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Corrigendum

Correction to “Cardiac rehabilitation improved oxygen uptake measured by cardiopulmonary exercise test in patients after aortic valve surgery” (Rev. Cardiovasc. Med. 2019, 20(1):47-52)

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Original Research

Cardiac rehabilitation improved oxygen uptake measured by cardiopulmonary exercise test in patients after aortic valve surgery

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Evidence for cardiac rehabilitation after valve surgery remains scarce. We retrospectively enrolled consecutive patients undergoing aortic valve surgery. The intervention group consisted of physical exercise for 3 months after surgery, while the control group underwent usual care without physical exercise. It was observed that cardiac rehabilitation has a beneficial effect on the peak oxygen uptake compared to the control group (24.2 ml/kg/min *vs.* 20.6 ml/kg/min) as measured by cardiopulmonary exercise testing 3 months after surgery. There was no significant difference observed in New York Heart Association class I or II between groups. Conversely, the intervention group underperformed the SF-36 Mental Component Scale at 3 months (50.3 *vs.* 53.8 points).

Keywords

Heart valve surgery; rehabilitation; physical exercise; cardiopulmonary exercise test; short-Form 36

1. Introduction

Heart valve diseases are common with an estimated prevalence of 2-3%. In this population, approximately one-fourth to one-half of patients has decreased exercise tolerance (Nkomo et al., 2006; Supino et al., 2006). Heart valve surgery has markedly improved survival and health-related quality of life during the last decade (Hansen et al., 2010). There were more than 61,000 cases of heart valve surgery in China in 2015 (Zhao et al., 2016). Patients undergoing heart valve surgery experienced abnormalities in physical activity before the surgery; however, during recovery, insufficient exercise led to impaired tolerance. Moreover, patients experienced great challenges in mentation and societal functions.

A large number of clinical studies showed that exercise-based cardiac rehabilitation (CR) as adjunctive therapy benefited patients with cardiovascular disease (Stoll et al., 2000; Lunel et al., 2003; Sire et al., 1987) and significantly improved cardiac function in patients with coronary heart disease after revascularization (Santaularia et al., 2013). Additionally, CR also improved the physical capacity and quality of life in patients with chronic heart failure (Izawa et al., 2014). However, studies exploring the effects of CR of patients treated for aortic valve surgery in China are scarce. As there was no evidence of the efficacy, the provided CR was presumably often suboptimal or totally lacking even though the European Society of Cardiology recommends rehabilitation of patients with valvular disease (Butchart et al., 2005).

The aim of the study was to determine the effect of CR after aortic valve surgery by comparing the usual treatment of improving the peak oxygen uptake (VO_2 peak) to the self-assessed mental health measured by the standardized questionnaire Short Form 36 (Ware, 2005).

2. Methods

2.1 Participants

This is a retrospective, single-center trial comparing comprehensive CR versus usual care according to current guidelines. Patients were enrolled from the Guangdong Provincial People's Hospital from January 2016 to December 2017. Inclusion criteria were 1) aortic valve open heart surgery; 2) aortic valve disease including aortic stenosis and/or aortic regurgitation; 3) age $\geq$ 18 years; 4) able to speak and comprehend Chinese, and 5) provide informed written consent. Exclusion criteria were 1) known ischemic heart

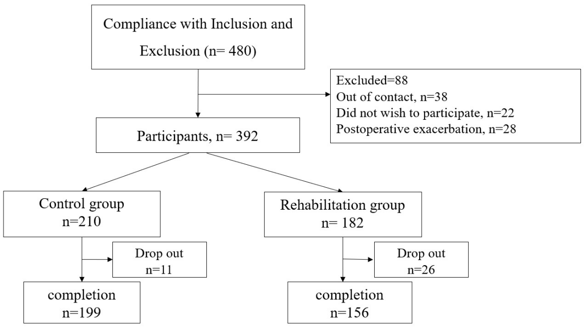

Figure 1. Flow diagram of the study.

disease prior to surgery; 2) current recruitment to other rehabilitation trials or participating in trials precluding patients to participate; 3) expected failure to cooperate according to the trial instructions; 4) diseases in the musculoskeletal system; 5) comorbidity complicating physical activity; 6) competitive sports, and 7) pregnancy and/or breastfeeding.

The study was approved by the research ethics committee of Guangdong Provincial People's Hospital (No.GDREC2016346H). The trial complied with the latest edition of the Helsinki Declaration and relevant regulatory requirements.

2.2 Intervention

Physical exercise was provided 3 months after aortic valve surgery. A training diary and electrocardiogram monitor were used (SNP9000N, China) to ensure adherence at home or in the hospital after discharge. Exercises include walking, Tai chi, jogging, cycling, and brisk walking. The continuing program, which consists of graduated cardiovascular training and strength exercise, was identical regardless of the training location. The patients who did the physical exercise in the hospital were guided by the physiotherapist. Physical exercise programs, based on the intensity of the Borg scale (Borg, 1982), were altered stepwise progressively during each training session. To monitor and regulate the training intensity, our study applied the Borg scale of perceived exertion (RPE) 6–20 scale (Borg, 1982). Rating of perceived exertion was measured by the Borg's scale and a point of 13 was an indication to stop exercise. Exercise frequency at home was observed twice a week and half an hour each session. Every patient who conducted the physical exercise at home had a notebook that recorded the type of activity, frequency, duration, intensity of physical exercise, complaints during activity, and Borg scale score. In addition, patients were familiarized with the content of the Borg RPE 6-20 scale, and the common signs and symptoms of adverse events during and after physical exercise. The physiotherapists offered consultation at the regular follow-up visits.

Usual care, according to current guidelines, was provided. The physician examined all patients 3 months after surgery including physical, biochemical, and echocardiographic assessments.

2.3 Outcomes

The primary outcome evaluated physical activity through peak oxygen uptake (VO_2 peak) at 3 months after surgery. Experienced CR therapists conducted the testing by cardiopulmonary exercise testing with a cycle ergometer (Ergo-Spiro CS-200, Schiller, Switzerland) (Mezzani et al., 2009).

The secondary outcome evaluated self-assessed mental health measured by the standardized questionnaire Short Form-36 (SF-36) at 3 months after sugery (Ware, 2005). Physical exploratory outcomes included distance walked on a 6-min walk test and New York Heart Association (NYHA) class.

2.4 Statistical analysis

All analyses were two-sided tests with a level of significance set at 5%. Data was analyzed with a Statistical Package for Social Sciences (SPSS; IBM Corporation; Armonk, New York USA) version 24.0. Continuous variables were outlined by means ± standard deviation or medians and interquartile ranges according to distribution. Categorical data are presented as absolute values and percentages. Continuous variables of baseline characteristics and comparison of primary outcomes were compared with Student *t*-test or Wilcoxon rank-sum test according to distribution. The $\chi 2$ or Fisher's exact test was used for categorical variables.

3. Results

During the recruitment period, between January 2016 and December 2017, 480 patients were complied with the inclusion criteria at the Guangdong Provincial People's Hospital. In this data set, 38 patients were out of contact, 22 patients did not wish to participate, and 28 were excluded due to postsurgical exacerbation. All patients received either CR (n = 182) or usual care according to current guidelines (n = 210). There were 11 dropouts in the control group and 26 dropouts in the intervention group. Finally, 355 participants were included in statistical analysis (Fig. 1).

3.1 Baseline characteristics

The included population was 60.3% men, mean age 60.9 years, 61.4% with aortic stenosis, 60.8% with aortic insufficiency. NYHA class ranged from I to IV. There were no significant baseline differences in gender, age, eGFR, EuroSCORE II, 6MWT distance, mean LVEF, or Preoperative LVEF ($\geq$ 45%). Moreover, there was a similar prevalence of aortic stenosis, aortic insufficiency, diabetes mellitus, and percentage of NYHA class I–II between 2 groups. The prevalence of atrial fibrillation was lower in the rehabilitation group (15.5% *vs.* 11.0%, $p = 0.043$). On the contrary, compared with the control group, patients in the rehabilitation group were more likely to suffer from hypertension (39.1% *vs.* 49.4%, $p = 0.018$) and dyslipidemia (30.4% *vs.* 35.3%, $p = 0.026$) (Table 1).

3.2 Outcomes

3.2.1 Primary outcome

There was a statistical difference in peak VO_2 (20.57 ml/kg/min *vs.* 24.23 ml/kg/min, $p = 0.049$), anaerobic threshold (9.3 ml/min/kg *vs.* 9.8 ml/min/kg, $p = 0.034$), and SBP at rest (124.5 mmHg *vs.* 130.6 mmHg, $p = 0.042$) between groups after 3 months (20.57 ml/kg/min *vs.* 24.23 ml/kg/min, $p = 0.049$). We found no difference in the VE/VCO_2 slope, maximal SBP, resting heart rate, maximal heart rate, rate pressure product, and total exercise time between groups after 3 months (Table 2).

3.2.2 Secondary outcome

No significant difference was observed for the distance of 6MWT and NYHA functional class between groups at 3 months.

Table 1. Baseline characteristics

	Control group (n = 199)	Rehabilitation group (n = 156)	p value
Male, n (%)	124 (62.3)	90 (57.9)	0.678
Age, years	60.2 ± 11.5	61.8 ± 10.8	0.376
Aortic stenosis, n (%)	121 (60.8)	97 (62.3)	0.273
Aortic insufficiency, n (%)	126 (63.3)	90 (57.9)	0.064
Diabetes mellitus, n (%)	34 (17.3)	22 (14.4)	0.056
Atrial fibrillation, n (%)	31 (15.5)	16 (11.0)	0.043
eGFR, ml/min/1.73m^2	53.34 ± 4.7	54.97 ± 5.1	0.485
Hypertension, n (%)	78 (39.1)	77 (49.4)	0.018
Dyslipidemia, n (%)	60 (30.4)	55 (35.3)	0.026
NYHA class I, n (%)	77 (38.7)	67 (42.9)	0.052
NYHA class II, n (%)	62 (31.2)	47 (30.1)	0.867
Mean LVEF, %	49.7 ± 5.6	50 ± 4.8	0.572
Preoperative LVEF ≥ 45%, n (%)	162 (81.2)	124 (79.4)	0.196
EuroSCORE II	1.08 ± 0.14	1.11 ± 0.12	0.073
Length of 6MWT, m	541.4 ± 7.5	553.9 ± 8.1	0.274

eGFR(ml/min/1.73 m^2) = 186 × (SCr) - 1.154 × (age) - 0.203 × (0.742 if female). eGFR, estimated glomerular filtration rate; Scr, serum creatinine; 6MWT, 6-minute walk test; LVEF, left ventricular ejection fraction.

The mental component scale of self-reported outcomes was lower in the rehabilitation group (50.3 *vs.* 53.8 pts, p = 0.042), while other concepts showed no statistical significance between two arms (Table 3).

3.2.3 Clinical outcomes

Regarding readmission for heart failure, 2 cases in the control group and 1 in the rehabilitation group were observed. Moreover, 1 patient in the control group died of pulmonary infection after surgery. After physical exercise, 3 patients had new-onset atrial fibrillation, 1 had atrial premature beats and 1 had ventricular premature beats. In addition, 11 patients felt chest pain and 2 patients had new musculoskeletal injuries after exercise. No symptom of palpitations or dyspnea was reported in the CR group.

4. Discussion

Although guidelines recommend specialized CR for patients after heart valve surgery (Butchart et al., 2005), evidence regarding its effectiveness, especially for the Chinese population, was lacking. Nowadays, CR is merely carried out during hospitalization in China, and attention to physical exercise after discharge was minimal (Heran et al., 2011; Davies et al., 2010; Keteyian et al., 2008; Hedman et al., 2012). Therefore, the current study was designed to investigate whether CR, in addition to usual care, is superior to treatment after aortic valve surgery.

The most commonly used indicator for assessing exercise tolerance is Peak Oxygen Consumption (Peak VO_2) (Keteyian et al., 2008). Kim et al. (2004) reported that Peak VO_2 was 23.1 ml/kg/min in patients before mitral valve repair surgery, while decreased to 22.9 ml/kg/min in one year after surgery and continued afterward. Hedman et al. showed that Peak VO_2 decreased from 25.6 ml/kg/min to 22.8 ml/kg from 6 months to 49 months after aortic valve replacement (Hedman et al., 2012). Other studies have also observed that exercise training could improve exercise tolerance (Newell et al., 1980; Haykowsky et al., 2012; Fiorina et al., 2007). A multi-center study conducted by Meurin et al. showed that the peak oxygen uptake increased from 16.3 ± 4.5 ml/kg to 20.0 ± 6.0 ml/kg/min after 3 weeks of exercise from 1 week to 1 month after mitral valve repair surgery (Meurin et al., 2005). Vanhees et al. reported that the peak oxygen uptake increased by 25.9% with a 3-month of exercise training after heart valve re-

Table 2. Comparison of Cardiopulmonary exercise test at 3 months

	Control group (n = 199)	Rehabilitation group (n = 156)	p value
Peak VO_2, ml/kg/min	20.6 ± 4.26	24.2 ± 3.89	0.049
VE/VCO_2 slope	26.3 ± 3.82	25.5 ± 4.11	0.242
Anaerobic threshold, ml/min/kg	9.3 ± 1.02	9.8 ± 0.89	0.034
SBP at rest, mmHg	124.5 ± 10.34	130.6 ± 9.37	0.042
Maximal SBP, mmHg	183.2 ± 9.38	188.9 ± 8.77	0.353
Heart rate at rest, bpm	87.5 ± 4.92	88.4 ± 4.18	0.634
Maximal heart rate, bpm	142.8 ± 9.38	144.6 ± 10.42	0.110
Total exercise time, min	6.57 ± 0.83	6.61 ± 0.77	0.058
Rate pressure product	16723 ± 834	17192 ± 738	0.062

SBP, systolic blood pressure; bpm, beats per minute; VO_2, oxygen consumption; VE/VCO_2, Ventilation/carbon dioxide production.

Table 3. Comparison of self-reported and physical exploratory outcomes at 3 months

	Control group (n = 199)	Rehabilitation group (n = 156)	p value
Length of 6MWT, m	503.6 ± 12.43	512.3 ± 11.97	0.324
NYHA function class I, n (%)	75 (37.7)	64 (41.0)	0.051
NYHA function class II, n (%)	61 (30.7)	45 (28.8)	0.763
Short Form-36			
Mental component scale, pts	53.8 ± 5.83	50.3 ± 6.12	0.042
Physical component scale, pts	40.6 ± 4.94	41.2 ± 4.38	0.463
General health perception, pts	71.7 ± 7.30	72.3 ± 8.02	0.353
Mental health index, pts	77.2 ± 6.93	78.1 ± 7.32	0.632
Physical functioning index, pts	71.5 ± 7.15	72.6 ± 7.83	0.521

6MWT, 6-minute walk test; NYHA, New York Heart Association; pts, points.

placement (Vanhees et al., 2004). Eder et al. (2010) and Russo et al. (2014) also reported that early exercise rehabilitation improved the quality of life in elderly patients after cardiac surgery. Given the data, it may be predicted that exercise tolerance was of great significance in patients after heart valve surgery.

The elevated VE/VCO_2 slope was inversely related to cardiac output at peak exercise and at least partly explained by a decrease in pulmonary perfusion (Reindl et al., 1998; Banning et al., 1995). Growing numbers of studies supported the concept that the VE/VCO_2 slope be a better predictor of outcome, including mortality and hospitalization, than peak VO_2 in the heart failure population (Francis et al., 2000; Arena and Humphrey, 2002; Arena et al., 2004). No data of VE/VCO_2 slope had been published on patients after valvular surgery.

The current study included consecutive patients with a reasonable number of inclusion and exclusion criteria securing external validity for the results. The findings, consistent with previous studies, demonstrated that physical exercise training was beneficial on VO_2 peak after heart valve surgery (Pardaens et al., 2014; Landry et al., 1984; Habel-Verge et al., 1987). It appeared that the 3-month exercise (2 times per week), with strength and resistance training, improved oxygen uptake. It was impossible to collect the peak VO_2 data and other measurements by CPET before surgery or CR because of the distinctive therapeutic effect and recovery from heart valve surgery. For the same reason, we could not assess the improvement in any of the self-reported outcomes such as SF-36. However, not every measurement of CPET showed a statistical difference between the CR and control group. The CR intervention did not seem to add improvement in VE/VCO_2 slope, maximal SBP, heart rate at rest, maximal heart rate, rate pressure product, or total exercise time. The mechanism could not be clarified based on the current study.

The exact mechanisms underlying the effect of CR; however, had not been clearly identified. Fukuda et al. found that Plasma PTX3, an inflammatory marker different from C-reactive protein and serum amyloid A, decreased during CR with exercise capacity improvement in patients with cardiovascular diseases (Fukuda et al., 2012). The study implied that exercise-based CR had anti-inflammatory effects, reducing levels of C-reactive protein and serum amyloid A, and improved endothelial function.

The 6MWT was feasible and reflected the daily activities of patients. It showed a good correlation with the peak VO_2 from cardiopulmonary exercise test in heart failure patients (Du et al., 2009). More investigators; however, opposed the idea and suggest that VO_2 peak was a better predictor of survival, particularly over longer follow-up periods (Zugck et al., 2000; Lainchbury and Richards., 2002; Pulz et al., 2008; Lederer et al., 2006). Moreover, the 6MWT distance correlates better with the measurement of quality of life than with VO_2 peak. This demonstrated that 6MWT was a better assessment of patients' ability in performing daily activities (ATS Committee, 2002). Several studies have reported that the 6MWT is associated with increased mortality among cardiac patients with the distance of less than 300 meters being a strong indicator of poor prognosis (Irfan et al., 2011). In patients with severe aortic stenosis admitted for surgery, the 6MWT distance predicted death, myocardial infarction, and stroke events independently from the EuroSCORE (de Arenaza et al., 2010). In the current study, no statistical difference was observed in 6MWT distance between the CR intervention and usual treatment nor did it show better improvement before surgery. This may be due to the insufficient time of CR since most patients gradually have increased exercise ability during surgery recovery. Further studies need to evaluate whether the 6MWT distance benefits from the prolonged CR program, and its effect on predicting the prognosis after aortic valve surgery.

Additionally, points of the mental component scale of SF-36 were lower in the CR group. There is still controversy of whether CR improved mental health status. Sibilitz et al. (2016) showed that CR after heart valve surgery had no effect on mental health and other measures of self-reported outcomes at 4 months. Nevertheless, the intervention consisted of monthly psycho-educational consultations.

Few studies reported that exercise rehabilitation increased the risk of the postsurgical adverse event. Pressler et al. (2011). believed that exercise acted on left ventricular remodeling in patients after aortic valve replacement by reducing left ventricular end-diastolic diameter and increasing left ventricular ejection fraction. Saito et al. (2014) reported only one life-threatening adverse event occurred during the amount of 383,096 patient-hours of exercise training, resulted from a 136-center-participating study. Russo et al. demonstrated the safety and effectiveness of the early exercise rehabilitation after aortic valve replacement or transcatheter aortic valve implantation under extracorporeal circulation in 158 patients aged 80 years or older (Russo et al., 2014).

In the current study, only 1 patient was admitted for heart failure in the rehabilitation group. After physical exercise, 16 (4.5%) patients had complications with arrhythmia, musculoskeletal injuries, or chest pain after exercise. Overall, postsurgical rehabilitation was safe with monitoring and proper guidance.

5. Limitation

The limitations of the trial were similar to those of other trials including physical exercise and physical testing. First, there were no standard CR prescription or testing of all physical exercise tests in the trial. CR prescription was designed by the CR therapists according to clinical guidelines (Butchart et al., 2005) and self-reported endurance and tolerance. Second, since the study included only patients transferred to the CR department, the trial population was not representative of the broad valvular heart disease population. Third, it was a retrospective study with small sample size, introducing selective bias and fewer predefined variables. Fourth, self-reported outcomes were by nature subjective to a risk of recall bias even though the patients completed questionnaires independently of the researchers (Berg et al., 2012). Finally, we did not collect data of parameters before surgery and before CR, which might indicate an imbalance of the baseline physical capability and mental status between groups. Also, the data including metabolic equivalent level was not collected by the time patients got discharged because surgery and insufficient exercise led to impaired tolerance for an extended amount of time during the postsurgical recovery. There were great challenges to the physical, mental, and social functions for patients undergoing heart valve surgery. In conclusion, it was expected that results from the trial should contribute to the development of heart valve specific CR. In order to assess the improvement of physical parameters and mental health contributed by CR, a further randomized control study is warranted.

6. Conclusion

This study investigated the effect of CR program comprising of physical exercise and conventional drug therapy in patients after aortic valve surgery. This was done in a single center setting showing CR after heart valve surgery. It was observed that there was a significantly improved VO_2 peak when cardiopulmonary exercise test was evaluated at 3 months. Conversely, patients undergoing CR underperformed on the SF-36 Mental Component Scale at 3 months.

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Conflict of Interest

The authors declared no competing interests.

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