ORIGINAL ARTICLE

Moderate Patient-Prosthesis Mismatch Has No Independent Effect on 30-Day Mortality After Isolated Aortic Valve Replacement

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Introduction and objectives. It remains unclear whether the presence of moderate patient-prosthesis mismatch after isolated aortic valve replacement can increase 30-day mortality. The aim of this study was to determine whether moderate mismatch is an independent predictor of early global or cardiac mortality after aortic valve replacement.

Methods. The study involved 272 adult patients (median age, 72 years; interquartile range, 66-76 years) undergoing isolated aortic valve replacement. Moderate mismatch was considered to be present if the projected indexed effective orifice area was ≤0.85 cm^2/m^2 and >0.65 cm^2/m^2. Severe mismatch was present if the projected indexed effective orifice area was ≤0.65 cm^2/m^2. Follow-up to assess 30-day survival was conducted in 100% of patients.

Results. Moderate mismatch was observed in 37.9% of patients. None had a severe mismatch. Multivariate analysis identified the following independent predictors of global mortality at 30 days: left ventricular ejection fraction <50% (*P*=.03) and age (*P*=.01). The same variables were identified as predictors of 30-day cardiac survival, but at a higher level of statistical significance: left ventricular ejection fraction <50% (*P*=.006) and age (*P*=.008). The analysis did not identify moderate mismatch as a predictor of global or cardiac 30-day mortality in our study population.

Conclusions. Our findings suggest that when patient-prosthesis mismatch is moderate it remains far from clear that the patient's survival will be compromised by inserting a prosthesis of the size measured into a small aortic annulus.

Key words: *Aortic valve. Valve prosthesis. Surgery. Survival.*

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El desajuste paciente-prótesis moderado no aumenta de modo independiente la mortalidad a 30 días tras la sustitución aislada de válvula aórtica

Introducción y objetivos. La cuestión de si un desajuste paciente-prótesis moderado tras la sustitución aislada de la válvula aórtica puede aumentar la mortalidad a 30 días continúa abierta. El objetivo de este estudio es verificar si un desajuste moderado es un factor predictivo de carácter independiente respecto a la mortalidad temprana total o cardiaca tras la sustitución valvular aórtica.

Métodos. Formaron la población del estudio 272 adultos (mediana de edad, 72 años; intervalo intercuartílico, 66-76 años) a los que se practicaron intervenciones de sustitución aislada de la válvula aórtica. Se consideró que había un desajuste moderado si el área efectiva del orificio indexada que se preveía era ≤ 0,85 y > 0,65 cm^2/m^2. Se consideró que había un desajuste grave si el área efectiva del orificio indexada prevista era ≤ 0,65 cm^2/m^2. El seguimiento a 30 días respecto a la supervivencia se cumplió en el 100% de los casos.

Resultados. Se detectó un desajuste moderado en el 37,9% de los pacientes. No hubo ningún caso de desajuste grave. Un análisis multivariable identificó los siguientes factores predictivos independientes para la mortalidad total a 30 días: fracción de eyección ventricular izquierda < 50% (p = 0,03) y edad (p = 0,01). Las mismas variables pero con un mayor nivel de significación estadística eran factores predictivos de la supervivencia por causas cardiacas a 30 días: fracción de eyección ventricular izquierda < 50% (p = 0,006) y edad (p = 0,008). Nuestro análisis no identificó que el desajuste moderado fuera un factor predictivo de la mortalidad total o cardiaca a 30 días en nuestra muestra de estudio.

Conclusiones. Nuestros resultados indican que la evidencia de que la implantación de la prótesis del tamaño medido en un anillo aórtico pequeño compromete la supervivencia del paciente está lejos de ser clara cuando el desajuste paciente-prótesis es moderado.

Palabras clave: *Válvula aórtica. Prótesis valvular. Cirugía. Supervivencia.*

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ABBREVIATIONS

AVR: aortic valve replacement
EOA: effective orifice area
IEOA: indexed effective orifice area
PPM: patient-prosthesis mismatch
TPG: transvalvular pressure gradient

INTRODUCTION

According to the original definition published by Rahimtoola in 1978, "mismatch can be considered to be present when the effective prosthetic valve area, after insertion into the patient, is less than that of a normal human valve."[1] Pibarot,[2] more recently, has divided mismatch into 2 entities: severe mismatch defined by the presence of an indexed effective orifice area (IEOA) ≤0.65 cm^2/m^2 and moderate mismatch with IEOA values between 0.65 cm^2/m^2 and 0.85 cm^2/m^2. Severe patient-prosthesis mismatch (PPM) is a rare condition that has been reported to be an independent risk factor for overall 30-day mortality after aortic valve replacement (AVR).[3] On the other hand, the question of whether the presence of moderate PPM does have an impact on post-operative survival is still open. In fact, contradictory data is available in the literature concerning this issue. Several confounding variables, including the pre-operative characteristics of the sample population and the time of effective orifice area (EOA) evaluation might help to explain these discordances. The aim of this study was to determine whether moderate mismatch is an independent predictor of early global or cardiac mortality in a sample population undergoing isolated aortic valve replacement.

METHODS

Between July 2000 and November 2008, a total of 463 patients underwent aortic valve replacement at our institution. We decided to include in our study all adult patients (≥18 years old) undergoing isolated AVR for aortic valve stenosis or mixed aortic valve disease in whom prosthesis type, model, labeled size and anticipated IEOA values were available.

The following patients were excluded: those with pure aortic regurgitation, those who had undergone previous cardiac surgical procedures, those undergoing a multiple valve operation or aortic surgery, those scheduled for surgery because of valve endocarditis, those undergoing emergency or urgent AVR, and those undergoing concomitant coronary artery bypass grafting. The sample population of our analysis was then constituted by 272 patients. As shown in Table 1, which lists operative data collected from a computerized database, our sample population mainly consisted of elderly patients (median age, 72 years; interquartile range, 66-76 years). Patient status at 1 month after the operation was obtained by hospital visit. Follow-up to assess 30-day survival was conducted in 100% of patients. The primary endpoint of our study was death. Deaths were classified as cardiac or noncardiac on the basis of review of medical records, including autopsy when this was performed.

Surgical Technique

A median sternotomy was performed as a standard approach, and cardiopulmonary bypass with mild systemic hypothermia (32°C) was utilized in all patients. Myocardial protection was achieved with a combination of antegrade intermittent cold blood cardioplegia and topical cooling. Prosthesis size was selected according to the size of the aortic annulus as measured with the manufacturer's gauge. The largest suitable valve was always selected for a given patient. Valvular prostheses were implanted in the supra-annular position with mattress sutures with Teflon pledgets.

Definitions

Body surface area (BSA) was derived from the Dubois formula. The in vivo EOA values were estimated by reference tables based on mean EOA values of the different prostheses, types and sizes (Table 2) available in the literature.[2,4-9]

The IEOA was obtained by dividing the in vivo EOA by the patient's body surface area. Moderate mismatch was assumed to be present if the anticipated IEOA was ≤0.85 cm^2/m^2 and >0.65 cm^2/m^2. Severe mismatch was assumed to be present if the projected IEOA was ≤0.65 cm^2/m^2. The remaining definitions have been previously described.[10]

Statistical Analysis

Initially, univariate and bivariate analyses were used to determine the main characteristics of the sample population. Continuous variables following a normal distribution according to the Kolmogorov-Smirnov test were expressed as mean (standard deviation). Continuous variables not normally distributed were expressed as median [25th-75th percentiles]. Comparisons of proportions between groups were performed using the χ^2 test or Fisher's exact test in the case of small proportions for categorical variables, the Student *t*-test for independent groups in the bivariate analysis for normal continuous variables and otherwise the

TABLE 1. **Sample Population Data**

Operative Data	Total (n=272)	Patients With PPM (n=103)	Patients Without PPM (n=169)	*P*
Preoperative				
Age, y[a]	72 (67-77)	74 (60-77)	72 (64-76)	.008
Female	130 (48%)	57 (55%)	73 (43%)	.06
BSA, m^{2}[,b]	1.74 (0.18)	1.76 (0.17)	1.73 (0.18)	.23
DM type 2	77 (28%)	33 (32%)	44 (26%)	.33
SAH	189 (70%)	83 (81%)	106 (63%)	.002
COPD	39 (14%)	15 (15%)	24 (14%)	1
BMI ≥30	98 (36%)	47 (46%)	51 (30%)	.01
CRF	12 (4%)	5 (5%)	7 (4%)	.77
AF	46 (17%)	14 (14%)	32 (19%)	.31
LVEF <50%	37 (14%)	11 (11%)	26 (15%)	.36
PH	43 (11%)	16 (16%)	27 (16%)	1
NYHA III/IV	134 (49%)	50 (49%)	84 (52%)	.90
Pure aortic stenosis	210 (77%)	83 (81%)	127 (75%)	.37
Previous MI	4 (1.5%)	1 (1%)	3 (2%)	1
Peripheral vascular disease	7 (3%)	1 (1%)	6 (4%)	.26
Previous stroke	16 (6%)	5 (5%)	11 (7%)	.79
Logistic euroSCORE[a]	5.1 (3.5-7)	5.1 (3.5-6.7)	4.5 (2.8-7.0)	.19
Intraoperative				
ECC time[b]	82 min (22)	85 min (21)	80 min (22)	.06
Clamp time[b]	61 min (17)	63 min (15)	60 min (18)	.09
Bioprosthesis	184 (68%)	93 (90%)	91 (54%)	<.001

AF indicates atrial fibrillation; BMI, body mass index; BSA, body surface area; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; ECC, extracorporeal circulation; LVEF, left ventricular ejection fraction; MI, myocardial infarction; min, minutes; PH, pulmonary hypertension; PPM, patient-prosthesis mismatch; SAH, systemic arterial hypertension.
[a]Values are median (interquartile range).
[b]Values are mean (standard deviation).

TABLE 2. **Effective Orifice Area (cm2) of Prosthetic Valves Used in This Study and Frequency (%) of Implantation of Each Valve Prosthesis**

Valve Prosthesis	19 mm	21mm	23 mm	25 mm	Reference
Mechanical					
St Jude M Regent (8.5%)	1.60 (5.1%)	2 (7.4%)	2.2 (5.9%)	2.5 (0.4%)	Bach[4]
Omnicarbon (4.7%)		1.3 (1.1%)	1.7 (1.8%)	2.3 (1.8%)	Bech-Hanssen[5]
St Jude M Standard (3.6%)	1.04 (1.8%)	1.38 (0.7%)	1.52 (1.1%)	2.08	Pibarot[2]
MCRI On-X (3.3%)	1.5 (0.4%)	1.7 (0.7%)	2 (2.2%)	2.4	Chambers[6]
Sorin Bicarbon (2.2%)	1.36	1.46 (1.1%)	1.98 (1.1%)	2.39	Rosenhek[7]
Bioprosthetic					
CE Perimount (24.7%)	1.1 (3.7%)	1.3 (8.5%)	1.5 (10.3%)	1.8 (2.2%)	Pibarot[2]
Mitroflow (26.8%)	1.2 (5.1%)	1.4 (14.4%)	1.6 (7.3%)		Tasca[8]
Soprano (8.1%)	18 mm 1.25 (0.4%)	20 mm 1.56 (1.5%)	22 mm 1.78 (4.8%)	24 mm 1.91 (1.5%)	Bleiziffer[9]
CE Perimount Magna (5.1%)	1.41 (1.1%)	1.49 (2.9%)	1.89 (0.7%)	2.09 (0.4%)	Bleiziffer[9]
St Jude Epic Supra (3%)		1.6 (0.8%)	2.38 (2.2%)		Bleiziffer[9]

Mann Whitney test. The 95% confidence interval (CI) for moderate patient-prosthesis mismatch was calculated using binomial proportions estimation approximation.

During analysis the statistician was blind to the presence of mismatch according to the IEOA. All variables listed in Table 1 were analyzed as independent variables by binomial multivariate logistic regression, where the dependent variable was global mortality or cardiac mortality (death=1, no death=0). In addition, 2 selection methods were used to enter the independent variables in the multivariate analysis: Forward Conditional Selection and Forward Wald Selection. Both

methods enter variables into the model sequentially according to an order that depends on the variable's association with the outcome (global and cardiac mortality) measured by the significance of the score statistic. In Forward Conditional Selection, removal testing is based on the probability of a likelihood-ratio statistic evaluated by conditional parameter estimates. In Forward Wald Selection, removal testing is based on the probability of the Wald statistic. The 3 selection methods used obtained the same results for each model studied.

The impact of predictor variables was expressed as odds ratios (OR) with 95% CI, calculated using the Woolf method.

Differences associated with *P* values <.05 were considered to be statistically significant. The SPSS (version 14, SPSS, Chicago, IL, USA) and MINITAB V.11 (Minitab, State College, PA, USA) packages were used for data analysis.

RESULTS

Moderate patient-prosthesis mismatch was detected in 37.9% (95% CI, 32.1-43.6; n=103) of the analyzed population. No patient suffered from severe PPM. Thirty-day overall mortality was 5.5% (n=15). Global early mortality was lower in the group with mismatch, without a chieving significance (no PPM group, 6.5%; PPM group, 3.9%; *P*=.42). Cardiac early mortality was 3.7% (n=10) abd was higher in the group with mismatch, without a chieving significance (no PPM group, 3.6%; PPM group, 3.9%; *P*=1). Noncardiac causes of 30-day mortality were mediastinitis (n=2), sepsis (n=1), pulmonary embolism (n=1), and respiratory distress syndrome (n=1).

According to logistic regression analysis, patients with moderate mismatch had higher incidence of obesity (*P*=.03; OR=1.9; 95% CI, 1.0-3.5) and more often received a bioprosthesis (*P*<.001; OR=0.1; 95% CI, 0.05-0.02) than those without mismatch.

Multivariate analysis identified the following independent predictors of 30-day global mortality: left ventricular ejection fraction <50% (*P*=.03; OR=3.8; 95% CI, 1.1-12.9) and age (*P*=.01; OR=1.3; 95% CI, 1.1-1.5).

The same variables, but with a higher level of statistical significance, were identified as predictors of 30-day cardiac survival: left ventricular ejection fraction <50% (*P*=.006; OR=9.7; 95% CI, 1.9-48.6) and age (*P*=.008; OR=1.2; 95% CI, 1.0-1.3). Moderate mismatch was not found to be an independent predictor of global or cardiac early mortality. To analyze the postoperative functional class, we established two groups: NYHA class I-II and NYHA class III-IV. Of the 257 survivors, 15 patients (5.8%) were in NYHA class III-IV, without a statistically significant difference between the mismatch and no mismatch groups (no PPM group, 1.9%, PPM group, 3.9%; *P*=.3).

DISCUSSION

The residual transvalvular pressure gradient (PG) is the most commonly used indicator to assess the residual obstruction of the prosthesis and is exponentially correlated with the IEOA. Thus, the IEOA can be decreased within a wide range without significantly changing the PG until reaching a value of 0.85 cm^2/m^2, when a steep increase in PG occurs.[11] On the basis of this hemodynamic principle, it is widely accepted that PPM (IEOA, ≤0.85 cm^2/m^2) should be avoided. Pibarot and Dumesnil[12] proposed a 3-step algorithm for its prevention, as follows: *a)* calculate the patient's BSA; *b)* determine the minimal valve EOA required to ensure an IEOA >0.85, >0.80, or >0.75 cm^2/m^2, given the patient's BSA as calculated in step 1; and *d)* select the type and size of prosthesis that has reference values for EOA greater than or equal to the minimal EOA value obtained in step 2.

Nevertheless, in those patients with a large BSA and relatively small aortic annulus requiring AVR, the native annulus may not fit the size of the prosthesis required and so the surgeon faces the problem of whether to perform an annular enlargement procedure or to possibly compromise the surgical result by accepting PPM.

A number of annular enlargement procedures have been described: the Nicks procedure,[13] the Manouguian technique[14] and the Konno procedure.[15] These techniques allow for the implantation of prosthetic valves 1 or 2 sizes larger than the original size of the aortic annulus.[16] Although these procedures have been frequently performed with good results, some authors have reported increased operative mortality.[12] It is clear that when performing these types of procedures, there is an increase in cross-clamp time.[17] This variable has been suggested to be associated with increased mortality following AVR, particularly in the elderly.[18] The use of a stentless bioprosthesis has been proposed as an alternative to annulus enlargement when facing the possibility of PPM. This type of prosthesis has been said to have an excellent hemodynamic profile, and resembles native aortic valve function when assessed by transthoracic echocardiography (TTE) postoperatively.[19] Nevertheless, according to a recent meta-analysis, the clinical significance of this hemodynamic advantage is not very clear.[20]

In our study, moderate PPM was not an independent risk factor for early mortality. Contradictory results on this issue exist in the literature. This is often due to the wide heterogeneity

between studies. For example, there are at least 2 different mismatch entities (severe and moderate PPM) and several parameters are used to define PPM: IEOA, indexed geometric orifice area and the Z value.[21] Bridges et al[22] published the largest study on PPM, which analyzed data acquired from a total of 42 310 patients undergoing isolated AVR. Small EOA were reported to be associated with increased operative mortality, but among patients receiving the same prosthesis model and size, those patients with a larger BSA had better outcomes. It was speculated that the impact of PPM on short-term mortality may be less important than several unmeasured confounding variables, including the BSA.[22]

We have recently reviewed the concept of mismatch as a risk factor for early and mid-term mortality after AVR and shown that severe mismatch could be a predictor of overall 30-day or mid-term overall mortality, whereas moderate PPM, which is much more frequent than severe PPM, could be an independent risk factor of early and mid-term overall mortality in the subgroup of patients with a poor ejection fraction.[1] In the present study, because of the small percentage of patients with a poor ejection fraction (14%), it was not possible to conduct any statistical analysis with sufficient power to show an association between this variable, PPM and early mortality.

In contrast to the abovementioned review on PPM,[3] in the present study we selected a homogeneous population, excluding patients with pure aortic regurgitation and those undergoing a multiple valve procedure, CABG or an aortic procedure.

No patient suffered from severe PPM, whereas moderate PPM was detected in 37.9% of the analyzed population. Even in our selected sample population, the analysis was not able to show any statistical association between moderate PPM and 30-day mortality.

It is also important to highlight that our sample population mainly consisted of elderly patients (median age, 72 years), a subgroup in which the presence of PPM has been previously reported not to be associated with higher postoperative mortality.[23]

Limitations

The main limitations of the present study are related to its retrospective nature and the relatively small size of the sample population. In particular, the low number of deaths after AVR precluded a powerful survival analysis. In addition, moderate PPM was predicted by reference tables based on mean EOA that may not reflect the actual in vivo value of the IEOA.

CONCLUSIONS

Although our results should be taken with caution due to the statistical limitations of the study, they suggest that when patient-prosthesis mismatch is moderate it remains far from clear that the patient's survival will be compromised by inserting a prosthesis of the size measured into a small aortic annulus.

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