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무심폐기하 관상동맥우회술에서의 중등도의 허혈성 승모판막부전증의 중요성

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Long-term Influence of Mild to Moderate Ischemic Mitral Regurgitation after Off-pump Coronary Artery Bypass Surgery

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Background: Our objective was to review the long-term prognosis of patients with preoperative mild to moderate ischemic mitral regurgitation who underwent off-pump coronary artery bypass grafting. ***Material and Method:*** We prospectively followed 1,000 consecutive and systematic off-pump coronary artery bypass grafting patients who were operated on between September 1996 and March 2004; follow-up was achieved for 97%. Sixty-seven patients (6.7%) had mild to moderate ischemic mitral regurgitation at the time of surgery. Operative mortality, actuarial survival and major adverse cardiac event free survival were compared to assess the effect of ischemic mitral regurgitation. ***Result:*** Average follow-up was 66±22 months. Patients with ischemic mitral regurgitation were older ($p<0.001$), had lower ejection fractions ($p<0.001$) and more comorbidities. Significantly more female patients presented with ischemic mitral regurgitation ($p=0.002$). There was no significant difference in operative mortality and perioperative myocardial infarction in ischemic mitral regurgitation patients ($p=0.25$). Eight-year survival was decreased in ischemic mitral regurgitation patients (39.6±11.8% vs 76.7±2.2%, $p<0.001$). However, after correcting for risk factors, mild to moderate ischemic mitral regurgitation was not found to be a significant independent risk factor for long-term mortality ($p=0.42$). Major adverse cardiac event free survival at 8 years was significantly lower in ischemic mitral regurgitation patients (53±12% vs 77±2%, $p<0.001$). After correction for risk factors, ischemic mitral regurgitation remained a significant independent cause of major adverse cardiac events (HR: 2.31), especially congestive heart failure and recurrent myocardial infarction. ***Conclusion:*** In our series, patients with preoperative mild to moderate ischemic mitral regurgitation had a higher prevalence of preoperative risk factors than patients without ischemic mitral regurgitation. They had comparable perioperative mortality and morbidity, but, in the long term, were found to be at elevated risk for recurrent cardiac events.

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Key words: 1. Mitral valve regurgitation
2. Off-pump
3. Survival
4. Coronary artery bypass graft

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INTRODUCTION

The coexistence of functional ischemic mitral regurgitation (IMR) in patients undergoing coronary artery bypass grafting (CABG) is often associated with poor operative and long-term outcomes[1-3]. There is general agreement among cardiac surgeons that severe IMR should be corrected at the time of CABG, and that trace to mild IMR can be left alone when treating isolated CABG. However, the optimal management of moderate IMR still remains controversial. There have been pros and cons about concurrent mitral valve reparative procedures at the time of CABG in managing IMR patients[1,2,4-8].

Nowadays, the safety and advantages of off-pump coronary artery bypass grafting (OPCAB) have been clearly established by many centers, especially in patients with many associated comorbidities[9]. However, performing OPCAB in a patient with severe functional IMR may induce ischemia and aggravate mitral regurgitation causing severe hemodynamic instability and unwanted conversion to on-pump bypass. Consequently, patients that undergo successful OPCAB surgery normally should not be affected by significant ischemic IMR. The purpose of this study is to evaluate perioperative and long-term outcomes after isolated OPCAB in patients with functional mild to moderate IMR.

MATERIAL AND METHOD

1) Patient population

We prospectively followed 1,000 consecutive and systematic OPCAB patients operated on between September 1996 and March 2004 at the Montreal Heart Institute by one surgeon representing more than 95% of the entire patient cohort operated for coronary revascularization during the same time frame.

Early and mid-term outcomes of these series have already been published[10]. Among these patients, 67 patients were preoperatively identified having mild to moderate IMR at the time of the surgery and will be the main topic of this report. Follow-up was completed in 97% of the patients. The grade of IMR was based on the pre and postoperative transthoracic echocardiography (TTE) and based on ACC/AHA 2006 guidelines[11].

2) Surgical technique

The surgical technique used has been consistent through the years and has been described in previous reports[10]. In summary, median sternotomy was used in more than 99% of the patients, and all procedures were performed under general anesthesia with continuous pulmonary artery pressure and TEE monitoring since 2000. A compression-type stabilizer (Cor-Vasc retractor-stabilizer; CoroNéo, Montreal, Canada) was used in all cases. Postoperatively, patients were maintained on oral aspirin (80 mg/day) and subcutaneous heparin (5,000 KIU, 3 times a day) throughout the entire hospital stay. Since August 2002, clopidogrel (75 mg/day) has been added to the post-operative medication for the first 3 months.

3) Clinical follow-up

All perioperative data were prospectively gathered. Clinical follow-up was completed through regular outpatient clinic, telephone interview by the attending surgeon, and/or chart reviews whenever applicable (such as in the case of ER visits or rehospitalization). In cases where patients were admitted to other hospitals, the reason for the visit and subsequent findings were obtained from the attending physician. All information collected was systematically entered into a computer-data base (SPSS13.0, SPSS Inc., Chicago, Ill).

Major adverse cardiac event (MACE) during the follow-up period were defined as one of the following: cardiac death or death of unknown cause, re-hospitalization for congestive heart failure (CHF), myocardial infarction, recurrent unstable angina, or repeat revascularization [surgical or percutaneous coronary intervention (PCI)].

Completeness of revascularization was defined according to the original Coronary Artery Surgery Study (CASS) trial defined as all 3 major vessels receiving a bypass graft in patients with triple-vessel disease[12].

4) Statistical analysis

Statistical analyses were performed using SPSS software (SPSS 13.0, SPSS Inc., Chicago, Ill). Results are presented as mean±standard deviation for continuous variable or as number and percentages for categorical variables.

Table 1. Demographic data and preoperative risk factors

Characteristics	No IMR (n=933)	IMR (n=67)	p-value
Age (year, mean±SD)	63.88±10.11	69.42±7.62	<0.0001
Female (%)	198 (21.22)	25 (37.31)	0.0022
Diabetes (%)	251 (26.90)	26 (38.81)	0.0355
Hypertension (%)	492 (52.73)	48 (71.64)	0.0016
Smoking (%)	277 (29.69)	11 (16.42)	0.0240
COPD	107 (11.47)	11 (16.42)	0.2060
Atrial fibrillation	32 (3.43)	5 (7.46)	0.0916
PVD	166 (17.79)	18 (26.87)	0.0641
Carotid stenosis	146 (15.65)	15 (22.39)	0.1471
LMCA	272 (29.15)	24 (35.82)	0.2482
Renal insufficiency	39 (4.18)	9 (13.43)	0.0006
LVEF	0.54±0.12	0.45±0.13	<0.0001
CHF	71 (7.61)	17 (25.37)	<0.0001
Old MI (>30 days)	367 (39.34)	31 (46.27)	0.2628
Recent MI (<30 days)	170 (18.22)	27 (40.30)	<0.0001
UA	636 (68.17)	56 (83.58)	0.0083
IABP (preoperative)	62 (6.65)	12 (17.91)	0.0007
Reoperation	66 (7.07)	3 (4.48)	0.4180
Emergency	44 (4.72)	10 (14.93)	0.0003
PHT	75 (8.04)	19 (28.36)	<0.0001
No. of diseased coronaries	2.68±0.57	2.78±0.45	0.2089
Parsonnet scores	11.0±8.2	19.7±8.3	0.001

IMR=Ischemic mitral regurgitation; COPD=Chronic obstructive pulmonary disease; PVD=Peripheral vascular disease; LMCA=Left main coronary artery stenosis; LVEF=Left ventricular ejection fraction; CHF=Congestive heart failure; MI=Myocardial infarction; UA=Unstable angina; IABp=Intraaortic balloon pump; PHT=Pulmonary hypertension.

Univariate analysis was performed to find the potential predictors for outcomes. Variables significant at 0.10 levels were included in the multivariate model. Because of the small number of some outcomes and in order to avoid over fitting of the multivariate model, a decision was made to limit the number of predictors to one per 10 outcomes. The IMR group was forced in all multivariate models. According to the type and available information, continuous outcomes were analyzed with generalized estimating equation (GEE) considering each pair as a repeated effect. Logarithmic transformations were used when a continuous outcome was not normally distributed. Categorical outcomes were analyzed with Cox regression or with logistic regression considering each pair as a separate stratum.

Table 2. Perioperative data

Characteristics	No IMR (n=933) (%)	IMR (n=67) (%)	p-value
Operative mortality	15 (1.6)	2 (3)	0.25
Number of grafts	3.2±0.9	3.3±0.9	0.41
Complete revascularization	882 (95)	61 (91)	0.71
Conversion to CPB	3 (0.3)	1 (1.5)	0.24
Perioperative MI	31 (3.3)	7 (10.45)	0.26
ICU stay (hours)	64±56	88.06±118	0.003
Hospital stay (days)	6.5±5.8	7.78±8.89	0.10
Infection	27 (2.9)	4 (6.0)	0.58
AF	245 (26)	22 (33)	0.13
IABP	6 (0.6)	1 (1.5)	0.38
Bleeding	36 (3.9)	5 (7.6)	0.18

CPB=Cardiopulmonary bypass; MI=Myocardial infarction; ICU=Intensive care unit; AF=Atrial fibrillation; IABp=Intraaortic balloon pump.

Adjusted survival curves were constructed for groups IMR- and IMR+, and compared using the log-rank test, $p<0.05$ was considered statistically significant.

RESULT

1) Patient characteristics and preoperative risk factors

Patient demographics and preoperative risk factors are displayed in Table 1. Among the 67 patients that presented with IMR 38 had 1+ IMR, 26 patients 2+ and 3 patients 3+. IMR patients were on average 5 years older, had lower EF, higher prevalence of diabetes, hypertension, chronic renal insufficiency, congestive heart failure (CHF), recent MI, unstable angina, preoperative intra-aortic balloon pump, emergency surgery, and a higher Parsonnet risk scores. Female patients also presented with IMR more frequently than men (37.31% vs 21.22%).

2) Perioperative data (Table 2)

Operative mortality was 3.0% (2 deaths) in IMR patients and 1.6% (15 deaths) in non-IMR patients (p=0.25). On average, the number of bypass grafts, the percentage of complete revascularization performed, conversion to CPB, and perioperative MI were similar for both groups. ICU stay, however, was longer in IMR patients.

Table 3. Long-term survival by Cox logistic regression analysis

	p-value	H. R.	C. I. 95%
Age	<0.001	1.07	1.05~1.09
CHF	0.04	1.82	1.18~2.81
PVD	0.01	1.63	1.12~2.35
Cerebral ASO	0.03	1.53	1.06~1.23
LVEF	0.002	0.13	0.04~0.46
Incomplete revasc.	0.002	2.23	1.43~3.60
Renal insufficiency	0.01	1.97	1.17~3.31
IMR	0.42		

HR=Hazard ratio; CI=Confidence interval; PVD=Peripheral vascular disease; ASO=Artherosclerosis.

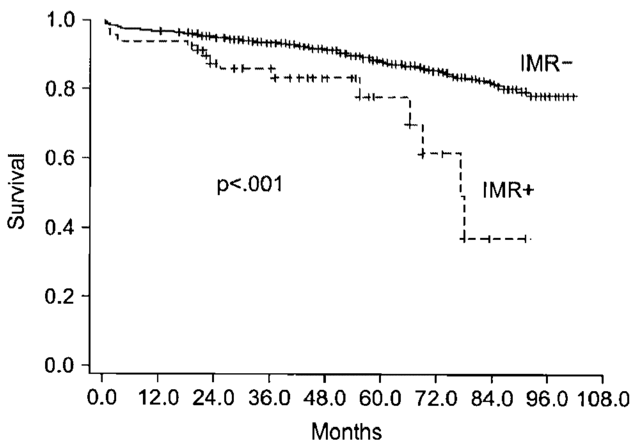

Fig. 1. Survival curve comparing patients with (dash line) and without (full line) ischemic mitral insufficiency after correcting for risk factors.

3) Long-term results

Long-term survival was significantly decreased in IMR patients compared to those without IMR (at 1 year (94.0±2.9% vs 97.0±0.6%), 5 years (78.0±6.8% vs 88.0±1.0%), and 8 years (42.0±11.3% vs 77±2.1%), respectively, $p<0.001$). After Cox logistic regression analysis only age at the time of operation, previous history of CHF, peripheral and cerebral vascular diseases, low EF, incomplete revascularization, and renal insufficiency were significant risk factors for the long-term survival (Table 3). After correcting for these factors, IMR patients had a comparable survival to non-IMR patients (Fig. 1).

MACE-free survival was also affected in IMR patients (86±4% vs 97.0±0.7%, 69±8% vs 88.0±1%, and 54±11% vs 76±2%, at 1 year, 5 years, and 8 years, respectively, $p<0.001$). After correcting for risk factors, IMR emerged as a cause of MACE occurrence at follow-up (Table 4, Fig. 2). By specifically breaking down for each cardiac events, IMR (HR: 2.54, CI 1.06~2.54) remained a significant factor of rehospitalization for CHF along with history of LVEF and CRI. Rehospitalization for new MI was also more frequent in IMR patients but remained at the limit of clinical significance (p=0.06).

Table 4. MACE-free survival by Cox logistic regression analysis

	p-value	H. R.	C. I. 95%
PVD	<0.001	1.96	1.37~2.82
Renal insufficiency	0.001	2.53	1.47~4.35
LVEF	0.01	0.21	0.06~0.71
Complete revasc.	0.03	0.54	0.31~0.93
Emergency	0.01	1.87	1.08~3.20
IMR	0.02		

MACE=Major cardiac adverse event; PVD=Peripheral vascular disease.

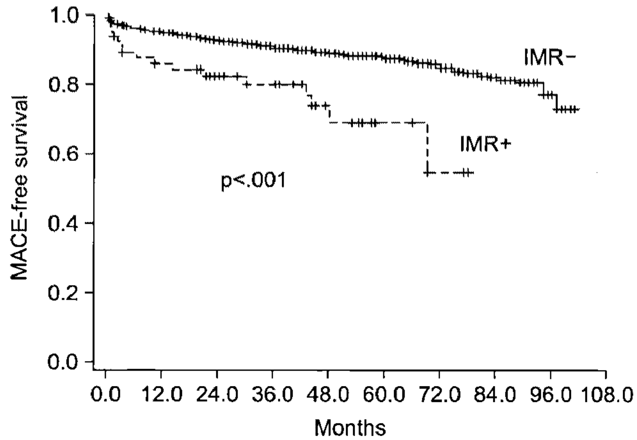

Fig. 2. MACE-free survival curve comparing patients with (dash line) and without (full line) ischemic mitral insufficiency after correcting for risk factors.

DISCUSSION

Patients with IMR complicated by myocardial infarction have a significantly worse prognosis than those without IMR [5,13-15]. Lamas and colleagues demonstrated that angiographically mild IMR after myocardial infarction, which is often clinically unrecognized, is a marker of a larger, more geometrically distorted LV and is associated with a significant increase in subsequent cardiac death[13]. These patients also showed a higher prevalence of cardiovascular mortality, severe heart failure, and recurrent myocardial infarction. Grigioni and colleagues showed that in the chronic phase of a myocardial infarction, the presence of IMR was associated with excess mortality independently of baseline characteristics and severe ventricular dysfunction[4]. Risk of death was directly related to the importance of IMR[4]. In patients undergoing primary percutaneous coronary intervention (PCI) in the set up of an acute MI[16], Pellizzon's study showed that survival was markedly reduced in patients with IMR at both 30 days and 1 year, and increased with severity of mitral regurgitation[17]. Even the presence of mild IMR at baseline has been recognized as an independent predictor of reduced survival after PCI[18].

Authors have questioned whether the presence of moderate IMR is simply a marker of high-risk patients or if it is a true risk factor for mortality at the time of coronary bypass procedure. Lam and colleagues reported that CABG patients with non-surgically repaired IMR at the time of surgery had reduced survival compared to patients without IMR, and that moderate IMR was an independent risk factor of mortality[9]. Paparella and colleagues reported similar observations in patients with poor LV function[19]. However, in their study, independent predictors of poor survival were mainly advanced age, LV dysfunction, heart failure, diabetes, prior stroke, PVD, and non-use of IMA. IMR was not an independent predictor of long-term mortality. They could not conclude whether the poorer outcomes in these patients were related to the dysfunctional valvular status or the presence of more extensive comorbidities, such as ventricular dysfunction. It has been suggested that the LV morpho-functional status (left ventricular regurgitation) might be a more important feature than the mitral regurgitation itself[20].

The operative strategies for IMR are mainly to improve late survival and functional status as well as late quality of life without increasing perioperative morbidity and mortality[7]. There is no clear consensus on the surgical indication of correcting moderate IMR, as well as a lack of consistency regarding the grading of MR based on either ventriculography or echocardiography (transthoracic or transesophageal). In the current study, we followed the ACC/AHA guidelines[11] in regard to mitral regurgitation for preoperative transthoracic echocardiographic evaluation. The great majority of our patients had 2+ or less IMR. It is a degree of regurgitation that we normally do not treat surgically in our institution.

Some authors have favoured concurrent mitral valve repair at the time of CABG[2,5,7,9]. whereas others have not [1,6,8,21]. The rationale for a conservative approach is that revascularization of the ischemic region will improve regional wall motion and correct the IMR. Even if some residual IMR persists, several studies suggest that long-term survival or functional status will not be affected. Mitral valve repair always has the potential to increase the surgical risk of the procedure[1,6,20,22-24]. The rationale for aggressive mitral repair is to decrease the risk of recurrent CHF especially in patients with previous CHF symptoms associated with an enlarged left atrium[5]. In this specific group, CABG alone may not correct moderate IMR. Significant residual IMR affects quality of life and may decrease long-term survival. Interestingly, ischemic patients who underwent surgical correction of IMR have been associated with diminished survival compared to those without IMR or degenerative mitral regurgitation due to an increased operative mortality[22-24]. As a result, patients with IMR have been more reluctantly referred for surgery than patients without IMR. But still the question remains whether the adverse outcome observed after repair of IMR is due to the more advance ischemic status of the myocardium or simply a reflection of a higher prevalence of preoperative risk factors.

Comparing ischemic and non-ischemic patients with mitral regurgitation, Glower and colleagues showed that long-term survival was more dependent of baseline patient characteristics and comorbidity than by the ischemic nature of the mitral regurgitation[22]. Other studies from Dalberg, Mayo Clinic[23] and Gillinov, Cleveland Clinic[24] reached similar conclusions confirming that survival after mitral valve surgery and CABG was better determined by extent of coronary artery disease and LV dysfunction than the etiology of the mitral disease. Our study has come to very similar result in excluding IMR as a significant factor for long-term mortality.

There are very few reports concerning OPCAB and residual IMR. Harris and colleagues reported on 17 patients out of 989 OPCAB patients who presented preoperatively moderate to moderately severe IMR[5]. Among them there were 11 men and 6 women. Three-year survival for these patients was 62%, which was comparable to a historical matched group operated on for routine CABG under cardiopulmonary bypass.

In our study, OPCAB patients with mild to moderate functional IMR were definitely sicker than those with normal mitral function. They were older, with more females presenting with IMR than without, and had more risk factors, which clinically translated in a higher Parsonnet score. However, they had comparable operative mortality and morbidity. After correction for risk factors their long-term survival they had a comparable to those without IMR. However, regression analysis established that IMR patients were at higher risk for rehospitalization due to cardiac failure and, to a lesser degree, new myocardial infarction which confirms the higher ischemic and dysfunctional status of the heart. On that point, our data came to the same conclusion as that of Glower's[22] and Gillinov's[24] series from the Mayo and Cleveland clinics.

1) Study limitations

This study presents several limitations. There were only a small number of OPCAB patients with IMR, which limits statistical analysis. Echocardiographic assessments were not systematically done for every patient, especially during the early phase of the study, and no specific echographic follow-ups were performed on IMR patients postoperatively to find out whether the residual IMR was persistent or not. Consequently, no direct correlation with persistent residual IMR and cardiac evolution could be established.

CONCLUSION

Our results suggest that patients with mild to moderate IMR undergoing OPCAB surgery are at higher risk to develop CHF at follow-up. A close medical management of these patients should help to prevent this complication. Regarding additional mitral procedure at the time of OPCAB, our data does not substantiate any aggressive surgical approach to correct the mild to moderate IMR at the time of surgery. Further studies are required.

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=국문 초록=

배경: 술전 경도 및 중등도의 허혈성 승모판막 폐쇄부전증이 동반된 환자들의 무심폐순환 관상동맥 우회로 조성술을 시행한 후의 장기 예후를 추적 조사하였다. **대상 및 방법**: 1996년 9월부터 2004년 3월까지 1,000명의 연속된 무심폐순환 관상동맥 우회로 조성술을 시행 받은 환자들의 데이터를 전향적으로 조사하였으며, 97%의 환자에서 추적 조사가 가능하였다. 육십칠명(6.7%)의 환자들이 수술 당시 경도 및 중등도의 허혈성 승모판막 폐쇄부전증이 동반되었다. 허혈성 승모판막 폐쇄부전증이 끼치는 영향에 대하여 수술사망율, 실제생존율 및 주요 심장 부작용이 없는 생존율 등을 비교하였다. **결과**: 평균 추적 조사 기간은 66±22개월이었다. 허혈성 승모판막 폐쇄부전증이 동반된 환자들의 연령이 더 높았으며($p<0.001$), 더 낮은 심박출량을 보였고($p<0.001$) 더 많은 위험 인자들을 갖고 있었다. 여성에게 의미있게 더 많았으며($p=0.002$), 수술사망율이나 술전후 심근 경색의 빈도에는 의미있는 차이는 없었다($p=0.25$). 팔 년 생존율은 허혈성 승모판막 폐쇄부전증이 동반된 환자들이 더 낮았다(39.6±11.8% vs 76.7±2.2%, $p<0.001$). 하지만 동반된 위험 인자들을 교정했을 때 술전 경도 및 중등도의 허혈성 승모판막 폐쇄부전증 자체가 장기 사망률의 의미있는 위험 인자는 아니었다($p=0.42$). 8년 간의 주요 심장 부작용이 없는 생존율은 허혈성 승모판막 폐쇄부전증이 동반된 환자들에서 의미있게 낮았다(53±12% vs 77±2%, $p<0.001$). 위험 인자들을 교정했을 때 허혈성 승모판막 폐쇄부전증은 주요 심장 부작용이 없는 생존율(HR: 2.31), 울혈성 심기능 저하와 재발성 심근 경색에 의미있는 위험 요소이었다. **결론**: 무심폐순환 관상동맥 우회로 조성술을 시행 받은 환자들 중 술전 경도 및 중등도의 허혈성 승모판막 폐쇄부전증이 동반된 경우 더 많은 술전 위험요소들을 갖고 있었다. 술전후의 사망률이나 유병율은 비슷하였으나, 장기적으로 심장 합병증의 유발율은 더 높았다.

중심 단어 : 1. 승모판막 폐쇄부전증
2. 무심폐순환
3. 생존율
4. 관상동맥 우회로 조성술