ORIGINAL RESEARCH ARTICLE

Exercise Hemodynamic and Functional Capacity After Mitral Valve Replacement in Patients With Ischemic Mitral Regurgitation

A Comparison of Mechanical Versus Biological Prostheses

BACKGROUND: In patients with ischemic mitral regurgitation requiring mitral valve replacement (MVR), the choice of the prosthesis type is crucial. The exercise hemodynamic and functional capacity performance in patients with contemporary prostheses have never been investigated. To compare exercise hemodynamic and functional capacity between biological (MVRb) and mechanical (MVRm) prostheses.

METHODS AND RESULTS: We analyzed 86 consecutive patients with ischemic mitral regurgitation who underwent MVRb (n=41) or MVRm (n=45) and coronary artery bypass grafting. All patients underwent preoperative resting echocardiography and 6-minute walking test. At follow-up, exercise stress echocardiography was performed, and the 6-minute walking test was repeated. Resting and exercise indexed effective orifice areas of MVRm were larger when compared with MVRb (resting: 1.30±0.2 versus 1.19±0.3 cm^2/m^2; *P*=0.03; exercise: 1.57±0.2 versus 1.18±0.3 cm^2/m^2; *P*=0.0001). The MVRm had lower exercise systolic pulmonary arterial pressure at follow-up compared with MVRb (41±5 versus 59±7 mm Hg; *P*=0.0001). Six-minute walking test distance was improved in the MVRm (pre-operative: 242±43, post-operative: 290±50 m; *P*=0.001), whereas it remained similar in the MVRb (pre-operative: 250±40, post-operative: 220±44 m; *P*=0.13). In multivariable analysis, type of prosthesis, exercise indexed effective orifice area, and systolic pulmonary arterial pressure were joint predictors of change in 6-minute walking test (ie, difference between baseline and follow-up).

CONCLUSIONS: In patients with ischemic mitral regurgitation, bioprostheses are associated with worse hemodynamic performance and reduced functional capacity, when compared with MVRm. Randomized studies with longer follow-up including quality of life and survival data are required to confirm these results.

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WHAT IS NEW?

- In patients with ischemic mitral regurgitation, mitral valve replacement with a mechanical valve was associated with better improvement in mitral valve hemodynamics (larger effective orifice areas and lower gradients) and patient's functional capacity as reflected by the larger increase in 6-minute walking test distance.
- Prosthesis-patient mismatch has a detrimental impact on the hemodynamic and functional outcomes of patients with ischemic mitral regurgitation undergoing mitral valve replacement.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Recent randomized trials suggest that mitral valve replacement may be superior to mitral valve repair for the treatment of ischemic mitral regurgitation. The present study suggests that when replacement is indicated in such patients, it may be preferable to select a mechanical valve rather than a bioprosthetic valve to optimize postoperative valve hemodynamic and patient's functional status.
- In patients with ischemic mitral regurgitation and heart failure, it is essential to implant a prosthetic valve that has superior hemodynamics and provides the largest possible effective orifice area.
- Larger studies with longer follow-up including exercise hemodynamic, quality of life, and survival data are required to confirm the superiority of mechanical valves for the surgical treatment of ischemic mitral regurgitation.

A growing body of evidence is challenging the long-standing trend favoring valve repair over mitral valve replacement (MVR) in patients with chronic ischemic mitral regurgitation (IMR).[1–4] Consequently, it seems reasonable to consider chordal-sparing MVR in patients with IMR.[5] Current guidelines for prosthetic heart valve selection recommend either type of prosthetic valve for patients aged 60 to 70 years and mechanical prosthetic valves for patients younger than 60.[6,7]

The comparison of biological versus mechanical prostheses has been already addressed by 2 trials[8,9] which, however, included the old generation models of prosthetic valves. On the other hand, retrospective analysis on contemporary prostheses investigated patient functional status and hemodynamics by using resting Doppler echocardiography.[10–15] However, resting echocardiographic parameters are not representative of the patient's daily activities. Exercise stress echocardiography (ESE) represents a more suitable and robust method to evaluate mitral valve hemodynamics and, along with 6-minute walking test (6-MWT), may also provide incremental value for risk stratification of patients with valvular diseases.[16–18] In a high-risk group of patients, such those with IMR, it is essential to optimize the hemodynamic and functional outcome. In this regard, the choice of the prosthesis (biological versus mechanical) seems to be a crucial decision, but there are few data to guide decision-making.[14,15]

The aim of this study was, therefore, to compare the exercise hemodynamic performance and functional capacity in patients with IMR who underwent chordal-sparing MVR with contemporary biological (MVRb) or mechanical (MVRm) prostheses and coronary artery bypass grafting.

METHODS

Study Population

We reviewed data of 155 consecutive patients with IMR undergoing MVR and coronary artery bypass grafting, at Ospedale Papa Giovanni XXIII, between January 2007 and June 2013. The definition of IMR was (1) mitral regurgitation >1 week after myocardial infarction; (2) >1 left ventricular (LV) segmental wall motion abnormalities; (3) significant coronary artery disease (≥75% stenosis of ≥1 coronary vessel) in the area creating the wall motion abnormality; (4) structurally normal mitral valve leaflets and chordae tendineae; and (5) type IIIb Carpentier classification, with or without annular dilatation.[19–21]

The choice between bioprosthesis versus mechanical prosthesis was a shared decision between the surgeon and patient, based on age, life expectancy, preference, and indication/contraindication for warfarin therapy.[6,22,23]

From the whole sample, we excluded 55 (35%) patients. A complete list of exclusion criteria is shown in Figure 1. Early mortality was observed in 4 (5%) patients (MVRm=2; MVRb=2, p=not significant). Late mortality was observed in 4 (5%) patients (MVRm=2; MVRb=2, p=not significant). These 8 patients who died were excluded from the study population because they did not have the chance to undergo ESE. Six patients were also excluded because unable to complete ESE. Final study sample was composed of 86 patients (MVRm: n=45, 52% and MVRb: n=41, 48%), on whom we performed a longitudinal data analysis of 2 assessments only (preoperative: clinical, 6-MWT, and resting echocardiography; last follow-up: clinical, 6-MWT, resting, and exercise echocardiography; Figure 1).

Postoperative mortality and adverse events (ie, including stroke, bleeding, endocarditis, dialysis, reoperation, valve thrombosis, readmission for cardiac cause, heart failure, and sepsis or deep wound infection) data were collected. Both groups received the same preoperative, operative, and postoperative care. Follow-up was completed in all patients.

The study complies with the Declaration of Helsinki and was approved by the Ethical Committee of our Institution. All the patients signed an informed consent. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

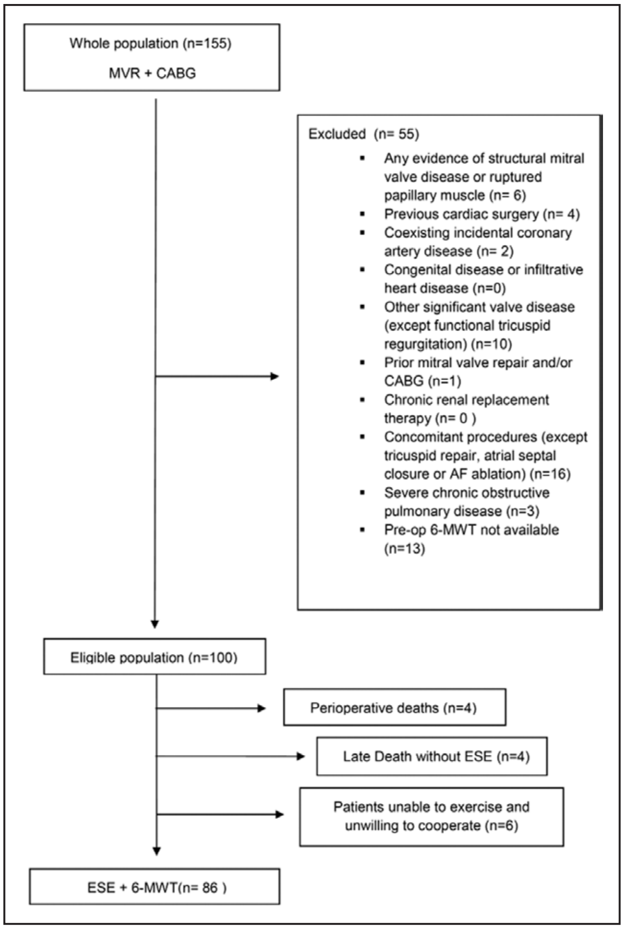

Figure 1. Study flow chart.
6-MWT indicates 6-minute walking test; CABG, coronary artery bypass grafting; ESE, exercise stress echocardiography; and MVR, mitral valve replacement.

Surgical Technique

The mitral prostheses were inserted with total preservation of subvalvular apparatus. Mechanical prostheses were implanted in the antianatomic position, rotating the valve as needed.[24] All patients underwent concomitant coronary artery bypass grafting with complete revascularization in all patients (more details are given in Surgical Technique section in Methods in the Data Supplement).

Preoperative Assessment

A physician performed the assessment of the 6-MWT[25] distance, along with resting standard 2-dimensional and Doppler echocardiogram.

Perioperative Management

After surgery, the mode of initiation of anticoagulation was based by using subcutaneous unfractionated heparin until therapeutic international normalized ratio was achieved. Additional antiplatelet agent was initiated and maintained in both group[22,26] (more details are given in Perioperative Management section in Methods in the Data Supplement).

Resting and ESE Protocol

Echocardiographic measurements were indexed to body surface area, and the Doppler tracings were averaged over 3 to 5 beats. The following parameters were measured: LV end-diastolic and end-systolic diameters, LV ejection fraction, mitral regurgitation severity assessed with the vena contracta width, LV diastolic function, LV stroke volume was determined by multiplied the LV outflow tract area to the time integral of the outflow tract velocity (pulsed-wave Doppler), cardiac output (more details are given in Resting and ESE Protocol section in Methods in the Data Supplement).

Mitral Valve Hemodynamics

The peak and mean transmitral pressure gradients were calculated. Mitral valve effective orifice area (EOA) was determined by the continuity equation. Systolic pulmonary arterial pressure (SPAP) was calculated by adding the systolic right ventricular pressure derived from the tricuspid regurgitation to the estimated right atrial pressure[27] (more details are given in Mitral Valve Hemodynamics section in Methods in the Data Supplement).

Statistical Analysis

Statistical analyses were performed with a commercially available software program (SPSS 16; IBM Ltd). Considering relatively small sample size per group and non-normal distribution, comparisons between groups for continuous variables were made by unpaired 2-sided *t* test or nonparametric Mann–Whitney test as appropriate; comparisons for categorical variables were performed using the χ^2 or Fisher exact test. Changes in echocardiographic parameters and 6-MWT distance between baseline (pre-operative) and follow-up evaluation were tested by paired *t* test or Wilcoxon matched-pairs signed rank-sum test. To identify joint predictors of 6-MWT at follow-up or changes in 6-MWT (postoperative–preoperative), linear regression and multiple linear regression models were used. Multivariable models were built using a backward stepwise strategy. Candidate variables for the final multivariable model selection were those with a P value <0.10 at the univariate analysis. The final model was built with demographic, clinical, and rest and stress echocardiographic measures as joint variables; in multivariable analysis, coefficients of determination (R^2) were used to determine strength of the association between a combination of echocardiographic parameters of LV function, cardiovascular hemodynamics or prosthesis characteristics, and the dependent variable (ie, 6-MWT). An F test of the overall significance was used to compare predictive accuracy of heretofore identified models. Median follow-up was 36 months (25th–75th percentiles=27–51). Cardiac-related hospitalization-free survival was analyzed using actuarial Kaplan–Meier curves; log-rank test for significant differences between the 2 groups.

RESULTS

Preoperative Data

Atrial fibrillation was present in 18 (21%) patients of the total sample without any difference between MVRb and MVRm. Six-minute walking test and body surface area were similar between the 2 groups. Medical therapy was similar between the 2 groups, except for the preoperative use of nitrates that was more frequent in the MVRm (*P*=0.04; Complete data are reported in Table 1)

Operative Data

A bioprosthesis was implanted in 41 (48%) patients, whereas 45 (52%) of the patients received a mechanical prosthesis (Table 2). In the MVRb group, 3 (7%) patients received a Carpentier-Edwards Perimount Pericardial bioprosthesis size 25 mm, 18 (44%) patients received size 27, 12 (29%) size 29, and 8 patients (20%) size 31 mm. In the MVRm group, a mechanical St Jude Medical valve, size 27 mm, was used in 9 (20%) patients; a size 29 was used in 16 (36%) and a size 31 in 6 (14%) patients; a Carbomedics size 27 mm valve was used in 7 (16%) patients, a size 29 in 3 (7%), and a size 31 in 3 (7%) of the patients (complete operative data are reported in Table 2).

Preoperative and Follow-Up Resting Echocardiographic Data

The median follow-up time (ie, time from surgery to the functional and echocardiographic assessment) was 25 months (interquartile, 14–38 months) without significant difference between the 2 groups (*P*=0.23). Stroke volume increased in the MVRm, whereas it decreased in the MVRb group, without any significant difference within and between the 2 groups (MVRm: from 55±06 to 57±16 mL; MVRb: from 55±11 to 53±9 mL; *P*=0.13). Cardiac index increased in both group, without any significant difference within and between group (MVRm: from 2.2±0.3 to 2.3±0.6 L min^{-1} m^{-2}; MVRb: from 2.2±0.3 to 2.3±0.3 L min^{-1} m^{-2}; *P*=0.86).

The prevalence of moderate prosthesis-patient mismatch (PPM) was higher in the MVRb group than in the MVRm (MVRb: 20 [49%] patients versus 10 [22%] patients in the MVRm group; *P*<0.05). SPAP was significantly reduced in both the MVRm and MVRb groups, without difference intergroup (complete data are reported in Table 3).

Follow-Up Exercise Echocardiographic Data

At peak exercise, cardiac index significantly increased to a larger extent in MVRm group when compared with MVRb (from 2.3±0.6 to 4.7±1.2 L min^{-1} m^{-2} in MVRm versus 2.3±0.3 to 3.25±0.3 L min^{-1} m^{-2} in MVRb; *P*=0.001; Table 4). Similarly, EOA and indexed EOA (i-EOA) significantly increased in the MVRm group, while decreased in patients with MVRb (EOA: from

Table 1. Preoperative Data

	All Patients; (n=86)	MVRm; (n=45)	MVRb; (n=41)	*P* Value*
Demographics				
Male, n (%)	60 (70)	31 (68)	29 (70)	0.96
Age, y	63.2±5.8	63.1±4.4	63.8±3.8	0.58
BSA, m^2	1.8±0.11	1.8±0.12	1.7±0.11	0.4
Clinical data				
Diabetes mellitus, n (%)	19 (22)	6 (13)	13 (31)	0.07
Hypertension, n (%)	48 (56)	25 (55)	23 (56)	0.86
Dyslipidemia, n (%)	49 (57)	27 (60)	22 (54)	0.70
Smoking history, n (%)	55 (64)	31 (68)	24 (58)	0.43
Cerebrovascular disease, n (%)	5 (6)	4 (8)	1 (2.4)	0.41
History of heart failure, n (%)	35 (41)	24 (53)	11 (27)	0.02
Preoperative IABP, n (%)	9 (10)	6 (13)	3 (7)	0.57
Atrial fibrillation, n (%)	18 (21)	10 (22)	8 (20)	0.75
Chronic renal insufficiency, n (%)	9 (10)	5 (11)	4 (10)	0.98
Euroscore	2.49±1.39	2.51±1.42	2.49±1.36	0.92
Functional				
NYHA class III/IV, n (%)	36 (42)	21 (47)	15 (36)	0.46
6-MWT distance, m	246±41	242±43	250±39	0.2
Echocardiographic				
LVEF, %	38±8	37±8	39±7	0.25
VC width, mm	7±0.7	7.2±0.76	7.1±0.58	0.71
LA, mm	51±5	51±5.6	50±5	0.42
EDV, mL	167±38	170±39	164±38	0.49
ESV, mL	89±37	88±36	92±40	0.72
Mitral annulus, mm	42.7±2.6	42.5±2.5	42.9±2.7	0.55
Moderate/severe TR, n (%)	5 (6)	3 (7)	2 (5)	0.62
Therapy				
ACE inhibitors, n (%)	61 (71)	33 (73)	28 (68)	0.78
β-blocker, n (%)	68 (79)	39 (87)	29 (70)	0.12
Diuretics, n (%)	53 (62)	25 (55)	28 (68)	0.32
Nitrates, n (%)	36 (42)	24 (53)	12 (29)	0.04
No. of diseased vessels				
1	4	2 (4)	2 (5)	0.67
2	19	11 (24)	8 (19)	0.45
≥3	63	35 (78)	28 (68)	0.45
Left main	12	8 (18)	4 (10)	0.44
LAD territory	77	40 (89)	37 (90)	0.88
Circumflex territory	40	21 (47)	19 (46)	0.85
RCA territory	59	35 (78)	24 (58)	0.09

ACE indicates angiotensin-converting enzyme; BSA, body surface area; EDV, end-diastolic volume; ESV, end-systolic volume; IABP, intra-aortic balloon pump; LA, left atrium; LAD, left anterior descending; LVEF, left ventricular ejection fraction; MVR, mitral valve replacement; MVRb, biological prostheses; MVRm, mechanical prostheses; 6-MWT, 6-minute walking test; NYHA, New York Heart Association; RCA, right coronary artery; TR, tricuspid regurgitation; and VC, vena contracta.

Chronic renal insufficiency defined by creatinine ≥2.5

**P* values refer to differences among MVRm and MVRb. Values are mean±SD when appropriate.

Table 2. Operative Data

	All Patients; (n=86)	MVRm; (n=45)	MVRb; (n=41)	*P* Value*
Cardiopulmonary bypass time, min	84±10	85±10	82±9	0.79
Aortic cross-clamping time, min	69±11	71±11	68±10	0.4
CABG, no. of grafts				
Anastomosis/patient	2.6±0.7	2.7±0.7	2.4±0.6	0.07
Arterial graft/patient	1.9±0.5	1.2±0.5	1.2±0.44	0.2
Prosthesis size distribution, n (%)				
25	3 (3)	3 (7)		0.2
27	34 (40)	16 (35)	18 (44)	0.56
29	31 (36)	19 (42)	12 (29)	0.3
31	17 (20)	9 (20)	8 (19)	0.83
33	1 (2)	1 (2)		0.96
Associate procedures				
Atrial septal defect closure, n (%)	2 (2)	0 (0)	2 (4)	0.22
Tricuspid repair, n (%)	3 (4)	1 (2)	2 (5)	0.60
AF ablation, n (%)	3 (4)	2 (2)	1 (2)	0.99
Conduits				
LIMA, n (%)	82 (95)	43 (95)	39 (95)	0.67
RIMA, n (%)	5 (6)	2 (4)	3 (7)	0.91
Radial artery, n (%)	16 (19)	10 (22)	6 (15)	0.53
Saphenous vein, n	1.3±0.7	1.3±0.9	1.3±0.6	0.8
Cardioplegia, n (%)				
Antegrade	61 (71)	32 (71)	29 (71)	0.84
Retrograde	25 (29)	13 (29)	12 (29)	0.98
Intra-aortic balloon pump, n (%)	3 (3)	2 (4)	1 (2)	0.93

AF indicates atrial fibrillation; CABG, coronary artery bypass grafting; LIMA, left internal mammary artery; MVR, mitral valve replacement; MVRb, biological prostheses; MVRm, mechanical prostheses; and RIMA, right internal mammary artery.

**P* values refer to differences among MVRm and MVRb. Values are mean±SD when appropriate.

1.98±0.44 to 2.23±0.5 cm² in MVRm versus 1.9±0.5 to 1.8±0.45 cm² in MVRb; *P*=0.001; i-EOA from 1.3±0.3 to 1.57±0.25 cm²/m² in MVRm versus 1.2±0.3 to 1.18±0.3 cm²/m² in MVRb; *P*=0.001; Table 4). Exercise-induced changes in transmitral mean and peak pressure gradients were significantly higher in MVRb when compared with MVRm (Table 4). In addition, exercise SPAP was significantly higher in MVRb, when compared with MVRm (*P*=0.001; Table 4; Complete data are reported in Table 4).

Functional Capacity Data

The 6-MWT distance improved from preoperative (baseline) to follow-up in MVRm group (from 242±43 to 290±50 m; *P*=0.001), whereas it remained similar in the MVRb group (from 250±40 to 220±44 m; *P*=0.13). The 6-MWT distance at follow-up and the absolute change from preoperative baseline to follow-up were significantly higher in the MVRm, when compared with MVRb (*P*<0.05 and *P*<0.0001, respectively; Figure 2). When adjusted by type of prosthesis implanted (mechanical or biological), a significant correlation was found between exercise i-EOA (Figure 3A) and exercise SPAP (Figure 3B) with changes in 6-MWT, from preoperative baseline to follow-up.

Exercise i-EOA and exercise SPAP also correlated with the 6-MWT distance at follow-up (Figures 4 and 5), but these correlation were no longer significant after adjusting by type of prosthesis implanted (Figures I and II in the Data Supplement).

Table 3. Comparison of Preoperative and Follow-Up Resting Echocardiographic Variables

	MVRm (n=45)		MVRb (n=41)	
	Pre-op	F-U	Pre-op	F-U
LV geometry				
LVEDD, mm	61±6	57±3.8*	58±9.5	55±4.7*
LVESD, mm	51±12	43±5.4*	55±8.6	42±6.3*
i-LVEDD, mm/m²	34±3.7	33±3.3*	35±3.5	33±2.9*
i-LVESD, mm/m²	26±5.7	25±4*	28±4.5	26±4.8*
Effective regurgitant orifice area, mm²	40±5	…	39±4	…
LV function				
LVEF, %	37±8	41±6*	39±7	41±4*
Heart rate, beats per minute	73±12	71±8	70±7	72±9
Stroke volume, mL	55±6	57±16	55±11	53±9
Cardiac index, L min^{-1} m^{-2}	2.2±0.3	2.3±0.6	2.2±0.3	2.3±0.3
Mitral valve hemodynamics				
Moderate PPM, n (%)		10 (22)	…	20 (49)†
Severe PPM, n (%)		4 (9)	…	5 (12)
Peak gradient, mm Hg	3.2±1	7.6±3	3.6±1*	8.3±2*
Mean gradient, mm Hg	1.6±0.2	4±1.5*	1.6±0.3	4.8±1.4*
SPAP, mm Hg	39±12	35±7*	39±10	35±7*

PPM defined moderate if >0.9 and ≤1.2 cm²/m², and as severe if ≤0.9 cm²/m². Values are mean±SD when appropriate. EF indicates ejection fraction; ESD, end-systolic diameter; F-U, follow-up; i, indexed; LV, left ventricle; LVEDD: left ventricular end-diastolic diameter; MVR, mitral valve replacement; MVRb, biological prostheses; MVRm, mechanical prostheses; PPM, prosthesis-patient mismatch; pre-op, pre-operative; and SPAP, systolic pulmonary arterial pressure.

**P*<0.05 (preoperative vs F-U).

†*P*<0.05 (MVRm vs MVRb).

Predictors of Functional Capacity

Table 5 presents the univariable and multivariable predictors of 6-MWT at follow-up and changes in 6-MWT (ie, difference between preoperative and follow-up). After adjustment for preoperative 6-MWT distance,

Table 4. Comparison of Resting and Exercise Doppler Echocardiographic Data at Follow-Up

	MVRm (n=45)		MVRb (n=41)	
	Rest	Exercise	Rest	Exercise
Exercise data				
Heart rate, beats per minute	71±8	114±13*	72±9	124±14*
Percentage of age-predicted hazard ratio, %	…	74±10	…	79±9
Systolic blood pressure, mm Hg	133±14	174±14*	136±12	174±14*
Workload, W	…	94±17	…	95±21
LV function				
LVEF, %	41±6	49±7*	41±4	42±5*†
Cardiac index, L min^{-1} m^{-2}	2.3±0.6	4.7±1.2*	2.3±0.3	3.25±0.3*†
Mitral valve hemodynamics				
Stroke volume, mL	57±16	80±21*	53±9	48±7*†
EOA, cm^2	1.98±0.44	2.23±0.5*	1.9±0.5	1.8±0.45*†
i-EOA, cm^2/m^2	1.3±0.3	1.57±0.25*	1.2±0.3	1.18±0.3*†
Mitral peak gradient, mm Hg	7.6±3	11.26±2.3*	8.3±2	16±5.5*†
Mitral mean gradient, mm Hg	4±1.5	6.7±1.86*	4.8±1.4	9.57±3.72*†
SPAP, mm Hg	35±7	41±5*	35±7	59±7*†

Values are mean±SD when appropriate. EF indicates ejection fraction; EOA: effective orifice area; i, indexed; LV, left ventricle; MVR, mitral valve replacement; MVRb, biological prostheses; MVRm, mechanical prostheses; and SPAP, systolic pulmonary arterial pressure.

**P*<0.05 (rest vs exercise).

†*P*<0.05 (MVRm vs MVRb).

exercise SPAP, and i-EOA, MVRm remained jointly associated with both 6-MWT at follow-up and changes in 6-MWT.

Having a moderate-to-severe PPM was not associated to the 6-MWT assessed at follow-up neither at the simple linear regression analysis nor at the multivariable analysis (Table 5). However, patients with moderate-to-severe PPM were able, on average, to walk 12 m less than patients with no or mild PPM. This difference was significantly associated to the 6-MWT delta (ie, the difference between distance at follow-up and preoperative) according to the univariate analysis, but PPM severity was no longer significantly associated with 6-MWT delta when the analysis was controlled by the type of prosthesis implanted (additional results are given in Data Analysis in the Data Supplement).

Clinical Outcomes

Clinical data are reported in the Clinical Outcome section in the Data Supplement (Table I in the Data Supplement; Figure III in the Data Supplement).

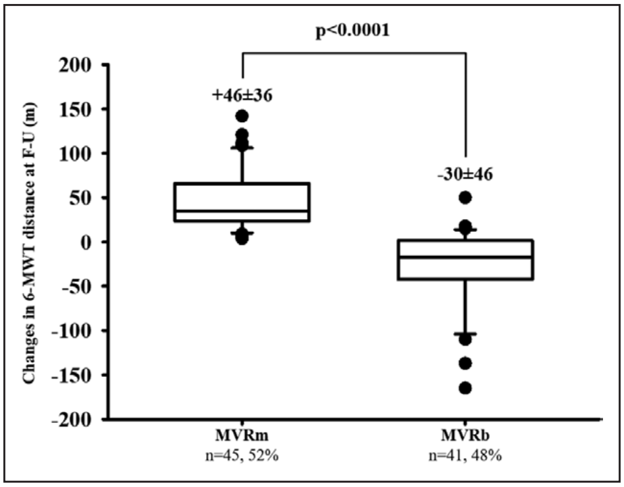

Figure 2. **Change in functional capacity, assessed by the difference in 6-minute walking test (6-MWT) distance from preoperative (baseline) to follow-up, in patients with a mechanical (MVRm) valve vs those with a biological valve (MVRb).**
MVR indicates mitral valve replacement.

DISCUSSION

This is the first study comparing exercise hemodynamics and functional capacity in patients with IMR undergoing MVRb or MVRm. The main findings are as follows: (1) MVRm have better postoperative exercise hemodynamics and higher functional capacity compared with MVRb; and (2) pre-operative 6-MWT, exercise i-EOA, and type of prosthesis implanted are joint predictors of changes in 6-MWT, at follow-up (Figure 6).

Two historic randomized clinical trials compared outcomes after valve replacement with a first-generation porcine bioprostheses and the Bjork-Shiley mechanical valve.[8,9] Hence, the ability to extrapolate these data to decisions made in modern practice is limited. The only data on contemporary prostheses are available from retrospective studies[10–12,28,29] which included aortic and mitral prostheses, along with differences in patients' baseline characteristics, making difficult to reach meaningful conclusions.

The evidence from the aforementioned studies favored biological prostheses over mechanical ones, specifically in patients ≥65 years old, in the light of comparable mortality, but lower bleeding risk.[8,10] Kulik et al[30] reported improved survival and lower risk of major prosthetic-related adverse events in middle-aged patients with mechanical prostheses, when compared with bioprostheses. A propensity score–matched analysis by Kaneko et al[12] showed that the use of a bioprosthesis was a significant predictor of long-term mortality for patients undergoing MVR. In a large multicenter propensity-matched series of MVR, Chikwe et al[13] found no difference in the long-term survival between the 2 group; however, echocardiographic and functional data

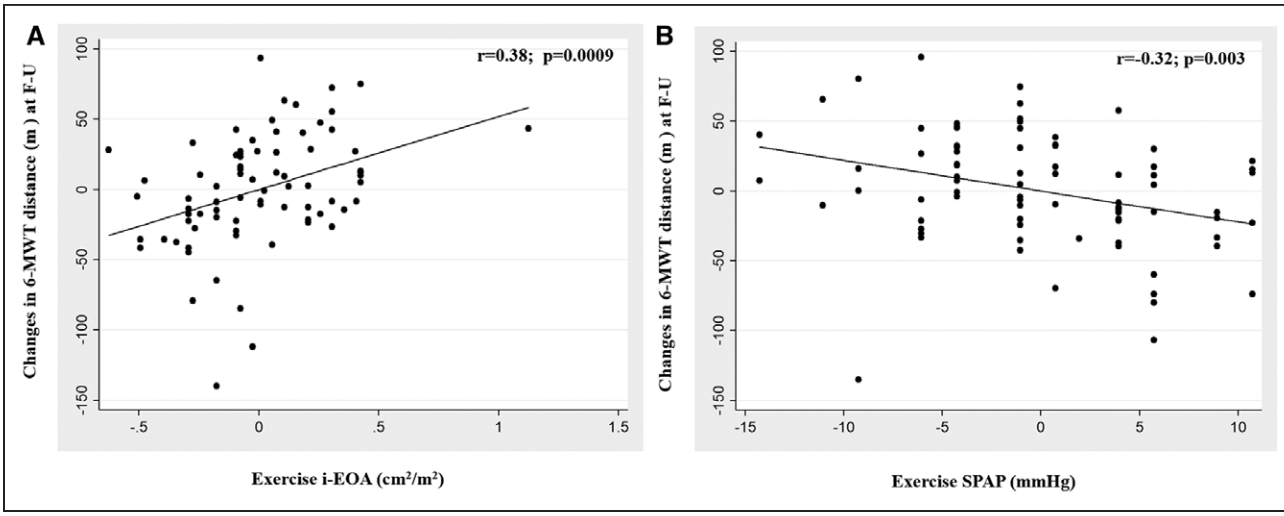

Figure 3. Correlation between change in functional capacity, assessed by the difference in 6-minute walking test (6-MWT) distance from preoperative (baseline) to follow-up and exercise indexed effective orifice area and systolic pulmonary arterial pressure.

Partial correlation between exercise indexed effective orifice area (i-EOA; **A**) and exercise systolic pulmonary arterial pressure (SPAP; **B**) with changes in 6-MWT by type of prosthesis implanted.

were not reported. Conversely, in our study, we have only analyzed patients with IMR and similar comorbidity profiles between MVRm and MVRb; moreover, ESE was used.[16]

Previous literature reported that a reduced i-EOA represents a joint predictor of mortality after MVR.[14,15] In our study, we observed a significant exercise reduction of i-EOA in the MVRb compared with the MVRm. This reduction was a joint predictor of change in 6-MWT at follow-up. On the contrary, a significant exercise increment of i-EOA was found in the MVRm, challenging the generally assumption which assume, in the aortic mechanical valves, an on/off phenomenon.[31] Many reasons, such as the type of effort or the method used for calculating the valve area, have been advocate, to explain this finding.[31] However, an on/off phenomenon cannot be translated to the mitral prostheses, in which the mechanism of valve opening is a complex interaction between left atrium and LV. Hobson et al[16] reported a significant dobutamine stress increase of the EOA. The exercise increment of i-EOA we observed in the MVRm could reflect a higher rate of change of valve leaflet opening and closing, along with a concomitant increase of stroke volume.

Moreover, the worsening hemodynamic and functional capacity of MVRb could be partially explained by their higher incidence of moderate PPM. However, in the multivariable analysis, PPM was not an independent predictor neither of 6-MWT nor of 6-MWT delta.

The reasons underlying the better exercise hemodynamics in the MVRm are unclear. The hemodynamic performance of the prostheses correlates to the total cross-sectional area effectively available for blood flow.[23,32] Bioprostheses have a central area available for flow, surrounded by the area occupied by the supporting stents, which may further steal some effective area for blood flow.[32] Conversely, bileaflet mechanical prostheses have a small central orifice and 2 larger semicircular orifices laterally. The greater cross-sectional area available for flow may account for the larger i-EOA in MVRm. This may allow for larger increase in transmitral flow and lesser increase in gradients and pulmonary arterial pressures during exercise. These favorable hemodynamic features observed in the MVRm may translate into better functional capacity. Furthermore, the durability of mitral bioprostheses is limited because of the high mechanical stress during systole[33] and this may compromise their outcome. However, further studies are needed to determine the underlying fac-

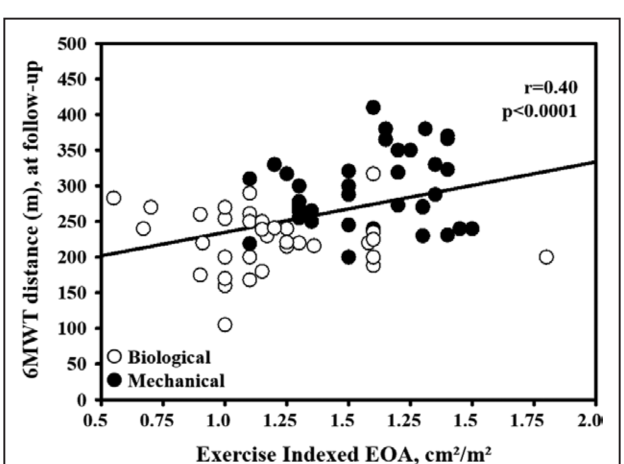

Figure 4. Unadjusted correlation between exercise indexed effective orifice area (i-EOA) and 6-minute walking test (6-MWT), at follow-up.

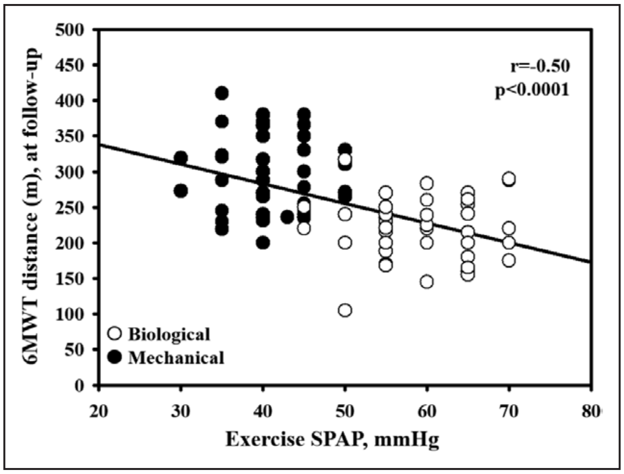

Figure 5. Unadjusted correlation between exercise systolic pulmonary arterial pressure (SPAP) and 6-minute walking test (6-MWT), at follow-up.

tors responsible for the better hemodynamic of the mechanical prostheses.

Clinical Implications

For patients who require MVR, the prosthesis can significantly influence outcome.[34] Primary goal of valve surgery should be relief of symptoms, improvement in functional capacity, and a favorable impact on mortality and morbidity,[15,35] particularly in patients with heart failure. In these patients, persistence of high postoperative SPAP will ultimately lead to an increased cardiovascular morbidity.[36] When MVR is indicated, the surgeon should implant a prosthesis with the largest possible i-EOA to optimize the hemodynamic and functional outcomes (Figure 6).[23]

Strengths and Limitations

This is the only study which addresses the exercise hemodynamic and the functional capacity in a consecutive highly homogeneous series of patients with ischemic cardiomyopathy undergoing MVR with contemporary prostheses. However, this is a single-center and retrospective study; it is thus subset to potential selection bias. Although this potentially increases the risk of unmeasured confounders, it also enhances consistency in preoperative evaluation, surgical techniques, and follow-up assessment of enrolled patients.

We reported only a single measurement of 6-MWT and ESE, rather than repeated measures over time; it would have been interesting to have a longitudinal data analysis of serial assessments.

We performed 6-MWT, rather than cardiopulmonary exercise testing. However, 6-MWT is widely used in patients with heart failure and is easier to apply in this population.

We do not have the data on preoperative myocardial viability in the 2 groups. Thus, it is unknown whether potential absence of ventricular remodeling might have

Table 5. Univariable and Multivariable Predictors of 6-MWT Distance at Follow-Up

	6-MWT Distance at Follow-Up						Change in 6-MWT From Baseline to Follow-Up					
	Univariable			Multivariable			Univariable			Multivariable		
	β	SE	*P* Value	β	SE	*P* Value	β	SE	*P* Value	β	SE	*P* Value
Variable												
Age, y	−0.094	1.57	0.4				0.07	0.006	0.5			
Sex	0.16	13.9	0.14				0.07	0.052	0.05			
BSA, m²	−0.072	56.26	0.5				0.042	0.2	0.7			
Pre-operative 6-MWT distance, m	0.43	0.14	0.001	0.75	0.11	0.0001						
Exercise EOA, cm²	0.20	13.2	0.07				0.5	0.04	0.001			
Exercise i-EOA, cm²/m²	0.66	0.18	0.001	0.42	0.15	0.008	0.6	0.06	0.0001	0.3	0.6	0.002
Exercise LVEF, %	0.39	0.84	0.001				0.4	0.003	0.001			
Exercise SPAP, mm Hg	−0.5	0.52	0.001				−0.71	0.002	<0.001	−0.3	0.002	0.018
Exercise mean gradient, mm Hg	−0.11	2	0.012				−0.38	0.07	0.0001			
Exercise peak gradient, mm Hg	−0.23	1.35	0.03				−0.54	0.004	0.0001			
Exercise cardiac output, L/min	0.43	3.6	0.001				0.67	0.11	0.0001			
Exercise cardiac index, L min⁻¹ m⁻²	0.12	7.18	0.3				0.41	0.024	0.001			
MVRm	68.1	10.6	0.0001	56	10	0.0001	−0.7	0.03	0.0001	−0.3	0.05	0.04
PPM (mod-severe)	−12.8	12.9	0.33				−33.9	11.6	0.004	0.96	10.3	0.92
Heart failure history	0.32	5.1	0.17				0.39	0.045	0.0001			

BSA indicates body surface area; EOA, effective orifice area; i, indexed; EF, ejection fraction; LV, left ventricle; 6-MWT, 6-minute walking test; MVR, mitral valve replacement; MVRm, mechanical prostheses; PPM, patient-prosthesis mismatch; and SPAP, systolic pulmonary arterial pressure.

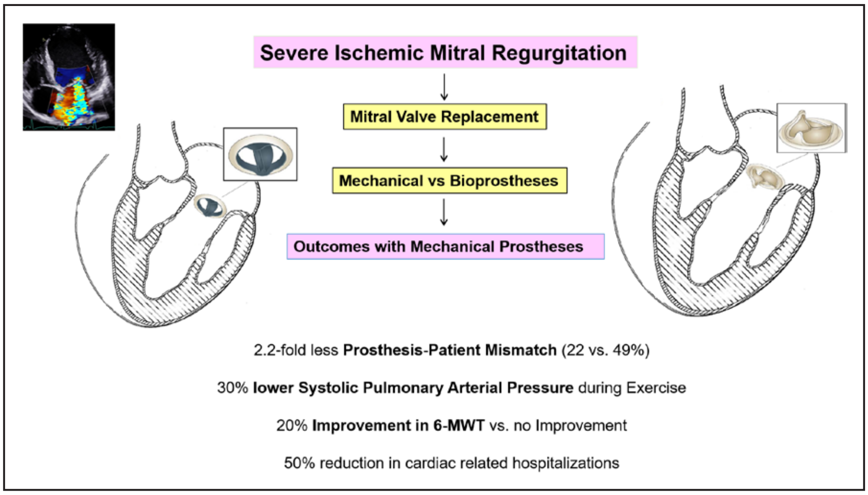

Figure 6. Impact of type of prosthetic valve on hemodynamic and functional capacity after mitral valve replacement in patients with ischemic mitral regurgitation. 6-MWT indicates 6-minute walking test.

influenced the results between the 2 groups. Furthermore, it would be interesting to know if a potential progression of coronary disease contributed to the different outcomes between the 2 types of prostheses. Given that we performed multiple comparison between MVRb and MVRm groups, type I error may be higher than 5%.

Conclusions

In patients with ischemic cardiomyopathy, mechanical prostheses are associated with better exercise hemodynamics and functional capacity compared with bioprostheses. These data provide support to the use of mechanical rather than biological valve in these patients (Figure 6). However, larger studies with longer follow-up including hemodynamic, quality of life, and survival data are required to confirm these results.

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DISCLOSURES

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FOOTNOTES

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Exercise Hemodynamic and Functional Capacity After Mitral Valve Replacement in Patients With Ischemic Mitral Regurgitation: A Comparison of Mechanical Versus Biological Prostheses

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SUPPLEMENTAL MATERIAL

Exercise Hemodynamic and Functional Capacity following Mitral Valve Replacement in Patients with Ischemic Mitral Regurgitation: A Comparison of Mechanical versus Biological Prostheses

Running Title: Comparison of Biological and Mechanical Prostheses

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Word Count:

SUPPLEMENTAL METHODS

Surgical technique

All operations were performed trough a midline sternotomy with bicaval cannulation and mild systemic hypothermia. Mitral valve was approached through conventional left atriotomy. In all patients visual inspection confirmed the preoperative inclusion criteria. Sizing was performed with the usual manufacturer’s sizers. Either biological or mechanical prostheses were inserted with total preservation of subvalvular apparatus. Mechanical prostheses were implanted in the anti-anatomic position, rotating the valve as needed (1).

In patients with chronic atrial fibrillation and enlarged left atrium, the ostium of the left atrial appendage was closed in almost every instance. All patients underwent associated CABG. Complete revascularization was accomplished when at least one graft was placed distal to an approximately 50% diameter narrowing in each of the three major vascular system in which arterial narrowing of this severity was noted in a vessel ≥1.5 mm of diameter. Following this definition, we achieved a complete revascularization in all patients (2). Transesophageal echocardiography was performed after cardiopulmonary bypass to exclude any residual periprosthetic leak or other intrinsic dysfunction

Perioperative Management

Immediately after valve surgery, the mode of initiation of anticoagulation was based by using subcutaneous unfractioned heparin until therapeutic INR was achieved (2.5 to 3.5). In patients with biological prostheses the above anticoagulation protocol was maintained only for 3 months. In patients with atrial fibrillation or other risk factors for thromboembolic sequelae, the same maintained indefinitely. Additional antiplatelet agent was initiated and maintained in both group (3,4).

All patients were discharged on appropriate guidelines-directed medical therapy.

Resting and ESE protocol

Resting and exercise echocardiogram were performed using commercially available instruments (Vivid 5 imaging device GE Healthcare). All echocardiographic and Doppler data were obtained at rest and at peak exercise in digital format and stored on a workstation for offline analysis (EchoPAC, GE Vingmed Ultrasound AS, Horten, Norway). Measurements were indexed to body surface area and the Doppler tracings were averaged from 3 to 5 beats.

According to the current guidelines and standard of the European Society of Echocardiography (5) the following parameters were measured: LV end-diastolic and end-systolic diameters; LVEF determined using the modified biplane Simpson method and MR severity assessed with the vena contracta width. LV diastolic function was assessed by conventional Doppler analysis of transmitral flow and by tissue Doppler imaging in the septal position of the mitral annulus, by measuring Doppler Ea-wave velocity. Outflow tract area was determined as $\pi D^2/4$, where D is the diameter measured from a zoomed systolic freeze-frame in the parasternal long-axis view. LV stroke volume (SV) was determined by multiplied the LV outflow tract area to the time integral of the outflow tract velocity (pulsed-wave Doppler). Because LV outflow tract area has been shown to remain constant during exercise, the resting value was used to calculate both rest and exercise SV. Cardiac output (CO) was calculated by multiplied the SV and the heart rate. Also prosthetic valve dysfunction was defined according to the current guidelines (5).

Mitral hemodynamics

The peak and mean transmitral pressure gradients were calculated using the modified Bernoulli equation. Mitral valve effective orifice area (EOA) was determined by the continuity equation using the SV divided by the integral of the mitral transvalvular velocity during diastole (5).

Systolic pulmonary arterial pressure (SPAP) was calculated by adding the systolic right ventricular pressure derived from the tricuspid regurgitation to the estimated right atrial pressure (6).

SUPPLEMENTAL DATA ANALYSES

Effect of prosthesis size (<u>either bio or mechanical</u>) on outcome (6-MWT at follow-up and the difference between follow-up and pre-op values, i.e. 6-MWT-delta).

a. The univariate linear regression model for 6-MWT at follow-up was not significant (p=0.249). Hence, prosthesis size is not associated with the 6-MWT at follow-up

b. Bi-variate linear regression model taking into account the group (bio vs. mechanical). The analysis aims to check whether there is an association between prosthesis size and 6-MWT at follow-up, among patients with a bioprosthesis or among those with a mechanical prosthesis:

c. No significant association has been found between prosthesis size and 6-MWT at follow-up (p=0.434).

d. Influence of the prosthesis size on 6-MWT-delta. The univariate linear regression model also shows no association (p=0.249).

d. Similar results with regression analysis of 6-MWT-delta vs. prosthesis size after controlling for prosthesis type (i.e. bivariate linear regression model) (p=0.718).

Effects of nitrates therapy on 6-MWT.

1. **Influence of nitrates treatment on 6-MWT at follow-up**

a. Univariate linear regression analysis shows no association between nitrates therapy and 6-MWT at follow-up, either as overall effect (p-value=0.42) or after having controlled for the type of prosthesis (bivariate analysis) (p-value=0.55)

2. **Influence of nitrates treatment on 6-MWT-delta at follow-up**

Conversely, a significant association was found between nitrates therapy and 6-MWT delta, so that, on average, the difference between 6-MWT at follow-up and pre-operative 6-MWT was 28 ± 12 m longer in patients on nitrates, as compared to patients without nitrates (p=0.023) The difference is statistically significant.

Since there is a significant association between 6-MWT at baseline and 6-MWT at follow-up, the difference (i.e. 6MWT-delta) is, in fact, mainly due to somewhat lower (-17.07 ± 8.9 m; p-value=0.06) 6-MWT distance at baseline (i.e. pre-op) in patients on nitrates compared to those without nitrates.

Furthermore, a bivariate model that includes the type of prosthesis implanted (bio vs. mechanical) and patients with or without nitrates, has been created. No significant relationship between prosthesis type and 6-MWT-delta has been found (i.e., patients with a mechanical prosthesis performed better than patients with a bioprosthesis, irrespective of the nitrates therapy) (on average, patients with mechanical walked 70.3±11 m more than patients with a bio-prosthesis, p<0.0001)

Clinical outcomes

The incidence of postoperative AF was as follows: N=21, (24%) in the total group; N=10, (12%) in the mechanical group; N=11 (13%) in the bioprostheses, without significant difference between the two groups (p=0.79).

In the group of patients with bioprosthetic valve, n=11 (13%) patients were on warfarin, at follow-up.

Seven patients (15%) in the MVRm and 1 (2%) in the MVRb group experienced a bleeding event during the study follow-up period (p= NS). Nine patients (10%) experienced embolic events at follow-up, 7 (15%) in MVRm group, and 2 (5%) in the MVRb group, (p = NS)

The rate of stroke and bleeding stratified groups was as follow:

1. **Bleeding**: within a total time at risk of 180.88 persons/years, we computed an incidence rate for MVR-mech group of 38.7 new bleedings/1000 patients/year, while MVR-bio patients, with a total time at risk of 203.83 persons/years, reached a computed incidence rate of 4.9 new bleedings/1000 patients/year
2. **Stroke**: within a total time at risk of 176.93 persons/years, we computed an incidence rate of 39.6 new strokes/1000 patients/year for mechanical group, whereas bioprostheses group had a total time at risk of 200.16 persons/years, with a computed incidence rate of 9.9 new strokes/1000 patients/year.

No cases of endocarditis, valve thrombosis and acute kidney failure requiring dialysis were recorded, so the actuarial freedom from this sequelae was 100%. All the events are listed in Table 1

At follow-up, improvement of at least 1 class of NYHA was found in 35.5% (n=16) of patients in the MVRm group vs. 14.6% (n=6) of patients in the MVRb group (p=0.04).

Thirty-seven (43%) patients were re-hospitalized during follow-up, 11 (24%) in the MVRm group (1 event at the first year, 3 events at 3 years, and 11 at 7 years) and 26 (63%) in the MVRb group (6 events at the first year, 9 at 3 years, and 26 at 7 years).

The cardiac-related hospitalization-free survival was significantly lower in MVRb, when compared to MVRm group (p=0.0004, Figure 1).

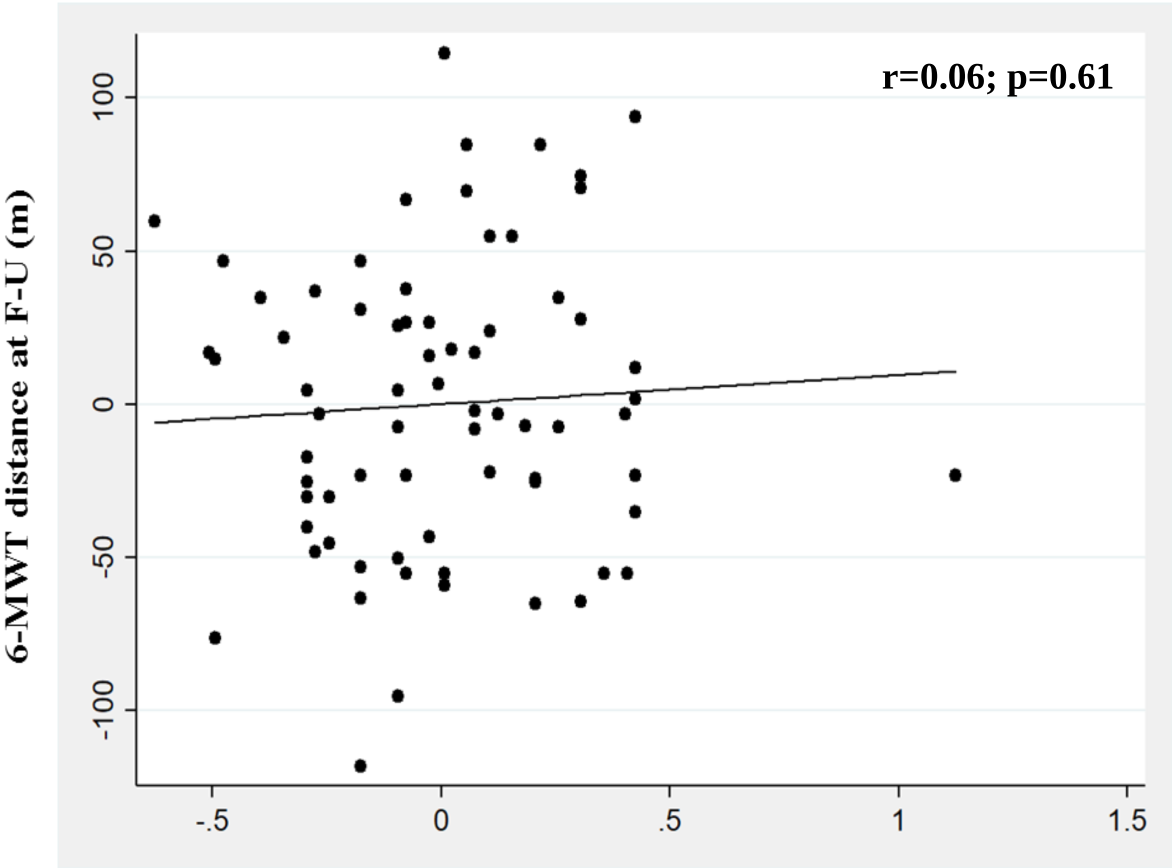
SUPPLEMENTAL TABLES

Supplemental Table 1: comparison of events during the follow-up.

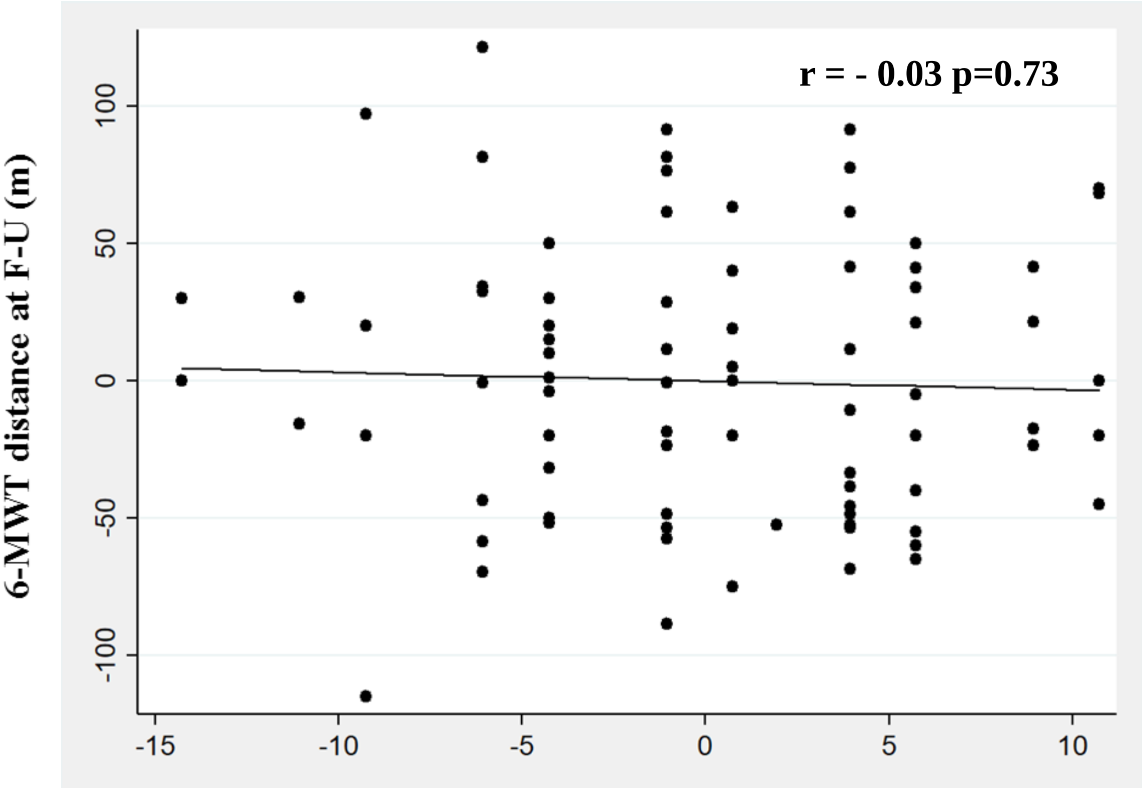
Events	MVRb	MVRm	p
Stroke	2	7	0.08
Bleeding Events	1	7	0.06
Endocarditis	0	0	N/A
Dialysis	0	0	N/A
Reoperation	0	0	N/A
Valve thrombosis	0	0	N/A
Readmission for cardiac cause	30	21	0.02
Sepsis/Deep wound infection	3	5	0.12

MVRm: mechanical; MVRb: biological prostheses

SUPPLEMENTAL FIGURES



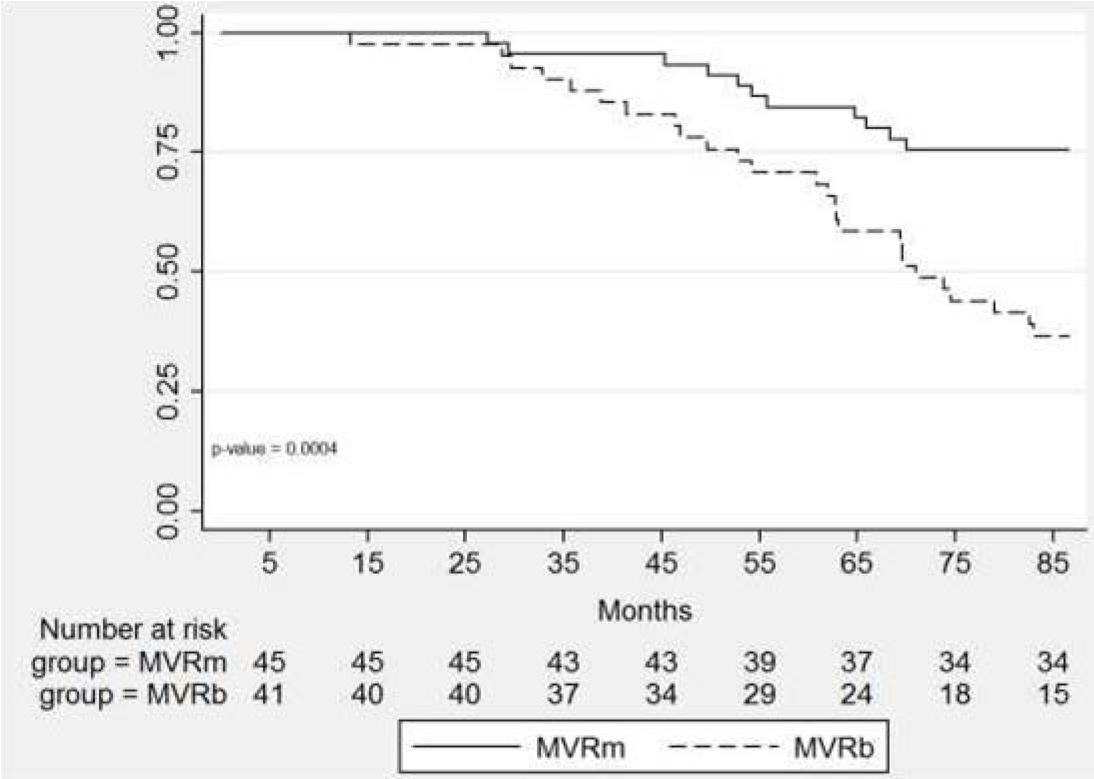
Supplemental Figure 1. Partial correlation of exercise indexed effective orifice area (i-EOA) with functional capacity, assessed by six-minute walking test (6-MWT) follow-up adjusted for the type of prosthesis implanted (mechanical or biological)



Exercise SPAP (mmHg)

Supplemental Figure 2. Partial correlation of exercise systolic pulmonary artery pressure (SPAP) with the change in 6-minute walking test distance (6-MWT) distance from preoperative baseline to follow-up (F-U) adjusted for the type of prosthesis implanted (mechanical or biological).

According to the partial correlation analysis, preoperative exercise SPAP is a confounder of the significant association between type of prosthesis implanted and 6-MWT at follow-up



Supplemental Figure 3. Freedom from cardiac-related hospitalizations. Analysis stratified by groups: mechanical prostheses (MVRm) vs. biological prostheses (MVRb).

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