

Does the Severity of Preoperative Symptoms Predict Operative Risk in Mitral Regurgitation?

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SUMMARY

Background

Patients with severe degenerative mitral regurgitation (SDMR) referred to surgery present diverse clinical presentations; while some patients are asymptomatic with preserved ventricular function, others have functional class IV dyspnea and systolic dysfunction. Current guidelines are helpful to recognize timing of mitral valve surgery; however, reality is sometimes far from ideal and defines daily practice.

Objective

To analyze the impact of preoperative functional class (FC) on in-hospital and on long-term outcomes of patients undergoing surgery for SDMR.

Material and Methods

We conducted a retrospective analysis of 254 consecutive patients who underwent surgery due to SDMR between July 1997 and July 2007. Patients were divided into two groups according to their NYHA FC for dyspnea. Group 1 included 87 patients in FC I-II and group 2 included 167 patients in FC III-IV.

Results

Patients in group 1 were more likely to undergo mitral valve repair (56.3% versus 37.7%; $p=0.005$); conversely, associated myocardial revascularization was less frequent (10.3% versus 27.5%; $p=0.002$). During postoperative, patients in group 2 presented greater morbidity and mortality rates (27.5% versus 13.7%; $p=0.01$) and greater in-hospital mortality (9.5% versus 2.3%; $p=0.03$). Global actuarial survival at 10 years was 92.9% with a median follow-up of 1,182 days/patient. During long-term follow-up, more patients in group 1 were free of associated events (mortality and readmission) than subjects in group 2 (HR 3.3; $p=0.01$, 95% CI 1.27-8.99). The degree of preoperative dyspnea was an independent predictor of adverse outcomes in multivariate analysis. The sub-analysis of patients without coronary artery disease also demonstrated that the severity of preoperative dyspnea is an independent predictor of in-hospital and long-term morbidity and mortality.

Conclusion

In patients with SDMR, preoperative FC III-IV dyspnea is associated with worse outcomes during hospitalization and long-term follow-up.

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Key words > Mitral Valve- Preoperative symptoms - Surgery Predictors - Survival

Abbreviations >

S	Stroke	ECG	Electrocardiogram
MV	Mechanical ventilation	EF	Ejection fraction
CPB	Cardiopulmonary bypass	MR	Mitral regurgitation
FC	Functional class	SDMR	Severe degenerative mitral regurgitation
CK	Creatine Kinase	NYHA	New York Heart Association
LVEDD	Left ventricular-end diastolic diameter		

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BACKGROUND

Patients with severe degenerative mitral regurgitation (SDMR) referred to surgery show diverse clinical presentations; while some patients are asymptomatic with preserved ventricular function, others have functional class IV dyspnea and systolic dysfunction. (1-4) Current guidelines are helpful to recognize the optimal timing of mitral valve surgery; however, reality is sometimes far from ideal and defines daily practice. (5-7)

Indications for SDMR surgery depend not only on the echocardiographic data of the mitral valvular apparatus but also on hemodynamic implications and on patients general characteristics. (8-10) The experience of the surgical team and the feasibility to perform mitral valve repair are particularly important when indicating surgery, specially in patients with no or mild symptoms. (11)

The aim of the present study is to analyze the impact of preoperative functional class (FC) on in-hospital and long-term outcomes of patients undergoing surgery for SDMR.

MATERIAL AND METHODS

From July 1997 to July 2007, 4537 consecutive patients were included in the database of the Department of Cardiovas-

cular Surgery; a retrospective analysis of 254 patients undergoing surgery due to SDMR (4.3%) was subsequently performed. All patients with mitral valve regurgitation due to myxomatous degeneration (chordal rupture, leaflets prolapse and Barlow's disease) were included. The diagnosis was made by preoperative and intraoperative echocardiography, and by the intraoperative findings. All the patients included had severe mitral regurgitation (MR) defined by clinical and echocardiographic parameters. Patients with associated coronary artery disease were included when this condition was not the cause of mitral regurgitation. Patients with the following conditions were excluded from the study: mitral regurgitation due to other diseases (ischemia, rheumatic valve disease, endocarditis, etc.), severe mitral stenosis and association with aortic valve disease, diseases of the ascending aorta, congenital heart defects and diseases of the pericardium. Indication for surgery in symptomatic and asymptomatic patients was determined according to the Consensus Statement on Valvular Heart Disease of the Argentine Society of Cardiology. (5)

Patients characteristics

Demographic variables and patient's preoperative cardiovascular history were analyzed (Table 1).

Patients were divided into two groups according to their New York Heart Association (NYHA) functional class (FC) for dyspnea: group 1 included patients in FC I-II and group 2 in FC III-IV. Preoperative left ventricular systolic function was defined by 2D echocardiography and Simpson's method. Systolic dysfunction was defined as left ventricular ejection fraction (EF) < 50%. Subgroups of patients

	Group 1 n = 87	Group 2 n = 167	p value
Age	59.2 ± 11.3	61.5 ± 12.2	0.1
Male, n (%)	59 (67.8)	90 (53.8)	0.01
HT, n (%)	33 (37.9)	82 (49.1)	0.09
DM, n (%)	4 (4.6)	8 (4.7)	0.9
CS, n (%)	28 (32.1)	55 (32.9)	0.9
Previous MI, n (%)	5 (5.7)	15 (8.9)	0.3
IABP, n (%)	0	2 (1.2)	0.1
CAD, n (%)	13 (14.9)	64 (38.3)	0.01
Previous CABGS, n (%)	3 (3.4)	10 (5.9)	0.3
LVSF < 50% n (%)	12 (13.7)	24 (14.3)	0.9
LVSF 30-49% n (%)	8 (9.1)	14 (8.3)	0.9
LVSF < 30% n (%)	4 (4.5)	10 (5.9)	0.4
LVEDD, mm	59.7 ± 8.1	56.7 ± 7.8	0.005
LVESD, mm	35.7 ± 7.3	34.6 ± 7.5	0.3
LA, mm	50.3 ± 9.4	50.4 ± 12.14	0.9
IVS, mm	11 ± 2.3	11.1 ± 2.2	0.8
Creatinine, mg/dl	1.11 ± 0.1	1.23 ± 0.5	0.06
Previous S, n (%)	3 (3.4)	10 (5.9)	0.3
AF, n (%)	15 (17.2)	44 (26.3)	0.1
Elective, n (%)	86 (98.8)	123 (73.6)	0.001

Table 1. Preoperative data

HT: Hypertension. DM: Diabetes mellitus. CS: Current smoking. LVSF: Left ventricular systolic function.

IABP: Intraaortic balloon counterpulsation pump. AF: Atrial fibrillation. LVEDD: Left ventricular-end diastolic

diameter. LVESD: Left ventricular-end systolic diameter. LA: Left atrium. S: Stroke. CAD: Coronary artery disease.

IVS: Interventricular septum

with EF between 30% and 49%, and < 30% were also analyzed.

The type of surgery performed (mitral valve repair or replacement), surgical times, and postoperative morbidity and mortality were also analyzed. In addition, we carried out a subanalysis of the effects of associated coronary artery disease on the outcomes.

Follow-up data were retrieved from the medical charts and telephone contacts performed every 6 months with the patients and/or with their family physicians. Rehospitalization was defined as any admission due to heart failure, stroke, bacterial endocarditis, syncope and need of reintervention.

Surgical technique

Surgery was performed using complete sternotomy, under cardiopulmonary bypass, hypothermia of 32 degrees, and antegrade/retrograde blood cardioplegia according to the Buckberg protocol. An annuloplasty ring device was implanted in all the procedures of mitral valve repair.

Statistical Analysis

Categorical variables are expressed as percentage and compared using chi square test or Fisher's exact test, when appropriate. Continuous variables with normal distribution are presented as mean and standard deviation and compared with *t* test. Continuous variables with non parametric distribution are presented as median and interquartile range, and compared using the Mann-Whitney test. Simple and multiple logistic regression analyses were applied to identify predictors of in-hospital mortality. Event-free survival after discharge (excluding in-hospital mortality) is presented as Kaplan-Meier curves. The association between the different variables with the prognosis was explored using Cox proportional hazards model. In all cases, a *p* value < 0.05 was considered statistically significant.

Definition of complications

The following major complications or events were evaluated during the postoperative period: acute myocardial infarction (development of new Q waves in at least two contiguous electrocardiographic leads and/or new regional wall motion abnormality and/or CK > 1000 UI/l), atrial fibrillation (presence of atrial fibrillation in a patient in previous sinus rhythm), prolonged mechanical ventilation (MV) (need for mechanical ventilatory support for more than 48 hours), mediastinitis (infection of the sternal surgical wound with positive cultures), stroke (with neurologic deficit at hospital discharge), acute renal failure (increase in serum creatinine levels of more than 100% above preoperative values, or greater than 2 mg/dl with normal preoperative values, or need for dialysis or ultrafiltration), low cardiac output (requirement of inotropic agents for more than 24 hours) and surgical bleeding (need for surgical re-exploration immediately after surgery due to bleeding > 300 ml during the first hour, > 250 ml during the second hour, > 200 ml during the third hour or 1000 ml in the first 6 hours or cardiac tamponade.)

Postoperative morbidity was defined by the presence of at least one major complication; in-hospital mortality was defined as any death, occurring within the operation until hospital discharge and/or 30 days after surgery; in-hospital morbidity and mortality during hospitalization included the presence of at least one major complication associated with in-hospital mortality.

The primary final endpoint was in-hospital mortality, and the association of rehospitalization and mortality during long-term follow-up were the secondary final endpoints.

RESULTS

Patients' basal characteristics

A total of 87 patients were included in group 1 and 167 in group 2. Patients in group 1 were predominantly men, with greater left ventricular-end diastolic diameter and lower prevalence of non-elective surgery and associated coronary artery disease (Table 1).

Intraoperative course

Aortic cross-clamp time and cardiopulmonary bypass time were similar in both groups (75.7 ± 27 versus 77.5 ± 24.7 min and 106.4 ± 42.2 versus 107.4 ± 33.4 min, respectively). Patients in group 1 were more likely to undergo mitral valve repair (56.2% versus 37.7%; *p* = 0.005); conversely, associated myocardial revascularization was less frequent (14.9% versus 38.3%; *p* < 0.01).

Postoperative course

During the immediate postoperative period, group 2 presented greater incidence of atrial fibrillation, prolonged mechanical ventilation, low cardiac output and increased in-hospital mortality (Table 2). The incidence of major complications was significantly lower in group 1 (13.7% versus 27.5%; *p* = 0.01).

Long-term course

Global actuarial survival at 10 years was 92.9% with a mean follow-up of 1182 (80-3.650) days/patient. Survival at 5 and 10 years was similar in group 1 and 2 (97.9% and 88.6% versus 90.5% and 81.2%, respectively (*p* = 0.2). Freedom from rehospitalization 5 and 10 years after surgery was greater in group 1 compared to group 2 (98.5% and 88.7% versus 83.9% and 77.3%, respectively; HR at 10 years 5.42, *p* = 0.02, 95% CI 1.23-23.84). Event-free survival was significantly greater in group 1 (mortality associated with rehospitalization) during follow-up, compared to group 2 (HR at 10 years 3.3, *p* = 0.01, 95% CI 1.27-8.99) (Figure 1).

Late mortality and rehospitalizations were significantly greater in patients with preoperative left ventricular dysfunction (HR 4.39, *p* = 0.03, 95% CI 1.14-16.92, and HR 3.28, *p* = 0.01, 95% CI 1.28-8.38, respectively).

Age, the presence of dyspnea, and CBP time were predictors of in-hospital morbidity and mortality, while dyspnea and age were predictors of long-term major events (Table 3).

Outcomes of patients without associated coronary artery disease undergoing mitral valve repair

When patients without associated coronary artery disease were excluded from the analysis, we found that patients with preoperative dyspnea in FC I-II were predominantly men (66.6% versus 48.7%; *p* = 0.01), the indication of surgery was elective in the great majority of cases (98.7% versus 77.7%; *p* < 0.01) and

	Group 1 n = 87	Group 2 n = 167	p value
LCO, n (%)	7 (8)	32 (19.1)	0.02
AF, n (%)	13 (14.9)	43 (25.7)	0.04
S, n (%)	0 (0)	2 (1.2)	0.3
Mediastinitis, n (%)	0 (0)	1 (0.6)	0.3
ARF, n (%)	3 (3.4)	10 (5.9)	0.3
Dyalisis, n (%)	1 (1.1)	8 (4.7)	0.1
MV, n (%)	1 (1.1)	14 (8.3)	0.02
Re-exploration, n (%)	5 (5.7)	11 (6.5)	0.5
Death, n (%)	2 (2.3)	16 (9.5)	0.03
Major complication, n (%)	12 (13.7)	46 (27.5)	0.01

Table 2. Perioperative complications

LCO: Low cardiac output. AF: Atrial fibrillation. S: Stroke. ARF: Acute renal failure. MV: Mechanical ventilation. Re-exploration: Surgical bleeding. Major complication: Please refer to section Definition of complications

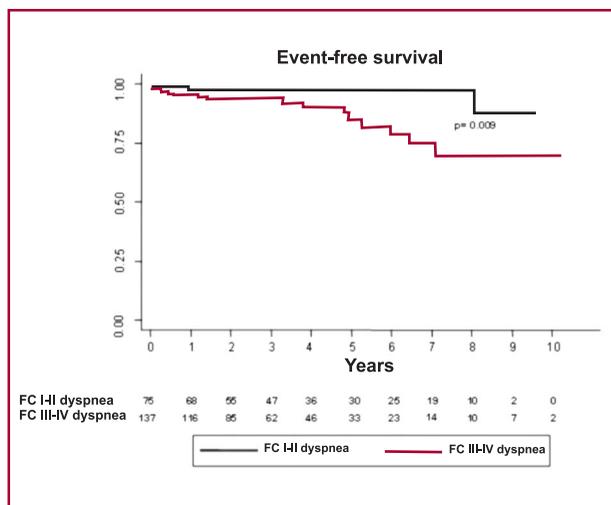


Fig. 1. Event free survival (late mortality associated with rehospitalization) according to functional class for dyspnea.

left ventricular-end diastolic diameter was greater (59.8 ± 8.4 mm versus 57.1 ± 7.9 mm; $p = 0.02$) compared to patients in FC III-IV.

Thirty days after surgery, patients with more severe symptoms had a strong trend towards major complications (12.8% versus 23.1%; $p = 0.06$) and mortality (8.2% versus 1.2%; $p = 0.05$). Multivariate analysis identified age and FC III-IV dyspnea as predictors of death and rehospitalization at 10 years of follow-up.

DISCUSSION

Our study has demonstrated the importance of preoperative symptoms in patients with SDMR to

predict operative morbidity and mortality, and its impact in long-term follow-up.

The Consensus Statement of the Argentine Society of Cardiology recommends surgery (class 1 indication) in symptomatic severe mitral regurgitation and in asymptomatic patients with severe mitral regurgitation who present parameters of left ventricular dysfunction. Surgery is also recommended (class 2 indication) in asymptomatic patients with moderate left ventricular dysfunction in whom mitral valve repair is feasible. (5)

It is well-known that patients undergoing mitral valve repair have low operative mortality; in addition, valve repair has an improved long-term durability; (12-16) for these reasons, this procedure is indicated even in asymptomatic patients in some experienced surgical centers. (17, 18) Sousa Uva et al. reported their experience with 175 patients in NYHA FC I-II undergoing surgery for degenerative mitral regurgitation with excellent outcomes; mitral valve repair was performed in almost 100% of patients and mortality during follow-up was 1.7%. (19) They recommend surgery in asymptomatic patients when mitral valve repair is feasible, regardless of myocardial performance. In addition, Bolling analyzed 93 consecutive patients with SDMR in NYHA FC I-II. (20) All patients underwent mitral valve repair; no deaths were reported and 100% remained asymptomatic at 5 years.

The feasibility to perform mitral valve repair may be determined by preoperative exams; (21-24) however, baring in mind that mitral this technique is associated with improved outcomes, this study tries to determine the relevance of preoperative symptoms regardless of the surgical technique. In our experience, in presence of minimal symptoms, the feasibility to perform mitral valve repair was the reason to indicate surgery; this might explain the greater incidence of elective surgery in patients undergoing mitral valve repair and the lower postoperative mortal-

Table 3. Predictors of mortality: multivariate analysis

In-hospital	OR	p value	95% CI
Dyspnea	2.39	0.02	1.10-5.16
Age	1.03	0.01	1.00-1.02
CBP time	1.01	0.01	1.00-1.06
Valve repair	0.51	0.06	0.26-1.02
Long-term	HR	p value	95% CI
FC III-IV dyspnea	3.3	0.02	1.27-8.99
HR per year of age	1.09	0.01	1.03-1.15

CBP: Cardiopulmonary bypass. LVSF: Left ventricular systolic function. CABGS: Coronary artery bypass graft surgery

ity rates. Nevertheless, only 56.2% of patients with preoperative FC I-II dyspnea could undergo mitral valve repair. Multivariate analysis identified that FC III-IV dyspnea was an independent predictor of unfavorable outcomes, and although mitral valve repair did not reach statistical significance with the same model, it showed a strong trend compared to mitral valve replacement.

According to consensus statements, an ejection fraction of 60% or lower is an index of ventricular dysfunction and a parameter to indicate surgery. (5) Data from ventricular function is entered in our database as normal, mild, moderate and severe, and considers ventricular dysfunction as an ejection fraction de 50%. We cannot identify patients with an ejection fraction between 50% and 60%; therefore, the conclusions related to ventricular function are limited.

Indication for surgery in patients with minimal symptoms was based on echocardiographic parameters, such a left ventricular-end diastolic diameter, flail mitral valve and pulmonary hypertension, and in the feasibility to perform mitral valve repair. These patients underwent elective surgery due to their clinical status. Conversely, in patients who remained symptomatic despite outpatient therapy with vasodilators and diuretics, the indication of surgery was decided during hospitalization due to dyspnea and heart failure.

It is well-known that coronary artery disease might justify the poor outcomes obtained in the global analysis of the population divided by symptoms; (25-27) however, our subanalysis of patients with mitral regurgitation without associated coronary artery disease showed a strong trend towards greater morbidity and mortality during hospitalization and at long-term follow-up. The studies published by Enriquez-Sarano (28) and Tirone David, (29) showed similar results; they reported that the prevalence of coronary artery disease was significantly greater in the group of patients with severe symptoms.

Enriquez-Sarano evaluated the long-term outcomes of surgery of 478 consecutive patients with SDMR and reported that preoperative functional class III-IV symptoms were associated with excess short-

and long-term postoperative mortality, compared to FC II-IV. Similarly to our experience, patients with severe symptoms were more likely to require coronary artery bypass graft surgery; yet, at multivariate analysis dyspnea was the only variable that prevailed as an independent factor of poor outcomes.

Tirone David et al. studied 488 patients with SDMR. The presence of preoperative associated coronary artery disease in patients with severe symptoms was twice as much as in patients with minimal symptoms; the postoperative course of these patients was similar to our findings. They also identified that an ejection fraction < 40% was a predictor of poor outcomes.

Patients undergoing non-elective surgery (urgent or emergency surgery) have worse outcomes than those going through elective surgery and these patients are hospitalized due to progression of symptoms. Patients admitted due to progressive dyspnea are referred to surgery during the hospitalization and have greater in-hospital morbidity and mortality. In group 2, 26.4% of patients underwent surgery during hospitalization and required medical therapy.

The optimal timing of mitral valve surgery in SDMR still remains controversial. Patients with mitral regurgitation may remain asymptomatic for many years until ventricular dysfunction becomes evident. (30-32)

It is essential to recognize the predictors of mortality and to perform an adequate follow-up and evaluation of echocardiographic parameters (ventricular function and diameters) in order to identify patients with severe organic mitral regurgitation with no or mild symptoms who may benefit from surgery before the progression of symptoms and the development of adverse outcomes.

Study limitations

This is a retrospective study based on the experience of a single cardiology center. The evaluation of the severity of dyspnea might be incorrect due to the fact that it is sometimes difficult to define the symptom for each patient. Current guidelines recommend a cutoff point of 60% of ejection fraction in these pa-

tients; however, our database did not allow us to evaluate that value of ejection fraction.

CONCLUSION

In our experience, the severity of preoperative symptoms is directly related to the outcomes of surgery; patients with NYHA FC I-II presented lower incidence of complications and mortality at 30 days compared to patients in NYHA FC III-IV. Patients without associated coronary artery disease had similar outcomes. Actuarial survival at 10 years was similar in both groups; however, patients with severe preoperative symptoms had greater incidence of rehospitalizations,

RESUMEN

¿La gravedad de los síntomas preoperatorios es predictora de riesgo en la cirugía de la insuficiencia mitral?

Introducción

Los pacientes que padecen insuficiencia mitral grave degenerativa (IMGD) son derivados a cirugía con diferentes presentaciones clínicas, desde asintomáticos con función ventricular conservada hasta pacientes en clase funcional IV y disfunción ventricular. A pesar de que existen guías que ayudan a conocer el momento oportuno para indicar la cirugía de la valvulopatía mitral, la realidad a veces dista de lo ideal y define la práctica diaria.

Objetivos

Analizar el impacto de la clase funcional (CF) preoperatoria en la evolución intrahospitalaria y en el seguimiento alejado de los pacientes operados por IMGD.

Material y métodos

Se analizaron retrospectivamente 254 pacientes consecutivos operados por IMGD entre julio de 1997 y julio de 2007 y se dividieron en dos grupos según la CF NYHA preoperatoria para disnea. El grupo 1 estuvo conformado por 87 pacientes en CF I-II y el grupo 2 por 167 pacientes en CF III-IV.

Resultados

Los pacientes del grupo 1 tuvieron mayor posibilidad de reparación valvular (56,3% *versus* 37,7%; $p = 0,005$) y menos revascularización miocárdica asociada (10,3% *versus* 27,5%; $p = 0,002$). En el posoperatorio, el grupo 2 tuvo mayor morbimortalidad (27,5% *versus* 13,7%; $p = 0,01$) y mayor mortalidad hospitalaria (9,5% *versus* 2,3%; $p = 0,03$). La sobrevida actuarial global fue del 92,9% a los 10 años con una mediana de seguimiento de 1.182 días/paciente. En el seguimiento alejado, el grupo 1 tuvo mayor libertad de eventos asociados (mortalidad y reinternación) que el grupo 2 (HR 3,3; $p = 0,01$, IC 95% 1,27-8,99). El grado de disnea preoperatoria fue un predictor independiente de mala evolución en el análisis multivariado. El subanálisis de pacientes sin enfermedad coronaria demostró también que la gravedad de la disnea preoperatoria es un predictor independiente de morbimortalidad hospitalaria y alejada.

Conclusión

La disnea CF III-IV preoperatoria en los pacientes con IMGD se asocia con peor evolución intrahospitalaria y alejada.

Palabras clave > Insuficiencia mitral - Disnea - Síntomas - Cirugía - Supervivencia

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