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# **Impact of mild patient prosthesis mismatch on quality of life in patients with preserved ejection fraction after isolated aortic valve replacement for aortic stenosis**

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## **ABSTRACT**

**Aim.** To analyze whether PPM affects QOL and functional status in patients after isolated AVR for aortic stenosis (AS) with preserved left ventricular ejection fraction (LVEF).

**Methods.** Consecutive patients who underwent AVR in University Hospital Center Zagreb for isolated severe symptomatic AS and preserved EF were enrolled. Echo data was obtained from complete transthoracic examinations prior and after surgery by offline analysis. Patients were divided into two groups according to presence of PPM (effective orifice area (EOA)/body surface area (BSA)  $<0,85\text{cm}^2/\text{m}^2$ ). QOL was assessed by telephone interview using Short Form 36-Item Health Survey (SF-36) along with functional NYHA status estimation.

**Results.** A total of 45 pts were included (23 female), and divided in PPM (n=26), and non PPM group (n=19). Both groups were similar in pts age, LVEF, AVA/BSA prior surgery. After surgery, 57% of pts had PPM categorized as mild PPM. During follow up of 2,5 years, 3 pts had died and 10 were lost from following. There was no difference in NYHA status after surgery between groups ( $p=0,758$ ). SF36 results showed no difference between groups. However, there was a significant improvement in Physical functioning (47,50% vs 75,47%, $p=0,000$ ) and Role limitation due to physical health (41,41% vs 81,25%, $p=0,007$ ) scores in the whole study population after AVR. Males had significantly better Energy/fatigue ( $p=0,034$ ), Social functioning ( $p=0,004$ ) and Pain ( $p=0,017$ ) scores.

**Conclusions.** Mild to moderate PPM showed no clinical relevance. All patients revealed improvement in QOL after AVR, while male sex was related to better functioning scores irrespectively of PPM.

## INTRODUCTION

Since it was first described by Rahimtoola in 1978, (1), patient prosthesis mismatch (PPM) has caused a lot of controversies. It means that the effective orifice area (EOA) of the implanted valve is too small for the patient's body surface area (BSA). PPM is more common in patients with large BSA, but it also depends on the left ventricular outflow tract (LVOT) diameter (2-4). In patients with aortic stenosis, due to left ventricular hypertrophy and excessive calcifications, LVOT diameter gradually gets smaller and precludes implantation of the prosthetic valve of appropriate size (4).

PPM is generally a relatively common finding, found in up to 70% AVR procedures (2,5-8). If the EOA/BSA ratio is  $<0,85\text{cm}^2/\text{m}^2$ , PPM is defined as mild or moderate, and as severe if the EOA/BSA ratio is  $<0,65\text{cm}^2/\text{m}^2$  (2). Patient outcomes mainly depend on the severity of PPM. Severe PPM has been shown to have worse long term survival, lower cardiac-related-death survival and lower left ventricular (LV) mass reduction (9).

However, the impact of patient prosthesis mismatch on the outcomes remains unresolved. In some studies, PPM did impact long term survival and cardiac related deaths (9-11) whereas in other there was no significant difference comparing to no PPM patients (8,11-12). Studies are more uniform regarding functional capacity, with no difference comparing to no PPM patients, especially in the elderly (5,7,12-16).

In younger, middle-aged patients, the impact of PPM on functional capacity and QOL remains unclear. Higher gradients and less positive remodeling of the left ventricle may have some impact on their functional capacity and the risk for reoperation (8). The aim of the study was to investigate the impact of PPM on survival, quality of life and functional status in general population with preserved ejection fraction after isolated AVR.

## METHODS

A retrospective observational study was conducted in the University Hospital Center Zagreb. Patients' demographic data and data regarding cardiac surgery were acquired from the hospital digital database and medical charts. Offline analysis of the previously recorded and digitally stored transthoracic echocardiographic exams was performed on the echo workstations using GE EchoPac software. Data concerning the quality of life and functional status were collected in December 2015 via telephone medical interview. Oral informed consent was obtained from each patient.

### Patients

Consecutive patients with preserved ejection fraction (LVEF > 45%) and severe symptomatic aortic stenosis who underwent isolated AVR in our institution, in the period from 2010-2014, were enrolled. Patients with reduced ejection fraction and concomitant coronary artery disease or other valvular disease regarding intervention, those with poor acoustic echo window and no preoperative TTE, were excluded from the study. Patient inclusion and exclusion criteria were met accordingly to medical charts data. Also, patients with poor acoustic echo window on echo data prior to surgery were excluded from the study.

### Echocardiography

We have retrospectively analyzed the digitally stored echocardiographic data - a complete standard transthoracic echocardiographic study was performed prior to surgery and in the early postoperative period.

Prior to surgery, the following echo parameters were analyzed: LVEF, global longitudinal strain (GLS), maximal and mean gradients over aortic valve and aortic valve area (AVA). The left ventricular ejection fraction was calculated using Simpson Biplane method and the global longitudinal strain (GLS) was measured using 2D speckle tracking. The aortic valve area was calculated using the continuity equation and indexed for body surface area (BSA).

After AVR, the same methods were used for the quantification of the LVEF and measurement of GLS, maximum and mean pressure gradients. The effective orifice valve area values were taken from the manufacturer's data. PPM was then calculated from the expected effective orifice area (EOA) for each valve type and size, and indexed by patient's body surface area (BSA).

#### Patient prosthesis mismatch

According to the calculated EOA/BSA after operation, patients were divided into two groups based on PPM presence. If EOA/BSA was  $< 0,85\text{cm}^2/\text{m}^2$ , the patient was classified into PPM group.

#### Quality of life survey

QOL was assessed in December 2015 by telephone interview using the Short Form 36-Item Health Survey (SF-36) questionnaire. The doctor performing the interview has read the questions exactly as written and recorded answers in numeric form. Patients were also asked additional questions in order to estimate their functional status according to the New York Heart Association (NYHA) classification. The results were recorded in numerical form (I-IV). Questions were also asked about additional data regarding mortality and hospitalizations due to heart failure.

Standard analysis of the SF-36 questionnaire was done, using the following scores calculated from the questionnaire: Physical functioning (PF), Role limitations due to physical health (RLPH), Role limitations due to emotional problems (RLEH), Energy/fatigue (EF), Emotional well-being (EMWB), Social functioning (SF), Pain (P) and General health (GH).

#### Statistical analysis

Descriptive statistics was done to analyze population characteristics, ECHO parameters and QOL data. When comparing the two populations adequate tests depending on variable type and data distribution were used (chi-square, Mann-Whitney, t-test, ANOVA). Statistical analysis was done using SPSS v21 IBM software.

## RESULTS

A total of 45 patients (23 female, 22 male), aged  $67,4 \pm 10,7$  years were included in the study. All patients had a preserved LVEF ( $57,3 \pm 8,05\%$ ). They all had an isolated severe aortic stenosis ( $0,65 \pm 0,2 \text{ cm}^2$ ). After AVR, 18 mechanical (40%) and 27 biological valves (60%) were implanted. Postoperative EOA/BSA was calculated and patients were divided into two groups: PPM group (n=26), and no PPM group (n=19). Mean EOA/BSA in no PPM group was  $1,0068 \text{ cm}^2/\text{m}^2$ . There were in total 57% patients with PPM (mean EOA/BSA  $0,76 \pm 0,05 \text{ cm}^2/\text{m}^2$ ,  $p=0,000$ ), categorized as mild to moderate PPM. Further subgroup analysis for moderate and severe PPM was not performed due to the small number of patients.

There was no significant difference in demographic parameters or in basic echocardiographic parameters prior to surgery between groups. Mean age of patients in no PPM group was  $66,61 \pm 11,07$  years and in PPM group  $62,5 \pm 18,25$  years,  $p=0,472$ ; body surface area was  $1,86 \text{ m}^2$  and  $1,95 \text{ m}^2$  respectively,  $p=0,215$ . All patients had a preserved left ventricular ejection fraction (LVEF) prior surgery:  $59,68 \pm 6,07\%$  (no-PPM group) vs  $55,58 \pm 8,95\%$  (PPM group),  $p=0,091$ . Global longitudinal strain (GLS) was reduced in both groups:  $-15,080\%$  vs  $-11,827\%$ ,  $p=0,363$ . Calculated aortic valve area was  $0,70 \pm 0,20 \text{ cm}^2$ , indexed  $0,36 \pm 0,09 \text{ cm}^2/\text{m}^2$  in no-PPM group and  $0,61 \pm 0,19 \text{ cm}^2$ , indexed  $0,31 \pm 0,09 \text{ cm}^2/\text{m}^2$  in PPM group ( $p=0,156$ ;  $p=0,065$  respectively).

Mechanical valves were implanted in 42% of no-PPM group and 38% of PPM group, and biological in 58% and 62% respectively ( $p=0,805$ ). The postoperative transthoracic echocardiography was performed within 6,79 days in no PPM and 8,04 days in PPM group ( $p=0,517$ ). In this early postoperative period, we found no significant difference in LV function, although a trend toward higher values was present among patients in no-PPM group: LVEF:  $60,63\%$  vs  $58,53\%$  ( $p=0,261$ ), GLS  $-14,75\%$  vs  $-12,08\%$  ( $p=0,428$ ). Maximum and mean pressure gradient (PG) across implanted valve also showed no difference between the patient groups (38 vs 45 mmHg maxPG,  $p=0,149$ ; 20 vs 25 mmHg meanPG,  $p=0,096$ ).

The mean follow up period was  $32,95 \pm 12,12$  months in no-PPM and  $31,23 \pm 10,97$  months in PPM group ( $p=0,683$ ). During this period, 3 patients had died (1 in no PPM and 2 in PPM group) and 10 pts were lost from following. In total, 32 of 45 patients (71,1%) were interviewed (13/19, 68,4% no PPM; 19/26, 73,1% PPM). No difference in functional NYHA status between groups was found ( $p=0,758$ ): all patients were in NYHA status I–III.

No significant differences between PPM groups were found in QOL SF-36 scores (Table 1). However, when compared to preoperative scores, a significant improvement in Physical functioning score (PF,  $p=0,000$ ) and Role limitation due to physical health score (RLPH,  $p=0,007$ ) was found in the whole study population, showed in table 2.

After subgroup analysis regarding sex category, males and females were matched in demographic and echocardiographic parameters as well as in PPM incidence. Interestingly when analyzing QOL, it was found that men had a significantly better Energy/fatigue (EFS,  $p=0,034$ ), Social functioning (SF,  $p=0,004$ ) and Pain (P,  $p=0,017$ ) scores (table 3).

## DISCUSSION

Patient prosthesis mismatch represents hemodynamic abnormality due to the inadequate artificial valve size according to the patient BSA (1,2). Ideally, taking into account patients BSA, a prosthesis with  $EOA/BSA > 0,85 \text{cm}^2/\text{m}^2$  should be implanted. In patients with isolated aortic stenosis, a large amount of calcification and also interventricular septum hypertrophy due to chronic pressure overload is present (4). These cause the LVOT narrowing and make impossible to implant adequate-sized prosthesis without performing the LVOT dilation procedures, which significantly prolong surgery and increase operative risk.

PPM is a common finding after AVR. It is mostly mild to moderate, with incidence ranging in studies from 20% to 70%, while severe PPM is rare (2%-11% in studies) (2,5-8). In our study, 57% pts had PPM, categorized as mild to moderate.



There is a lot of debate in literature about patient prosthesis mismatch concerning outcomes and LV reverse remodeling (9-11). In general, mild to moderate PPM did not show in previous studies impact on survival (9-10). Our results also did not show a significant difference in mortality or hospitalization rate due to heart failure in PPM group, which is in accordance with previous studies.

However, some smaller studies have found difference in functional status and the quality of life in elderly, 70-80 years old patient population (5,7,12-16). However, in these studies, patients were dispersive concerning the type of the procedure (isolated AVR, or AVR+CABG) and systolic LV function prior operation, two factors interfering with mortality rate and physical functioning. We have studied the impact of PPM in general, younger population. It is expected that this group of patients have a more active life style than octogenarians and less symptoms. The patients with reduced LVEF or coronary artery disease were excluded from the study, and a homogenous population that underwent isolated AVR for severe AS and had preserved ejection fraction prior operation was analyzed, so that any difference in QOL or functional status would be more specific for PPM influence.

Prior AVR, there were no significant differences between groups in demographic parameters, gender, severity of aortic stenosis or LV function. In the early postoperative period, echocardiography revealed a trend to better LV ejection function and GLS in both groups, but no statistical significance was reached. The average mean gradient was found to be higher in PPM group (24,85 mmHg vs 20,05 mmHg in no PPM), which is in concordance with previous studies (17). This difference is important because, during exercise, the mean gradient is increasing, getting close to values measured in mild to moderate native aortic stenosis, while in patients without mismatch mean gradients remain normal (3,18). These higher gradients in high flow rate state could cause difference in functional capacity and impact QOL in more active patients.

In our study, after AVR, all patients had relief of symptoms with significant improvement of functional status and QOL in the late follow up of about 2,5years. The most prominent improvement was noticed in „Physical functioning“ and „Role limitation due to physical health“ after AVR in the whole population

(table 2). These are the scores that are the most related to functional status and physical activity. But, there was no significant difference between PPM groups in these scores (table 1). This means that pressure unloading is significant enough to decrease symptoms, even if some degree of hemodynamic obstruction is still present. These findings are similar like those in previous studies with elderly patients (5,7,12-13,15-16), even though elderly patients have less demanding life style.

Gender subgroup analysis showed significant differences between males and females in Energy/Fatigue and Social functioning scores (table 3). This is probably more related to psychological aspect concerning surgery, social functioning and self-esteem, which needs a further investigation. It is important to notice that there was no difference in genders relating to physical functioning and functional status.

#### Limitations of the study

The main limitation of the study was the small study population. It would be interesting to analyze, on a bigger sample, the difference between mild and severe PPM as well as differences between mechanical and biological prostheses.

#### CONCLUSION

Our results have shown that a mild to moderate PPM in patients with preserved ejection fraction undergoing isolated AVR, has no influence on survival, functional capacity and QOL. According to this, the patient's cardiologist and surgeon should decide on performing higher risk surgery procedures only to avoid severe PPM, irrespective of age.

**Table 1.** Quality of life scores in patients with and without patient prosthesis mismatch after aortic valve replacement.

	PPM	N	Mean	SD	Sig.
PF	No-PPM	13	72,31	28,18	0,564
	PPM	19	77,63	23,23	
RLPH	No-PPM	13	82,69	31,26	0,850
	PPM	19	80,26	37,80	
RLEH	No-PPM	13	94,87	12,52	0,985
	PPM	19	94,74	22,94	
EF	No-PPM	13	59,23	4,00	0,478
	PPM	19	57,37	10,18	
EMWB	No-PPM	13	75,39	2,21	0,113
	PPM	19	71,79	9,08	
SF	No-PPM	13	69,23	18,12	0,505
	PPM	19	64,47	20,52	
P	No-PPM	13	77,12	17,17	0,915
	PPM	19	76,32	22,54	
GH	No-PPM	13	63,08	15,08	0,666
	PPM	19	60,00	24,78	

PPM=patient prosthesis mismatch, PF=Physical functioning, RLPH=Role limitations due to physical health, RLEH=Role limitations due to emotional problems, EF=Energy/fatigue, EMWB=Emotional well-being, SF=Social functioning, P=Pain, GH=General health

**Table 2.** Postoperative improvement in quality of life scores in the whole study population

	Mean	N	SD	Sig.
PF preAVR	47,50	32	24,56	0,000
PF postAVR	75,46	32	25,05	
RLPH preAVR	41,40	32	45,61	0,000
RLPH postAVR	81,25	32	34,78	

AVR=aortic valve replacement, PF=Physical functioning, RLPH=Role limitations due to physical health

**Table 3.** Gender differences in quality of life scores after aortic valve replacement

	Sex	N	Mean	SD	Sig.
PF	F	16	71,56	22,41	0,387
	M	16	79,38	27,62	
RLPH	F	16	70,31	40,02	0,076
	M	16	92,19	25,36	
RLEH	F	16	89,58	26,44	0,136
	M	16	100,00	0,00	
EF	F	16	55,00	10,33	0,034
	M	16	61,25	3,42	
EMWB	F	16	71,00	9,74	0,089
	M	16	75,50	2,00	
SF	F	16	57,03	18,24	0,004
	M	16	75,78	16,12	
P	F	16	68,28	22,34	0,017
	M	16	85,00	14,05	
GH	F	16	54,38	25,03	0,067
	M	16	68,13	14,01	

M=male, F=female; PF=Physical functioning, RLPH=Role limitations due to physical health, RLEH=Role limitations due to emotional problems, EF=Energy/fatigue, EMWB=Emotional well-being, SF=Social functioning, P=Pain, GH=General health.

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