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The Effect of Leg and Arm Exercises on Physical and Psychosocial Functions in Patients with Coronary Artery Bypass Surgery

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Abstract

Aim: The aim of this study was to compare the effects of bicycle and arm ergometer exercises on physical and psychosocial functions in patients who underwent Coronary Artery Bypass Surgery. **Methods:** A total of 107 cases (64 males, 43 females) were included in the study, with 23 participants aged between 52 and 65 using bicycle ergometers and a group of 58 people who performed arm ergometers opposite. After the demographic data were recorded, physical functions of all individuals participating in the study were evaluated with a 6-minute walk test, bioimpedance analysis, HDL, LDL, Triglyceride and Total cholesterol values, and psychosocial functions were evaluated with the Beck depression scale, modified borg scale and SF 36 questionnaires before and after the training. All participants were given bicycle or arm ergometer exercises for 6 weeks, 5 sessions per week, for a total of 30 sessions. **Result:** When the results were examined, it was observed that there was a statistically significant increase in walking distance of the people in the bicycle ergometer group compared to the arm ergometer group ($p < 0.05$). In addition, it was revealed that there was a statistically significant difference in the general health parameter, which is one of the sub-parameters of SF 36, in the arm ergometer group compared to the bicycle ergometer group ($p < 0.05$). **Conclusion:** When we look at the results of this study, it is important in terms of revealing that bicycle and arm ergometer exercises similarly improve the physical and psychosocial functions of patients who have undergone Coronary Artery Bypass Surgery. However, it has been shown that cycling exercises are much more advantageous in improving functional capacity. **Summary Statement:** What is already known about this topic? 1) Walking and arm exercises are good for heart diseases. What this paper adds? 2) Demonstrated that cycling and arm ergometer exercises have curative aspects for patients undergoing Coronary Artery Bypass Surgery. As a result of our

study, it has emerged that leg and arm ergometry techniques are good imagers in individuals who have undergone coronary artery bypass surgery.

Keywords

CABG, Leg and Arm Ergometry, Physical Function, Psychosocial Function, Quality of Life

1. Introduction

In the 21st century, the development in education and income levels in the world, the differentiation of nutritional habits, and efforts to control infectious diseases cause an increase in the expected life span. Increasing the life expectancy is a desirable situation, but this has increased the incidence of non-communicable chronic diseases and 60% of the causes of death in the world are non-communicable chronic diseases [1].

While the rate of increase in diseases decreases in developed countries, it increases in developing countries due to lifestyle differences [2].

Coronary artery disease (CAD) is considered one of the most common causes of death in developed countries. Today, deaths related to CAD are decreasing due to the decrease in risk factors, the widespread use of medical treatment, and the developments in revascularization techniques [3]. Coronary artery bypass graft surgery (CABG) continues to be the gold standard of revascularization in many patients, especially cardio-vascular patients, for over 50 years [4]. The main reason why mortality in coronary artery diseases is number one in the world is not due to the interventions made in the acute stages of the diseases, but to the inadequate application of secondary prevention methods. Cardiopulmonary rehabilitation is stated as a multidisciplinary treatment application with the highest scientific evidence level [5] as a secondary prevention method [6].

Cardiac rehabilitation (CR) is a physical, physiological, psychological, social or work-related exercise that includes individually planned exercise practices for heart patients, medical evaluations, identification of risk factors, education and counseling for patients, medical treatment, and behavioral changes according to coronary risk factors. It is known as a program that aims to keep the quality of life of people at the highest level in terms of efficiency [7] [8].

Physiotherapist, in the field of CR, plays an important role in protecting and improving respiratory functions, providing optimal circulatory regulation, preventing muscle atrophy, helping to control pain, increasing independence and general function, and improving quality of life by providing patient education [9]. For these purposes, many physiotherapy methods are used and compared in the literature. Although the benefit of physiotherapy is a fact emphasized in almost every study, there is no definite conclusion about which method is superior. It is known that CABG surgery is an important operation that adversely affects many systems, especially the cardiopulmonary system, and causes serious

complications in the postoperative period [10]. The importance of physiotherapy is evident in the prevention and reduction of these complications. When the negative effects of post-surgical immobilization are added to CABG patients who are at serious risk for complications, planned applications are required to regain the patient's adaptation to daily life despite the success of the operation [7] [11].

When the literature is examined, there are studies in this field, but it is noteworthy that comparative studies are limited. With this study, it is foreseen that it will be a guide in the selection of the appropriate method for both the patient and the patient by determining in which aspects the methods may be more advantageous. This study was planned to compare the effects of cycling and arm ergometer exercises on physical and psychosocial functions in patients undergoing CABG. The hypotheses we established in our study;

H1: Leg ergometer exercise training is more effective than arm ergometer exercise training in improving physical functions in patients undergoing CABG surgery.

H2: Leg ergometer exercise training is more effective than arm ergometer exercise training in improving psychosocial functions in patients undergoing CABG surgery.

2. Materials and Methods

2.1. Purpose of the Study

This study was planned to compare the effects of cycling and arm ergometer exercises on physical and psychosocial functions in patients undergoing CABG.

2.2. Sample of the Study

Necessary permissions were obtained by local ethical committee. This study was carried out in Diyarbakır state hospital.

2.3. Study Time

This study was carried out between April 2021 and September 2021.

2.4. Participants

We interviewed 110 patients who had undergone stable CABG surgery, who applied to cardiology and physical therapy outpatient clinics between April 2021 and September 2021. Eleven of these cases were not included in the study because they did not attend the sessions regularly for different reasons such as transportation difficulties and lack of sufficient time, and 3 cases did not sign the consent form. As a result, the study was carried out with 107 patients who agreed to participate in the study and signed a voluntary consent form after being informed about the study.

2.4.1. Inclusion Criteria in the Study

1) According to exercise-related cardiac event risk assessment, individuals

with low and moderate levels (EF > 40% - 49% AND MET VALUE > 5),

2) Those between the ages of 18 - 65,

3) With an assistive deviceable to stand independently,

4) Body mass index 24 - 36 kg/m^2,

5) EF over 40%,

6) It was determined as individuals who voluntarily participated in the study.

2.4.2. Exclusion Criteria

1) Having a neurological problem,

2) Having an active infection,

3) Having an orthopedic problem that prevents the use of lower and upper extremity bikes,

4) Cancer patients receiving radiotherapy and chemotherapy,

5) Individuals who are psychiatric patients and use antidepressants were determined.

2.5. Evaluation

2.5.1. Demographic and Descriptive Data

A patient evaluation form questionnaire was used to determine the demographic and descriptive characteristics of the participants, such as age, height, body weight, background, family history.

2.5.2. Evaluation of Physical Functions

1) Determination of Functional Capacity

In order to determine the functional capacity, the 6-minute walking test (6 MWT) was applied twice, before and after the exercise training. 6 MWT was held on a flat track suitable for walking, with a 30-meter start and end point marked. Before the test, the subjects were rested on a chair at the beginning of the track for 15 minutes, and the level of fatigue felt during rest, resting HR and BP were recorded. Before starting the test, all participants will walk on the track, whose start and end points are marked with signs, for 6 minutes at the walking speed you set, with the command "Test has begun. In any situation such as dizziness, nausea, palpitations, severe shortness of breath, severe fatigue, or whenever you want.", you can slow down, stop, rest and continue the test again, or you can end the test completely. You must continue the test until the test finished command is given". At the end of the test, the total distance the participant walked in 6 minutes was recorded in meters. The data recorded before the test was recorded again after the test. Blood pressure, HR, respiratory frequency and oxygen saturation were measured before and after the test. Patients were asked to walk as long as possible in their own rhythm and with standard commands for 6 minutes in a 30-meter hospital corridor. Patients were seated when they wanted to rest. At the end of 6 minutes, the distance walked was measured in meters.

2) Evaluation of Body Composition

Body composition, body mass index and fat percentage were calculated using

the Tanita body composition analyzer TBF-300 Instrument using the bioelectric-electrical impedance method. Measurements were repeated at the beginning and end of exercise training. Participants were asked to come to the measurement in the morning hungry and the measurement was made with bare feet. Height, body weight, lipid ratio and percentages of the participants were recorded.

3) Determining Cholesterol Level

HDL, LDL, Trglyceride and total cholesterol findings in blood values were evaluated separately before and after exercise training with laboratory tests.

2.5.3. Evaluation of Psychosocial Functions

1) Evaluation of Quality of Life

The Turkish version of the short form health questionnaire (SF-36) was used to evaluate the quality of life. SF-36 is a very common general health assessment questionnaire. It evaluates many aspects of health. It consists of 36 questions consisting of 8 sub-titles; while physical health score is obtained by adding physical function, physical role difficulty, pain, general health scores, mental health score is obtained by adding vitality (vitality, energy), social function, emotional role difficulty and mental health scores. The higher the calculated scores, the better the health status [12]. The validity and reliability study of the SF-36 questionnaire was conducted by Koçyigit *et al.* [13] [14].

2) Evaluation of Depressive Symptoms

The Turkish version of the 21-item Beck Depression Inventory (BDI) was used to evaluate depressive symptoms. BDI is a self-report inventory developed by Beck in 1961 to measure emotional, cognitive, somatic and motivational components. BDI is one of the most frequently used self-informing tools in research and clinics. Although its main purpose is to comprehensively evaluate the symptoms of depression, it also allows the evaluation of cognitive content. The scale consists of 21 items and two items are for emotions, eleven items are for cognition, two items are for behaviors, five items are for somatic symptoms, and one item is for interpersonal symptoms. Patients are asked to choose the most appropriate one of these questions for their situation. Scores ranging from 0 to 63 are obtained by giving points as 0, 1, 2, 3 for each question. Results are evaluated as 0 - 9 no/minimal depression, 10 - 18 mild depression, 19 - 29 moderate depression, 30 - 63 severe depression [15]. The validity and reliability of the BDI, which was used to determine the intensity of depression, for Turkish society was made by Tegin.

3) Assessment of fatigue

While the severity of dyspnea was rated between 6 - 20 points in the Borg scale, which was first developed by Borg in 1970, it was later modified to become a modified scale marked between zero and ten points, which is still in use [16].

This scale is used in clinics to determine the severity of dyspnea during bicycle or treadmill exercise tests and in tests such as 6 MWT, in which functional capacity is measured, and is an assessment method with proven reliability and va-

lidity [17]. The data obtained at the end of the first session and the last session of the exercise training was evaluated.

3. Finding

Descriptive Characteristics of Participants

This study was carried out in a total of 107 cases (64 males, 43 females) between the ages of 50 - 65, consisting of two groups, 58 (23 M, 35 F) in the Cycling Ergometer Group (BEG) and 49 (41M, 8F) in the Arm Ergometer Group (KEG) was performed with.

The mean age, height, body weight and BMI of BEG were 54.69± 4.29 years, 170.1 ± 9.59 cm, 71.98 ± 13.49kg and 24.81 ± 3.81 kg/It was determined as cm^2. The mean age, height, weight and BMI of CEG were 56.45± 4.86 years, 167.1 ± 7.62 cm, 70.10 ± 11.6 kg and 25.21 ± 4.80 kg/cm^2, respectively. When the groups were compared, no statistically significant difference was determined. The data of these findings are shown in Table 1 ($p > 0.05$), Table 2 and Table 3.

The pre-training data of the groups were compared and no statistically significant difference was found between the walking distance in BEG and CEG.

AEG group triglyceride score was significantly higher. There was no significant change in other physical and psychosocial parameters compared to other data ($p > 0.05$). These data are in Table 4.

When the physical and psychosocial functions of BEG before and after training

Table 1. Demographic characteristics of the cases by groups.

	BEG n (58) X ± SS	AEG n (49) X ± SS	P
Age (year)	59.26 ± 4.28	56.45± 4.86	0.086
Height (cm)	170.1 ± 9.59	167.1 ± 7.62	0.607
Weight (kg)	71.98 ± 13.49	70.10 ± 11.6	0.950
BMI (kg/m^2)	24.81 ± 3.81	25.21 ± 4.80	0.051

X: mean, SD: standard deviation, n: number of cases, %: percent, cm: centimeters, kg: kilograms, kg/m^2: kilograms/square meter, BMI: body mass index, CEG: Cycling Ergometer Group, AEG: Arm Ergometer Group p: Significance level, *: Variable for which difference was detected.

Table 2. Frequency of patients.

Frequency		n %	n %
Gender	Woman	35 (81.4%)	8(18.6%)
	Man	23 (35.9%)	41 (61.9%)
Educational Status	Primary school	21 (50.0%)	21 (50.0%)
	Middle School	22 (56.4%)	17 (43.6%)
	High school	7 (53.8%)	46 (42.6%)
	University	8 (61.5%)	5 (38.5%)

Table 3. Comparison of the groups' pre-training data.

Variables	BEG n (58) X ± SS	AEG n (49) X ± SS	P
Physical Functions Walking distance (m)	437.4 ± 28.4	437.7 ± 28.94	0.961
Body fat percentage (%)	33.52 ± 7.83	32.43 ± 7.60	0.470
HDL	42.95 ± 2.40	43.17 ± 2.88	0.669
LDL	102.1 ± 23.08	96.99 ± 21.28	0.241
Trigliserid	219.8± 40.01	235.0 ± 32.20	0.035*
Total kolesterol	227.6 ± 36.16	233.7 ± 45.17	0.436
BMI (kg/m^2)	24.81 ± 3.81	25.21 ± 4.80	0.629
Psychosocial Functions Borg score	4.00 ± 0.83	3.91 ±.99	0.646
Beck depression	17,48 ± 14.85	12.55 ± 10.84	0.056
Physical Function	69.10 ± 22.39	66.61 ± 23.00	0.581
Role limitation	70.11 ± 22.18	69.00 ± 25.48	0.809
Emotional Function	65.55 ± 20.05	66.91 ± 25.30	0.758
General Health	68.78 ± 23.25	69.98 ± 21.34	0.782
Vitality	74.49 ± 22.40	66.20 ± 22.92	0.062
Social Function	75.81 ± 25.89	67.50 ± 23.30	0.087
Ache	75.61 ± 23.52	83.69 ± 25.04	0.089
Mental Health	71.54 ± 23.67	72.11 ± 23.92	0.902

X: mean, SD: standard deviation, n: number of cases, %: percent, cm: centimeters, kg: kilograms, kg/m^2: kilograms/square meter, BMI: body mass index, BEG: Cycling Er-gometer Group, CEG: Arm Ergometer HDL: high-density lipoprotein LDL: low-density lipoprotein p: Significance level, *p < 0.05, **p < 0.01, ***p < 0.001, m: meters.

were compared, it was found that there was no statistically significant difference between the groups in physical functions such as walking distance, lipid value, triglyceride and total cholesterol values, and BMI values. It was found that there was a significant difference between the groups that only the walking distance variable increased after exercise. These data are shown in Table 4.

4. Discussion

Our study was conducted to compare the effects of cycling and arm ergometer exercises on physical and psychosocial functions in patients undergoing CABG. As a result of our study, there was no significant difference between the patients' bicycle ergometer exercises and walking distance, body fat percentage, triglyceride and total cholesterol, modified borg scale values, but positive significance was observed in the increase in the triglyceride score in the AEG group. The SF-36 sub-parameters of exercise and general health were higher in the arm ergometer exercise group than in the bicycle ergometer exercise group.

Table 4. Comparison of the pre-training and post-exercise values of the bicycle ergometer in terms of physical and psychosocial functions.

Variables	Pre-training	Post training	P
Physical Functions Walking distance (m)	437.5 ± 28.54	453.1 ± 44.68	0.001***
Body fat percentage (%)	33.02 ± 7.71	33.41 ± 7.53	0.727
HDL	43.05 ± 2.62	43.38 ± 2.54	0.357
LDL	99.75 ± 22.32	97.53 ± 23.80	0.945
Trigliserid	224.2 ± 36.76	219.2 ± 30.07	0.192
Total kolesterol	226.7 ± 40.87	224.8 ± 39.24	0.714
BMI (kg/m^2)	24.99 ± 4.27	24.28 ± 3.70	103
Psychosocial Functions Borg score	3.963 ± 0.91	3.813 ±.93	0.227
Beck depression	16.77 ± 12.98	20.02 ± 16.22	0.056
Physical Function	67.96 ± 23.13	65.43 ± 24.00	0.404
Role limitation	69.60 ± 23.64	70.53 ± 22.28	0.779
Emotional Function	66.17 ± 22.51	70.78 ± 26.00	0.145
General Health	69.33 ± 22.30	68.51 ± 22.30	0.792
Vitality	70.70 ± 22.91	65.17 ± 19.74	0.063
Social Function	72.00 ± 24.97	66.73± 25.14	0.111
Ache	73.31 ± 24.45	76.03 ± 24.34	0.331
Mental Health	71.80 ± 23.67	71.48 ± 22.56	0.922

X: mean, SD: standard deviation, n: number of cases, %: percent, cm: centimeters, kg: kilograms, kg/m^2: kilograms/square meter e, BMI: Body Mass Index, BEG: Cycling Ergometer Group, p: Significance level, *: Variable with difference, m: meters

According to the data published by the World Health Organization in 2008, 17.3 mil-lion people died worldwide due to various diseases. 30% of these deaths were caused by coronary heart diseases. It has been stated that 23.3 million people will die due to cardiovascular diseases in 2030 [18]. Although the exact number is not known exactly, the number of heart surgeries performed in Turkey is about 50,000 per year, and the majority of these surgeries consist of coronary heart surgery [19].

KR; exercise, psychosocial support and patient education. The purpose of KR is to facilitate the re-adjustment of individuals with cardiovascular disease to normal life, to reach the maximal functional state and to reduce risk factors [20]. In recent years, it has been agreed that exercise is effective in the treatment of cardiovascular diseases. Deaths due to cardiovascular diseases in Canada, Japan and England decreased by 70% with the introduction of CR [21]. While participation in CR programs reaches 10% - 20% among over 2 million patients per year in the United States (USA) [22], it was stated in the study of Çiftçi *et al.* in

our country that CR programs are not adequately implemented in cardiology [16].

Age and gender are controversial variables in terms of postoperative complications. It has been determined that cardiac operations performed in patients aged 80 and over have a higher risk of mortality and morbidity compared to the younger population [23] [24]. Bagheri *et al* used the data of 393 male and 997 female patients in their study in which they investigated the effect of gender on the results of CABG surgery. As a result, they stated that female patients should be paid more attention due to the high mortality rate [25]. According to statistical studies carried out for men and women between the ages of 45 - 74 in Turkey for 21 years, the mortality rate of heart diseases was recorded as 7.6 per thousand for men and 3.8 per thousand for women. Both CAD mortality and new coronary event rate in Turkish people were higher than normal in both genders, especially in women, and these data increased the importance and necessity of taking preventive measures from coronary disease in our country.

Evidence has increased in recent years that the elderly benefit from exercise training. According to the study of Williams *et al.,* the benefits of CR are similar in elderly and young patients [26]. According to the study of Audelin *et al*., while improvements in quality of life and physical function scales were higher in patients over 75 years of age, the absolute increase in functional capacity was found to be less than in younger patients [27]. According to the study evaluating the functional capacity after CABG, it was stated that the increase in age negatively affects the functional capacity increase [28].

When the groups were compared in our study, no significant difference was found in age, height and weight values. This shows that the groups included in the study are homogeneous. We think that the similarity of the values contributes to the objectiveness of examining the effect of individualized regular and planned exercise program on cardiac functions.

After regular CR applications, a decrease in BMI value is observed with weight loss [29]. A BMI of more than 25 (overweight) increases the risk of coronary artery disease [30]. Kuo *et al.* stated that an appropriate BMI should be maintained to prevent secondary complications after CABG; stated that BMI is inversely proportional to quality of life [31]. Lavie *et al.* found a massive 10% reduction in BMI in 259 young patients. They stated that this different result was due to the fact that the pre-rehabilitation BMI was higher than the patient groups in other studies [32]. Al-Ajlan and Mehdi, in the study in which 474 cases participated, according to the physical activity level of the participants; classified them as sedentary, low, moderate, and high, and reported that there was an inverse relationship between BMI and activity level [33].

In our study, BMI value decreased significantly only in the arm ergometer exercise group after exercise training compared to before. According to the BMI formula developed considering body weight and height, it was determined that the pre-measurement values of the groups fell into the category of overweight,

and despite the significant decrease in body weight in the final measurements, the groups still remained in the category of overweight.

Of the patients participating in CR, 47% - 65% were also diagnosed with hypertension [34]. In a meta-analysis including the last 54 studies, it was shown that aerobic exercise decreased 3 - 4 mmHg in systolic BP and 2 - 3 mmHg in diastolic BP [35]. In a study involving 1500 participants between 1962 and 1977, the risk of hypertension was found to be 35% higher in sedentary people. AHA (American Heart Association) included exercise in the scope of non-pharmacological treatment in hypertension [36]. In our study, the rate of patients diagnosed with hypertension was 15.4%. 46.2% of the cases in our study had never smoked, and 53.8% quit smoking. The high rate of smoking in both groups supports studies that reveal the harmful effects of smoking on heart diseases. Almost all of the patients included in the study had a smoking history that would be considered as severely dependent. We think that this situation affects the vascular structures of the patients, negatively affects the rate of CABG surgery, and subsequently prevents the development of physical functions and quality of life. In the light of this information, we think that it is important to evaluate all parameters that affect exercise efficiency, such as demographic characteristics, comorbidities, and smoking in exercise training after CABG surgery.

The 6 MWT is a test affected by many factors [37] [38]. These factors include age, weight, height, gender, mood at the time of the test, mental function, supplemental oxygen use, courage given to the patient during walking, the area where the test was performed, and the diseases possessed [39].

According to the study of Trevisan *et al.* in 2015 comparing 27 patients who underwent bicycle ergometer exercises and aerobic exercise after CABG surgery, the increase in walking distance in BEG was found to be statistically significant after 6 MWT in both groups [40]. Jelinek *et al.* applied an ergometer exercise program to 22 PCI and 16 CABG patients 3 times a week for 6 weeks. The 6 MWT results at the beginning and end of the treatment showed a statistically significant increase in CABG patients compared to PCI. In the study conducted to investigate the effectiveness of cycling and arm ergometer on walking distance in individuals with Peripheral Arterial Disease (PAD), there was a significant increase in walking distance in both groups at the end of 24 weeks, while there was a statistically higher increase in bicycle ergometer compared to arm ergometer application. Measurements were made at the 6^{th}, 12^{th}, 18^{th}, and 24^{th} weeks, and significant changes began to occur in the results from the 12^{th} week [41].

In 2012, Ghrouni *et al.* compared the effects of cycling ergometer and isokinetic dynamometer and strengthening programs on body composition in patients after CABG surgery. According to the study conducted with 32 patients, there was no statistically significant difference between the ergo-meter group and the group that strengthened with isokinetic dynamometer, while body fat percentages decreased in both groups at the end of the 6-week program [42]. According to the study conducted by Pierson *et al.* on 36 coronary artery patients, a statistically significant decrease was observed in body fat percentage at

the end of 6 weeks when resistance exercises were added to ergometer exercises [43]. In a study conducted by Onishi *et al.* in 2009, resistance exercises were added to 32 patients in addition to bicycle ergometer exercises, and a significant decrease in body fat percentage was found as a result [44]. The positive effects of an active lifestyle and regular aerobic exercises on body fat percentage have been emphasized in many studies [7]. In a study in which 34 patients were compared in a randomized controlled manner, it was stated that early aerobic activity was beneficial in a study performed with conversional physiotherapy after CABG surgery and a bicycle ergometer [45].

Quality of life refers to the vital functions, social and physical well-being of individuals in general, as well as the emotional well-being of the person [45]. The quality of life of cardiac patients is adversely affected by symptoms such as fatigue, dyspnea, edema, and sleep disturbances [46].

Korkmaz *et al.* conducted a study with a total of 195 patients (159 men, 36 women) who were over the age of 18 and had no communication problems, who had undergone CABG surgery in a training and research hospital in Istanbul. Quality of life was measured with SF-36 before surgery and six weeks and one year after surgery. The patients' quality of life sub-dimension score averages at six weeks and one year after surgery increased significantly compared to preoperative values [47].

5. Conclusions

As a result of our study:

- Functional capacity increased after cycling and arm ergometer exercise training.
- The positive effects of both exercise training on cholesterol level were determined.
- Positive effects on body composition were found in both groups after cycling and arm ergometer exercise.
- Both exercise training decreased the BMI value.
- Both exercise training increased the quality of life.
- Depressive symptoms decreased after exercise training.
- While the fatigue value after exercise decreased in BEG, no change was found in CEG.
- In order for the results to be more objective, it is recommended that future studies be planned with a larger sample size.
- Since the positive effects of bicycle and arm ergometer exercise training on physical and psychosocial functions are different, which method to choose should be decided according to the desired functions. In addition, it should not be forgotten that they can be used as alternatives to each other according to the motivations of the patients.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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