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5 **A Pilot study Examining the Safety and Effectiveness of 8-weeks of early**  
6 **cardiac rehabilitation on physical function and psychological well-being in**  
7 **patients following aortic root replacement**

8 **Abstract.**

9 **Aim.** To determine the effects of a structured, moderate-intensity, early cardiac rehabilitation (CR)  
10 program on physical function and psychological wellbeing in patients following aortic root  
11 replacement. **Materials and methods:** Patients were randomly assigned to either an 8-week (24  
12 sessions) cardiac rehabilitation (CR) program, 4 to 6 weeks after aortic root replacement using the  
13 Bentall procedure, or to an age- and sex-matched control group undertaking no structured exercise.  
14 Physical function (via exercise treadmill test (ETT)) and psychological wellbeing (assessed via  
15 DASS-21 and SF36) were assessed before and following 8-weeks of CR. **Results:** 30 patients (15  
16 in the control (mean age: 37±10 years) and 15 in the intervention group (mean age: 38±11 years))  
17 completed the 8-week CR programme and no adverse events were reported over the intervention  
18 period. In the CR group, all sub-components of the SF-36 and DASS-21 increased (all  $P<0.05$ ),  
19 showing an overall improvement in psychological function, anxiety, and depression following the  
20 intervention. Distance walked on the ETT (improved significantly following 8-weeks of CR ( $490$   
21  $\pm 167$  m v  $659 \pm 141$ m;  $\Delta$  improvement = 169 m;  $P<0.05$ ). There were no changes in physical  
22 function and psychological wellbeing in the controls ( $P>0.05$ ). A significant group-by-time  
23 interaction effect was evident for physical function and all sub-components of the SF-36 and  
24 DASS-21 (all  $P<0.05$ ) highlighting significant improvements in outcomes in the CR group  
25 compared to controls. **Conclusions:** This small sample, aerobic-based, moderate-intensity CR is  
26 safe and effective, and can be tolerated only 4-6 weeks after complex aortic root replacement  
27 surgery.

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29 **Keywords:** cardiac rehabilitation, Bentall procedure, depression, anxiety

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32        **1. Introduction**

33

34 For individuals requiring aortic root replacement, the Bentall technique is considered the “gold  
35 standard” procedure [1]. This technique is commonly performed on the bicuspid aortic valve due  
36 to a congenital abnormality of the aortic root affecting 0.5 to 2% of the general population [1]. The  
37 vast majority of procedures undertaken involves the replacement of the aortic root with a  
38 mechanical valved conduit [2,3]. The mechanical valve is rarely used in patients over 70 years of  
39 age; in older populations, the biological valve has been shown to be more effective [1]. A  
40 limitation of the mechanical valve is that whilst it provides a robust solution it requires life-long  
41 anti-coagulation therapy associated with increased bleeding risk. A recent meta-analysis indicates  
42 that rates of aortic root re-operation have decreased in recent years as techniques have been refined.  
43 However, rates of late mortality, thromboembolic complications, and incidents of major bleeding  
44 still exist highlighting the risks associated with the procedure even in the light of modern surgical  
45 procedures [4].

46 Cardiac rehabilitation (CR) is a multi-dimensional strategy combining structured exercise training,  
47 education, and psychological and nutritional interventions to improve physical function and mental  
48 wellbeing in patients with a history of cardiac disease [5,6]. Previous work has shown how CR can  
49 help improve physical function, health-related quality of life (HRQoL) and reduce stress, anxiety,  
50 and depression [7]. Following cardiac intervention, post-surgical complications are most likely to  
51 affect the pulmonary system (33%), cardiac system (30%), and negatively affect psychological  
52 wellbeing (26%) [8]. Such complications will often lead to increased length of hospital stay,  
53 increased bed rest, and may exacerbate symptoms of stress, depression and anxiety resulting in  
54 decreased functional capacity, muscle wasting, joint stiffness and a decrease in HRQoL [8].

55 The evidence-base strongly indicates that structured comprehensive CR helps to improve  
56 physical function, recovery from surgery and psychological wellbeing due to the work of an  
57 effective multi-disciplinary team including dieticians, counsellors, smoking cessation  
58 practitioners, and exercise specialists [9,10]. From a surgical perspective, there may be some  
59 anxiety associated with the impact of prolonged exercise on a recently fitted valve replacement, at  
60 least in the short term. Resistance (strength) training is known to significantly increase diastolic  
61 and systolic blood pressure and would appear to be contraindicated, at least in the short term, for  
62 patients recently undergoing aortic root replacement [3]. However, the role of CR on patient  
63 outcomes following aortic root replacement compared to usual care has received little attention.  
64 Most CR studies which have followed surgical intervention have focused on outcomes following  
65 coronary artery bypass graft or angioplasty. To our knowledge, little is known about the impact of  
66 CR following aortic root replacement using the Bentall procedure as it is rarely performed [1].  
67 Therefore, this pilot study aimed to investigate the safety and efficacy of an 8-week CR program  
68 on physical function and psychological wellbeing in patients following aortic root replacement  
69 surgery using the Bentall procedure compared to patients receiving usual care.

70

## 71 **2. Material and methods**

### 72 **2.1. Participants**

73 The pilot study received full ethical approval from the local medical ethics board (approval code:  
74 IR.TUMS.NI.REC.1399.046), and all patients provided full written informed consent before  
75 participation in the study. Patients who underwent aortic root replacement surgery using the  
76 Bentall procedure in Shariati Hospital (Tehran University of Medical Sciences, Iran) between the  
77 years 2016-2019 were referred to a CR center 4 to 6 weeks following surgery.

78 Prior to enrolment in CR, patients underwent echocardiography, completed a symptom-limited  
79 exercise test with treadmill (modified Bruce protocol), and medication was reviewed by a  
80 cardiologist. Patients assigned to the CR group were subsequently referred to the Department of  
81 Cardiac Rehabilitation, where they underwent a supervised 8-week exercise training program  
82 including three sessions per week (24 sessions in total). Controls did not engage in any structured  
83 exercise rather they were advised to undertake physical activity by walking daily and to stop  
84 smoking as per usual care.

85 The inclusion criteria were: clinically stable and deemed suitable for engaging in regular exercise  
86 sessions, optimal medical treatment for cardiac and other underlying diseases, left ventricular  
87 ejection fraction (LVEF) >40%, able to follow study instructions, able to complete study  
88 questionnaires. Exclusion criteria: unstable cardiac conditions including uncontrolled arrhythmias,  
89 uncontrolled cardiac risk factors including hypertension or diabetes mellitus, co-existing  
90 respiratory disease, orthopaedic limitations, and post-surgical complications resulting in the  
91 inability to participate in structured exercise sessions.

92

## 93 **2.2.CR program**

94 Patients were enrolled onto the local 8-week CR program, 4 to 6 weeks after receiving aortic root  
95 replacement surgery. The program consisted of 24 structured exercise training sessions, plus an  
96 education session focused on cardiovascular risk factors, lifestyle modification after surgery, stress  
97 management, quit smoking, and warfarin therapy.

98 At baseline, clinical history, risk factors, and medication usage were logged [11]. Bodyweight and  
99 height were recorded, and subsequently, body mass index (BMI) was calculated. The exercise  
100 program was performed according to the American Association of Cardiac Rehabilitation

101 (AACVPR) guidelines. The patients were divided into 3 groups of low, moderate, and high risk  
102 based on cardiac risk stratification. An individualized aerobic exercise training program consisting  
103 of treadmill walking, cycling, and arm ergometer exercise was provided. Exercise training sessions  
104 were completed 3 times per week for 8 weeks (24 exercise training sessions). Patients trained  
105 between 40-60% of their percentage heart rate reserve (%HRR), with a rating of perceived exertion  
106 (RPE) between 11-14 on the Borg scale [12,13]. Each training session lasted 30-60 minutes which  
107 also included a 15-minute warm-up and 10-minute cool-down. At the beginning and end of each  
108 training session, blood pressure was measured and heart rate was monitored with heart rate and  
109 blood pressure monitors. The INR levels were monitored regularly throughout the intervention, if  
110 the INR was  $\geq 4.5$  the training session would be postponed until it dropped within a normal range  
111 [14]. In addition, patients received weekly counselling sessions which were themed around dealing  
112 with anxiety and depression, managing risk factors, smoking cessation, and making positive  
113 lifestyle changes. On completion of the 8-week CR program, patients were re-referred to a  
114 cardiologist and underwent an echocardiographic investigation, treadmill-based exercise tolerance  
115 test, and medication review.

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### 118 **2.3.SF-36 and DASS-21**

119 Patients completed two psychological outcome measures on two occasions, before and following  
120 their engagement in the 8-week CR program, and at the same time-points for controls. These  
121 included including quality of life assessment (SF-36), and the depression, anxiety, and stress scale  
122 (DASS-21). The SF-36 questionnaire consists of 36 questions with eight health-related concepts:  
123 physical functioning; role limitations due to physical problems; bodily pain; general health

124 perceptions; vitality; social functioning; role limitation due to emotional problems; and mental  
125 health. A higher quality of life is associated with a higher score. The reliability and validity of the  
126 SF-36 questionnaire have been previously established in the Persian language [15]. The DASS-21  
127 is a 21-item self-reported measure of psychological distress. This questionnaire consists of three  
128 subscales, which evaluate depression (7 items), anxiety (7 items), and stress (7 items). The  
129 reliability and validity of the DASS-21 questionnaire have been previously established in the  
130 Persian language [16]. Each questionnaire was completed at baseline and within one week of  
131 completing the CR program.

132

#### 133 **2.4.Exercise tolerance test**

134 An exercise tolerance test was conducted before and immediately following the 8-week CR  
135 program. Patients performed a modified Bruce protocol (symptom-limited) on a treadmill. The  
136 modified Bruce protocol increased speed or gradient every 3 minutes; the first stage started at 2.7  
137 km/h speed and 0% grade, and increased every 3 minutes thereafter until volitional exhaustion.  
138 Heart rate, blood pressure, and a 12-lead electrocardiogram were monitored throughout. The test  
139 was terminated when patients reached volitional exhaustion. Distance walked (m) on the treadmill  
140 (with BMS, Treadmill Track Master) was recorded. Before conducting the ETT, all patients were  
141 instructed to prepare for the test by (1) not eating, drinking alcohol or caffeine, or smoking in a 3  
142 hour period before the test; (2) hydrating regularly in the 24 hours before the test; (3) not engaging  
143 in moderate to vigorous physical activity for at least 12 hours before the test; and (4) wearing  
144 appropriate footwear to perform the test. Heart rate and a 12-lead electrocardiogram were  
145 monitored throughout the test. blood pressure was recorded before the test and every 2 minutes

146 during the test. The test was terminated when patients reached maximum fatigue and were unable  
147 to continue based on self-reported symptoms [17].

148

### 149 **2.5.Echocardiography**

150 A cardiac echocardiographic assessment was performed before and immediately after the 8-week  
151 CR program using standard 2-D echocardiography (Medison EKO 7, Samsung, South Korea). The  
152 Simpson method using the apical four-chamber view was used to estimate LVEF [18,19].

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### 154 **2.6.Data analysis**

155 Data were reported as mean  $\pm$  standard deviation. Repeated measures analysis of variance  
156 (ANOVA) with a two-by-two design (two groups by two points) was used to compare the CR  
157 group and controls for physical function and psychological wellbeing parameters. An alpha level  
158 of  $P<0.05$  was considered statistically significant. Data were analyzed using SPSS version 25  
159 (IBM, NY, USA).

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161

## 162 **3. Results**

163

164 Thirty patients were randomly assigned to the CR group (mean age  $38 \pm 11$  years; 67% male) or  
165 usual care (mean age  $37 \pm 10$  years; 73% male). We recruited 15 patients in the CR group (mean  
166 age  $38 \pm 11$  years; 67% male), and 15 controls (mean age  $37 \pm 10$  years; 73% male), who had all  
167 undergone aortic root replacement within the past 4-6 weeks. Baseline clinical characteristics are

168 presented in Table 1. There were **no** between-group differences in anthropometric variables,  
169 physical function, or in sub-domains of the SF-36 and DASS-21 at baseline (all  $P<0.05$ ).  
170 All fifteen patients (CR group) completed the 8-week CR program and no adverse events were  
171 reported over the intervention period. Table 2 shows that all sub-components of the SF-36 and  
172 DASS-21 improved (all  $P<0.05$ ), showing an overall improvement in QoL, stress, anxiety, and  
173 depression following the intervention. Physical function based on mean distance walked following  
174 an ETT improved significantly following 8-weeks of CR ( $490 \pm 167$  m v  $659 \pm 141$ m;  $\Delta$   
175 improvement = 169 m;  $P<0.05$ ). There were no changes in physical function and psychological  
176 wellbeing in the controls ( $P>0.05$ ). A significant group-by-time interaction effect was evident for  
177 physical function and all sub-components of the SF-36 and DASS-21 (all  $P<0.05$ ) highlighting  
178 significant improvements in outcomes for the CR group compared to controls.

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## 180 TABLES 1-2 ABOUT HERE

181

### 182 4. Discussion

183

184 Our pilot study showed that early CR is safe and effective in patients following aortic root  
185 replacement using the Bentall technique. Patients who undertook early CR following aortic root  
186 replacement surgery in the past 4-6 weeks showed significant improvements in physical function  
187 and psychological wellbeing compared to age- and sex-matched controls. The CR program was  
188 well tolerated with no adverse events being reported. Patients in the CR group improved  
189 significantly in all components of the SF-36 and DASS-21, and in physical function (metres  
190 walked on a treadmill) compared to controls.



191 A large body of evidence has shown that CR programs improve physical function in coronary heart  
192 disease and heart failure cohorts [20,21], as well as in those who have undergone coronary artery  
193 bypass grafting [22]. However, the evidence for the safety and efficacy of CR programs on patients  
194 following valvular surgery is far less established [23]. Recently, Tabet et al. [24] showed that mean  
195 peak oxygen consumption and first ventilatory threshold increased by 32% and 19%, respectively  
196 following 3-5 weeks of moderate-intensity CR. in 50 patients who had recently undergone aortic  
197 valve repair. This is in agreement with our findings as we found a ~26% increase in walking  
198 capacity following a symptom-limited exercise tolerance test.

199 A novelty of our study is the focus on psychological wellbeing which shows the benefits of CR in  
200 this population. Previous studies have shown the benefits of CR for cardiac patients following  
201 surgery [25], for improving depressive symptoms and quality of life [26], and stress and anxiety  
202 [27]. Psychological function and quality of life should continue to be assessed in the longer term  
203 following CR intervention. Longer-term interventions should focus on stress management, self-  
204 care coaching, and wellbeing counseling [28].

205 Cardiac rehabilitation has been well established for having beneficial effects on both physical  
206 function and mental wellbeing. Physical function is improved through increased maximal aerobic  
207 capacity due to improved endothelial function, increased muscle mass, and improvement in  
208 oxygen delivery and utilization [29]. Cardiovascular risk factors are positively modified,  
209 myocardial oxygen demand is reduced, autonomic tone is improved, and the likelihood of  
210 myocardial ischemia is reduced [30]. Epidemiological evidence indicates that CR can improve all-  
211 cause and cardiovascular mortality, reduce CVD events, reduce hospitalization rates, and enhance  
212 HRQoL in patients with coronary heart disease [29,30].

213 Limitations: Our pilot study was small with only 30 patients included so we must recognize this  
214 as a potential confounder. We recommend larger-scale studies be developed to confirm our  
215 tentative findings. Our study was focused on aerobic-based, moderate-intensity training and it  
216 would be interesting for other studies to focus on the viability of conducting higher intensity  
217 training with a resistance training component for the patient undergoing complex aortic root  
218 surgery. This may need to be conducted under close clinical supervision in a hospital setting to  
219 maximize safety considerations.

220

## 221 **5. Conclusion**

222 We found significant improvements in physical function and psychological wellbeing after an 8-  
223 week, aerobic-based, moderate-intensity CR program compared to age- and sex-matched controls  
224 who had all received aortic root replacement surgery using the Bentall technique in the past 4–6  
225 weeks.

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## 227 **Conflict of interest**

228 None to report.

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**Table 1.** Baseline clinical characteristics of people in the CR group and controls (n=30)

Variables	CR group (Mean $\pm$ SD)	Controls (Mean $\pm$ SD)	<i>P</i> -value
Age (years)	38 $\pm$ 11	37 $\pm$ 10	0.12
Stature (cm)	169 $\pm$ 10	168 $\pm$ 11	0.45
Body mass (kg)	77.7 $\pm$ 12.3	76.5 $\pm$ 11.4	0.32
Sex (male/female)	(10/5)	(11/4)	0.22
<b>SF36</b>			
Physical functioning	71 $\pm$ 17.2	73 $\pm$ 16.2	0.23
Physical limitations	41.3 $\pm$ 11.8	40.3 $\pm$ 10	0.76
General health	57.6 $\pm$ 8	56.6 $\pm$ 6	0.10
Vitality	28 $\pm$ 7	29 $\pm$ 6	0.54
Social function	14.6 $\pm$ 4	12.8 $\pm$ 3	0.63
Pain	27 $\pm$ 15.5	26 $\pm$ 14	0.55
Emotional limitations	28.6 $\pm$ 9.9	27 $\pm$ 10	0.16
Mental health	36 $\pm$ 9.1	35 $\pm$ 9.4	0.32
<b>DASS 21</b>			
Stress	14.6 $\pm$ 5.7	13.2 $\pm$ 4.6	0.66
Depression	12.1 $\pm$ 4.5	13.1 $\pm$ 3.5	0.82
Anxiety	10.9 $\pm$ 4.2	11.5 $\pm$ 3.2	0.43
Distance walked during ETT (m)	489.9 $\pm$ 166.6	460.9 $\pm$ 154.2	0.12

DASS-21: The Depression, Anxiety, and Stress Scale; SF36: Quality of life assessment; ETT: exercise tolerate test.

349 **Table 2:** Comparative changes in physical function and psychological wellbeing between the CR  
 350 group and controls (N=30)

	CR group Mean +SD		P-value (change within group)	Controls Mean +SD		P-value (change within group)	P-value (interaction effect)
	Pre	Post		Pre	Post		
SF36							
Physical function	71 ± 17.2	86.3 ± 12.02*	0.02	70 ± 16	71 ± 14.2	0.09	0.02
Physical limitations	41.3 ± 11.8	28 ± 12.07	0.001	42 ± 12	41 ± 11	0.12	0.01
General health	57.6 ± 8.7	61.6 ± 8.9	0.04	58 ± 9.1	57 ± 10.2	0.23	0.01
Vitality	28 ± 7.7	32.3 ± 7.7	0.04	26 ± 7.2	25 ± 6.2	0.53	0.04
Social functioning	14.6 ± 4.4	17.3 ± 4.08	0.06	15.1 ± 4.1	14.8 ± 3.2	0.27	0.01
Body pain	27 ± 15.5	15.6 ± 8.5	0.01	25.2 ± 14	26.1 ± 8.1	0.76	0.01
Emotional limitations	28.6 ± 9.9	19.3 ± 8.8	0.02	29.6 ± 8.2	30 ± 6.4	0.16	0.02
Mental health	36 ± 9.1	43 ± 7.9	0.04	34 ± 7.2	35 ± 7.5	0.54	0.04
DASS16							
Stress	10.9 ± 4.2	11 ± 4.4*	0.01	12.3 ± 3.6	12.2 ± 3.3	0.88	0.01
Depression	12.13 ± 4.5	9.06 ± 2.8*	0.03	11.8 ± 3.6	11.5 ± 3.3	0.21	0.01



Anxiety	14.6 ± 5.7	8.4 ± 2.8*	0.02	13.9 ± 5.2	13.2 ± 6.3	0.92	0.01
Distance walked following an ETT (m)	489.9 ± 166.6	658.8±140.6*	0.01	482 ± 162.3	485±164.6	0.51	0.01

351 DASS 21: The Depression, Anxiety, and Stress Scale; SF36: Quality of life assessment; ETT:  
352 exercise tolerance test; \* indicates a significant difference, CR: cardiac rehabilitation;  $P < 0.05$ .

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