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Incidence, associated factors and evolution of non-severe functional mitral regurgitation in patients with severe aortic stenosis undergoing aortic valve replacement

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Abstract

Introduction: In order to improve the prognosis, repair of severe mitral regurgitation should be undertaken at the same time as aortic valve replacement in patients with severe aortic valve stenosis. However, mitral regurgitation may be secondary to pressure overload or ventricular dysfunction and improve after surgery. **Aim:** To assess the incidence of non-severe functional mitral regurgitation before and after isolated aortic valve replacement and determine its influence on the postoperative course. **Methods:** The clinical and surgical characteristics were compared in a cohort of 577 consecutive patients who underwent isolated aortic valve replacement. **Results:** The mean age was 68.4 ± 9.2 years (44% women). Non-severe functional mitral valve regurgitation was detected prior to surgery in 26.5% of the patients. These patients were older ($p = 0.009$), more often had ventricular dysfunction ($p = 0.005$) and pulmonary hypertension (0.002), and had been admitted more frequently for heart failure (0.002), with fewer of them conserving sinus rhythm ($p < 0.001$). Additionally, the pre-surgery existence of mitral regurgitation was associated with greater morbidity and mortality (10.5% vs 5.6%; $p = 0.025$). The mitral regurgitation disappeared or improved prior to hospital discharge in 56.2% and 15.6%, respectively. Independent factors predicting this improvement were the presence of coronary lesions (OR 3.7, $p = 0.038$), and the absence of diabetes (OR 0.28, $p = 0.011$) and pulmonary hypertension (0.33, $p = 0.046$). **Conclusions:** The presence of intermediate degree mitral regurgitation in patients undergoing isolated aortic valve replacement increases morbidity and mortality. However, a high percentage of those who do survive experience disappearance or improvement of the mitral regurgitation.

Keywords: Aortic stenosis; Functional mitral regurgitation; Prosthesis

1. Introduction

In usual clinical practice, patients with severe aortic stenosis (AS) with an indication for surgical treatment who also have important accompanying valve disease, or who may do so in the short- or medium-term, usually undergo combined replacement. In the specific case of mitral regurgitation (MR) associated with severe AS, patients with a severe degree of MR have a worse prognosis, and should undergo mitral valve surgery even though the MR appears functional [1]. However, MR in those patients with intermediate degrees of MR with no structural involvement is usually attributed to the pressure overload caused by the resulting aortic stenosis and deformations in ventricular anatomy and geometry. Although it is generally assumed that MR in these patients will improve or disappear after surgery [2—5], no clear agreement exists about this [6].

Functional MR is a common finding in patients with AS, with an incidence above 60% [1,7,8]. Its management, therefore, is of great importance as simultaneous repair or replacement of MR is associated with greater postoperative morbidity and mortality [9,10].

1.1. Aims

The aims of our study were to determine the incidence of non-severe functional MR in patients undergoing isolated aortic valve replacement at our centre due to severe AS, and assess the factors associated with the MR, its prognosis and evolution.

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2. Materials and methods

2.1. Study population

This retrospective study involved a cohort of patients who underwent surgery for aortic valve replacement due to severe AS from February 1996 to April 2007 and who just received a prosthesis in the aortic position (biological or mechanical). Patients were excluded if the aortic valve replacement was: (a) due to predominant aortic regurgitation or coronary disease with a concomitant aortic valve lesion; (b) in the context of type A aortic dissection with valvular involvement; (c) accompanied by repair or replacement of another heart valve; (d) accompanied by mitral valve disease of rheumatic or endocarditic origin or prolapse; or (e) secondary to SAM associated with dynamic left intraventricular obstruction.

Data were recorded on the demographic, epidemiologic, clinical, electrocardiographic and echocardiographic characteristics of the patients, as well as the results of a coronary arteriography (we defined significant or important coronary lesion when the lumen is narrowed more than 70%), and the type and size of the prosthesis, morbidity and mortality during the perioperative period (defined as the time from hospital admission immediately prior to surgery up to the time of discharge), and the need for reoperation.

2.2. Doppler echocardiogram

Echocardiographic examination was performed prior to surgery and before hospital discharge using Acuson Sequoia (Siemens Co.), Acuson Aspen (Siemens Inc.) and VingMed (GE) devices. The standard examination included M-mode, two-dimensional (2D), spectral and colour Doppler, obtaining the usual planes including the long and short parasternal axis, and apical 3, 4 and 5 chamber planes.

The norms of the American Society of Echocardiography [11] were followed to analyse parameters associated with the aortic valve (maximum and mean gradient, and valve area estimated from the continuity equation, and the presence or absence of aortic regurgitation), the mitral valve (morphology and function) and the tricuspid valve, as well as the presence and degree of left ventricular hypertrophy, systolic function and pulmonary systolic pressure when it could be estimated.

The severity of the regurgitation was estimated semi-quantitatively, from the regurgitant jet area with colour Doppler, pulsed Doppler tracings, and pulmonary vein flow, according to the norms of the American Society of Echocardiography [12].

2.3. Statistical analysis

The continuous variables were expressed as mean $\pm$ stan-standard deviation and the qualitative variables as percentages. The χ^2-test was used for qualitative variables and Student's t-test for continuous variables. Values were considered to be statistically significant if the $p < 0.05$. A stepwise logistic regression multivariate analysis was done, expressing the results as OR with confidence interval.

Table 1
Echocardiography findings in the study population

Maximum gradient (mmHg)	79.2 ± 23.1
Mean gradient (mmHg)	55.0 ± 17.8
Aortic valve area (cm^2)	0.60 ± 0.19
Aortic regurgitation (%)	69
Mitral regurgitation (%)	34.2
Mitral annular calcium (%)	24.3
Left atrial dilatation (%)	22.5
Tricuspid regurgitation (%)	19.2
Left ventricular hypertrophy (%)	85.8
Ejection fraction (%)	60.3 ± 12.3
Systolic pulmonary artery pressure (mmHg)	45.0 ± 18.9

3. Results

3.1. Study population

The mean age of the 577 patients who underwent isolated aortic valve replacement during the study period and who fulfilled the inclusion criteria was 68.3 ± 9.2 years (44% women). The incidence of cardiovascular risk factors was: 59.1% had hypertension, 25.3% were active or ex-smokers, 28.4% had diabetes mellitus and 21.8% dyslipidaemia. Their symptoms were dyspnoea in 73.1% of the patients, angina in 42.8%, effort syncope in 12.7% and heart failure in 56.9%.

Table 1 shows the main echocardiographic details. Prior to surgery, 84.2% of the patients were in sinus rhythm. Coronary arteriography was performed in 82.3% of the patients, with 26.3% of these having important coronary lesions.

3.2. Incidence of mitral regurgitation and associated factors

Of the 577 patients who underwent aortic valve replacement due to AS, 153 (26.5%) had non-severe MR prior to surgery. Comparison of the group of patients with MR prior to surgery (group 1) with the other patients (group 2) showed that the older patients more often had accompanying MR. Compared with group 2, the patients with MR had a greater incidence of left ventricular dysfunction, mitral annular calcium, tricuspid regurgitation and aortic regurgitation, as well as a greater prevalence and severity of pulmonary hypertension, a larger left atrium, and more commonly had dyspnoea and heart failure (Table 2). Additionally, the patients with severe AS and accompanying functional MR were less often in sinus rhythm.

3.3. Surgical results

A biological prosthesis was implanted in 297 patients (51.5%), more often in the patients with accompanying MR. Important associated coronary lesions were present in 25.5% and a concomitant aortocoronary bypass was performed in 80.1% of the patients for whom it was indicated, not being performed by technical reasons (diffuse lesions, small vessels or total occlusions with viability absence) in 19.9% of them. Of the whole group of 577 patients who underwent isolated aortic valve replacement, 9.9% died during the postoperative period. The presence of MR prior to surgery was associated with a greater rate of infections (6.5% vs 2.3%; $p = 0.018$), kidney failure (11.1% vs 6.2%; $p = 0.028$) and low output

Table 2
Univariate analysis of the preoperative presence of mitral regurgitation

	MR (n = 153)	No MR (n = 419)	p-Value
Age	69.8 ± 7.6	67.5 ± 9.4	0.009*
Sex (female)	72 (47.1%)	125 (41%)	0.1
Hypertension	91 (59.5%)	181 (59.3%)	0.080
Smokers	37 (24.2%)	87 (28.5%)	0.055
Dyslipidaemia	30 (19.6%)	76 (24.9%)	0.042*
Diabetes mellitus	40 (26.1%)	89 (29.2%)	0.070
Dyspnoea	106 (76.3%)	197 (70.6%)	0.045*
Prior MI	9(6.4%)	16 (5.7%)	0.1
Angina	45 (32.6%)	132 (47.5%)	0.001*
Syncope	13 (9.4%)	41 (14.6%)	0.040*
Admission for heart failure	92 (66.2%)	145 (52.2%)	0.002*
Sinus rhythm	95 (74.2%)	240 (89.6%)	0.000*
Coronary disease	36 (23.8%)	78 (25.8%)	0.083
Maximum aortic gradient (mmHg)	76.9 ± 23.2	79.7 ± 23	0.2
Mean aortic gradient (mmHg)	54.5 ± 17	55.0 ± 18	0.8
Aortic valve area (cm^2)	0.57 ± 0.16	0.63 ± 0.23	0.2
Aortic regurgitation	121 (80.1%)	190 (65.7%)	0.001*
Tricuspid regurgitation	61 (41.2%)	23 (8%)	0.000*
Mitral annular calcium	60 (40%)	54 (18.2%)	0.000*
Left atrial dilatation	64 (42.4%)	37 (12.5%)	0.000*
Biological prosthesis	95 (63.3%)	148 (49.2%)	0.001*
Ejection fraction (%)	57.0 ± 13.7	61.8 ± 11.5	0.000*
Ejection fraction <55%	99 (35.3%)	56 (18.4%)	0.000*
Ejection fraction <40%	29(19%)	32 (10.5%)	0.005*
Left ventricular hypertrophy	127 (87.6%)	253 (86.3%)	0.1
Systolic pulmonary artery pressure (mmHg)	48.4 ± 15.7	36.2 ± 21.5	0.004*
Pulmonary hypertension	33 (21.6%)	34 (11.1%)	0.003*

* $p < 0.05$.

(28.1% vs 23.3%; p = 0.048) during the immediate postoperative period, as well as greater perioperative mortality (10.5% vs 5.6%%; p = 0.025) (Table 3).

3.4. Evolution of the mitral regurgitation in survivors after surgery

Of the 153 patients with MR prior to surgery, improvement was noted in 110, of whom 86 had no MR on the pre-discharge echocardiogram following aortic valve replacement (Fig. 1). The degree of mitral regurgitation in the postoperative recording worsened in eight patients. Comparison of the group of patients who experienced an improvement in MR with the others (Table 4) showed that an improvement in MR was associated with angina (38.5% vs 21.5%; p = 0.040) and the presence of coronary lesions prior to surgery (29.4% vs 14.3%; p = 0.037), while no improvement in MR after aortic valve replacement was associated with diabetes mellitus (20.9% vs 41.7%; p = 0.01) and pulmonary hypertension (30.6% vs 14.5%; p = 0.022). Multivariate analysis also showed that the presence of prior coronary lesions was an independent marker for MR improvement after surgery (OR 3.7; 95% CI 1.08—12.97; p = 0.038), and that diabetes mellitus (OR 0.28; 95% CI 0.10—0.74; p = 0.011) and pulmonary hypertension (OR 0.33; 95% CI 0.11—0.97; p = 0.046) were independent markers for lack of MR improvement after surgery (Table 5).

Table 3
Univariate analysis of complications according to the presence or absence of mitral regurgitation prior to surgery

	MR	No MR	p-Value
Low output	43 (28.1%)	71 (23.3%)	0.048*
Kidney failure	17 (11.1%)	19 (6.2%)	0.028*
Perioperative MI	3 (2%)	6 (2%)	0.2
Neurological complications	10 (6.5%)	11 (3.6%)	0.069
Respiratory complications	17 (11.1%)	28 (9.2%)	0.1
Infectious endocarditis	2 (1.3%)	5 (1.6%)	0.3
Superficial infection	5 (3.3%)	8 (2.6%)	0.2
Postoperative block	5 (3.3%)	11 (3.6%)	0.2
Reoperation due to bleeding	3 (2%)	3 (1%)	0.2
Suture dehiscence	0 (0%)	6 (2%)	0.086
Death	16 (10.5%)	17 (5.6%)	0.025*

* $p < 0.05$.

4. Discussion

We found that 26.5% of our patients with severe AS with criteria for surgery had intermediate degrees of MR with no clear organic substrate. This was possibly due to the pressure overload that characterises this entity and the resulting anatomic and geometric modification of the ventricle [4]. A recent study found a correlation between improvement in

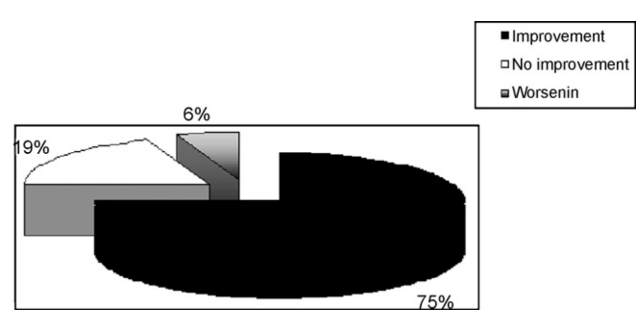

Fig. 1. Evolution of the mitral regurgitation in survivors after surgery.

Table 4
Univariate analysis of the presence or absence of improvement of mitral regurgitation after aortic surgery

	Improvement MR (n = 110)	No improvement MR (n = 36)	p-Value
Age	69.8 ± 7.3	70.4 ± 8.9	0.6
Sex (female)	49 (44.5%)	16 (44.4%)	0.5
Hypertension	64 (58.2%)	20 (55.6%)	0.1
Smokers	24 (21.8%)	12 (33.3%)	0.066
Dyslipidaemia	23 (20.9%)	6 (16.7%)	0.1
Diabetes mellitus	23 (20.9%)	15 (41.7%)	0.010*
Dyspnoea	72 (74.2%)	27(84.4%)	0.1
Angina	37 (38.5%)	7 (21.9%)	0.040*
Syncope	7 (7.2%)	3 (9.4%)	0.2
Admission for heart failure	62 (63.9%)	24 (75%)	0.092
Previous AMI	6 (6.2%)	2 (5.9%)	0.3
Sinus rhythm	64 (70.3%)	21 (67.7%)	0.1
Coronary disease	32 (29.4%)	5 (14.3%)	0.037*
Maximum aortic gradient (mmHg)	76.8 ± 20.6	76.7 ± 25.44	0.9
Mean aortic gradient (mmHg)	57.1 ± 19.2	48.6 ± 16.3	0.1
Aortic valve area (cm^2)	0.56 ± 0.15	0.59 ± 0.18	0.6
Aortic regurgitation	88 (81.5%)	29(85.3%)	0.1
Tricuspid regurgitation	40 (38.5%)	17 (48.6%)	0.090
Mitral annular calcium	43 (40.2%)	14 (41.2%)	0.1
Left atrial dilatation	45 (41.7%)	17 (50%)	0.1
Ejection fraction (%)	53.3 ± 13.1	57.82 ± 14.6	0.3
Ejection fraction <55%	34 (30.9%)	12 (29.3%)	0.1
Ejection fraction <40%	20 (18.2%)	5 (13.9%)	0.1
Left ventricular hypertrophy	91 (89.2%)	32 (94.1%)	0.2
Pulmonary hypertension	16 (14.5%)	11 (30.6%)	0.022*
Systolic pulmonary artery pressure (mmHg)	50.8 ± 15.7	45.0 ± 13.7	0.2
Biological prosthesis	72 (64.9%)	29 (72.5%)	0.2
Size of prosthesis	21.1 ± 1.8	21.2 ± 1.6	0.7
Coronary revascularisation	30 (81.1%)	11 (84.6%)	0.5

AMI: acute myocardial infarction.
* $p < 0.05$.

mitral regurgitation and its aetiology, although we attempted to avoid this possible confounding bias in our series by excluding all those MR of non-functional aetiology [13].

Mitral regurgitation in our population is more common among those patients with left ventricular dysfunction and, although this left ventricular dysfunction is associated with a greater presence of coronary lesions [14] and the association between coronary lesions and aortic stenosis with ventricular dysfunction is known [15], this does not occur with the MR these patients presented, suggesting an additional mechanism apart from the that of the ischaemic MR itself.

The patients in our series with non-severe MR were older, a factor that also favoured the presence of greater accompanying valve disease, had a greater amount of mitral calcium and a greater left atrial dilation, with the resulting lower preservation of sinus rhythm. These factors explain the more unfavourable haemodynamic status that, in turn, could account for the greater presence of pulmonary lesions in the patients with MR, and a greater incidence of admissions due to heart failure.

Table 5
Multivariate analysis of the factors associated with improvement of mitral regurgitation after surgery

	OR	95% CI	p-Value
Smoking	0.49	0.18—1.31	0.1
Diabetes mellitus	0.28	0.10—0.74	0.011*
Angina	1.88	0.62—5.73	0.2
Admission for heart failure	0.89	0.30—2.65	0.8
Coronary disease	3.74	1.08—12.97	0.038*
Tricuspid regurgitation	1.09	0.42—2.82	0.8
Pulmonary hypertension	0.34	0.11—0.97	0.046*

* $p < 0.05$.

The presence of intermediate degrees of MR seemed in our series, unlike the series of Absil et al. [2] to increase perioperative mortality during surgery for aortic valve replacement. This may be explained mostly by the fact that our patients were older, and had greater left ventricular dysfunction and greater associated valve disease, which would partly agree with the results of Barreiro et al. [16] where the presence of moderate MR was an independent factor predicting long-term survival, although this study included various aetiologies (with myxomatous involvement and calcified or ischaemic degeneration in 70% of the patients).

The immediate postoperative evolution in the patients who had intermediate degrees of MR was excellent, as has been seen in other studies [2—4], with a high percentage of improvement (71.8%). A search for markers predicting this improvement in the MR showed that it was associated with the presence of coronary disease prior to surgery, while absence of improvement was associated with pulmonary hypertension and diabetes mellitus. However, improvement was not associated with the mitral calcification or atrial dilation reported elsewhere [3], though this may be due to the low prevalence of mitral calcification (24.3%) in comparison with other studies [17]. Moreover, the association between a greater presence of coronary disease and improvement in the MR could be related with the coronary revascularisation, which would reduce the restrictive component of the MR, thus favouring its improvement after surgery.

The role of diabetes mellitus in the lack of improvement of the MR after surgery may be explained by two mechanisms; first, the indirect association between diabetes mellitus and coronary atherosclerosis, which in both its acute symptomatic form and its silent form does little or nothing to favour ventricular remodeling. However, in our series this first possibility would not appear to be especially relevant in the lack of short-term improvement in non-severe MR, but rather the opposite, as explained above for coronary disease. Second, the role of diabetic cardiomyopathy should be considered. A recent review by Boudina et al. [18] discussed the relation between diabetes mellitus and the development of heart failure, and the role played in this latter by myocardial fibrosis or diabetic microangiopathy [19], suggesting that, in this case, patients with diabetes mellitus, even in the absence of important coronary atherosclerosis, may have a less favourable ventricular geometry as a direct consequence of the diabetes on the ventricle, thus hindering improvement of the MR after surgery.

The results of our study could be relevant in older patients with severe aortic stenosis and functional non-severe mitral regurgitation with high perioperative risk and poor prognosis who could be candidates to transcatheter aortic valve implantation as a new therapeutic option.

4.1. Limitations

The study was retrospective, and its results do not enable identification of patients who would most benefit from combined replacement. Nonetheless, it is a large series that has produced valuable information about the perioperative repercussions of MR. Additionally, a semiquantitative measurement was made of the MR, mainly because the long study period prevents use of a reliable quantitative measurement from the outset of the analysis, such as PISA.

5. Conclusion

In patients with severe aortic stenosis scheduled for valve replacement surgery, the accompanying presence of intermediate degrees of mitral regurgitation represents an additional risk. This is mainly because the patients are older with greater ventricular dysfunction, more tricuspid regurgitation and more heart failure. This mitral regurgitation decreases or disappears in a high percentage of patients after surgery, although the improvement is influenced by the diabetic status of the patient.

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