Impact of Prosthesis-Patient Mismatch on Cardiac Events and Midterm Mortality After Aortic Valve Replacement in Patients With Pure Aortic Stenosis

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Background—Prosthesis-patient mismatch (PPM) occurs when the effective orifice area (EOA) of the prosthesis being implanted is too small in relation to body size, thus causing abnormally high transvalvular pressure gradients. The objective of this study was to examine the midterm impact of PPM on overall mortality and cardiac events after aortic valve replacement in patients with pure aortic stenosis.

Methods and Results—The indexed EOA (EOAi) was estimated for each type and size of prosthesis being implanted in 315 consecutive patients with pure aortic stenosis. PPM was defined as an EOAi $\leq$0.80 cm^2/m^2 and was correlated with overall mortality and cardiac events. PPM was present in 47% of patients. The 5-year overall survival and cardiac event-free survival were 82$\pm$3% and 75$\pm$4%, respectively, in patients with PPM compared with 93$\pm$3% and 87$\pm$4% in patients with no PPM ($P\leq$0.01). In multivariate analysis, PPM was associated with a 4.2-fold (95% CI, 1.6 to 11.3) increase in the risk of overall mortality and 3.2-fold (95% CI, 1.5 to 6.8) increase in the risk of cardiac events. The other independent risk factors were history of heart failure, NHYA class III-IV, severe left ventricular hypertrophy, and absence of normal sinus rhythm before operation.

Conclusions—PPM is an independent predictor of cardiac events and midterm mortality in patients with pure aortic stenosis undergoing aortic valve replacement. As opposed to other risk factors, PPM may be avoided or its severity may be reduced with the use of a preventive strategy at the time of operation. **(*Circulation*. 2006;113:&NA;-.)**

Key Words: echocardiography ■ hemodynamics ■ prognosis ■ stenosis ■ valves

Prosthesis-patient mismatch (PPM) occurs when the effective orifice area (EOA) of the prosthesis being implanted is less than that of the normal human valve.[1,2] This is a frequent problem in patients undergoing aortic valve replacement (AVR), especially in patients with aortic stenosis (AS), and its main hemodynamic consequence is to generate high transvalvular pressure gradients through normally functioning prosthetic valves.[1–7] The issue of PPM still generates much controversy with regard to its clinical relevance and, in particular, with regard to its effect on survival after operation. Whereas some authors have found that the persistence of PPM results in lower postoperative survival,[8,9] others have reported that PPM and/or small prostheses have no significant impact on survival,[10–13] and on this basis they concluded that PPM is not an important issue. However, the parameter used to define PPM was different from one study to the other, thus making difficult the comparison and interpretation of the results of these previous studies. To this effect, it should be emphasized that the only parameter yet demonstrated as being valid to define PPM is the prosthesis EOA indexed to the patient's body surface area (EOAi).[3–5,14–16] This index has consistently been shown to correlate with postoperative gradients as well as being predictive of adverse outcomes.[3–9,14–24]

Clinical Perspective p 0000

The objective of this study was thus to analyze the impact of PPM, defined on the basis of EOAi, on midterm mortality and cardiac events in patients with pure AS undergoing AVR.

Methods

Patients

Between September 1997 and September 2003, 320 consecutive patients underwent AVR for pure AS. Hospital mortality was 1.6% (5/320), and only the 315 patients who were discharged from the hospital were included in this study. Clinical, echocardiographic, operative, and outcome data were prospectively collected in a

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TABLE 1. Reference EOA for Each Size and Model of Prosthesis

		Prosthesis Size, mm					
	No. of Patients (%)	19	21	23	25	27	Reference
Medtronic Freestyle	18 (6)	...	1.35	1.5	2.0	2.3	21
St Jude Medical Toronto SPV	25 (8)	...	1.3	1.5	1.7	...	21
Carpentier-Edwards Perimount	149 (47)	1.1	1.3	1.6	1.8	...	21
Mitroflow (Sulzer)	31 (10)	1.2	1.4	1.6	...	...	*
Carbomedics	81 (25.7)	1.0	1.5	1.6	2.0	...	21
Prima-Plus Edwards	5 (2)	...	1.1	1.5	1.8	...	21
Carbo-Seal (Carbomedics)	6 (2)	...	1.5	1.6	2.0	...	21

*Data obtained from our echocardiography laboratory.

computerized database. The data were collected as part of a larger observational study aiming to identify the independent risk factors for postoperative morbidity and mortality in patients undergoing AVR. All patients had a follow-up visit at the hospital at 3 months. This visit included a physical examination, the determination of NYHA functional class, and an ECG. Thereafter, the patients were interviewed by telephone annually to assess their status. If any fatal or cardiac event occurred, these events were documented by communicating with the patient's treating physician(s). For the purpose of the present study, we selected the patients who had undergone surgery at least 12 months before the closing date of the study (September 30, 2004), and a final telephone follow-up was conducted within 1 month after this date. The follow-up was complete in 99% (313/315) of the patients, and the mean follow-up time was 3.7±1.7 years.

Doppler-Echocardiographic Data

Preoperative echocardiographic data were obtained at our institution 0 to 7 days before operation in 94% (296/315) of patients. The Doppler-echocardiographic measurements were performed as previously described.[24,25] Briefly, the dimensions of the left ventricle (LV) were assessed with 2-dimensionally guided M-mode tracings, with the measurements being made according to the recommendations of the American Society of Echocardiography. Left ventricular mass (LVM) was calculated with the corrected American Society of Echocardiography formula.[26] LVM was indexed to patient height with an allometric power of 2.7 to compensate for the effect of overweight or obesity on LVM indexation, and the normal values were considered <50 g/m$^{2.7}$ for men and <47 g/m$^{2.7}$ for women.[27] Severe LV hypertrophy was considered present when the preoperative LVM index was in the 90th percentile of the studied cohort. The relative wall thickness was calculated as previously described.[24,25] The LV ejection fraction was determined by the Simpson method.

End Points

Study end points were (1) overall mortality[28] excluding in-hospital mortality and (2) cardiac events, defined as cardiac death, sudden death, hospital readmission for angina, heart failure, or lipothymia/syncope.

Definition of PPM

Previous studies have shown that PPM as well as its consequences on morbidity and mortality can be predicted at the time of operation by calculating the projected EOAi.[5,8,9,16,23] In the present study the projected EOAi was derived from the published normal in vivo EOA values[5] for each model and size of prosthesis implanted in this cohort except for the Mitroflow prosthesis (Table 1). Indeed, for this prosthesis model, the normal in vivo EOA values have not yet been reported. We thus used the normal EOA values established in our echocardiography laboratory from the data measured 1 year after operation in the cohort of patients with the Mitroflow prosthesis (Table 1). This information was used in the present study to determine the projected EOA of the patients who received Mitroflow prosthesis. The projected EOA was then divided by body surface area, and PPM was defined as a projected EOAi ≤ 0.8 cm^2/m^2. The selection of this value was based primarily on the results of previous studies.[19,23] In addition, we did a preliminary analysis that confirmed that this cutoff value provides the best compromise between sensitivity and specificity to predict the studied end points.

Statistical Analysis

Continuous variables were expressed as mean±SD values and compared with a 2-tailed *t* test. The normality of the distributions in the 2 groups was tested by means of the Kolmogorov-Smirnov test, and, when not normal, the data were log transformed. Categorical variables were expressed as percentage of total and compared with the χ^2 test. Cumulative probability values of survival and cardiac event-free survival were estimated by the Kaplan-Meier method, reported as mean±SEM, and compared with the log-rank test. The effect of the preoperative and operative variables on survival and event-free survival was assessed with the Cox proportional hazard model in a stepwise manner. The variables with a probability value <0.1 were inserted in the final models. The variables tested in the models were as follows: (1) preoperative variables: age, gender, body mass index, NYHA functional class, severity of AS, hypertension, diabetes, coronary artery disease (presence and severity: number of diseased vessels), history of myocardial infarction, LV ejection fraction, history of heart failure, arteriopathy, chronic renal insufficiency, chronic obstructive pulmonary disease, sinus rhythm, left bundle branch block, LVM index, relative wall thickness ratio, presence of severe LV hypertrophy; and (2) operative variables: urgent/emergent operation, way of delivering cardioplegia, aortic cross-clamp time, bicuspid aortic valve, etiology of valve disease, coronary artery bypass graft, type of prosthesis implanted (stentless bioprosthesis, stented bioprosthesis, mechanical prosthesis), implantation of the prosthesis in supra-annular position, EOAi, PPM, aortic root replacement, isolated replacement of ascending aorta, and septal myectomy. To assess the effect of PPM on outcome variables, we developed a first model with PPM entered as a dichotomous variable (PPM: EOAi ≤ 0.8 cm^2/m^2 versus no PPM) and then a second model with EOAi entered as a continuous variable. The proportional hazards assumption was verified for all models. The data were statistically analyzed with the use of SPSS 13.0 (SPSS Inc).

Results

Preoperative and Operative Data

Forty-seven percent of patients had PPM, and their mean EOAi was 0.71±0.05 cm^2/m^2 versus 0.91±0.09 cm^2/m^2 in the patients with no PPM ($P<0.0001$). Five percent of patients had severe PPM (EOAi ≤ 0.6 cm^2/m^2). Tables 2 and 3 show the preoperative and operative data, respectively. When compared with patients with no PPM, patients with PPM were older and had higher body surface area, body mass index, prevalence of female gender, and proportion of 21-mm

TABLE 2. Preoperative Data

	Mismatch (n=149)	No Mismatch (n=166)	P
Age, y	74±8	68±11	<0.001
Age >75 y	90 (60)	42 (25)	<0.001
Sex (female)	88 (59)	70 (42)	0.003
Body surface area, m^2	1.85±0.21	1.76±0.19	0.007
Body mass index, kg/m^2	27±5	25±4	<0.001
Diabetes	22 (15)	31 (19)	NS
Hypertension	81 (54)	116 (70)	0.005
Coronary artery disease	71 (48)	56 (37)	0.03
≥2-vessel disease	40 (27)	27 (16)	0.04
Sinus rhythm	134 (90)	150 (90)	NS
Arteriopathy	22 (15)	40 (24)	NS
Chronic renal insufficiency	4 (3)	15 (9)	0.01
COPD	13 (9)	10 (6)	NS
Preoperative NYHA class III-IV	55 (37)	46 (28)	NS
Myocardial infarction	9 (6)	8 (5)	NS
Preoperative heart failure*	46 (31)	38 (23)	NS
LVEF, %	59±11	56±12	0.05
LVEF ≤40%	13 (9)	22 (14)	NS
LVEDD, mm	50±7	52±8	0.01
IVS, mm	14±2	14±2	NS
LVPW, mm	12.9±1.5	12.6±1.6	NS
LVM, g	281±65	298±78	0.04
LVMi, $g/m^{2.7}$	74±17	77±19	NS
Preoperative LV hypertrophy	135 (96)	152 (97)	NS
Preoperative severe LV hypertrophy	8 (6)	22 (14)	0.02
RLVWT	0.52±0.11	0.49±0.09	<0.001
Aortic valve EOA, cm^2	0.86±0.18	0.83±0.17	NS
Aortic valve EOAi, cm^2/m^2	0.48±0.09	0.46±0.08	0.04
Mean aortic valve gradient, mm Hg	50±14	48±13	NS

Values are expressed as mean±SD or number (%). COPD indicates chronic obstructive pulmonary disease; LVEF, LV ejection fraction; LVEDD, LV end-diastolic diameter; IVS, interventricular septum; LVPW, LV posterior wall; RLVWT, relative LV wall thickness; and LVMi, LVM index.

*History of preoperative hospital admission for heart failure.

prosthesis. Conversely, patients with no PPM had a higher prevalence of hypertension and chronic renal failure, and they tended to have worse preoperative LV ejection fraction. They also had a lower relative wall thickness ratio, higher preoperative LVM, and, according, a higher prevalence of severe LV hypertrophy.

Follow-up Data

The mean follow-up time was similar in both groups (PPM: 3.9±1.7 years versus no PPM: 3.4±1.7 years; *P*=NS). During follow-up, 23 patients died in the PPM group versus 6 patients in the no PPM group (*P*<0.001). The causes of death are reported in Table 4. The 5-year cumulative survival was 82±3% in patients with PPM and 93±3% in patients with no PPM (*P*=0.01) (Figure 1).

During the same follow-up period, 30 patients with PPM and 11 patients with no PPM (*P*<0.001) had cardiac events.

TABLE 3. Operative Data

	Mismatch (n=149)	No Mismatch (n=166)	P
Urgent/emergent	10 (7)	12 (7)	NS
Bicuspid aortic valve	16 (11)	43 (26)	0.001
Stented bioprosthetic valve	109 (74)	71 (43)	0.006
Stentless bioprosthetic valve	23 (15)	25 (15)	NS
Full-root implantation	8 (35)	14 (56)	NS
Valve replacement implantation	15 (65)	11 (44)	NS
Mechanical valve	17 (11)	70 (42)	<0.0001
Prosthesis size ≤21 mm	119 (80)	53 (32)	<0.0001
Projected EOAi, cm^2/m^2	0.71±0.05	0.91±0.09	<0.0001
CABG	62 (42)	52 (31)	NS
CABG ≥2 grafts	26 (17)	14 (8)	0.03
Supra-annular prosthesis implantation	21 (14)	32 (19)	NS
Aortic root replacement	8 (5)	19 (11)	NS
Aortic root enlargement	0 (0)	3 (2)	NA
Isolated ascending aorta replacement	4 (3)	11 (7)	NS
CPB time, min	120±34	119±32	NS
Aortic cross-clamp time, min	82±24	84±26	NS

Values are expressed as mean±SD or number (%). CABG indicates coronary artery bypass graft; CPB, cardiopulmonary bypass.

The 5-year event-free survival was 75±4% in the PPM group and 87±4% in the no-PPM group (*P*=0.005) (Figure 2). In multivariate analysis, PPM was a strong independent predictor of both overall mortality (Table 5) and cardiac events (Table 6). PPM was associated with a 4.2-fold (95% CI, 1.6 to 11.3) increase in the risk of mortality and 3.2-fold (95% CI, 1.5 to 6.8) increase in the risk of cardiac events. PPM remained a strong independent predictor of mortality (hazard

TABLE 4. Cause of Death and Types of Cardiac Events

	Mismatch (n=149)	No Mismatch (n=164)	P
Cause of death			
Cardiac	11 (7.4)	1 (0.6)	...
Sudden death	1 (0.7)	2 (1.2)	...
Hemorrhage	1 (0.7)	1 (0.6)	...
Cancer	6 (4.0)	1 (0.6)	...
Infection	2 (1.3)	0 (0)	...
Unknown	1 (0.7)	1 (0.6)	...
Other	1 (0.7)	0 (0)	...
Overall mortality	23 (15)	6 (3.6)	0.003
Cardiac events			
Cardiac death	11 (7.4)	1 (0.6)	...
Sudden death	1 (0.7)	2 (1.2)	...
Heart failure	13 (8.7)	5 (3.0)	...
Syncope/lipothymia	4 (2.7)	3 (1.8)	...
Angina	1 (0.7)	0 (0)	...
Total cardiac events	30 (20.2)	11 (6.6)	0.006
Follow-up time interval, y	3.9±1.7	3.4±1.7	NS

Values are expressed as mean±SD or number of patients (%).

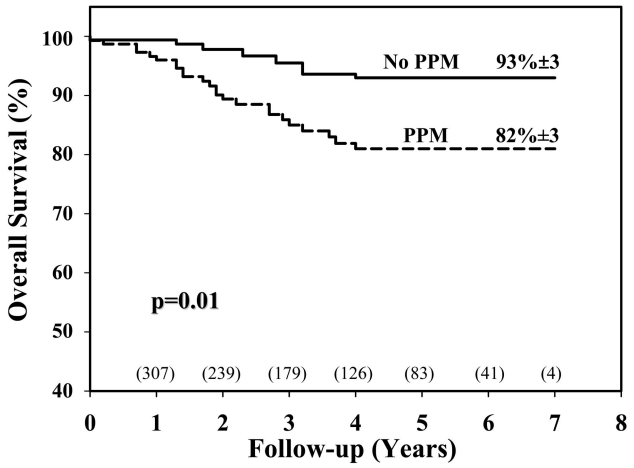

Figure 1. Overall survival in patients with PPM vs those with no PPM. Numbers between parentheses indicate the number of patients at each follow-up year.

ratio, 4.01; 95% CI, 1.5 to 11.2) and cardiac events (hazard ratio, 2.9; 95% CI, 1.3 to 6.5) when age and gender were forced into the models. A second model was developed by incorporating into the multivariate model EOAi as a continuous variable instead of PPM (Tables 5 and 6). In this model, higher EOAi (ie, lower degree of PPM) was independently associated with reduction in the risk of overall mortality (hazard ratio, 0.67; 95% CI, 0.46 to 0.97 for 0.1 cm^2/m^2 increase in EOAi) and cardiac events (hazard ratio, 0.63; 95% CI, 0.47 to 0.84). EOAi also remained an independent predictor of mortality (hazard ratio, 0.65; 95% CI, 0.43 to 0.98) and cardiac events (hazard ratio, 0.66; 95% CI, 0.48 to 0.90) when age and gender were forced into the models. The other independent risk factors were history of heart failure and absence of normal sinus rhythm for overall mortality and severe LV hypertrophy, NYHA class III-IV, and absence of normal sinus rhythm for cardiac events.

Discussion

The major finding of this study is that PPM is a strong and independent risk factor for cardiac events and midterm

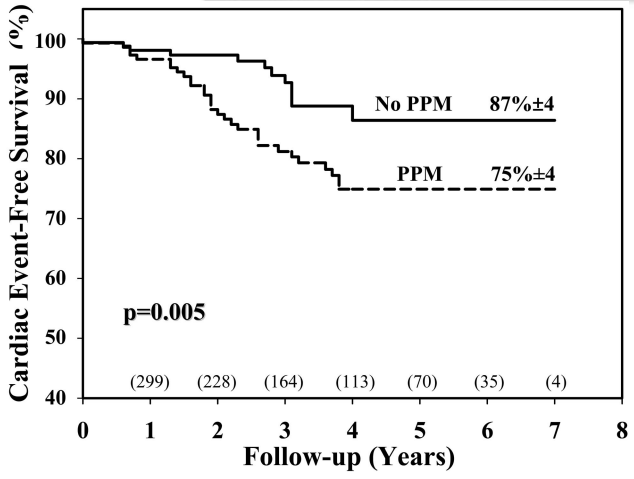

Figure 2. Cardiac event–free survival in patients with PPM vs those with no PPM. Numbers between parentheses indicate the number of patients at each follow-up year.

TABLE 5. Multivariate Predictive Models for Overall Mortality

	Model 1		Model 2	
Variable	*P*	HR (95% CI)	*P*	HR (95% CI)
Preoperative variables				
History of heart failure	0.023	2.5 (1.1–5.4)	0.04	2.3 (1.02–5.1)
Sinus rhythm	0.006	0.2 (0.09–0.52)	0.001	0.2 (0.1–0.48)
Operative variables				
EOAi, cm^2/m^2	...	...	0.04	0.67 (0.46–0.97)*
PPM (EOAi ≤0.80 cm^2/m^2)	0.004	4.2 (1.6–11.3)	...	...

In model 1, we entered PPM, defined as an EOAi ≤0.80 cm^2/m^2; in model 2, we entered EOAi as a continuous variable. Only the variables that reached statistical significance in multivariate analysis are shown in this table.

*In the case of model 2, the hazard ratio (HR) of the EOAi variable represents the decrease in the risk of mortality per 0.1 cm^2/m^2 increase in EOAi.

mortality in patients undergoing AVR for pure AS. Indeed, the risk of cardiac events and mortality was increased ≈3- to 4-fold in patients with PPM as opposed to those with no PPM.

The issue of PPM still generates controversy concerning its effects on postoperative morbidity and mortality. Whereas some authors have found that the persistence of PPM results in higher incidence of cardiac events and lower survival rates,[8,9,17,18,21,23] others have reported that PPM and/or small prosthesis size has no or minimal impact on morbidity and mortality.[10–13]

Definition of PPM

The discrepancies between these previous studies are likely due to the fact that they did not use the same parameter to define PPM. Some authors have indeed attempted to characterize PPM using the internal geometric orifice area (GOA) of the prosthesis rather than the EOA because it is more reproducible.[10,11,13,28,29] The GOA is a static manufacturing specification based on the ex vivo measurement of the diameter of the prosthesis. The criteria used for its measurement unfortunately differ from one type of prosthesis to the other so that, for instance, the IGA grossly overestimates the EOA but to a much larger extent in the case of a bioprosthesis than in the case of a mechanical prosthesis (Figure 3).[6] In the present study the indexed GOA varied from 1.1 to 1.9 cm^2/m^2 for an EOAi of 0.80 cm^2/m^2. Hence, the relation between GOA and EOA varies extensively depending on the type and size of prosthesis, and it has been shown that the indexed GOA cannot be used to predict postoperative gradients.[16,28] Most studies using the indexed GOA have failed to find any significant relation between this parameter and adverse clinical outcomes.[10,11,13,28,29] This should, however, come as no surprise because, as mentioned, the indexed GOA does not bear any relationship whatsoever to postoperative hemodynamics. In contrast, the indexed EOA has consistently been shown to correlate with postoperative gradients as well as being highly predictive of adverse outcomes.[3,5,8,9,16,21–24,30]

Impact of PPM on Cardiac Events

Our results are consistent with previous studies reporting that PPM is independently associated with a higher occurrence of cardiac events.[17,18,21,23] Milano et al[21] reported that the free-

TABLE 6. Multivariate Predictive Models for Cardiac Events

	Model 1		Model 2	
Variable	*P*	HR (95% CI)	*P*	HR (95% CI)
Preoperative variables				
Sinus rhythm	0.003	0.3 (0.13–0.65)	0.001	0.25 (0.1–0.6)
Severe preoperative LV hypertrophy	0.018	2.8 (1.2–6.6)	0.01	3.0 (1.3–7.1)
Preoperative NYHA	0.045	1.9 (1.02–3.8)	0.03	2.1 (1.2–3.1)
Operative variables				
EOAi	...	...	0.003	0.63 (0.47–0.84)*
PPM (EOAi $\leq$0.80 cm^2/m^2)	0.003	3.2 (1.5–6.8)	...	...

In model 1, we entered PPM, defined as an EOAi $\leq$0.80 cm^2/m^2; in model 2, we entered EOAi as a continuous variable. Only the variables that reached statistical significance in multivariate analysis are shown in this table.

*In the case of model 2, the hazard ratio (HR) of the EOAi variable represents the decrease in the risk of mortality per 0.1 cm^2/m^2 increase in EOAi.

dom of late cardiac events (new episodes of angina, congestive heart failure, or myocardial infarction) was 56±15% in patients with severe PPM (EOAi $\leq$0.60 cm^2/m^2), 80±5% in patients with moderate PPM (EOAi $\leq$0.90 cm^2/m^2 and $>$0.60 cm^2/m^2), and 94±4% in patients with no PPM (EOAi $>$0.90 cm^2/m^2). Moreover, in a recent study including 1681 patients, Ruel et al[23] reported that PPM defined as an EOAi $\leq$0.80 cm^2/m^2 is associated with a 60% increase in the risk of congestive heart failure after AVR.

Impact of PPM on Survival

Several studies reported that PPM has a significant impact on in-hospital mortality.[8,9,12] This finding may be related to the fact that patients' LV function and hemodynamic status are more vulnerable during the early postoperative period and that an increase in afterload due to PPM may contribute to the development of irreversible LV failure, especially in patients already having depressed LV function before operation.[9] In the present study the number of perioperative deaths was, however, too small to allow meaningful analysis of the impact of PPM on in-hospital mortality.

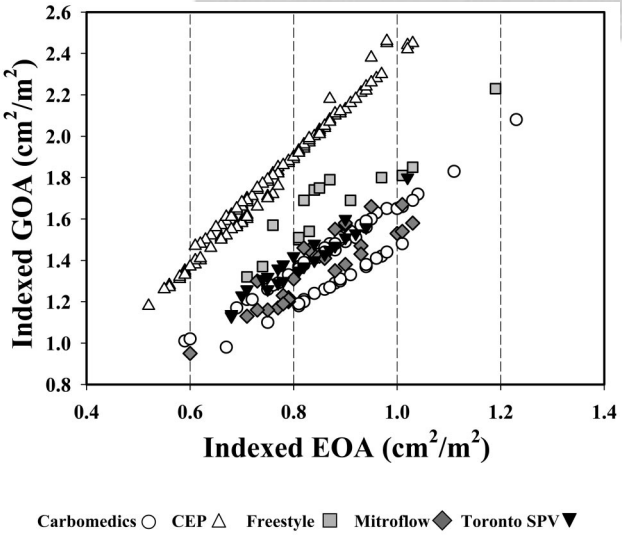

Figure 3. Comparison between the indexed GOA and the EOAi. CEP indicates Carpentier-Edwards Perimount.

In a study of 2516 patients who underwent AVR with a stented bioprosthetic valve, Rao and colleagues[8] reported that freedom from valve-related mortality at 12 years was significantly lower in patients with an indexed EOA of $\leq$0.75 cm^2/m^2 compared with those with a larger indexed EOA (75.5% versus 84.2%; P=0.004). However, other studies with shorter follow-up failed to demonstrate any significant impact on midterm mortality.[12,18,23] The present study is thus the first study to report that PPM is an independent risk factor for midterm mortality. The absence of significant association between PPM and midterm mortality reported in previous studies may be due to the fact that, as opposed to the present study, these previous studies were performed in heterogeneous populations of patients including patients with pure AS, pure aortic insufficiency, and mixed aortic valve disease. Patients with aortic insufficiency are more likely to receive a larger valve with lower probability of having PPM, but their postoperative survival is generally lower than that of patients with AS probably because they have eccentric rather than concentric LV hypertrophy.[31]

Potential Mechanisms Responsible for the Adverse Effects of PPM

Mehta et al[32] reported that LV hypertrophy is a strong risk factor for in-hospital mortality after AVR. In the present study the presence of severe LV hypertrophy before operation was also found to be an independent risk factor for cardiac events after AVR. Previous studies have suggested that the residual pressure overload due to PPM may hamper the regression of LV hypertrophy after AVR,[19,24,33] and this may have contributed to the higher occurrence of cardiac events and deaths in the PPM group. Beyond the persistence of LV hypertrophy after AVR, other mechanisms may explain the worse outcome of patients with PPM. In this regard, Rajappan et al[34] demonstrated that, in patients with AS and angiographically normal coronary arteries, the improvement of coronary flow reserve after AVR is directly dependent on the improvement of valve EOA that is achieved with AVR. Hence, the increased LV systolic pressure associated with PPM may compromise the normalization of coronary flow reserve after AVR[34–36] and may thus predispose to the

development of LV dysfunction and the occurrence of adverse events.

Clinical Implications

The practical implications of these findings are important given that PPM is a frequent occurrence with a prevalence of 47% in the present study, which is consistent with the results generally reported in the literature (19% to 70%).[5,6,9,16] More importantly, as opposed to other risk factors for cardiac events and mortality, PPM is a modifiable risk factor that can, in large part, be avoided with the use of a prospective strategy at the time of operation.[5,9,16,37] As proposed by Pibarot and Dumesnil,[5] this strategy consists of the systematic calculation of the projected EOAi before the implantation of the prosthesis. If the projected EOAi is lower than the recommended value (0.8 to 0.9 cm^2/m^2), the surgeon may either use another type of prosthesis with a better hemodynamic profile and hence a larger EOA (eg, bileaflet mechanical valves of new generation or stentless bioprostheses)[16,38,39] or perform an aortic root enlargement procedure to accommodate a larger prosthesis.[37] Castro et al[37] have demonstrated that this prospective strategy to avoid PPM can be applied with success. Nonetheless, it is also possible that, given the operative circumstances (eg, comorbidities, anatomy of the aortic root), the surgeon may have to accept the PPM, and if such is the case, the calculation of the projected EOAi is useful to forecast how the selected prosthesis will perform thereafter in the patient. Particular attention should be given to completely avoid PPM, ie, provide a minimum EOAi of $\geq$0.8 to 0.9 cm^2/m^2, in young, physically active patients as well as in patients with depressed LV function since they are the most vulnerable to PPM.[9] However, lesser values of EOAi are probably acceptable in older sedentary patients with preserved LV function. This underscores the importance of individualizing the PPM preventive strategy according to the patient's age, level of physical activity, and status of LV function. If PPM cannot be completely avoided, however, every effort should be made to implant a prosthesis that would provide the largest possible EOA because it has been suggested that the postoperative regression of LV mass as well as the improvement of coronary flow reserve is directly related to the magnitude of valve EOA improvement achieved with AVR.[30,34]

Study Limitations

The number of patients with severe PPM was not sufficient to allow for separate analysis in these patients and determine whether severe PPM was associated with significantly more adverse outcomes compared with mild/moderate/no PPM. Nevertheless, the fact that the EOAi emerged as an independent predictor of adverse outcomes when entered as a continuous variable in multivariate analysis (Tables 5 and 6) supports the notion that the adverse effects of PPM increase with its degree of severity, as suggested in previous studies.[9,18,21]

The body surface area may overestimate the cardiac output requirement in obese patients, and, consequently, the utilization of the EOA indexed to body surface area would then overestimate the degree of PPM in these patients. Hence, the difference between the PPM and non-PPM groups may have been overstated because of the significantly greater proportion of obese patients (49% versus 27%) in the PPM group.

Finally, this study was not of randomized design, and it is possible that unrecognized biases may have influenced the results.

Conclusion

PPM is a strong and independent predictor of cardiac events and midterm mortality in patients with pure AS undergoing AVR. As opposed to most other risk factors for postoperative morbidity and mortality, PPM is a modifiable risk factor that can be avoided, or its severity may be reduced with the use of a preventive strategy at the time of operation.

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CLINICAL PERSPECTIVE

Prosthesis-patient mismatch (PPM), defined as a projected indexed valve effective orifice area (EOA) ≤ 0.8 cm^2/m^2, was present in 47% of the patients. The major finding of this study is that PPM is a strong and independent risk factor for cardiac events and midterm mortality in patients undergoing aortic valve replacement for pure aortic stenosis. Indeed, the risk of cardiac events and mortality was increased $\approx$3- to 4-fold in patients with PPM as opposed to those with no PPM. In contrast, values derived from geometric measurements of the prosthesis (eg, label size, internal diameter, or geometric area) were not found to be independent predictors of postoperative outcomes. The clinical implications of these results are important given that PPM is a frequent and modifiable risk factor. As opposed to other risk factors, PPM may be avoided or its severity may be reduced with the use of a preventive strategy at the time of operation. To achieve this goal, the projected indexed EOA should be systematically calculated before prosthesis implantation to estimate the risk of PPM and, if PPM is anticipated, alternative options should be considered including (1) the implantation of another type of prosthesis with a larger EOA or (2) the enlargement of the aortic root to accommodate a larger prosthesis. These alternative options should always be considered in light of the patient's overall clinical conditions and risk-benefit ratio.

Impact of Prosthesis-Patient Mismatch on Cardiac Events and Midterm Mortality After Aortic Valve Replacement in Patients With Pure Aortic Stenosis

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