Original Article

Effect of Mitral Valve Repair on Cardiopulmonary Exercise Testing Variables in Patients with Chronic Mitral Regurgitation

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Abstract

Background: **Mitral valve repair is the surgical procedure of choice for patients with chronic Mitral Regurgitation (MR). The good early and late results allow surgical indication before symptom onset. The cardiopulmonary exercise test (CPET) can objectively assess functional capacity, but little is known about the effect of surgery on their variables.**

Objectives: **Evaluate the effects of mitral repair on CPET variables in patients with chronic MR.**

Methods: **A total of 47 patients with severe MR were selected; these patients underwent mitral valve repair and were submitted to CPET ± 30 days before surgery, as well as six to 12 months after the surgery.**

Results: **There was a predominance of males among 30 patients (63.8%) and 34 patients (72.3%) were NYHA-FC I or II. A significant decrease in oxygen consumption (VO_2) was observed after surgery, from 1,719 ± 571 to 1609 ± 428 mL min-1, p = 0.036. There was a decrease in Oxygen Uptake Efficiency Slope (OUES) from 1,857 ± 594 to 1763 ± 514, p = 0.073 and oxygen pulse (O_2) increased after surgery, from 11.1 ± 3.2 to 11.9 ± 3, 2 mL.beat-1 (p = 0.003).**

Conclusion: **The mitral valve repair did not increase peak VO_2 and OUES despite positive cardiac remodeling observed seven months after surgery. However, O_2 pulse increased postoperatively, suggesting improved LV systolic performance. The CPET is a useful tool to assist in the medical management of patients with MR (Arq Bras Cardiol 2013; 100(4):368-375).**

Keywords: **Mitral Valve Insufficiency/surgery; Exercise; Rehabilitation.**

Introduction

In recent decades, remarkable progress has occurred regarding the understanding of pathophysiology, clinical management and treatment of mitral regurgitation (MR). Advances in diagnostic and surgical techniques, with the possibility of increasing preservation of valve apparatus and left ventricular function, has attracted increasing interest in this disease.

The presence of heart failure symptoms is an important tool to evaluate patients with MR and a strong indicator of quality of life and surgical indication, according to current guidelines[1-3].

In the patient with asymptomatic MR and good ventricular function, surgery may be considered if there is high probability of successful mitral valve repair, but this strategy is not universally accepted[4].

However, in patients with chronic MR, symptoms may appear only in the later stages of the disease and sometimes coincide with irreversible myocardial damage. Furthermore, assessment of functional class (FC) is subjective and may be influenced in several situations, such as in sedentary life style, common in the elderly, in exercise restriction, in the presence of obesity or orthopedic problems.

The cardiopulmonary exercise test (CPET) more objectively assesses the capacity to exercise, minimizing the subjective aspects of obtaining the medical history. In patients with valvular heart disease, the CPET can assess the presence of symptoms, functional capacity and hemodynamic effect.

Few studies have been carried out using CPET in patients with MR and the effects of mitral valve repair, including the preservation of left ventricular function, on exercise capacity[5,6].

Objectives

to evaluate the influence of mitral valve repair on the cardiopulmonary exercise testing (CPET) variables in patients with chronic, nonischemic, severe, organic MR.

Methods

Consecutive patients with a diagnosis of chronic, nonischemic, severe, organic MR and surgical repair indication were selected based on the guidelines of AHA/ACC[1]; these

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patients were followed at the preoperative outpatient clinic of the Valve Disease Medical Section of Instituto Dante Pazzanese de Cardiologia, from August 2008 to January 2011.

Patients with coronary artery disease, associated valvular heart disease, previous cardiac surgery, dilated cardiomyopathy unrelated to MR and moderate or severe lung disease were excluded.

The CPET was performed on an Inbramed treadmill and a Medical Graphics Corporation® (Minnesota, USA) Cardio O_2 gas analyzer was used to measure exhaled gases, using sensors that allow breath-by-breath analysis with real-time plotting of the mean of seven exhalations. The patients breathed exclusively through a plastic mouthpiece attached to a disposable differential pressure Pitot pneumotachometer with 20 mL of dead space after they had the nasal cavity occluded with a clamp.

Bruce's modified protocol was applied for CPET on a treadmill to make it similar to a ramp, with small increments every two minutes. The recovery phase was active in the first two minutes with a velocity of 2.7 km/h, with no inclination and the remaining four, with the patient in the sitting position.

The exercise intensity was considered satisfactory and the exercise classified as maximum, if the respiratory exchange ratio (RER) reached values ≥ 1.10, associated with symptoms of maximal effort, fatigue or breathlessness.

The following variables were obtained for analysis and expressed in tables or charts: oxygen consumption (VO_2) at anaerobic threshold and peak, oxygen pulse (VO_2 / HR), VE/VCO_2 slope, respiratory exchange ratio - RER (VCO_2 / VO_2) and the slope of the curve representing the logarithmic relationship between ventilation and oxygen consumption, the Oxygen Uptake Efficiency slope (OUES).

Initially, all variables were submitted to an exploratory, descriptive and graphical assessment (Box-Plot), used to observe the behavior of measures and also identify possible typos and outliers. The results were summarized as mean and standard deviation (SD), median and 25 (25th Per) and 75 (75th Per) percentiles for quantitative variable and in frequencies, absolute (n) and relative (%) for qualitative variables.

The distribution of quantitative measurements was also assessed by the normality test of Kolmogorov-Smirnov. When the normal distribution was not rejected, the paired Student's *t* test was used to compare before and after surgery. When normality was rejected or to obtain ordinal qualitative measure, the nonparametric Wilcoxon test was used in this comparison.

The present investigation was approved by the Ethics Committee of Instituto Dante Pazzanese de Cardiologia during a meeting on 01.04.2008, according to Resolution N. 3596. All participants signed the free and informed consent form.

Results

Between August 2008 and January 2011, 47 patients (mean age 48.5, SD = 17.5 years), of which 30 were males (63.8%) were prospectively and consecutively evaluated. The predominant etiology was degenerative (35 patients - 74.5%), 34 patients (72.3%) were in NYHA functional class I or II and three patients (6.4%) had permanent AF.

The main preoperative clinical characteristics expressed in frequency (n and %) are shown in Table 1.

The description of the surgical techniques performed in the 47 study patients is summarized in Table 2.

Of the 47 patients who underwent mitral valve repair, 33 patients (70.2%) had absent, minimal or mild residual regurgitation; three patients (6.4%) had mild to moderate, seven patients (14.9%) had moderate, two patients (4.3%) had moderate to severe and two patients (4.3%) had significant residual regurgitation. The two patients with significant residual MR did not undergo CPET postoperatively, having been submitted to previous surgery and were excluded from the CPET database. The other patients with residual MR are being clinically monitored.

The pre- and postoperative echocardiographic studies were performed on average 42.2 (7.8) days (median = 22.5 days) before and 218.1 (37.2) days (median = 203.0 days) after surgery.

After surgery, there were significant reductions in echocardiographic measurements of cardiac remodeling, as shown in Table 3.

The CPETs were carried out on average 31.6 (29.4) days (median = 22.0 days) before and 219.1 (38.3) days (median = 201.0 days) after surgery.

After mitral valve repair, there was a significant reduction in peak VO_2. The variable VE/VCO_2 slope showed no significant difference in mean values pre- and postoperatively and OUES values showed a slight reduction after surgery, from 1857 (594) to 1763 (514), $p = 0.073$. O_2 pulse after surgery increased from 11.1 (3.2) to 11.9 (3.2) mL.beat-1, $p = 0.003$. Table 4 shows the pre- and postoperative comparisons of CPET variables and Figure 1 shows the individual profiles of pre- and postoperative VO2, O2 pulse and OUES values.

Discussion

Chronic MR has a complex pathophysiology and causes LV volume overload, which can lead to irreversible decline of its contractility. The favorable LV loading conditions during the long period of its natural history allows the patient to remain asymptomatic or exhibit few symptoms, even in the presence of LV contractile dysfunction[7,8].

Definitive treatment of chronic and severe MR is surgical and includes mitral valve replacement and mitral valve repair. Mitral valve repair has some advantages over valve replacement, including not requiring anticoagulant therapy in patients with sinus rhythm, preserving the ventricular-valvular integrity, maintaining LV function and showing lower mortality in the immediate and late postoperative period[9,10].

Current guidelines[1-3] recommend surgical intervention in severe and chronic MR and in the presence of heart failure symptoms or when there is evidence of LV dysfunction, PAH or atrial fibrillation. In the absence of symptoms and markers of poor prognosis, the ideal time for surgical intervention is controversial, even in the presence of high probability of successful mitral valve repair[4]. In a study by Rosenhek et al[11], patients with asymptomatic MR were clinically followed in a strategy known as 'watchful waiting', with good clinical results until the onset of symptoms or evidence of LV dysfunction, PAH or atrial fibrillation.

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Table 1 – Patient preoperative characteristics

	Mitral valve repair (n = 47)	%
Male sex	30	63.8
Age (years)	48.5 (17.5) 52.0	
Etiology		
MVP	35	74.5
Rheumatic Others	10 2	21.3 4.2
Functional class NYHA	2.0 (0.8) 2.0	
I	13	27.7
II	21	44.7
III	12	25.5
IV	1	2.1
ECG		
Atrial fibrillation	3	6.4
Hypertension	23	48.9
Diabetes	3	6.4
Obesity	11	23.4
Active smoker	4	8.5
Dyslipidemia	7	14.9
Medications used:		
Diuretics	21	44.7
Beta-blockers	17	36.2
ACEI	22	46.8
ARB	3	6.4
Amiodarone	2	4.3

MVP: mitral valve prolapse; NYHA: New York Heart Association; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-1 receptor blocker.

Table 2 – Mitral valve repair: description of the surgical techniques performed in the 47 study patients

Surgical techniques	N = 47	%
Annuloplasty of the posterior mitral annulus	47	100.0
Quadrangular resection of the posterior cusp	30	63.8
Partial resection the anterior cusp	6	12.8
Shortening of the anterior cusp chordae	5	10.6
Closure of the anterior cusp cleft	2	4.3
Transfer of the posterior cusp chordae to the anterior cusp	2	4.3
Increase of posterior cusp with bovine pericardium	1	2.1
Posterior leaflet neochordae	1	2.1
Mitral commissurotomy	1	2.1
Anterior and posterior chordotomy	1	2.1

Table 3 – Mitral valve repair: comparison of pre- and postoperative echocardiographic measurements of cardiac remodeling

Mitral repair ECHO	PREOP. Mean (SD) Median	POSTOP. Mean (SD) Median	p
Atrial volume Left, mm^3	112.7 (32.5) 107.8	68.1 (29.1) 63.5	< 0.001tp
LV end-diastolic diameter, mm	61.8 (4.5) 61.5	52.9 (6.0) 53.0	< 0.001W
LV end-systolic diameter, mm	38.8 (4.3) 38.0	35.8 (6.6) 35.0	< 0.001W
LV end-diastolic volume, mL	154.2 (32.4) 152.5	113.7 (46.2) 110.0	< 0.001W
LV end-systolic volume, mL	47.7 (18.3) 43.5	45.5 (30.4) 38.0	0.017W
Ejection fraction, %	69.6 (6.2) 70.0	61.2 (8.7) 62.0	< 0.001W
Pulmonary artery systolic pressure, mm Hg	45.7 (15.1) 41.5	35.0 (11.7) 34.0	< 0.001W

pT: paired t test; W: Wilcoxon.

Table 4 – Pre and postoperative CPET: comparison of results

Cardiopulmonary exercise test	PREOP. Mean (SD) Median (per 25; per 75)	POSTOP. Mean (SD) Median (per 25; per 75)	p
Time of exercise, min.	9.12 (1.9) 9.7 (8.2 ; 10.4)	8.7 (2.0) 8.8 (7.6 ; 10.3)	0.079w
Peak gas exchange ratio (GER)	1.13 (0.15) 1.16 (1.03 ; 1.24)	1.14 (0.16) 1.16 (1.03 ; 1.28)	0.698 tp
VO_2 (LA), $mL.min^{-1}$	1.107 (381) 1.120 (814 ; 1405)	1.060 (309) 1.010 (799 ; 1225)	0.262W
Peak VO_2, $mL.min^{-1}$	1.719 (571) 1.690 (1.263 ; 2110)	1.609 (428) 1.635 (1.257 ; 2014)	0.036W
VO_2 (LA), $mL.kg^{-1}.min^{-1}$	15.3 (4.4) 15.1 (12.8 ; 17.1)	14.4 (3.1) 14.0 (11.5 ; 16.7)	0.136W
Peak VO_2, $mL.kg^{-1}.min^{-1}$	23.8 (6.7) 23.4 (20.0 ; 27.1)	22.0 (4.9) 21.8 (18.2 ; 25.5)	0.019W
VO_2 (LA) % predicted	49.1 (13.2) 49.0 (42.0 ; 57.5)	46.3 (10.0) 45.0 (39.0 ; 51.0	0.115 tp
VO_2 max % predicted	75.5 (16.9) 78.6 (62.4 ; 87.0)	70.1 (10.8) 68.8 (63.4 ; 76.9)	0.017 tp
Peak O_2 Pulse, $mL.beat^{-1}$	11.1 (3.2) 11.0 (9.0 ; 14.0)	11.9 (3.2) 11.0 (9.5 ; 14.0)	0.003W
VE/VCO_2 slope	35.34 (9.11) 33.36 (29.04 ; 38.98)	34.43 (4.61) 33.96 (30.66 ; 37.58)	0.906W
OUES	1857 (594) 1814 (1386 ; 2370)	1763 (514) 1650 (1357 ; 2070)	0.073W
OUES % predicted	78.6 (15.5) 76.8 (68.6;89.5)	74.7 (14.6) 74.2(65.6;80.8)	0.108pt

VO_2: oxygen consumption; AT: anaerobic threshold; VE/VCO_2 slope: minute ventilation/carbon dioxide production slope; OUES: Oxygen Uptake Efficiency Slope; pt: paired t test; W: Wilcoxon.

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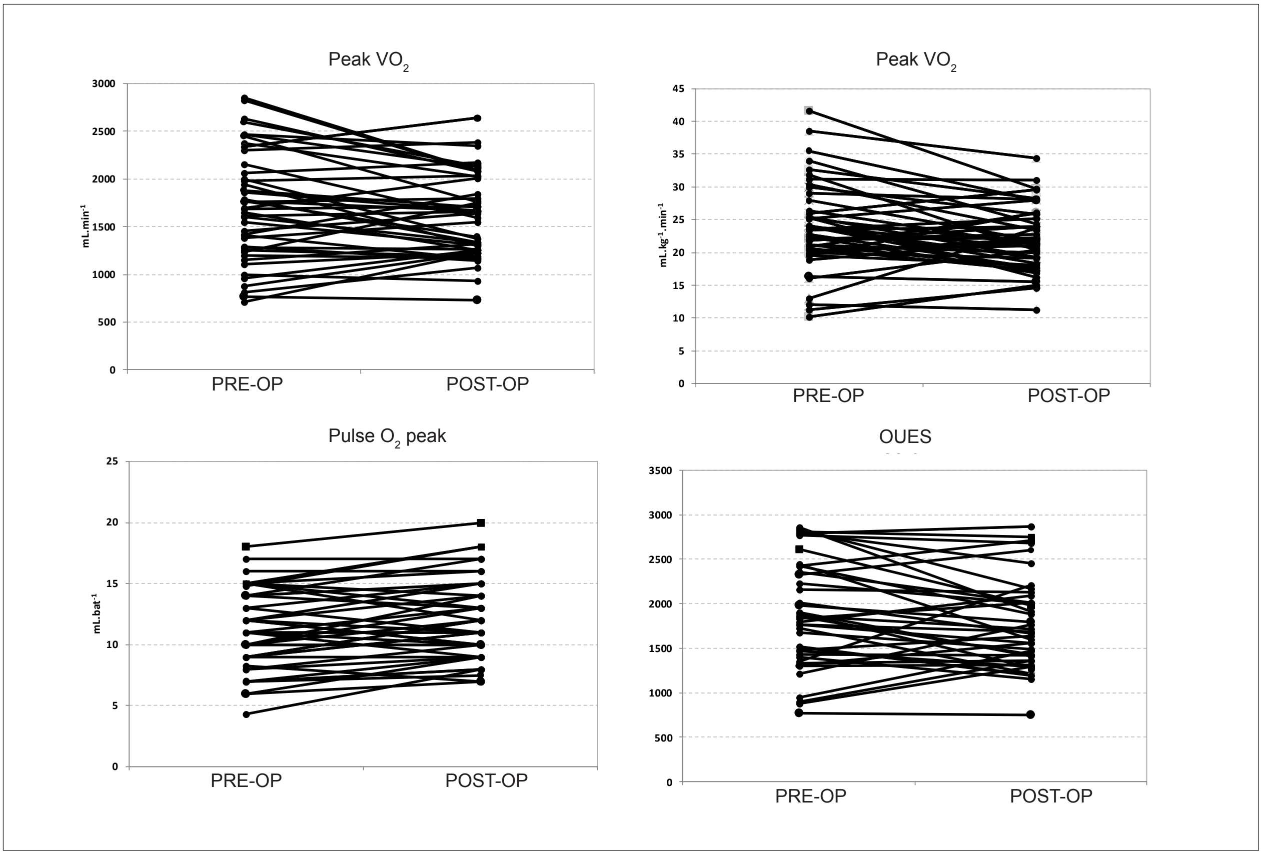

Figure 1 – *VO_2, O_2 Pulse and pre and postoperative OUES.*

The guidelines of the Brazilian Society of Cardiology[3] recommend clinical follow-up of asymptomatic patients with good LV systolic function, with sporadic reassessments every six to 12 months, as well as monitoring of echocardiographic parameters.

Therefore, the presence of symptoms is an important marker of surgical indication. The limitations and difficulties of adequately quantifying functional class, especially in sedentary individuals, suggest the need for a more accurate assessment[12]. The CPET fills that gap by providing a quantitative and noninvasive assessment of FC, as well as several variables for prognostic stratification[13]. However, CPET remains poorly understood and underutilized in current clinical practice. This is mainly due to the costs related to the collection and analysis of expired gases and lack of trained personnel to apply and interpret test results.

The combined evaluation of conventional exercise testing and direct measurement of oxygen consumption (VO_2), carbon dioxide production (VCO_2) and ventilation (VE), analyzed individually or associated in different combinations, provide a detailed and integrated analysis of responses to exercise involving the cardiovascular, pulmonary, hematopoietic, neuropsychological and muscular systems.

Few studies have evaluated exercise capacity after cardiac surgery, particularly in patients with valvular disease[14-16]. In a study by Le Tourneau et al[5], CPET, radionuclide angiography and blood samples for assessment of neurohormonal status were obtained before and one year (216 ± 80 days) after surgery in 40 patients with non-ischemic MR (24 patients successfully submitted to valve repair and 16 patients to valve replacement). In spite of the improvement in NYHA FC, the exercise performance did not change after surgical correction of MR (VO_2 peak of 19.3 ± 6.1 mL.kg-1.min.-1 to 18.5 ± 5.6-mL.kg -1.min.-1 and achieved percentage of predicted VO_2 max. of 79.5% ± 18.2 to 76.8 ± 16.9%) in all patients, regardless of the type of surgery performed.

There were no differences between the groups before and after surgery, regarding tolerance to exercise assessed by peak O_2 pulse or percentage of predicted VO_2, as well as in patients classified according to preoperative EF (< 60% in 14 patients and ≥ 60% in 26 patients) regarding the percentage of postoperative predicted VO_2 max. (74.2% ± 16.5 *versus* 77.1 ± 17.7%) or VO_2 max. (18.1 ± 6.9 mL.kg^{-1}.min.$^{-1}$ *versus* 18.1 ± 4.7 mL.kg^{-1}.min.$^{-1}$). Therefore, there was no improvement in exercise tolerance after surgical correction of MR in untrained patients and the author considers that this result can be explained by the physical deconditioning induced by valvular heart disease or by the postoperative course.

Moreover, in the early postoperative period of cardiac surgery, many factors can contribute to a decrease in exercise capacity compared to preoperative level, among them:

worsening in ventilation (by pleural effusion, atelectasis or phrenic nerve paralysis), congestive heart failure, anemia, decreased mobility of the ribs and the sternum, sinus tachycardia, atrial fibrillation, transient left ventricular dysfunction, and overall fatigue[17-19].

The main objective of this study was to evaluate the effects of mitral valve repair on the CPET variables in patients with chronic and isolated MR. The pre- and postoperative results of CPET variables were compared and the postoperative CPET was performed after a period of significant and progressive cardiac remodeling, as shown by echocardiography performed an average of eight months after valve surgery.

As might be expected, the postoperative echocardiogram showed a significant reduction in left atrial and ventricular volumes, in addition to a decrease in pulmonary artery pressure. Ejection fraction decreased significantly after surgery, but remained within the normal range at the postoperative period. These observations suggest that the patients involved in the study had their indication and surgical intervention performed before the onset of irreversible left ventricular dysfunction.

In both the pre- and postoperative periods, the quality or intensity of effort was considered satisfactory, as shown by the gas exchange ratio (RER) > 1.10, thus meeting the maximal effort criteria.

After surgery, VO_2 peak decreased significantly, from 1719 ± 571 to 1609 ± 428 mL min^{-1} ($p = 0.036$) and the percentage of predicted VO_2 max achieved decreased from 75.5 ± 16.9% preoperatively to 70.1 ± 10.8% postoperatively ($p = 0.017$).

VO_2 max is an important CPET variable as it is considered the measurement that defines the limit of the cardiopulmonary system[13] and represents the maximum level of oxidative metabolism involving large muscle groups[20]. This variable, according to Fick's equation, it is the product of cardiac output and oxygen arteriovenous difference (O_2 av. diff). The main determinants of VO_2 max. are genetic factors and the amount of muscles involved in the exercise and also depends on sex, age and body surface, as well as the level of training or physical conditioning[17]. VO_2 max. is considered impaired when < 80% of its predicted value.

Although there was individual variation in our study, the absence of increase in VO_2 peak or its predicted percentage has been observed in a few previous studies carried out in patients with MR who underwent surgery[5,6]. In the study by Kim HJ et al[6] of 31 patients undergoing mitral valve repair, CPET performed before and one year after surgery showed no significant improvement in peak VO_2 (preoperative peak VO_2 of 23.1 ± 6.2 mL.kg-1.min-1 and postoperative of 22.9 ± 6.4 $mL.kg^{-1}.min^{-1}$, $p = 0.82$). The authors of this study suggest that CPET can be helpful in determining the timing of surgery and a preoperative value of VO_2 peak of 18.5 mL.kg-1.min-1 could be used as a marker of functional degree improvement.

The O_2 pulse provides an estimate of LV systolic volume and reflects the amount of O_2 transported and consumed by the body at each heartbeat. It is considered a strong predictor of mortality in patients with chronic cardiovascular disease[21]. In our study, the peak O_2 pulse showed a significant increase after surgery, from 11.1 ± 3.2 to 11.9 ± 3.2 $mL.bat^{-1}$ ($p = 0.003$), suggesting improvement in left ventricular performance.

The variable VE/VCO_2 slope was not significantly different after mitral valve repair surgery, with a postoperative value of 34.43 ± 4.61. This ratio describes ventilatory efficiency during exercise, showing the amount of air that must be ventilated to remove 1L of CO_2 and normal values are between 20.00 and 30.00[18]. In the study by Arena et al[22] a VE/VCO_2 slope > 34.00 was a marker for poor prognosis in patients with heart failure and left ventricular dysfunction. We found no information in the literature on the behavior of this variable in patients with MR who underwent mitral valve repair, but the results of our study showed postoperative values close to the threshold of poor prognosis.

After surgery, OUES decreased from 1857 ± 594 (78.6 ± 15.5% of predicted value) to 1763 ± 514 (74.7 ± 14.6% of predicted value). There are no data in the literature on the behavior of this variable after cardiac surgery in patients with MR; however, a reduction in OUES was observed in patients with coronary artery disease undergoing coronary artery bypass surgery, when compared to patients undergoing percutaneous transluminal angioplasty, as well as a significant improvement of this variable after physical training[23]. The improvement in OUES has also been observed after exercise training in patients with HF[24], suggesting that a certain VO_2 is reached at a lower ventilatory cost. Previous studies suggest that OUES is strongly correlated with the peak VO_2 [25,26].

In our study, it is likely that the reduction in OUES and VO_2 observed seven months after surgery occurred due to physical deconditioning and lack of training of patients in rehabilitation programs.

The benefits of physical reconditioning programs after mitral valve repair were observed in a previous multicenter study, with a significant increase of 22% in VO_2 peak and anaerobic threshold of 16%, regardless of age, sex, left ventricular function, presence of AF, hemoglobin concentration or medication use (beta-blocker or angiotensin-converting enzyme inhibitor)[27].

Author contributions

Conception and design of the research: Togna DJD, Abizaid AAC, Meneghelo RS, Ramos AIO, Meneghelo ZM; Acquisition of data: Togna DJD, Abizaid AAC, Meneghelo RS, Le Bihan DCS, Ramos AIO, Nasr SK, Maia FS, Meneghelo ZM; Analysis and interpretation of the data: Togna DJD, Abizaid AAC, Meneghelo RS, Le Bihan DCS, Ramos AIO, Nasr SK, Maia FS, Meneghelo ZM; Statistical analysis: Togna DJD; Writing of the manuscript: Togna DJD, Abizaid AAC, Meneghelo RS, Ramos AIO, Meneghelo ZM; Critical revision of the manuscript for intellectual content: Togna DJD, Abizaid AAC, Meneghelo RS, Le Bihan DCS, Ramos AIO, Meneghelo ZM, Sousa AGM

Conclusions

We can conclude that in this prospective study of patients with chronic MR submitted to mitral valve repair and who did not participate in cardiac rehabilitation programs after surgery, there was no improvement in exercise capacity measured by CPET seven months after surgery, despite the significant positive cardiac remodeling. The O_2 pulse increased after surgery, suggesting improvement in left ventricular systolic performance.

The results of this study reinforce the need for patients to perform physical rehabilitation after surgery for mitral valve repair. The physical reconditioning programs allow a more complete and appropriate approach for patients during their postoperative course.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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