[21]. With a larger patient population, including >1000 CABG patients with either mild or moderate MR, the current study is able to show that even mild MR is a significant risk factor for death, as well as heart failure hospitalization.

Another unique aspect of this study is that all of the included patients underwent intraoperative, preprocedural TEE as the method to assess MR severity. In contrast, much of the cited literature has relied on either TTE or, more commonly, ventriculography to assess MR.[1,7,21] Whereas general anesthesia can reduce afterload and lead to the underestimation of MR severity, we maintain that TEE is the most accurate method to assess this condition.[8] TEE avoids catheter-induced MR and possible ischemia that can be encountered with ventriculography. Additionally, TEE can study MR over multiple cardiac cycles, and, in the vast majority of patients, echocardiogram windows are excellent. In this study, patients underwent intraoperative TEE performed under varying afterload conditions to avoid the effects of general anesthesia and to reproduce baseline systemic blood pressure. We believe that intraoperative TEE is the most precise modality for MR assessment in the CABG patient, and its use in all of the patients represents an important strength of the current study.

This report serves to delineate the natural history of uncorrected, mild, and moderate MR in CABG patients. Importantly, it does not address whether mitral repair is warranted for mild MR in this population. Probably most of the MR could be eliminated by surgical annuloplasty, typically with a ring device. This study, however, is unable to comment on whether such an aggressive strategy would result in improved, long-term outcomes. Nevertheless, the study does emphasize that even mild MR in CABG patients predicts increased risk of death. Furthermore, revascularization alone does not appear to negate this risk. Additional studies should focus on the identification of subsets of CABG patients with mild MR that may benefit from surgical repair. Additionally, these results support efforts to develop less invasive methods to repair MR in patients with coronary artery disease.

An important limitation of this report is that the extent of medical treatment for MR after CABG is not assessed. Our database does not uniformly acquire information on the use of antihypertensive or afterload reducing agents. It is possible that the mild MR cohort did not receive an aggressive medical regimen to reduce afterload and minimize the effect of MR. Such a regimen may significantly reduce death or heart-failure readmission. Additional limitations include those inherent to its observational nature, including the need to adjust for different baseline characteristics.

In conclusion, this report emphasizes that uncorrected, mild, or moderate MR in CABG patients is not a benign or insignificant condition. When compared with patients with no or trace MR, this subset of patients appears to be at higher risk for death or heart-failure hospitalization. More aggressive medical treatment, including closer follow-up and reassessment of MR, is indicated. Additional investigation, possibly including a randomized trial, may be necessary to assess the effect of valve repair on long-term outcomes in this patient population.

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