Influence of Patient-Prosthesis Mismatch on Myocardial Mass Regression and Clinical Outcome in Physically Active Patients after Aortic Valve Replacement

Jacob Zeitani, Fabio Bertoldo, Paolo Nardi, Giuseppe Iaci, Patrizio Polisca, Ruggero De Paulis, Alfonso Penta de Peppo[1], Luigi Chiariello

Division of Cardiac Surgery, Tor Vergata University of Rome, [1]2nd University of Naples, Italy

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Native aortic valve replacement (AVR) with a mechanical or biological prosthesis has become a standard procedure for significantly diseased aortic valves.

The ideal prosthesis should guarantee durability and the absence of (or at least minimal) residual transprosthetic gradients. These gradients progressively increase as the size of the valve prosthesis decreases and/or the patient's body surface area (BSA) increases. The concept of patient-prosthesis mismatch (PPM) was first described by Rahimtoola (1). In practice, in order to avoid PPM, based on data from in-vitro experiments (2), the effective orifice valve area indexed by the BSA (EOAI) should be >0.9-1.0 cm^2/m^2. To respect these limits in patients with a small aortic annulus, the utilization of aortic root enlargement or a stentless bioprosthesis has been proposed. These techniques are, however, more complex, and stentless bioprostheses also have a limited durability. The clinical consequences of PPM remain controversial: recently, myocardial mass regression, improvement of clinical symptoms and event-free survival have been found to be independent of EOAI (3-5). In these studies, however, patients had a mean age of 73-79 years, though with a large range (42 to 89 years). It is expected that patients of advanced age would have a low physical activity, and hence the EOAI might be less influential on myocardial mass regression and clinical outcome. In fact, Dumesnil et al. (6) and Gonzalez-Juanatey and colleagues (7,8) clearly showed the increase of transprosthetic gradient in correlation with exercise. The aim of the present study was to evaluate the effect of different values of EOAI on myocardial mass regression, the improvement in clinical status, and on event-free survival in physically active, young patients.

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Address for correspondence:
Zeitani Jacob MD, Cardiac Surgery Division, Tor Vergata University of Rome, European Hospital, Via Portuense 700, Rome, Italy
e-mail: zeitani@hotmail.com

Materials and methods

Between September 1991 and February 2002, 706 patients underwent isolated AVR at the authors' institution. Patients aged <60 years at the time of surgery and with a postoperative EOAI <1.3 cm^2/m^2 were included, whereas those undergoing aortic root enlargement or AVR with bioprosthesis were excluded. Consequently, 70 patients (10% of the total patient population), comprising 50 males and 20 females (mean age 45 ± 7 years; range: 22 to 55 years) participated in the present study. Based on EOAI values, the patients were allocated to three groups: group 1 (n = 23; 20 males) were considered as no mismatch (EOAI >1.03 cm^2/m^2; mean 1.12 ± 0.08 cm^2/m^2); group 2 (n = 24, 17 males) were considered as borderline (1.03 < EOAI > 0.90 cm^2/m^2; mean 0.98 ± 0.03 cm^2/m^2); and group 3 (n = 23, 13 males) were considered as mismatch (EOAI <0.90 cm^2/m^2; mean 0.83 ± 0.03 cm^2/m^2). The preoperative clinical data are listed in Table I.

Surgical technique

After median sternotomy and heparin administration, a standard cardiopulmonary bypass (CPB) was established with mild to moderate systemic hypothermia (32-34°C). Myocardial protection was achieved with tepid blood cardioplegia. After performing an oblique aortotomy, the valve was excised and the prosthesis implanted with 2-0 polyester mattress sutures reinforced with Teflon pledgets. The prostheses implanted included 38 CarboMedics (CarboMedics, Inc., Austin, TX. USA), 17 St. Jude Medical (St. Jude Medical, Inc., St. Paul, MN, USA) 10 Sorin (Sorin Biomedica, Saluggia, Italy), and five ATS (ATS Medical, Inc., Minneapolis, MN, USA). The mean CPB time was 77 ± 19 min, and mean aortic cross-clamp time 54 ± 14 min (Table II).

Echocardiography

Transthoracic echocardiography was performed before the operation and at the last follow up by only two physicians. The echocardiographic data included left ventricular end-diastolic (LVED) and left ventricular end-systolic (LVES) volumes, left ventricular ejection fraction (LVEF), mean and peak gradients, left ventricular mass (LVM), left ventricular mass indexed by body surface area (LVMI), and EOAI. For echocardiography, a Hewlett Packard Sonos 2500 was used between 1991 and 1997, and a Sonos 5500 since 1998 (Hewlett Packard, Andover, MA, USA), interfaced with 2.5 MHz transducer. All data were recorded with the patient in the left lateral position during end-expiration apnea, and recorded on SVHS videotape. Echocardiographic views were obtained according to the recommendations of the American Society of Echocardiography (9). LVM was calculated using the Devereux formula and then indexed by height (LVMI [H]) and by BSA (LVMI [BSA]). Aortic transprosthetic mean and maximal gradients were calculated using the Bernoulli formula. Comparison of mean and maximal peak gradient values was performed between the two prevalent types of implanted valve.

Clinical follow up

Patients were followed for between 5 and 140 months (mean 61 ± 34 months).

Statistical analysis

Comparisons between groups were performed using either a *t*-test, chi-square test or Fisher exact test, as appropriate. A two-way repeated-measures analysis of variance was used to assess the influence of time and EOAI on LVM. Survival and freedom from cardiac events were computed by using the Kaplan-Meier method; the log-rank test was used to compare estimates.

Results

In group 3 (EOAI <0.90 cm^2/m^2), the mean body weight was higher than in groups 1 and 2 ($p < 0.05$), and the mean value of BSA was significantly higher than in group 1 ($p < 0.05$). Pure aortic valve stenosis was prevalent in groups 2 and 3 compared with group 1 ($p < 0.05$). Female sex was statistically prevalent in group 3 ($p < 0.05$). There was no difference in the time of discharge after surgery between groups (6 ± 2 days in groups 1 and 3; 6 ± 1 days in group 2; p = NS) (Table II). There was no 30-day mortality.

The overall nine-year survival was 92 ± 3% (Fig. 1). Freedom from cardiac-related death was similar in groups 1, 2 and 3 (94 ± 6%, 100% and 89 ± 10%, respectively; p = 0.2) (Fig. 2). Causes of late death included sudden cardiac death (one in group 1, one in group 3), chronic heart failure (one in group 3), malignancy (two in group 3) and gastric ulcer (one in group 3). There were no valve-related or anticoagulant-related complications.

At follow up, all patients experienced a reduction in LVED and LVES diameters (51 ± 6 and 35 ± 6 mm versus preoperative values 61 ± 11 and 43 ± 11 mm; p <0.01), improvement of LVEF (57 ± 6% versus 51 ± 10%; p <0.0001), NYHA functional class (from 2.2 ± 0.4 to 1.2 ± 0.4; p <0.0001) and regression of LVM (237 ± 57

Table I: Preoperative characteristics in the three groups of patients.

Characteristic	Group 1 (EOAI >1.03) (n = 23)	Group 2 (1.03< EOAI >0.90) (n = 24)	Group 3 (EOAI <0.90) (n = 23)
Gender ratio (M:F)	20:3	17:7	13:10*
Age (years)	44 ± 8	45 ± 7	46 ± 6
NYHA class	1.8 ± 0.8	2.5 ± 0.7*	2.2 ± 0.6
LVEF (%)	49 ± 7	50 ± 9	54 ± 13
Body weight (kg)	68 ± 11	73 ± 12	82 ± 17*†
Height (m)	1.67 ± 0.9	1.67 ± 0.1	1.66 ± 0.1
BSA (m^2)	1.78 ± 0.18	1.84 ± 0.21	1.93 ± 0.23*
LVM (g)	343 ± 108	316 ± 117	299 ± 64
LVMI [H] (g/m^2)	83 ± 26	78 ± 22	74 ± 15
LVMI [BSA] ($g/m^{2.7}$)	193 ± 64	171 ± 53	154 ± 27
Valve stenosis (n)	6 (26)	15 (62.5)*	16 (70)*
Valve mixed lesion (n)	17 (74)	9 (37.5)	7 (30)

Values are mean ± SD.
Values in parentheses are percentages.
*p <0.05 versus group 1.
†p <0.05 versus group 2.
BSA: Body surface area; EOAI: Effective orifice area index; LVEF: Left ventricular ejection fraction; LVM [BSA]: Left ventricular mass indexed by body surface area; LVM [H]: Left ventricular mass indexed by height; LVM: Left ventricular mass.

Table II: Operative and postoperative characteristics in the three groups of patients.

Characteristic	Group 1 (EOAI >1.03) (n = 23)	Group 2 (1.03 < EOAI >0.90) (n = 24)	Group 3 (EOAI <0.90) (n = 23)
Prosthesis			
CarboMedics (n)	13	12	13
St. Jude Medical (n)	4	7	6
Sorin (n)	2	5	3
ATS (n)	4	0	1
Prosthesis size (mm)			
19	0	0	2 (8.7)
21	1 (4.3)	6 (25)	12 (52.2)
23	5 (21.7)	12 (50)	7 (30.4)
25	17 (74)	6 (25)	2 (8.7)
CPB time (min)*	78 ± 13	77 ± 19	78 ± 24
ACC time (min)*	54 ± 10	55 ± 14	53 ± 16
Postop. in-hospital stay (days)*	6 ± 2	6 ± 1	6 ± 2
Operative mortality (n)	0	0	0

*Values are mean ± SD.
Values in parentheses are percentages.
ACC: Aortic cross-clamp; CPB: Cardiopulmonary bypass; EOAI: Effective orifice area index.

versus 325 ± 100 g; $p < 0.01$), LVMI [H] (58 ± 12 versus 79 ± 21 g/m$^{2.7}$; $p < 0.01$), and LVMI [BSA] (129 ± 29 versus 175 ± 52 g/m^2; $p < 0.01$).

Mean and peak transprosthetic gradients were significantly higher in group 3 than in group 1 ($p = 0.0029$ and $p = 0.0148$, respectively); nevertheless, there was no significant difference in LVM mass regression, improvement in NYHA class and LVEF (Tables III and IV). Comparison of mean and peak transprosthetic gradients between the two most frequently used valve prostheses in group 3 (CarboMedics, n = 13, and St. Jude Medical, n = 6) did not reveal any statistical difference (18 ± 5 and 30 ± 10 versus 18 ± 6 and 29 ± 11 mmHg, respectively; p = NS).

Discussion

Aortic valve replacement has become a standard procedure for the treatment of aortic valve disease, improving left ventricular function, symptoms, and long-term survival.

The goal of surgery is to replace the diseased aortic valve with a competent, non-stenotic prosthesis that allows relief of the patient's symptoms and normalizes

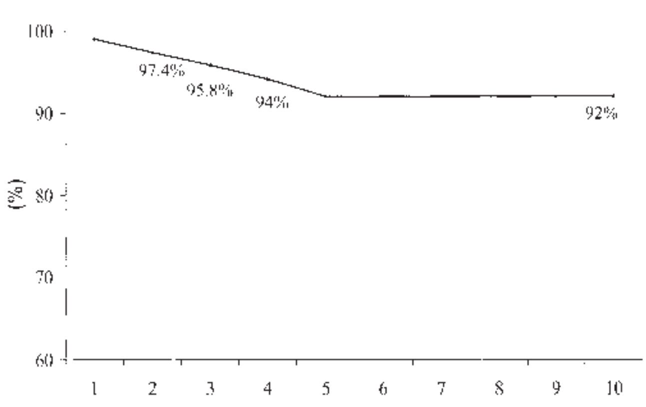

Figure 1: Overall actuarial survival in all population of patients submitted for aortic valve replacement.

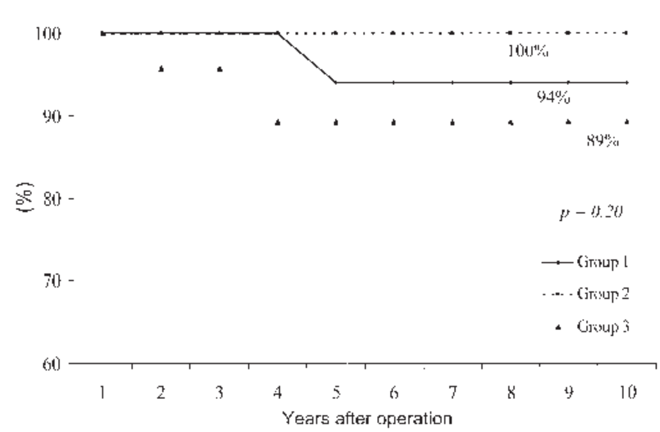

Figure 2: Actuarial freedom from late cardiac death in group 1 (EOAI >1.03 cm²/m²), group 2 (1.03 < EOAI > 0.90 cm²/m²) and group 3 (EOAI <0.90 cm²/m²).

Table III: Preoperative and postoperative left ventricular mass data in the three groups.

Parameter	Group 1 (EOAI >1.03)		Group 2 (1.03 < EOAI > 0.90)		Group 3 (EOAI <0.90)		p-value between groups
	Pre-op. (n = 23)	Follow up (n = 22)	Pre-op. (n = 24)	Follow up (n = 24)	Pre-op. (n = 23)	Follow up (n = 18)	
LVM (g)	343 ± 108	243 ± 53*	316 ± 117	225 ± 56*	299 ± 64	245 ± 66*	0.216
LVMI [H] ($g/m^{2.7}$)	83 ± 25	58 ± 10*	78 ± 22	56 ± 11*	74 ± 15	64 ± 15*	0.312
LVMI [BSA] (g/m^2)	193 ± 64	133 ± 29*	171 ± 53	122 ± 25*	154 ± 27	131 ± 35*	0.445

*p <0.0001 versus preoperative values.
EOAI: Effective orifice area index; LVM [BSA]: Left ventricular mass indexed by body surface area; LVM [H]: Left ventricular mass indexed by height; LVM: Left ventricular mass.

the hemodynamics parameters. Hence, the ideal prosthesis should guarantee an absence of (or at least a minimum) any transprosthetic gradient. Stented prosthetic valves are theoretically stenotic, however, because the valve sewing ring and stent reduce the EOA. Postoperative transprosthetic gradients progressively increase as the size of the prosthesis decreases and/or the patient's BSA becomes greater.

Several studies (7,10,11) have demonstrated less symptom improvement, poor regression of LVM and reduced survival with an EOAI <0.85-0.90 cm^2/m^2. In order to avoid lower EOAI values, Castro et al. (12) proposed the regular use of aortic annulus enlargement; however, an average of 19 minutes additional aortic cross-clamp time was required, and CPB time was found to be an independent risk factor of mortality.

The implantation of a stentless bioprosthesis - another possible solution - also requires a prolonged CPB time, and poses the risk of limited durability of the prosthesis in young patients. Therefore, in the presence of a small aortic root, the complexity associated with annulus enlargement or the choice of a stentless bioprosthesis with limited durability, should be weighed against the risk of a small EOAI and its expected transprosthetic gradient.

However, in recent investigations into PPM and the performance of small aortic valve prostheses, myocardial mass regression, improvement of clinical symptoms and event-free survival were found to be independent of EOAI (13-16). Izzat et al. (17) showed that PPM might be negligible with modern aortic valve prostheses in a series of patients examined at rest and during dobutamine-stress testing. Hanayama et al. (14) analyzed, in a prospective study, the effect of severe PPM (EOAI <0.60 cm^2/m^2) on LVM regression, symptomatic status and long-term survival, and found no

Table IV: Comparison of functional and clinical data preoperatively and at follow-up between the three groups.

Parameter	Group 1 (EOAI >1.03)		Group 2 (1.03 < EOAI > 0.90)		Group 3 (EOAI <0.90)	
	Pre-op. (n = 23)	Follow up (n = 22)	Pre-op. (n = 24)	Follow up (n = 24)	Pre-op. (n = 23)	Follow up (n = 18)
NYHA class	1.8 ± 0.8	1.2 ± 0.4	2.5 ± 0.7	1.1 ± 0.3	2.2 ± 0.6	1.3 ± 0.5
LVEF (%)	49 ± 7	57 ± 7	50 ± 9	57 ± 6	54 ± 13	58 ± 6
Mean gradient (mmHg)	12 ± 4	-	14 ± 6	-	17 ± 5†	
Peak gradient (mmHg)	23 ± 6	-	27 ± 9*	-	29 ± 10‡	
LVEDd (mm)	67 ± 1	53 ± 5	58 ± 12	51 ± 6	56 ± 8	49 ± 5
LVESd (mm)	44 ± 10	37 ± 5	41 ± 6	34 ± 6	38 ± 9	32 ± 5
IVST (mm)	11 ± 2	11 ± 1	12 ± 3	11 ± 1	12 ± 2	12 ± 2
PWT (mm)	10 ± 2	11 ± 1	11 ± 2	11 ± 1	12 ± 1	11 ± 1

†p = 0.0029 versus group 1.
*p = 0.0581 versus group 1.
‡p = 0.0148 versus group 1.
EOAI: Effective orifice area index; IVST: Interventricular septum thickness; LVEDd: Left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction; LVESd: Left ventricular end-systolic diameter; PWT: Posterior wall thickness.

significant effect of mismatch. It should be noted that patients in the present series often presented with advanced age and with a presumably low physical activity; the EOAI might therefore be less determinant on myocardial mass regression and clinical outcome. In fact, Dumesnil et al. (6) and Gonzalez-Juanatey and colleagues (7,8) demonstrated an increase in transprosthetic gradient which correlated with exercise.

In the present study, the effect of different values of EOAI was evaluated in young patients undergoing AVR with non-compliant mechanical prostheses. In the expected mismatch group (group 3), NYHA functional class and LVEF improved similarly to the other two patient groups. Moreover, no significant difference was found between the three groups in terms of cardiac-related death at long-term follow up. There was also a comparable regression of LVM and LVMI in all groups, despite the fact that the mean and peak gradient values were higher in group 3 than in the two other groups. These findings were justified by the larger number of 21- and 19-mm prostheses used in this group (61% of patients).

The satisfactory recovery of functional status and regression of LVM in patients with expected mismatch may be due to full utilization of the internal orifice area during exercise, as demonstrated in previous studies (17,18).

In conclusion, in physically active patients a smaller value of EOAI and a higher postoperative transprosthetic gradient does not appear to influence LVM regression and improvements in either LVEF, NYHA functional class, and survival.

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