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ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2020;9(4):1045-52

Patient-prosthesis mismatch in patients with mechanic aortic valve replacement: Which method is better: *In vitro* or *in vivo* measurement?

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Received 23 August 2020; Accepted 21 October 2020
Available online 25.11.2020 with doi: 10.5455/medscience.2020.08.172

Abstract

Patient-prosthesis mismatch is usually accepted to be associated with poor outcomes in patients with aortic valve replacement (AVR). This study aims to evaluate prevalence, sensitivity and specificity of mismatch measured with *in vivo* and *in vitro* methods, look for a relationship between mismatch and obesity, and investigate the effect of mismatch on left ventricle mass index (LVMI) regression and mortality. A total of 72 consecutive patients who underwent mechanical AVR between December 2011 and May 2013, were prospectively evaluated. EOA was measured with echocardiography in all patients on the 6th postoperative month and an Indexed Effective Orifice Area (EOA) $\leq 0.85 cm^2/m^2$ was accepted as mismatch with the *in vivo* measurement method. For the *in vitro* measurement method, charts provided by the valve manufacturers were used for EOA prediction. LVMI was also evaluated on the 6th and 12th postoperative months. Postoperative follow-up is 100% complete with 68.5±14.4 months. *In vivo* and *in vitro* mismatch prevalences were 43.5% and 25.0% with slight concordance (kappa=0.172). Sensitivity of *in vitro* measurements was poor (35.7%), but specificity was 80.5%. LVMI regressions were significant with both mismatch methods ($p<0.001$ for all). Obesity prevailed in mismatch patients ($p=0.021$ with the *in vivo* and $p=0.004$ with the *in vitro* method) and mortalities and survival curves did not differ between PPM+ and PPM- patients with both approaches ($p>0.05$ in both). *In vitro* EOA measurements have a poor sensitivity to predict mismatch preoperatively. Left ventricular mass regressions were significant in all groups with no difference in early and late mortality.

Keywords: Aortic valve replacement, prosthesis-patient mismatch, *in vivo* indexed EOA, *in vitro* indexed EOA

Introduction

After first described by Rahimtoola in 1978, patient-prosthesis mismatch (PPM) is considered to be moderate when indexed effective orifice area (IEOA = EOA / body surface area (BSA) of the heart valve prosthesis in the aortic position is $\leq 0.85 cm^2/m^2$, severe when IEOA $<0.65 cm^2/m^2$ [1,2]. This situation can delay left ventricular mass (LVM) regression and increase mortality [3]. However, especially in patients with aortic stenosis(AS) LVM regression may improve due to a relative increase in EOA and resultant decrease in transvalvular pressure gradients [4].

Obesity was associated with lower IEOA, higher LVM index (LVMI) and increased late mortality in a study [5]. Given the unfavorable effects of PPM, efforts for preopereative prediction and prevention of mismatch are encouraged [6]. *In vitro* EOA values supplied by the manufacturer or *in vivo* measurements done with echocardiography (ECHO) after aortic valve replacement (AVR) are used in the literature.

This study aims to evaluate prevalence, sensitivity and specificity of mismatch measured with *in vivo* and *in vitro* methods, look for a relationship between mismatch and obesity, and investigate the effect of mismatch on LVMI regression and mortality.

Materil and Methods

A total of 72 consecutive patients (mean age:54.1±16.2 years; range:19-84), who underwent bileaflet mechanical AVR between December 2011 and May 2013 were included in the study. The study protocol was approved by the local ethics committee (Date: Dec 23, 2011; No. 20048). The study was conducted in accordance with the principles of the Declaration of Helsinki and Informed consent was obtained from all of the patients. Patients with concomitant mitral and/or tricuspid valve procedure, reoperations,

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permanent pacemaker, complete heart block were excluded. The decision as to the size and product of the prosthesis is given in the operating room by various surgeons whose tendency is to implant a prosthesis as large as possible according to the body size of the patient. If an aortic valve prosthesis less than 23 no is to be used, usually products with higher performances are chosen if available. Prosthesis were implanted with interrupted simple sutures in intra-annular position or for large prosthesis (>25 mm) with pledgetted mattress sutures in supra-annular position. Concomitant procedures were coronary artery bypass grafting (CABG) in 19(26.4%), replacement of ascending aorta in 20(27.8%), Bentall procedure in 12(16.7%), aortic root enlargement in 6 (4 patients with Nicks, 2 patients with Manouguian technique, 8.3%), hemiarc replacement in 5(6.9%), aortic root abscess removal and patch repair in 1(1.4%) patients.

Patients were regarded as PPM+ with an IEOA≤0.85cm^2/m^2, (moderate mismatch) according to EOA measurements done by echocardiography on the 6th postoperative month after prosthetic valve implantation (*in vivo* measurement method, reference test) and manufacturer derived *in vitro* EOAI (*in vitro* measurement method). As 3 patients died in the first postoperative month 69 patients could be evaluated with the *in vivo* measurement method. Accordingly, statistical subgroups as *in vivo* PPM+ (30 patients) and PPM- (39 patients) and *in vitro* PPM+(18 patients) and PPM-(54 patients) were constituted in order to make a comparison. Among these 72 consecutive patients severe PPM was observed in only 5 patients with the *in vivo* and 1 patient with the *in vitro* method yielding mostly a group with a moderate mismatch. Patients with body mass index (BMI)≥30 were considered obese.

The preoperative and postoperative echocardiographic studies were performed by two experienced echocardiographers using a VIVID-3® (with 3s probe, equipped with 2.5- to 3.5-MHz transducers, General Electric, 2008, Japan) in the 6th and 12th postoperative months. Peak and mean pressure gradients of the aortic valve were obtained by continuous wave (CW) doppler. The EOA was calculated by the continuity equation (EOA= Stroke Volume/VTIPrV). VTIPrV is the Velocity-Time Integral (VTI) through the prosthesis determined by CW Doppler. Stroke volume is usually derived as cross-sectional area just proximal to the prosthesis multiplied by the VTI of flow by pulsed wave (PW) Doppler at that site. The *in vivo* EOA value was divided by BSA (Du Bois Method) to find IEOA [7].

Left ventricular wall thickness was recorded at the end of the diastole in the parasternal long axis image. LVM calculated by the formula, $0.8[1.04(LVEDd+LVPWTd+IVSd)^3-(LVEDd)^3]-(13.6)$. IVSd is the end-diastolic interventricular septum thickness, LVEDd is the LV end-diastolic internal diameter, and the LVPWTd is left ventricle posterior wall thickness [8]. Left ventricular ejection fraction (EF) was calculated by the Modified Simpson rule.

Early postoperative period is the first 30-days. The follow-up was 100% complete as of July 3rd, 2019 with a mean value of 68.5±14.4 months (median: 70.7, range: 0- 81.5).

Statistical analysis

Data was coded and recorded on the computer in SPSS Statistics Release 22.0.0.0 (1989-2013 IBM®). For the methodological component of this study, *in vivo* PPM was accepted as "reference test" and *in vitro* PPM as "new test"; and sensitivity, specificity, positive and negative predictive values, accuracy and a kappa statistics was calculated in order to find discordance between *in vivo* and *in vitro* PPM calculations. The scale variables were shown as average±standard deviation, median, min-max in tables. Distribution of subgroups in cross tables was compared by using "Pearson $\chi 2$; Fisher's exact test". The variables determined by the measurement of binary groups were compared using "Student's t test" in parametric data and "Mann- Whitney U test" in nonparametric ones. Changes of peak and mean gradients, EOA, EOAI, EF, IVS, PW thickness, LVM and LVMI among the preoperative (native), postoperative 6th and postoperative 12th months (totally 3 repeated measurement) in PPM+ and – groups of both in *in vivo* and *in vitro* approach, were compared by "ANOVA with repeated measurements" in parametric, and by "Friedman test" in non-parametric data. After statistically significant results of these two tests, post hoc multiple comparison test (Bonferroni) was used in order to identify significant pairs. Survival of the patients was compared with "Kaplan Meier logrank test". Agreement between *in vivo* and *in vitro* approach was investigated by Kappa statistics. $p<0.05$ was considered statistically significant.

Results

The mismatch prevalances were 25.0% and 43.5% according to *in vitro* and *in vivo* calculations, respectively. Early mortality is 4.2% with 3 patients. No patient-prosthesis mismatch was observed in 6 patients who underwent root enlargement.

BSAs of the PPM+ patients with both measurement methods were generally higher compared to the PPM- patients (Table 1). The mean BMI of all *in vitro* PPM+ patients were also significantly higher in all measurements (p=0.005 preoperatively, p=0.002 postoperative 6th and p=0.019 12th months). Diabetes mellitus and dyslipidemia were more prevalent in PPM+ patients when evaluated with the *in vitro* method (p=0.038 and p=0.013 respectively). Patient characteristics are given in Table 1.

There was a slight compatibility between *in vitro* and *in vivo* PPM measurement methods (kappa statistics=0.172). The *in vitro* PPM method's sensitivity was low (35.7%) but it had a better specificity (80.5%). Its positive predictive value was 55.6%, negative predictive value was 64.7%, accuracy ratio was 62.3%. Sensitivity, specificity, positive and negative predictive values, accuracy, false positive and false negative values are listed in Table 2.

Table 2. Methodological component of study: Concordance or discordance between in vivo and *in vitro* PPM calculations

New Test	**Reference Test**		
	in vivo PPM(+)	*in vivo* PPM(-)	Total
in vitro **PPM(+)**	a(n=10)	b(n=8)	a+b(n=18)
in vitro **PPM(-)**	c(n=18)	d(n=33)	c+d(n=51)
Total	a+c(n=28)	b+d(n=41)	a+b+c+d(n=69)

PPM:Prosthesis-patient mismatch
Sensivity: a/(a+c) x 100=10/28=35.7%
Spesificity: d/(b+d) x100=33/41=80.5%
Positive Predictive Value: a/(a+b)x100=10/18=55.6%
Negative Predictive Value: d/(c+d)x100=33/51=64.7%
Accuracy: [(a+d)/{2x(a+b+c+d)]}x100=(10+33)/69=62.3%
False positive: b=8 and false negative:c=18.
For the concordance or discordance between in vivo and *in vitro* PPM kappa statistics=0.172; Decision: Slight agreement

Table 1. Patient characteristics

	In vivo (n=69)			*In vitro* (n=72)		
	PPM+	PPM-	p	PPM+	PPM-	p
n(%)	30(43.5)	39(56.5)	-	18(25.0)	54(75.0)	-
Female(n:21) %30.4	10(33.3)	11(28.2)	0.646	6(33.3)	15(27.8)	0.653
Male(n:48) %69.6	20(66.7)	28(71.8)		12(66.7)	39(72.2)	
Age(Mean±SD)	51.0±16.1	55.5±16.0	0.257	53.8±15.4	53.2±16.8	0.889
BSA(m^2) preoperative	1.9+0.2	1.8+0.2	0.022	1.9+0.2	1.8+0.2	0.087
6 month	1.9+0.2	1.8+0.2	0.019	1.9+0.2	1.8+0.2	0.055
12 month	1.9+0.2	1.8+0.2	0.137	1.9+0.1	1.8+0.2	0.019
p	0.145	0.680		0.898	0.732	
BMI(kg/m^2) preoperative	28.8+5.9	26.8+4.0	0.09	30.6+5.0	26.8+4.8	0.005
6month	29.0+5.2	26.9+4.1	0.069	30.8+4.4	26.8+4.4	0.002
12month	29.0+4.7	26.7+4.5	0.084	30.2+2.9	26.8+4.9	0.019
p	0.029	0.725		0.389	0.208	
Aortic Root Diameter (Mean+SD)	2.4+0.5	2.2+0.3	0.568	2.5+0.5	2.3+0.4	0.029
BMI<30 (n:49) 71.0%	17(56.7)	32(82.1)	0.021	8(44.4)	43(79.6)	0.004
BMI≥30 (n:20) 29.0%	13(43.3)	7(17.9)		10(55.6)	11(20.4)	
NYHA class 1-2(n:62) 89.9%	27 (90.0)	35 (89.7)	1.000	17(94.4)	46(85.2)	0.434
NYHA class 3-4(n:7) 10.1%	3 (10.0)	4 (10.3)	1.000	1(5.6)	8(14.8)	0.434
Hypertension(n:26) 37.7%	10 (33.3)	16 (41.0)	0.513	8(44.4)	20(37.0)	0.577
D.Mellitus(n:8) 11.6%	6 (20.0)	2 (5.1)	0.070	5(27.8)	4(7.4)	0.038
Cronic heart failure	0.0	0.0	-	0.0	0.0	
Renal failure(n:1) 1.4%	0 (0.0)	1 (2.6)	1.000	0.0	2(3.7)	1.000
COPD (n:7) 10.1%	2 (6.7)	5 (12.8)	0.690	0.0	7(13.0)	0.181
CAD (n:18) 26.1%	6 (20.0)	12 (30.8)	0.313	4(22.2)	15(27.8)	0.764
Cerebrovascular disease (n:4) 5.8%	2 (6.7)	2 (5.1)	1.000	0.0	4(7.4)	0.566
Dyslipidemia(n:22) 31.9%	11 (36.7)	11 (28.2)	0.455	10(55.6)	13(24.1)	0.013
Angina pectoris (n:37) 53.6%	16 (53.3)	21 (53.8)	0.966	11(61.1)	28(51.9)	0.495
Syncope(n:6) 8.7%	3 (10.0)	3 (7.7)	1.000	1(5.6)	5(9.3)	1.000
Atrial fibrillation	0.0	0.0	-	0.0	0.0	-
Arrhythmia (n:1) 1.4%	1 (3.3)	0 (0.0)	0.435	0.0	1(1.9)	1.000
Aortic stenosis (n:19) 27.5	8 (26.7)	11 (28.2)	0.887	5(27.8)	15(27.8)	1.000
Aortic insufficiency (n:5) 7.2%	2 (6.7)	3 (7.7)	1.000	1(5.6)	4(7.4)	1.000
Aortic stenosis-insufficiency (n:45) 65.2%	20 (66.7)	25 (64.1)	0.825	12(66.7)	35(64.8)	0.886
Root Enlargement	0 (0.0)	6 (15.4)	-	0 (0.0)	6 (11.1)	-

BSA: Body surface area; BMI: Body mass index; NYHA: New York Heart Association; COPD: Chronic obstructive pulmonary disease; CAD: Coronary artery disease.

Postoperative transvalvular mean gradients and fall in mean and peak gradients were more pronounced when the PPM- patients were evaluated with both methods (p=0.020 and p=0.031 for mean, p=0.015 and p=0.021 for peak gradients respectively). According to post hoc Bonferroni test, these differences occurred between the preoperative - postoperative 6th months and preoperative - postoperative 12th months' pairs. Transprosthetic mean gradients in the 6th and 12th months showed similar results (p=0.025 and p=0.013 for the *in vivo* and p=0.001 and p<0.001 for the *in vitro* measurements respectively). There was a statistically significant fall in postoperative EOA and IEOA values in the *in vivo* PPM+ (p= 0.032 and p=0.035) and *in vitro* PPM- patients (p<0.001 and p<0.001 respectively) (Table 3).

Table 3. Hemodynamic data of the patients native or prosthetic valves in the preoperative and postoperative period

	***In vivo* PPM+**	***In vivo* PPM-**	**p**	*In vitro* ***PPM+***	*In vitro* **PPM-**	**p**
Peak gradient(mmHg)						
Preoperative Native/Projected	57.4+34.0	58.7+33.8	0.870	61.5+27.4	57.9+34.7	0.682
Postoperative 6th month	32.1+14.2	26.6+11.1	0.078	37.4+17.2	26.0+9.2	0.008
Postoperative 12th month	31.0+13.0	25.8+10.7	0.079	37.9+15.3	24.5+8.1	0.001
p	0.154	0.015		0.138	0.021	
Mean Gradient(mmHg)						
Preoperative Native/Projected	37.1+23.7	36.6+21.0	0.929	39.3+18.6	36.8+23.4	0.680
Postoperative 6th month	18.2+9.5	14.0+6.0	0.025	21.3+11.4	13.9+5.2	0.001
Postoperative 12th month	17.7+7.9	13.7+5.7	0.013	21.4+9.6	13.3+4.1	< 0.001
p	0.183	0.020		0.145	0.031	
EOA (cm^2)						
Preoperative Native/Projected	1.8+0.4	1.8+0.4	0.855	1.5+0.2	1.9+0.3	< 0.001
Postoperative 6th month	1.4+0.2	1.8+0.3	< 0.001	1.6+0.3	1.6+0.3	0.754
Postoperative 12th month	1.5+0.4	1.7+0.3	0.067	1.6+0.4	1.6+0.4	0.744
p(preoperative vs 6th and12th month)	0.032	0.121		0.076	< 0.001	
EOAI(cm^2/m^2)						
Preoperative Native/Projected	0.9+0.2	1.0+0.2	0.064	0.8+0.1	1.1+0.1	< 0.001
Postoperative 6th month	0.8+0.1	1.0+0.2	< 0.001	0.8+0.1	0.9+0.2	0.180
Postoperative 12th month	0.8+0.2	1.0+0.2	0.011	0.8+0.2	0.9+0.2	0.217
P (preoperative vs 6th and 12th month)	0.035	0.121		0.060	< 0.001	
EF %						
Preoperative Native/Projected	57.1+9.4	57.8+9.3	0.512	60.3+2.6	56.2+10.5	0.370
Postoperative 6th month	59.8+4.2	57.5+8.1	0.493	60.3+2.1	57.9+7.6	0.556
Postoperative 12th month	59.5+5.1	57.5+6.2	0.186	59.4+4.3	58.0+6.2	0.648
p	0.424	0.599		0.648	0.343	

EOA: Effective orifice area; IEOA:Indexed effective orifice area; EF: Ejection fraction

All patients either with PPM+ or not in both measurements had significant regression in left ventricular mass and mass index values in the postoperative period compared to the preoperative values ($p<0.001$ for all). Left ventricular wall thicknesses in the ventricular septum and posterior also displayed significant reductions in all patients except with the *in vitro* PPM+ measurement (p=0.069). According to post hoc Bonferroni test, these significances occurred between the preoperative - postoperative 6th months and between preoperative - postoperative 12th months' pairs (Table 4).

According to the Kaplan-Meier survival analysis, there was no statistically significant difference between the survival curves of these PPM + or PPM- patients, when measured with the *in vitro* and *in vivo* approach (p = 0.948 and p=0.535, respectively) (Figure 1 and 2).

Table 4. Left ventricular wall thicknesses and mass indexes preoperatively and postoperatively

	In vivo PPM+	***In vivo PPM-***	**p**	*In vitro* ***PPM+***	*In vitro* ***PPM-***	**p**
IVS thickness (mm)						
Preoperative Native/Projected	1.3+0.2	1.3+0.2	p:0.825	1.3+0.2	1.3+0.2	p:0.864
Postoperative 6th month	1.2+0.2	1.2+0.2	p:0.499	1.2+0.2	1.2+0.2	p:0.933
Postoperative 12th month	1.1+0.2	1.2+0.2	p:0.873	1.1+0.1	1.1+0.2	p:0.892
p	**0.001**	**< 0.001**		**0.001**	**< 0.001**	
PW thickness (mm)						
Preoperative Native/Projected	1.2+0.2	1.2+0.2	p:0.985	1.2+0.2	1.2+0.2	p:0.901
Postoperative 6th month	1.1+0.1	1.1+0.2	p:0.781	1.1+0.1	1.1+0.2	p:0.680
Postoperative 12th month	1.1+0.1	1.1+0.1	p:0.629	1.1+0.1	1.1+0.1	p:0.290
p	**0.005**	**0.001**		**0.069**	**< 0.001**	
LVM (gr)						
Preoperative Native/Projected	316.4+83.5	302.0+70.8	p:0.441	286.0+58.1	323.2+89.7	p:0.104
Postoperative 6th month	239.4+58.4	228.4+53.4	p:0.421	235.4+46.8	232.5+58.7	p:849
Postoperative 12th month	221.0+52.8	230.2+55.9	p:0.696	232.2+39.5	222.7+58.6	p:0.049
p	< 0.001	< 0.001		< 0.001	< 0.001	
LVMI(gr/m2)						
Preoperative Native/Projected	169.7+46.7	172.1+43.1	0.932	152.1+31.2	180.9+50.5	p:0.023
Postoperative 6th month	127.5+29.7	129.6+29.5	p:0.781	124.7+24.5	130.1+31.0	p:0.506
Postoperative 12th month	119.4+30.6	130.2+31.8	p:0.229	123.7+23.4	126.0+34.0	p:0.822
p	**< 0.001**	**< 0.001**		**< 0.001**	**< 0.001**	

IVS: Interventricular septum; PW: Posterior wall; LVM: Left ventricular mass; LVMI: Left ventricular mass index.

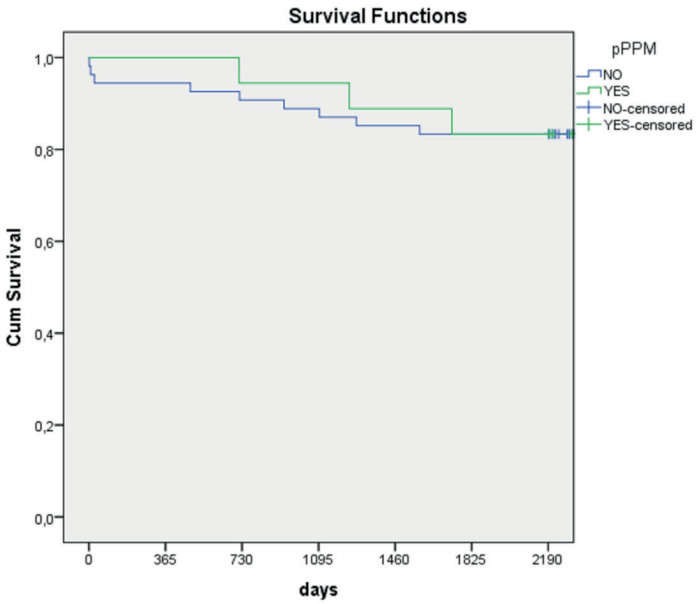

Figure 1. *In vitro* (Projected) PPM Survival. pPPM: Projected patient-prosthesis mismatch

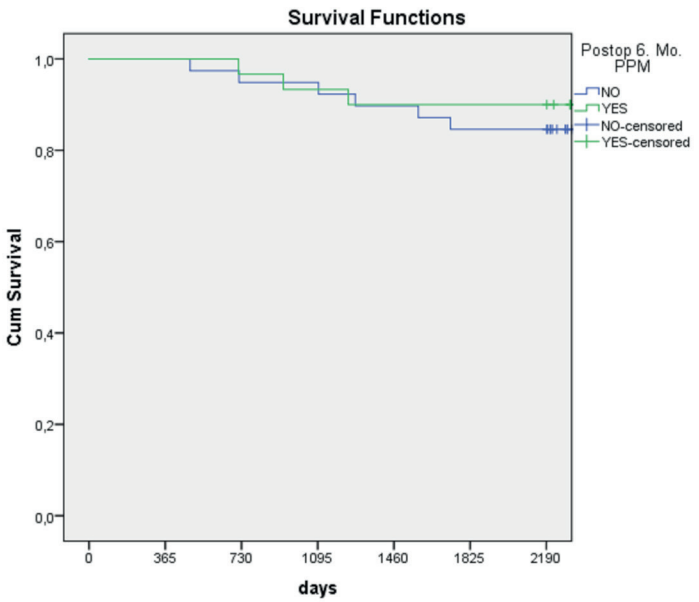

Figure 2. *In vivo PPM Survival. PPM: Patient-prosthesis mismatch*

Discussion

In the present study, *in vivo* calculated mismatch prevalance was found higher than *in vitro* measurements and obesity was found relation with PPM. In addition, it was found that *in vitro* PPM method's sensitivity was low but it had a better specificity. On the other hand, it was observed that LVMI value of all of the patients regressed in the postoperative period compared to the preoperative measurements. In addition, there was no statistically significant difference between the groups in terms of mortality.

PPM is predicted in various ways in the literature. *In vitro* EOA measurement values derived from a pulse duplicator or geometric orifice area (GOA) measurements are supplied by the manufacturer for each size and type of prosthesis [9]. *In vivo* EOA measurements are done with Doppler echocardiography after prosthesis implantation. *In vivo* EOA charts obtained with postoperative echocardiography are also available from the previous published literature [6,9]. GOA is significantly greater than the EOA values measured by ECHO and its use leads to erroneous results [9,10]. Bleiziffer S. et al.[11] compared four EOA measurement methods in their patients and reported the sensitivity and the specificity of PPM prediction as 53% and 83% by their own institutional *in vivo* EOA data, 0% and 17% by GOA method, 9-17 % and 96-100% according to *in vitro* EOA charts, and 71% and 67% by published *in vivo* EOA data in the literature. They concluded that *in vitro* and GOA methods were not reliable and the best method was *in vivo* EOA measurements. *In vitro* PPM prediction yielded a poor sensivity (35.7%) in the present study as well. Specificity was also comparable (80.5%).

According to a recent meta-analysis it is the incidence of PPM that varies according to the method used for estimation of EOA [3]. According to our results, for those willing to predict PPM preoperatively the use of *in vitro* EOA values poorly exhibits patients with positive PPM but more correctly determines patients with improbable PPM. Therefore using predetermined *in vitro* values or creating one's own institutional *in vivo* measurement charts is more appropriate. However EOA may decrease postoperatively due to endothelization, pannus formation, tissue development in the prosthesis or hypertrophy of the interventricular septum (ie. left ventricular outflow tract) [6]. Amorim PA et al. claim that EOA is a patient-specific parameter and not applicable to other patients [2]. Technological development and new generation prosthesis with greater EOA seem promising in this ongoing controversial PPM debate.

Mismatch prevalences (moderate and severe) are between 3.3 and 70% in the literature [10-12]. In the present study less PPM prevalence was found with the *in vitro* measurements compared to the *in vivo* calculations (25.0% vs 43.5%). This result is not surprising given the fact that *in vitro* values supplied by the manufacturer for EOAs are claimed to be overestimated by 10 to 15% and PPM is rare with *in vitro* measurements [6,10,11]. Also it is suggested that higher mismatch results can be estimated by Doppler ECHO due to the localized high velocity jets regarding *in vivo* EOA value measurements for bileaflet mechanical valves [6]. By the end of 6th postoperative month, PPM+ patients evaluated with the *in vivo* method had gained significant weight which we think is one of the reasons of finding high PPM prevalance with the *in vivo* measurement method as measurements were done on the 6th postoperative month (p=0.029).

Higher BMI was one of the determinants of PPM [13,14]. Patients with moderate or severe PPM had larger BMI in one study but interestingly, patients with a BMI <30 kg/m^2 and severe PPM was found to have 2.1 fold higher mortality (95% CI: 1.26 to 3.19; p 0.006) [15]. They speculate that the use of the body surface area for normalization of EOA may overestimate the prevalence and severity of PPM in obese patients [15]. Fat free body mass was the main determinant of cardiac output in the Strong Heart Study [16]. As they suggested, it may bring a new insight into PPM prediction if fat free body mass is taken into consideration while defining PPM. Fat tissue included in obese patients' weight has a significant contribution to the BSA calculation and may cause overestimation of PPM severity [17]. Prevalence of obese patients was higher in PPM+ patients in the present study as well.

High residuel postoperative aortic gradient may delay LVM regression and left ventricular hypertrophy has long been recognized as-a risk factor for survival [3,6]. Besides, LVM regression may be affected by preoperative ventricular hypertrophy grade, postoperative hypertension, age, gender, hemodynamic factors, prosthetic valve types, myocyte changes, interstitial structures, ethnic origin as well as PPM. These factors may lead to changes in myocardial metabolism and coronary artery circulation after AVR [18]. In this context, poor LVM regression may not always accompany increased valve gradients with decreasing valve sizes [19]. In a study conducted with 19 size bileaflet mechanical prosthesis, significant regression of LVM was observed with no difference in 8 year survival or quality of life between patients with or without PPM [20]. LVMI reductions postoperatively in our study may also be explained the rarity of patients with severe PPM.

Postoperative transvalvar fall in mean and peak gradients was observed in all patients regardless of PPM in the present study. However this was statistically significant only in the PPM- patients. LVM regression was also observed in all patient groups regardless of PPM. We think that even statistically insignificant but a small increase in EOA after AVR may account for this improvement in our patients as Tasca et al. [21] have also proposed in their patients with aortic stenosis. The predominant pathology was aortic stenosis (AS) in all study groups (>90%) in the present study.

Controversy exists regarding the relevance of PPM on patient survival. Overall survival was 77% in patients with minimal, 63% in patients with moderate and 47% in patients with severe PPM (p<0.001) in a study [13]. Similarly, severe PPM but not moderate PPM was associated with early, midterm and overall mortality [3,22]. A meta-analysis reported a significant increase in all-cause mortality in patients with PPM (HR ¼ 1.34, 95% CI: 1.18–1.51) [23]. On the other hand, Kulik et al.[24] report that the presence of mismatch in patients with small aortic valve prosthesis (size 19-21) does not have any impact on perioperative morbidity - mortality and long-term outcomes compared to patients with aortic root enlargement and larger prosthesis (size 21-23). Garatti et al. [25] also did not find PPM as an independent risk factor for early and late mortality in patients receiving modern 17-mm mechanical prosthesis. Yılmaz et al. [26] in their recent study comparing surgical and transcatheter aortic valve implantation found no difference between PPM+ and PPM– patients in terms of postoperative outcomes and mortality. In these last 3 studies

there were no groups with severe PPM like the present study. Howell et al. [27] also states that PPM neither increases hospital mortality nor has any effect on 5 year survival in their study comprising of patients with moderate and severe PPM. Moreover their patients with PPM were older, had more comorbidities like diabetes, hypertension and higher Euroscore [27]. We also did not find any relation between PPM and mortality. It is suggested the adverse effect of PPM is more pronounced in patients with poor left ventricular function and moderate PPM on the other hand has a relatively mild effect on mortality in patients with preserved left ventricular function [28]. Another argument supporting our results can be the well preserved left ventricular ejection fractions of the patients in the present study (Table 3). There were no significant differences between the survived and non-survived cases with respect to left ventricular ejection fraction, residual aortic gradients, age, gender distribution, LVM regression according to either *in vitro* or *in vivo* prediction methods.

Regarding implanted prosthesis, this is a prospective study comprising of consecutive patients with AVR in a series. Therefore, a heterogeneous group with different sizes, products and concomitant procedures (including aortic root enlargement) were included. This is one of the drawbacks of the study. However Wang et al.[29] reported that EOAIs increased and transvalvular pressure gradients decreased significantly even in patients with 19 mm high performance prosthesis in the 3rd and 12th postoperative months compared to the preoperative values. No significant difference was observed regarding these parameters and left ventricular diameters between patients having 19 mm aortic prosthesis and root enlargement procedures with larger prosthesis. We also had small prosthesis and improved postoperative EOA, transvalvar pressure gradients and LVMI in our series consistent with the above mentioned study. In addition our patients mainly had moderate PPM.

Our study has some limitations. Our study is non-randomized trial. Surgical procedures were performed according to the standard of our clinic and to the individual discretion of the surgeon. In these patients, the surgeon may remain in dilemma between insertion of a small-sized valve and root enlargement taking into account his own experience or the individual risks of the patient. The high number of surgeons with different surgical experience performing this surgery in the clinic where the study was conducted can be considered as the reason for the higher number of valve insertions that will cause moderate mismatch calculated *in vitro*. In addition, the patient population is heterogeneous, including patients with pure AS, pure AI and mixed aortic valve diseases. Patient number is small and number of cases with severe PPM is very few. Confounding factors may affect the LVMI regression, mortality and, after 1 year of follow-up, the reasons of death for some patients are lacking.

Conclusions

The diagnosis of PPM should not be based solely on *in vitro* EOA measurements. It has a poor sensitivity to predict PPM preoperatively. *In vivo* EOA determination charts derived from previous studies, physical characteristics and activity of the patient should also be taken into consideration to predict the size of the valve to be used during surgery in order to avoid severe PPM. Presence of moderate PPM has no detrimental effect on the short and long-term survival of patients in our era of heart valve prosthesis with high hemodynamic performance. When a patient presents with high transvalvar gradient postoperatively, *in vivo* EOA determination of the prosthesis with echocardiography should be performed in addition to a thorough evaluation of the patient with symptomatic status, functional capacity and clinical examination. According to the experience of the surgeon based on preoperative aortic root measurements, we think that choosing the surgical treatment method that will have the least PPM will be more beneficial for positive reflection on postoperative echocardiography and clinical parameters. More useful results can be obtained with a larger number of homogenous, and randomized patient populations.

Conflict of interests
The authors have no conflicts of interest to declare.

Financial Disclosure
This study received no financial support.

Ethical approval
Ethics committee approval was obtained from the Turkey Yuksek Ihtisas Training and Research Hospital (no: 23.12.2011/20048)..

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