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Incidence of prosthesis-patient mismatch in patients receiving mitral Biocor® porcine prosthetic valves

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Abstract

Background: *The aim was to assess the incidence of prosthesis-patient mismatch (PPM) after mitral valve replacement (MVR) in patients receiving Biocor® porcine or mechanical valves, and to evaluate the effect of PPM on long-term survival.*

Methods: *All patients undergoing MVR between 2009 and 2013 received either mechanical or bioprosthetic valves (Biocor® porcine). PPM was defined as severe when the indexed effective orifice area was < 0.9 cm^2/m^2, moderate between 0.9 cm^2/m^2 and 1.2 cm^2/m^2 or absent > 1.2 cm^2/m^2. The primary endpoint was all-cause long-term mortality.*

Results: *Among a total of 136 MVR, PPM was severe in 27%, moderate in 44% and absent in 29% of patients. Implanted valves were 57% mechanical and 43% bioprosthetic. Only 3% of patients with mechanical valves had severe PPM vs. 59% with bioprostheses ($p < 0.0001$). Sixty-month survival with severe mismatch was 0.559 (SE 0.149) and with no mismatch 0.895 (SE 0.058) ($p = 0.043$). Survival of patients suffering from severe mismatch, or moderate mismatch with pulmonary hypertension (PH) was 0.749 (SE 0.101); while for patients with no mismatch or with moderate mismatch without PH, survival was 0.951 (SE 0.028) ($p = 0.016$).*

Conclusions: *About one-fourth of patients had severe PPM and almost all of them had received a bioprosthesis. Sixty-month survival was significantly lower in patients with severe mismatch, or moderate mismatch with PH. Specifically, when a bioprothesis is chosen and while further evidence on the impact of PPM on clinical outcomes appears, surgeons are recommended to follow a preoperative strategy to implant a mitral prosthesis of adequate size in order to prevent PPM.* (Cardiol J 2016; 23, 2: 178–183)

Key words: prosthesis-patient mismatch, mitral valve replacement, bioprosthetic valves, pulmonary hypertension, long-term survival

Introduction

In contrast to prosthesis-patient mismatch (PPM) associated to aortic valve surgery, PPM after mitral valve replacement (MVR) is a concept rarely explored. Prosthesis-patient mismatch occurs when the effective orifice area (EOA) of the prosthetic valve is too small relatively to the patient's body surface area (BSA), resulting in increased postoperative transvalvular gradient. The ratio between EOA and BSA is known as indexed EOA (iEOA). Usually, moderate mitral PPM is

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defined for iEOA ≤ 1.2 cm^2/m^2 and ≥ 0.9 cm^2/m^2; while severe mismatch is considered for iEOA < 0.9 cm^2/m^2.

At present, around two dozen retrospective cohort studies have been reported with controversial outcomes about long-term survival of patients with severe mitral PPM [1]. Nevertheless, some evidence supports the notion that increased long-term mortality in severe PPM may be associated to preoperative pulmonary hypertension (PH) [2, 3]. Recently, Aziz et al. [4] reported that severe PPM after MVR with bioprosthetic valves adversely affects long-term survival in older patients. However, in this study, poor outcomes may be explained by confounding variables, since almost 25% of patients had undergone previous cardiac surgery, and 52% had received concomitant coronary or aortic surgery procedures. Considering that bioprosthetic valves have in general lower EOA than mechanical prostheses, and are preferentially implanted in older patients, further research is needed to evaluate the incidence of PPM in this age group. Furthermore, there is little information regarding the incidence of mitral PPM in older patients receiving the Biocor® porcine bioprosthesis (Biocor Industria e Pesquisas Ltda, Belo Horizonte, Brazil), in spite of being widely used in South American countries [5]. Based on these observations, the objective of this study was to assess the incidence of PPM after MVR in patients receiving Biocor® porcine prosthetic valves compared with mechanical valves, and to evaluate the effect of mitral PPM on early mortality and long-term survival.

Methods

All patients undergoing MVR between 2009 and 2013 at the Buenos Aires University Hospital of Argentina and its associated Clinics were included in this study. Baseline and operative data were collected retrospectively from a clinical registry. Patients with concomitant procedures such as tricuspid annuloplasty, aortic valve replacement, or coronary artery bypass grafting were also incorporated. All the patients had standard surgical procedures for cardiopulmonary bypass through median sternotomy and transseptal biatrial approach. Cardiac arrest was obtained with antegrade infusion of St. Thomas solution and mild hypothermia. Implanted prostheses included mechanical and bioprosthetic valves. All tissue valves were Biocor® porcine bioprostheses, while mechanical valves were of different types. Estimates of EOA for each valve type and size were obtained from reference normal values as summarized in Table 1. Indexed EOA was defined as prosthetic EOA divided by BSA, and PPM was defined as severe for iEOA < 0.9 cm^2/m^2, moderate for iEOA between 0.9 cm^2/m^2 and 1.2 cm^2/m^2 or absent for iEOA > 1.2 cm^2/m^2. Valve size selection relied on surgeon's preference, and PPM was preset after the operation. Severe PH was defined as systolic pulmonary artery pressure > 55 mm Hg.

To assess long-term outcomes, postoperative follow-up was conducted by telephone interviews, questionnaires, or examination of hospital records. The endpoint was all-cause long-term mortality. The protocol was assessed and approved by the Institutional Ethics Committee (ENERI Ethics Committee; Chairperson Lylyk P.; file number of approval: ENERI-056; date of approval: November 8th, 2014). No specific informed consent was required since this work was a retrospective analysis, and the institutional review board waived the need for patient consent.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or standard error (SE). Kolmogorov-Smirnov goodness-of-fit test was used to analyze normal distributions. Univariate comparison of dichotomous variables was performed using χ^2 and odds ratio (OR) with the associated 95% confidence interval (95% CI). Yates' corrected χ^2 was used when cell expected values were between 3 and 5, and 2-tailed Fisher's exact test when values were below 3. Continuous variables were compared using Student's t test, Mann-Whitney U or ANOVA. The Kaplan-Meier method was used to assess the time-related survival probability. Survival curves were compared with the Mantel-Cox log-rank test. Statistical analysis was performed with SPSS Statistics for Windows, Version 17.0. Chicago, SPSS Inc. A 2-tailed p value ≤ 0.05 was considered statistically significant.

Results

Preoperative and intraoperative variables are shown in Table 1. For the total series of 136 MVR, PPM was severe in 27% (n = 36), moderate in 44% (n = 60) and absent in 29% (n = 40) of patients. Mechanical valves were implanted in 57% of cases (n = 78) and bioprostheses in 43% (n = 58). Table 2 includes specific valve types; all the tissue valves implanted were Biocor® porcine prostheses [3, 6–10]. Table 3 summarizes selected preoperative and

Table 1. Patient preoperative and intraoperative characteristics (n = 136).

Variables	All type (n = 136)	Bioprosthesis (n = 58)	Mechanical (n = 78)	P
Age [years]	67.0 ± 11.5	74.0 ± 5.64	67.3 ± 11.5	0.00008
Age ≥ 70 years	72 (52.9%)	51 (87.9%)	12 (15.4%)	< 0.00001
Sex (female)	74 (54.4%)	33 (56.9%)	41 (52.6%)	0.616
Body surface area [m^2]	1.84 ± 0.20	1.83 ± 0.20	1.84 ± 0.17	0.774
Pulmonary systolic pressure [mm Hg]	46.9 ± 11	49.3 ± 10.4	45.1 ± 11.6	0.031
Preoperative atrial fibrillation	49 (36.0%)	19 (32.8%)	30 (38.5%)	0.493
Emergent/urgent status	26 (19.1%)	9 (15.5%)	17 (21.8%)	0.357
Endocarditis	14 (10.3%)	5 (8.6%)	9 (11.5%)	0.777
Ejection fraction < 50%	24 (17.6%)	12 (20.7%)	12 (15.4%)	0.422
Previous cardiac surgery	5 (3.7%)	2 (3.4%)	3 (3.8%)	1.000
EuroSCORE II (median, $P_{25\%,75\%}$) [%]	2.34 (1.41–5.21)	2.49 (2.06–4.28)	1.51 (0.95–4.67)	0.043
Associated procedures:				
Tricuspid annuloplasty	3 (2.2%)	0 (0.0%)	3 (2.2%)	–
Aortic valve replacement	13 (9.6%)	6 (10.3%)	7 (9.0%)	–
Coronary bypass surgery	15 (11.0%)	8 (13.8%)	7 (9.0%)	–
Arrhythmia surgery	2 (1.5%)	0 (0.0%)	2 (1.5%)	0.213
Bypass time (median, $P_{25\%,75\%}$) [min]	70.0 (60–88)	75.0 (60–90)	70.0 (60–89)	0.583
Cross-clamp time (median, $P_{25\%,75\%}$) [min]	50.0 (40–60)	50.0 (45–60)	50.0 (40–60)	0.718
Chordal preservation	15 (11.0%)	6 (10.3%)	9 (11.5%)	1.000

Table 2. Types of prosthetic mitral valve implanted and effective orifice area based on reference normal values.

Effective orifice area [cm^2]	n	25 mm	27 mm	29 mm	31 mm	33 mm	References
Mechanical valves:							
ATS	8	1.8 ± 0.5	2.8 ± 0.3	2.8 ± 0.3	2.9 ± 0.2	2.9 ± 0.2	[6]
Carbomedics	17	2.2	2.4	2.4	2.3	2.3	[3, 6]
On-X	4	2.2 ± 0.9	2.2 ± 0.9	2.2 ± 0.9	2.2 ± 0.9	2.2 ± 0.9	[3, 6]
St. Jude Medical	49	1.9	2.0	2.3	2.3	2.4	[3, 6, 7]
Bioprosthetic valves:							
Biocor (SJM)	58	1.4	1.5 ± 0.3	2.3 ± 0.6	2.2 ± 0.6	2.3 ± 0.7	[8, 9, 10]

Effective orifice areas are expressed as mean or mean ± standard deviation

Table 3. Patient characteristics based on the occurrence of prosthesis-patient mismatch (PPM) (n = 136).

Variable	No PPM	Moderate PPM	Severe PPM	P
Number of patients	40 (29%)	60 (44%)	36 (27%)	–
Mean age [years]	65.1 ± 12.9	63.7 ± 11.8	74.1 ± 6.3	0.0001
Age ≥ 70 years	20 (50%)	22 (37%)	30 (83%)	< 0.0001
Female	26 (65%)	25 (42%)	23 (64%)	0.030
Body surface area [m^2]	1.74 ± 0.17	1.89 ± 0.17	1.84 ± 0.19	0.0002
Pulmonary pressure [mm Hg]	47.9 ± 12.1	44.8 ± 11.3	48.5 ± 12.6	0.614
Atrial fibrillation	11 (28%)	20 (35%)	18 (47%)	0.179
Emergent/urgent status	9 (23%)	8 (14%)	9 (24%)	0.392
Bioprosthetic valve	10 (25%)	14 (23%)	34 (94%)	< 0.0001

Emergent/urgent status includes endocarditis and postinfarction mitral valve dysfunction

intraoperative characteristics of patients based on the occurrence of PPM. Severe PPM was more common in older patients, women and in individuals receiving a bioprothethic valve. Only 3% (n = 2) of patients with mechanical valves had severe PPM vs. 59% (n = 34) of patients with bioprosthetic valves ($p < 0.0001$). Among the 34 Biocor® valves implanted and associated with severe mismatch, 59% (n = 20) were 25 mm in diameter and the rest 27 mm. The incidence of moderate or severe PPM after mechanical and bioprosthetic MVR was not different in patients younger or older than 70 years (Fig. 1).

Overall operative mortality was 9.6% (13/136 patients) and isolated non-urgent MVR mortality was 6.3% (6/95 patients), while mortality after combined or urgent MVR was 15.5% (5/33 patients), showing worse results as the complexity of the procedure increased. Univariate analysis only identified previous mitral valve surgery to be associated with operative mortality (OR 7.27, 95% CI 1.09–48.3). Acute endocarditis (OR 3.05, 95% CI 0.73–12.8), urgent or emergent status (OR 1.30, 95% CI 0.33–5.12), bioprosthetic valve implantation (OR 1.17, 95% CI 0.37–3.69) and severe PPM (OR 0.81, 95% CI 0.21–3.15) failed to demonstrate an association with operative mortality. The total follow-up period was 310.3 patient-years (mean time 37 months). Sixty-month survival after MVR for patients with severe mismatch (iEOA < 0.9 cm^2/m^2) was 0.559 (SE 0.149). In contrast, long-term survival of patients with moderate mismatch (iEOA 0.9–1.2 cm^2/m^2) was 0.937 (SE 0.043) and with no mismatch (iEOA > 1.2 cm^2/m^2) 0.895 (SE 0.058) (log rank p = 0.043) (Fig. 2). Cumulative survival of patients suffering from severe mismatch, or moderate mismatch with severe PH was 0.749 (SE 0.101), while in patients with no mismatch or with moderate mismatch without severe PH, survival was 0.951 (SE 0.028) (log rank p = 0.016) (Fig. 3). Finally, for the group of patients exclusively receiving a bioprosthetic valve, long-term survival in the presence of severe PPM or moderate mismatch with PH was 0.440 (SE 0.169), while in individuals with no PPM, or with moderate mismatch without PH, survival was 0.766 (SE 0.125) (log rank p = 0.556).

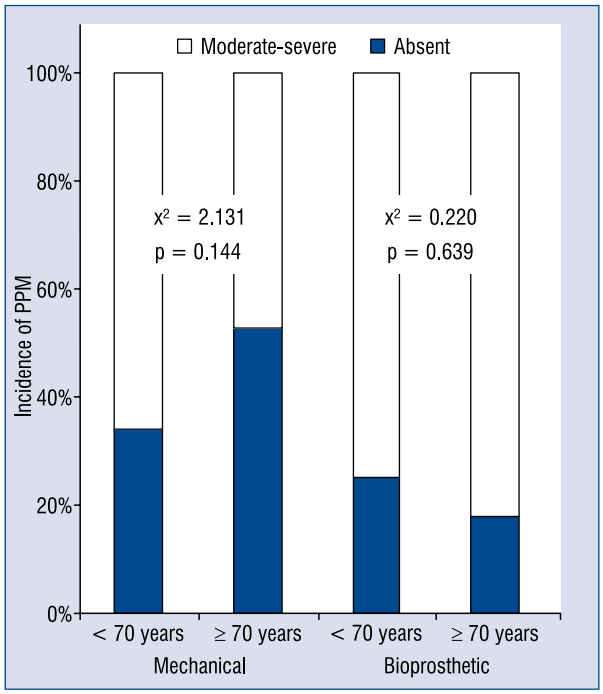

Figure 1. Incidence of prosthesis-patient mismatch (PPM) after mechanical and bioprosthetic mitral valve replacement in patients < 70 years and ≥ 70 years.

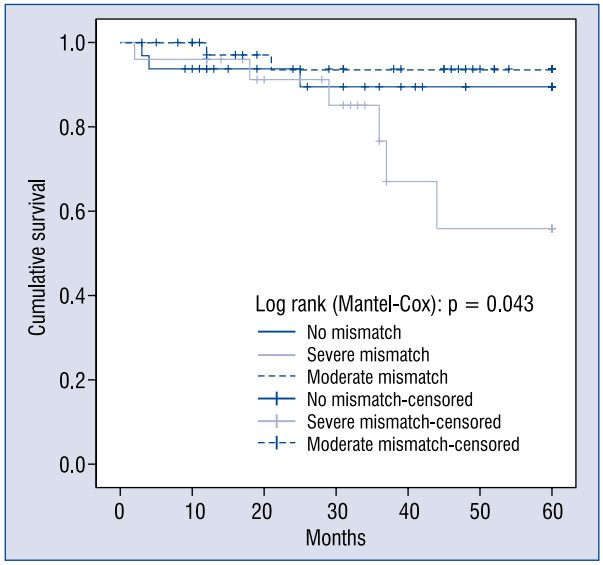

Figure 2. Kaplan-Meier cumulative 60-month survival, stratified by an indexed effective orifice area < 0.9 cm^2/m^2 (severe mismatch group), between 0.9 and 1.2 cm^2/m^2 (moderate mismatch group), or > 1.2 cm^2/m^2 (no mismatch group).

Discussion

Approximately one-fourth of our patients undergoing MVR had severe PPM based on the immediate postoperative theoretical estimation, according to EOA reference values of each prosthesis implanted. Furthermore, 94% of patients with severe PPM had received a bioprosthetic valve, and almost 60% of them had the smallest diameter bioprosthesis (Biocor® 25 mm). The overall incidence

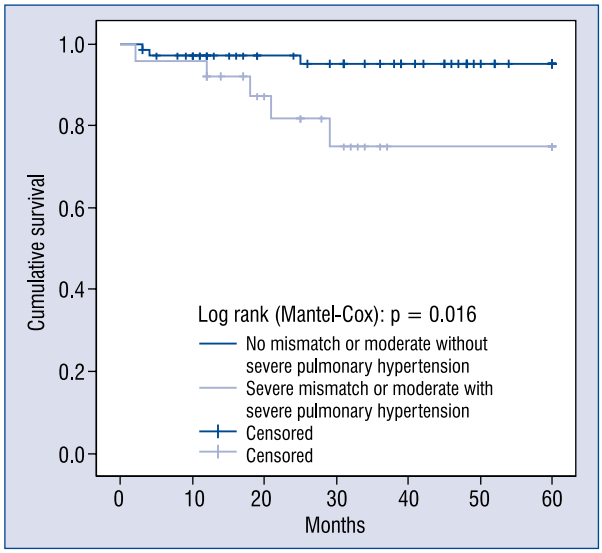

Figure 3. Kaplan-Meier cumulative 60-month survival, stratified in two groups: severe mismatch or moderate mismatch with systolic pulmonary artery pressure > 55 mm Hg vs. no mismatch or moderate mismatch with systolic pulmonary artery pressure ≤ 55 mm Hg.

of PPM (iEOA ≤ 1.2 cm^2/m^2) after MVR ranges from 3.7% to 85.9%; moderate PPM varies from 37.4% to 69.5%, and severe PPM from 8.7% to 16.4% [1, 3, 4, 7, 9, 11–14]. When considering values lower than 1.2 cm^2/m^2 to define PPM, Bouchard et al. [14] found only 3.7% of mismatch in patients receiving a mechanical valve. In contrast, Matsuura et al. [11] found 58.9% of PPM with the same cut-off value, including mechanical prostheses and approximately one-third of bioprosthesis.

Aziz et al. [4] observed that with mechanical valves the incidence of moderate or severe PPM was higher in patients younger than 65-years-old, while with bioprosthetic valves the incidence of PPM was higher in older patients. In the current study, an association between type of prosthesis, age and mismatch was not confirmed; nevertheless, the absence of statistical significance could depend on the power of the sample. Since bioprosthetic valves are commonly implanted in older people, we have concluded that PPM exclusively depends on the comparative lower EOA of bioprostheses, with age acting as a confounding variable. Based on theoretical speculations, we established that by avoiding 25 mm-diameter Biocor® porcine valves, the incidence of severe PPM may be drastically reduced from 59% to 24%. Truly, one should abandon these small valves with small EOAs if there are other marketed valves of same outer ring diameter and larger EOAs. Nevertheless, this is not an intra-operative surgeon decision, but more a department strategy decision.

In addition to PPM, outcomes of MVR may be related to several other pathophysiological conditions, such as preoperative right and left ventricular function, mitral valve disease (stenosis or regurgitation), previous atrial fibrillation and PH, concomitant coronary artery bypass grafting or aortic valve replacement, previous cardiac operation and preservation of mitral sub-valvular apparatus during surgery [1]. In our series, operative mortality was significantly associated with previous mitral valve surgery, and poorer outcomes were also observed with combined surgery or urgent MVR.

Some evidence supports that only severe PPM is associated with higher mortality (HR: 3.2, 95% CI 1.5–6.8), while moderate PPM does not significantly affect long-term survival [7]. On the contrary, other studies did not detect a deleterious impact of PPM on long-term survival after MVR [11–13, 15]; however, there is apparently an interaction between preoperative PH and long-term outcome in patients with both moderate and severe PPM [2, 3]. In our series, not only patients with severe mitral PPM associated or not to preoperative PH but also those presenting moderate mismatch with preoperative systolic pulmonary pressure > 55 mm Hg showed lower long-term survival.

Most studies assessing long-term effects of mitral PPM practically only include patients with mechanical prosthesis, since they are less prone to late degenerative calcification that may change EOA over time, as occurs in those receiving a bioprosthesis. Therefore, the interpretation of these unpredictable bioprosthesis changes throughout time must be based on the theoretical estimation of immediate postoperative PPM. To eliminate a possible confounder, patients with mechanical prosthesis were removed for an extra survival analysis. In this case, comparative cumulative survival showed worse results in patients with severe PPM or moderate mismatch plus PH, in contrast to those having no mismatch or suffering a moderate PPM without PH. Nevertheless, the low power of the sample must be pondered again to interpret these findings.

Finally, though only a small proportion of our patients had posterior leaflet and chordal preservation to protect left ventricular function, this must be considered a common reason for implanting smaller prosthesis.

The present study has some limitations. Firstly, its design was non-randomized and retrospective; hence, selection bias or unidentified confounders may have influenced the results. There are no uniform EOA values of Biocor® prosthesis in the literature and at present, no clear reference values have been firmly established for each valve size. Since iEOA is a hemodynamic measure and very much dependent on individualized hemodynamic conditions, EOA would have been ideally determined postoperatively for each patient's prosthesis, but postoperative echocardiography showed to be inconsistent in the retrospective series [4]. Therefore, estimates of EOA for each type and size were obtained from referenced normal values. Moreover, a probable high type II error must be considered when assessing factors associated with operative mortality. The major complication of porcine tissue valves in mitral position is structural valve deterioration; hence, the resultant valve cusp calcifications may reduce EOA and worsen PPM. Another limitation of our work is that long-term structural deterioration or bioprosthesis dysfunction was not systematically assessed with echocardiography.

Conclusions

PPM after MVR is a poorly explored concept and current evidence is not conclusive to determine whether mitral PPM affects early mortality and long-term survival. In this study, approximately one-fourth of patients had severe PPM and almost all of them had received a bioprosthesis. PPM failed to demonstrate an association with operative mortality; however, 60-month cumulative survival was significantly lower in patients suffering from severe mismatch, or moderate mismatch with severe PH. Especially, when a bioprothesis is chosen and while further evidence on the impact of PPM on clinical outcomes appears, surgeons are recommended to follow a preoperative strategy to implant a mitral prosthesis of adequate size in order to prevent PPM.

Conflict of interest: None declared

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