ORIGINAL RESEARCH

The Effect and Possible Mechanism of Cardiac Rehabilitation in Partial Revascularization Performed on Multiple Coronary Artery Lesions

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Purpose: To observe the effect of cardiac rehabilitation (CR) in patients with partial revascularization performed on multiple coronary artery lesions and explore its possible mechanism.

Patients and Methods: A total of 400 patients with multiple coronary artery lesions were enrolled and randomly divided into a complete revascularization group and a CR group, with 200 cases in each group. Target lesion revascularization was performed radically in the complete revascularization group, while it was partially completed in the CR group, and postoperative CR was performed. All the patients were put under conventional treatment. Left ventricular end diastolic dimension (LVEDD), left ventricular ejection fraction (LVEF), 6-minute walking distance (6-MWD), quality-of-life scores, safety and levels of serum nitric oxide (NO), nitric oxide synthase (NOS), superoxide dismutase (SOD), and vascular endothelial growth factor (VEGF) were evaluated and compared between two groups before and after training.

Results: There was no significant difference in LVEDD, LVEF, 6-MWD, quality-of-life scores, levels of serum NO, NOS, SOD, and VEGF between two groups before training ($p>0.05$). 1 year later, compared with the complete revascularization group, the occurrence of major adverse events in the CR group declined ($p>0.05$); the measurements of LVEDD decreased and LVEF increased ($p>0.05$), 6-MWD increased significantly ($p<0.05$), quality-of-life scores were higher ($p<0.05$), the levels of serum NO, NOS, and SOD increased noticeably, and the levels of serum VEGF decreased significantly in the CR group ($p<0.05$). There were significant differences within the same group, before and after training ($p<0.05$).

Conclusion: Cardiac rehabilitation training, not increase in the incidence of adverse events, is effective and safe after partial revascularization in patients with multiple coronary artery lesions, which has notable clinical advantages in promoting patients' exercise endurance and quality-of-life by improving the nitric oxide synthase system and antioxidant system and reducing the level of VEGF.

Keywords: multiple coronary artery lesions, cardiac rehabilitation, coronary revascularization, 6-MWD, quality-of-life, NO/NOS

Introduction

At present, chronic diseases such as coronary heart disease (CHD) are still the leading cause of death in China and throughout the world.[1] A large number of evidence-based medical studies have shown that cardiac rehabilitation can significantly reduce the days and cost of hospitalization, the mortality, and cardiovascular events in patients with CHD, which is a key measure when building a comprehensive prevention and treatment network for CHD.[2,3] Studies showed that outpatient cardiac rehabilitation programmes could provide some substantive benefits for patients, such as

convenience, fitness, improved functional capacity, quality-of-life, as well as lipid profile and blood pressure and endothelial function.[3–5]

Cardiac rehabilitation has been recognized as secondary prevention and effective treatment for CHD, which should be commenced as soon as possible after percutaneous coronary intervention (PCI) and continued after discharge, even needing to become a part of life to improve the quality-of-life.[6] Left ventricle ejection fraction (LVEF) is a strong hemodynamic factor influencing the clinical outcome of patients with CHD.[7] Reduced LVEF is associated with increased mortality in patients with ST-elevation myocardial infarction.[8] It has been reported that nitric oxide (NO)-dependent vasodilation was impaired in patients with CHD and impaired NO-dependent vasodilation is an independent predictive factor of cardiac events in CHD patients.[9] Aerobic exercise could improve LVEF and vascular endothelial dysfunction.[10–12]

Complete revascularization should be recommended to patients with multiple coronary artery lesions.[13] Although there are many studies on cardiac rehabilitation in patients with multiple coronary artery lesions after PCI at home and abroad, it is reported that global access to cardiac rehabilitation is poor, with only 5–50% of eligible patients with cardiac disease receiving rehabilitation.[14] Besides, complete revascularization for multiple coronary artery lesions may affect the anxiety and other emotional fluctuations about the effect of PCI and postoperative complications of the patients, to some extent. Furthermore, for multiple coronary artery lesions, complete revascularization is difficult to achieve due to the complexity of the lesion. In practice, there are a proportion of patients who choose partial revascularization, with many factors influencing the strategy selection, such as clinical characteristics, comorbidities of the patient, and reimbursement, etc.[7] What's more, there are few studies on cardiac rehabilitation and its related mechanisms in patients with partial revascularization performed on multiple coronary artery lesions.

In this context, compared with complete revascularization for multiple coronary artery lesions, the researchers proposed to perform cardiac rehabilitation on patients with multivessel coronary artery lesions who underwent partial revascularization and observe its efficacy and safety, and to explore the possibly protective mechanism of cardiac rehabilitation through the further determination of the levels of serum nitric oxide (NO), nitric oxide synthase (NOS), superoxide dismutase (SOD), and vascular endothelial growth factor (VEGF).

Patients and Methods

Sample Size

Through this study, we intend to test the hypothesis that the effect in the complete revascularization group and cardiac rehabilitation group would be comparable in improving cardiac function, 6-minute walking distance (6-MWD), quality-of-life, and biomarkers such as NO/NOS, SOD and VEGF, which were usually recorded at the baseline and 12th month. It has been found through calculation that the group samples of 336 patients (168 patients in each group) would provide 90% power to reject the null hypothesis of equal means at a two-sided alpha of 0.05. Given an anticipated dropout rate of 20% in this study, we initially planned to include 400 patients (200 in each group).

Patients

This was a randomized controlled single blind study. Four hundred patients with multiple coronary artery lesions treated by the the Heart Center of the people's Hospital Of Liaoning Province from March 2017 to July 2021 were selected. Based on the inclusion and exclusion criteria, in accordance with a random number table, they were divided into a complete revascularization group and a cardiac rehabilitation group randomly, with 200 cases in each group. The complete revascularization group was the control group, while the partial revascularization & rehabilitation intervention group was the observation group. The whole process of the study is described in the flow chart in Figure 1. Baseline data were obtained from the patients before the study (Table 1). The patients' underlying diseases and main medications after PCI are outlined in Table 1. The study was in accordance with the Declaration of Helsinki and approved by a local ethics committee, and all patients provided written informed consent. The authors had no access to any information that could identify individual participants during and after data collection.

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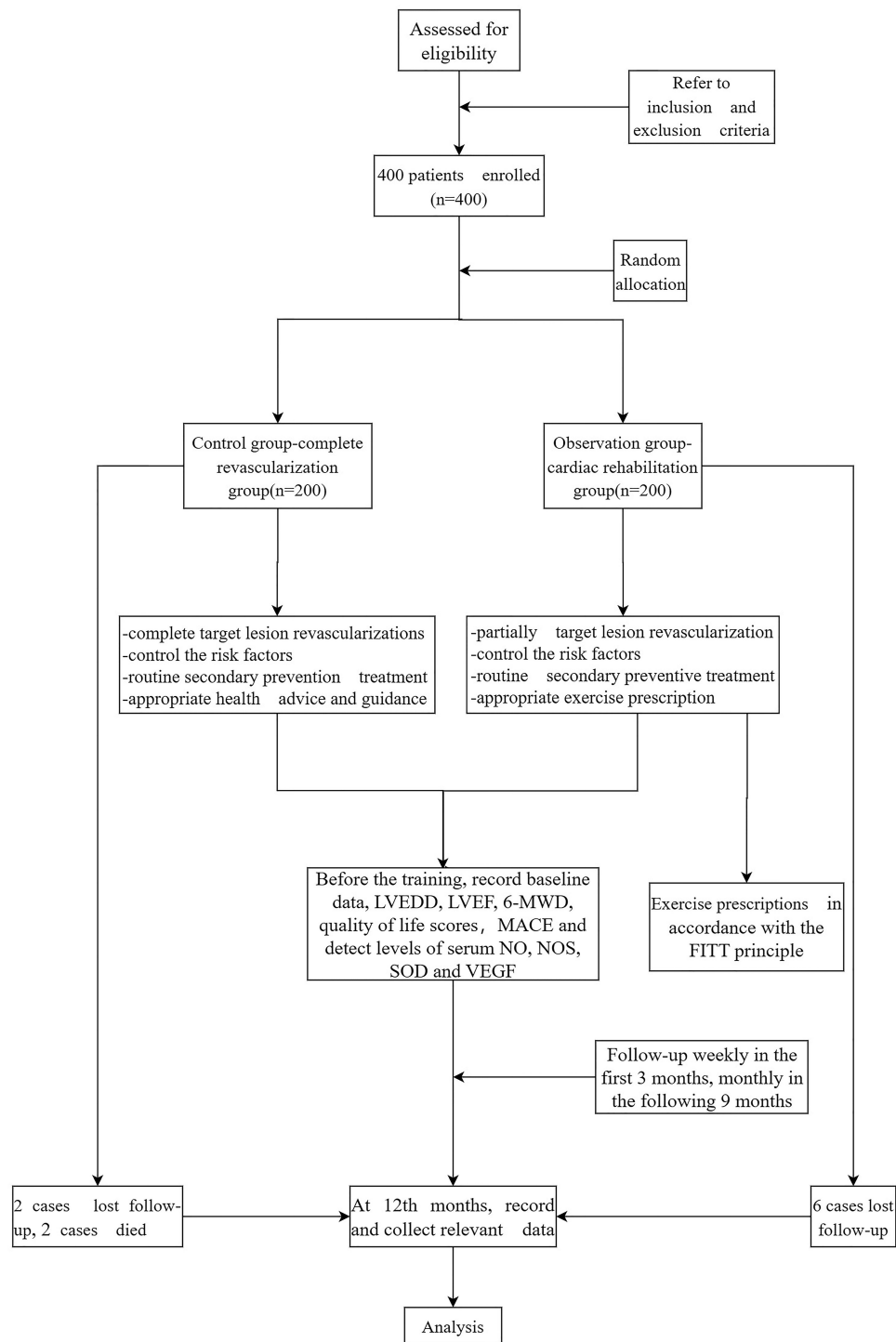
Figure 1 Study design and flowchart.
Abbreviations: LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; 6MWD, 6-min walk distance; MACE, major cardiac adverse events; NO, nitric oxide; NOS, nitric oxide synthase; SOD, superoxide dismutase; VEGF, vascular endothelial growth factor.

Inclusion Criteria

1) Diagnosis of CHD according to the diagnostic criteria and coronary artery interventional therapy performed in accordance with the European Society of Cardiology guidelines;[15] 2) at least two coronary arteries (the left main, left anterior descending, left circumflex, and right coronary artery, with a target vessel diameter ≥2 mm) with ≥70% stenosis,

Table 1 Baseline Data of the Patients in Two Groups

Variables	Complete Revascularization Group (n=200)	Cardiac Rehabilitation Group (n=200)	t/χ^2	p
Male, n (%)	106(53)	124(62)	1.66	0.20
Age, yr	71.60±9.32	72.00±6.73	−0.11	0.91
BMI, kg/m^2	24.22±1.80	23.01±2.19	1.35	0.20
Smoking, %	114(57)	128(64)	1.03	0.31
The underlying diseases, n (%)				
Hypertension	144(72)	130(65)	1.14	0.29
Atrial fibrillation	30(15)	40(20)	0.87	0.35
HFpEF	22(11)	32(16)	1.07	0.30
Diabetes	130(65)	108(54)	2.51	0.11
Non-malignant Arrhythmia	28(14)	18(9)	1.23	0.27
TG, mmol/L	2.00±0.27	2.21±0.43	−1.31	0.21
HDL-C, mmol/L	1.12±0.13	1.25±0.18	−1.86	0.08
LDL-C, mmol/L	4.41±0.68	4.78±0.59	−1.33	0.20
Heart rate, beats per min	80.40±9.13	77.70±8.25	0.69	0.50
Systolic pressure, mmHg	140.40±11.26	138.40±11.92	0.37	0.70
Diastolic pressure, mmHg	85.40±11.15	82.20±11.45	0.63	0.54
Main medications, n (%)				
Antiplatelet drug				
Aspirin Enteric-coated Tablets	170(85)	174(87)	0.17	0.68
Clopidogrel sulfate	92(46)	74(37)	1.67	0.20
Ticagrelor	108(54)	126(63)	1.67	0.20
Beta-blockers	190(95)	182(91)	1.23	0.27
Metoprolol	76(38)	60(30)	1.43	0.23
Bisoprolol	114(57)	122(61)	0.33	0.57
HMGR inhibitor	190(95)	186(93)	0.36	0.55
Atorvastatin	84(42)	76(38)	0.33	0.56
Rosuvastatin	46(23)	58(29)	0.936	0.33
Simvastatin	40(20)	36(18)	0.13	0.72
Fluvastatin	20(10)	16(8)	0.05	0.82
ACE inhibitor	124(62)	128(64)	0.09	0.77
Enalapril	32(16)	26(13)	0.36	0.55
Perindopril	28(14)	34(17)	0.34	0.56
Ramipril	34(17)	30(15)	0.15	0.70
Fosinopril	30(15)	38(19)	0.57	0.45
ARB	76(38)	72(36)	0.09	0.77
Losartan	26(13)	20(10)	0.44	0.51
Valsartan	20(10)	30(15)	1.14	0.29
Irbesartan	16(8)	10(5)	0.74	0.39
Telmisartan	14(7)	12(6)	0.08	0.77
Antidiabetic drugs	112(56)	100(50)	0.72	0.40
Metformin	16(8)	12(6)	0.31	0.58
Sitagliptin	24(12)	20(10)	0.20	0.65
Acarbose	40(20)	34(17)	0.30	0.59
Dapagliflozin	30(15)	26(13)	0.17	0.68
Insulin	48(24)	56(28)	0.42	0.52
Oral anticoagulants	30(15)	26(13)	0.17	0.68
Warfarin	6(3)	4(2)	0.21	0.65
Rivaroxaban	12(6)	16(8)	0.31	0.58
Dabigatran	12(6)	6(3)	1.05	0.31

Note: Before training, there were no statistically significant differences on baseline data of patients in the complete revascularization group and cardiac rehabilitation group, $p>0.05$.
Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HFpEF, heart failure with preserved ejection fraction; HMGR, 3-hydroxy-3-methyl glutaryl coenzyme A reductase; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

with or without major branching lesions; 3) New York Heart Association functional class from grade I to II; 4) the ability to communicate well with the researchers and be open to rehabilitation training in this study; and 5) all selected patients were required to sign the informed consent form. The whole design of the study was in accordance with the requirements of the Declaration of Helsinki and approved by the ethics committee of the people's Hospital Of Liaoning Province, China.

Exclusion Criteria

1) New York Heart Association functional class from grade III to IV; 2) complications of serious arrhythmia, hyperthyroid cardiopathy, congenital and idiopathic cardiomyopathy, valvular heart disease, cardiomyopathy, chronic obstructive pulmonary disease, cor pulmonale, idiopathic cardiomyopathy blood disorder, and autoimmune disease; 3) wearers of cardiac pacemakers and heart transplantation patients; 4) serious diseases of the liver, kidney, or other important organs; 5) pregnancy or lactation and family planning during trial period; 6) exercise intolerance or non-cardiac illness that might be aggravated by exercise; 7) mental illness; 8) poor compliance; 9) definitive diagnosis of malignancy; 10) surgery, trauma, gastrointestinal bleeding, or complications of PCI; and 11) refusal to sign the informed consent.

Methods

Complete Revascularization Group

Complete target lesion revascularizations were performed for the main target vessels. Postoperatively, to strictly and actively control the risk factors for CHD, coronary secondary prevention treatment, appropriate health advice, and important guidance on daily life were offered. We started a file on every selected case and called on or visited them weekly in the first 3 months and every month in the following 9 months. The whole process lasted 1 year. The outpatients were followed-up at 12 months and the relevant data was recorded.

Cardiac Rehabilitation Group

Cardiac rehabilitation is a complex form of intervention, which includes exercise training, physical activity promotion, health education, cardiovascular risk management, and psychological support, with personalized treatment to the individual needs of patients with a confirmed diagnosis of heart disease.[14,16] In China, prescriptions for cardiac rehabilitation mainly include medication, exercise, nutrition, smoking cessation, and psychological management,[17] as displayed in Table 2.

Table 2 Cardiac Rehabilitation Components and FITT Parameters

Cardiac Rehabilitation Components	**FITT Parameters**
Medications prescriptions: Coronary secondary prevention treatment (Anti-platelet drug, beta-blocker, ACE inhibitor/ARB, HMGR inhibitor, etc). Individualization, offer appropriate health advice and important guidance on daily life.	Frequency: 3–4 times a week.
Exercise prescriptions: Individualization, exercise frequency, exercise intensity, exercise time, exercise type.	Intensity: Formulate based on 6-MWT. Before discharge, 6-MWT was performed and exercise prescription was formulated depending on 6-MWD, in order to ensure the safety, the target heart rate, did not exceed 60% to 80% of the maximal heart rate after exercise and returned to the pre-exercise level after 5 minutes. The exercise intensity was adjusted monthly.
Nutrition prescriptions: Ameliorate unhealthy lifestyle; draw up individualized nutrition prescriptions according to blood glucose, blood pressure, exercise habits, and so on, and guide the patients and their families to form a healthy diet.	Time: 20 minutes in the first 3 months, adjusted monthly for the next 9 months, to about 1 hour each session, until the patient felt tired.
Smoking cessation prescriptions: Make a smoking cessation plan, guide on smoking cessation methods and drug treatment, give psychological support and conduct the regular follow-up.	
Psychological prescriptions: Patients with CHD are prone to suffer from psychological problems such as depression and anxiety. Appropriate identification and intervention are needed.	Type: Aerobic exercise: cycling, dancing, walking, tai chi, and housework, etc.; Resistance exercise: such as dumbbells, sit-ups, etc.

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CHD, coronary heart disease; HMGR, 3-hydroxy-3-methyl glutaryl coenzyme A reductase; 6-MWT, 6-minute walk test; 6-MWD, 6-minute walk distance.

In this group, target lesion revascularization was partially completed. Postoperative control of risk factors of CHD, routine secondary preventive treatment of CHD, and appropriate exercise prescription for out-of-hospital rehabilitation were offered three times a week. Patients were instructed to conduct a telephone or door-to-door follow-up every week in the first 3 months and every month in the following 9 months and outpatient follow-up at 12 months and the data were recorded. The specific exercise prescriptions were in accordance with the FITT principle in this study, as described in Table 2.

The FITT Principle

The FITT principle refers to the components of exercise prescription, which involves frequency, intensity, time, and type.[18]

Frequency. After discharge, the average exercise prescription was 3–4 times a week.

Intensity. The intensity of exercise, assessed by heart rate, was formulated based on 6-minute walk test (6-MWT) with a wearable electrocardiogram and blood pressure monitor under professional instruction. Before discharge, 6-MWT was performed following the clinical practice guidelines with a continual electrocardiogram and blood pressure monitor and exercise prescription that was formulated depending on 6-MWD. At the same time, in order to ensure the safety and efficacy, the target heart rate did not exceed 60% to 80% of the maximal heart rate after exercise and returned to the pre-exercise level after 5 minutes.[12,19,20] According to the patients' degree of tolerance, the exercise intensity was adjusted monthly for the next 9 months.

Time. Sessions lasted 20 minutes in the first 3 months and, according to the patients' degree of tolerance, the time was adjusted monthly for the next 9 months, to about 1 hour each session, until the patient complained of tiredness.

Type. Currently, exercise-based cardiac rehabilitation, which involves aerobic exercise supplemented with resistance training, is the primary training for most CR programs.[21] Aerobic exercise mainly consisted of cycling, dancing, walking, tai chi, and housework, etc. Resistance exercise, such as dumbbells, sit-ups, etc., could also be chosen (1 time/week).

If any discomfort occurred during this period, including refractory angina, heart rate change >20 beats/min, blood pressure charge >20 mmHg, ST segment depression ≥0.1mV or elevation ≥0.2 mV during activity, or arrhythmia, chest distress, palpitation, dizziness, syncope, pallor, sweating, oxygen saturation (SpO_2, measured using a portable oxygen saturation monitor) ≤85% and so on, activity was to be stopped immediately and the follow-up doctor informed to decide whether to adjust the program to continue the rehabilitation or withdraw from the study.

Observed Indicators

Evaluation of Cardiac Function and Athletic Endurance

Before and 1 year after training, the left ventricular end diastolic dimension (LVEDD) of all the enrolled patients was measured with a Doppler ultrasonic diagnostic apparatus (CX50, Philips, Holland), and LVEF was calculated along with the 6-minute walk distance (6-MWD) based on the 6-MWT according to a standardized protocol simultaneously.

Evaluation of Safety

Adverse events were recorded, including refractory angina, myocardial reinfarction, malignant arrhythmia, heart failure, stroke, sudden cardiac death, rehospitalization, revascularization, and fatal bleeding events.

Evaluation of the Quality-of-Life

The quality-of-life was measured by the Medical Outcome Survey Short Form (SF-12) questionnaire, which contained a physical component summary (PCS) and mental component summary (MCS).

Laboratory Indicators

Before and 1 year after training, the serum levels of NO, NOS, SOD, and VEGF were detected. Four milliliters of fasting blood was drawn from all the patients into tubes with separating gel. The blood was incubated for 10 minutes and then centrifuged for 10 minutes at 3,500 rpm. Levels of NO, NOS, SOD, and VEGF were detected by colorimetric assay, the xanthine oxidase method, and enzyme-linked immunosorbent assay (ELISA), respectively. All operations were carried

out strictly in accordance with the kit manufacturer's instructions. Nitrate ester medication was stopped for 2 days before testing in both groups.

Types of Outcome Measures
According to the inclusions and exclusions, the study should assess the following outcomes. We extracted the results at baseline and 12 month follow-ups (medium–long-term) to assess the efficacy and safety and explore the possible mechanism.

Primary Outcomes
Cardiac Function; 6-MWD; quality-of-life assessed by 12-item Short Form (SF-12).

Secondary Outcomes
Major adverse cardiac events.

Statistical Analysis
Measurement data were presented as means±SDs, a *t*-test was performed to analyze the differences between the complete revascularization and cardiac rehabilitation groups if the variance was homogeneous, or the Wilcoxon rank sum test was used. Enumeration data were presented as ratios, and the chi-square test or Fisher's exact test was used to analyze differences between the two groups. All the data were analyzed with the Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS, Inc., Chicago, IL). The level of significance was set at $p < 0.05$ for all results.

Results
Among the 400 enrolled patients, two cases were lost follow-up and two cases died in the complete revascularization group, while six cases were lost to follow-up in the cardiac rehabilitation group.

Evaluation of Cardiac Function and Athletic Endurance
As shown in Table 3, before training, the measurements of LVEDD, LVEF, and 6MWT in the complete revascularization group were 57.90±5.38 mm, 46.10±4.10%, and 258.70±20.15 m, respectively, lower than those in the cardiac rehabilitation group, which were 58.70±2.91 mm, 48.20±4.13%, and 267.90±14.28 m, respectively, but there was no statistically significant difference (p=0.68, 0.25, 0.25). After 1 year, the measurements of LVEDD in the complete revascularization group decreased to 49.50±3.54 mm and 48.70±2.26 mm in the cardiac rehabilitation group, and the difference between the two groups was not statistically significant (p=0.56). By contrast, the measurements of LVEF in the complete revascularization group increased to 54.20±6.05% and 56.50±3.03% in the cardiac rehabilitation group, also with no statistical significance (p=0.30). Meanwhile, 6MWD in the complete revascularization group increased to 418.80 ±24.42 m and 556.70±55.67 m in the cardiac rehabilitation group, with statistical significance (p=0.001). There were also significant differences within the same group before and after training because of the obvious improvement of the

Table 3 The Levels of LVEDD, LVEF, and 6-MWD Before and After Training in Two Groups ($\bar{x} \pm s$)

Indicators / Groups	LVEDD (mm)		LVEF (%)		6-MWD (m)	
	Baseline	**1 Year Later**	**Baseline**	**1 Year Later**	**Baseline**	**1 Year Later**
Complete revascularization group (n=196)	57.90±5.38	49.50±3.54[#]	46.10±4.10	54.20±6.05[#]	258.70±20.15	418.80±24.42[#]
Cardiac rehabilitation group (n=194)	58.70±2.91	48.70±2.26[#]	48.20±4.13	56.50±3.03[#]	267.90±14.28	556.70±55.67*[#]
t/p	−0.413/0.68	0.603/0.56	−1.142/0.27	−1.075/0.30	−1.178/0.25	−7.147/0.001

Notes: Before training, the measurements of LVEDD, LVEF, and 6-MWD had no statistically significant difference (p=0.68, 0.27, 0.25) in two groups. One year later, compared with the complete revascularization group, the measurements of LVEDD decreased and the measurements of LVEF increased in the cardiac rehabilitation group, p>0.05; while 6MWD increased greatly in the cardiac rehabilitation group, *p<0.05. Within the same group, the improvement of the measurements of LVEDD, LVEF, and 6MWD were obvious after training, [#]p<0.05.
Abbreviations: LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; 6MWD, 6-min walk distance.

Table 4 The Occurrence of Major Adverse Cardiac Events After the Training in Two Groups (n, %)

Major Adverse Cardiac Events	Complete Revascularization group (n=196)	Cardiac Rehabilitation group (n=194)	χ^2/p
Refractory angina	6 (3.06)	4 (2.06)	0.00/1.00
Myocardial reinfarction	0	0	
Malignant arrhythmias	6 (3.06)	4 (2.06)	0.00/1.00
Heart failure	10 (5.10)	4 (2.06)	0.57/0.45
Stroke	0	0	
Sudden cardiac death	2 (1.02)	0	0.00/1.00
Rehospitalization	20 (10.20)	10 (5.15)	1.75/0.19
Revascularization	4 (2.04)	4 (2.06)	0.00/1.00
Fatal bleeding events	0	0	
Totle	32 (16.33)	22 (11.34)*	1.02/0.31

Notes: 1 year later, compared with complete revascularization group, the occurrence of major cardiac adverse events in cardiac rehabilitation group declined, but *p>0.05.

measurements of LVEDD, LVEF, and 6MWT (Complete revascularization group: p=0.001, 0.001, 0.001; Cardiac rehabilitation group: p=0.001, 0.001, 0.001).

Evaluation of the Safety

The occurrence of major adverse cardiac events in the complete revascularization group was 16.33% (32 cases, including refractory angina (6 cases), malignant arrhythmias (6 cases), heart failure (10 cases), sudden cardiac death (2 cases), rehospitalization (20 cases), and revascularization (4 cases)), compared to 11.34% (22 cases, including refractory angina (4 cases), malignant arrhythmias (4 cases), heart failure (4 cases), rehospitalization (10 cases), and revascularization (4 cases)) in the cardiac rehabilitation group (Table 4). This difference was not statistically significant (p=1.00, 1.00, 0.45, 1.00, 0.19, 1.00, 0.31).

Evaluation of Quality-of-Life

Before training, PCS and MCS in the complete revascularization group were 24.04±11.95 and 31.50±7.09, and they were 23.67±8.18 and 32.75±3.62 in the cardiac rehabilitation group, respectively, with no statistically significant difference (p=0.94, 0.32). However, 1 year later, PCS and MCS in the complete revascularization group increased to 55.27±7.86 and 55.50±11.95, and 78.91±16.89 and 80.75±6.35 in the cardiac rehabilitation group, respectively. The differences between the two groups were statistically significant (p=0.002, 0.001). The improvement was obvious in the same group before and after training, a difference that was also statistically significant (Complete revascularization group: p=0.001, 0.001; Cardiac rehabilitation group: p= 0.001, 0.001), as presented in Table 5.

The Levels of Serum NO, NOS, SOD, and VEGF

Before training, the levels of serum NO, NOS, SOD, and VEGF in the complete revascularization group were 40.00±5.94 μmol/L, 37.00±4.69 U/mL, 60.40±5.36 U/mL, and 386.80±31.62 ng/L, while they were 42.90±5.47 μmol/L, 38.30±3.40

Table 5 The Score of PCS and MCS of Two Groups Before and After Training ($\bar{x} \pm s$, Score)

Score of Quality-of-Life / Groups	PCS		MCS	
	Baseline	1 Year Later	Baseline	1 Year Later
Complete revascularization group (n=196)	24.04±11.95	55.27±7.86[#]	31.50±7.09	55.50±11.95[#]
Cardiac rehabilitation group (n=194)	23.67±8.18	78.91±16.89*[#]	32.75±3.62	80.75±6.35*[#]
t/p	0.08/0.94	−4.01/0.002	−0.50/0.63	−5.90/0.001

Notes: Before training, PCS and MCS in the complete revascularization group and cardiac rehabilitation group had no statistically significant difference (p=0.94, 0.63). One year later, compared with the complete revascularization group, the score of PCS and MCS in the cardiac rehabilitation group were higher, *p<0.05. The improvement was obvious in the same group before and after training, [#]p<0.05.
Abbreviations: MCS, mental component summary; PCS, physical component summary.

Table 6 The Levels of Serum NO, NOS, SOD, and VEGF Before and After Training in Two Groups ($\bar{x} \pm s$)

Biomarker / Groups	NO (μmol/L)		NOS (U/mL)		SOD (U/mL)		VEGF (ng/L)	
	Baseline	I Year Later	Baseline	I Year Later	Baseline	I Year Later	Baseline	I Year Later
Complete revascularization group (n=196)	40.00±5.94	78.80±3.94[#]	37.00±4.69	68.90±2.42[#]	60.40±5.36	101.00±2.98[#]	386.80±31.62	280.10±24.76[#]
Cardiac rehabilitation group (n=194)	42.90±5.47	104.80±6.80[*#]	38.30±3.40	87.70±5.58[#]	63.10±6.64	113.80±5.57[*#]	386.90±24.08	223.10±12.07[*#]
p	−1.14/0.27	−10.45/0.001	−0.71/0.49	−9.77/0.001	−1.00/0.33	−6.40/0.001	−0.01/0.99	6.54/0.001

Notes: Before training, the levels of serum NO, NOS, SOD and VEGF had no statistically significant difference in the two groups (p=0.27, 0.49, 0.33, 0.99). One year later, compared with the complete revascularization group, the levels of serum NO, NOS, and SOD increased noticeably and the levels of serum VEGF decreased significantly in the cardiac rehabilitation group, *p<0.05. The levels of serum NO, NOS, SOD, and VEGF were improved obviously within the same group before and after training, #p<0.05.
Abbreviations: NO, nitric oxide; NOS, nitric oxide synthase; SOD, superoxide dismutase; VEGF, vascular endothelial growth factor.

U/mL, 63.10±6.64 U/mL, and 386.90±24.08 ng/L in the cardiac rehabilitation group, respectively. There was no statistically significant difference (p=0.27, 0.49, 0.33, 0.99). One year later, the levels of serum NO, NOS, and SOD in the complete revascularization group increased to 78.80±3.94 μmol/L, 68.90±2.42 U/mL, and 101.00±2.98 U/mL, respectively, while there were noticeably higher levels of 104.80±6.80 μmol/L, 87.70±5.58 U/ mL, and 113.80±5.57 U/ mL in the cardiac rehabilitation group, respectively, and the levels of serum VEGF decreased to 280.10±24.76 ng/L in the complete revascularization group and 223.10±12.07 ng/L in the cardiac rehabilitation group. The differences between two groups was statistically significant (p=0.001, 0.001, 0.001, 0.001). The levels of serum NO, NOS, SOD, and VEGF were improved obviously within the same group before and after training, a difference that was also statistically significant (p=0.001). All of the above results are displayed in Table 6.

Discussion

At present, the purpose of the treatment of CHD is to alleviate symptoms, reduce the occurrence of myocardial infarction, and improve the quality-of-life and long-term survival of patients; the means to achieve the above requirements is to perform complete revascularization.[13] However, incomplete revascularization is very common clinically due to advanced age, complex coronary lesions, chronic coronary arterial total occlusion, left ventricular dysfunction, past medical history of myocardial infarction, diabetes, and chronic renal insufficiency, etc., with an incidence of about 47.2–69.0%.[22] How to improve the survival rate of these patients and reduce the incidence of myocardial infarction is particularly important. Cardiac rehabilitation refers to ensuring the patients achieve the best physical, psychological, and social status through a variety of combined therapies, so that these patients suffering from chronic or acute cardiovascular diseases can maintain or regain optimal social functional status through their own efforts, and delay or reverse the disease process through healthy behaviors.[23] Many studies have shown that cardiac rehabilitation can significantly reduce the morbidity and mortality of patients with CHD after myocardial infarction, PCI, and coronary artery bypass grafting (CABG),[24–26] decrease the risk factors of CHD, and improve the quality-of-life of patients with CHD. Therefore, cardiac rehabilitation is recommended as a primary intervention treatment for CHD.[27–29]

In this study, through the observation and comparison of the patients who underwent complete revascularization and partial revascularization and cardiac rehabilitation, it was found that the 6-MWD in the cardiac rehabilitation group was superior to that in the complete revascularization group after 1 year, and the difference was significant. The possible reason for this change might be that, although it takes a long time for the formation of multi-vessel coronary artery disease, coronary blood flow and cardiac functional reserve have changed, yet, as the time is prolonged, cardiac rehabilitation could dramatically improve the coronary blood flow and cardiac functional reserve of patients after PCI so as to save more cardiomyocytes and open or establish vascular channels further, which could significantly reduce the oxygen consumption of cardiomyocytes, reduce myocardial tissue remodeling after myocardial infarction, and improve myocardial tissue compliance.[30] Moreover, cardiac rehabilitation from an earlier stage after PCI could significantly strengthen cardiopulmonary functions, enhance exercise tolerance, reduce myocardial oxygen consumption, and improve quality-of-life,[31] which may be related to the fact that exercise training could increase the density and volume of mitochondria, as well as the ratio of the formation of Adenosine Triphosphate (ATP), to improve the ability of oxidative

metabolism and exercise tolerance. This is a greater alignment with the result of the improvement of 6-MWD in the cardiac rehabilitation group compared with it in the complete revascularization group in our study.

6-MWT, an important indicator of cardiopulmonary function in patients with CHD could be influenced by stature, age, sex, BMI, gait mechanics, comorbidities, and motivation, as well as the test operators' encouragement and/or motivation given to patients,[6,32–35] is safe, reliable, cost-effective, easy to perform, does not require specialized equipment, and also has practical value.[12,36] After 1 year, 6-MWD in the cardiac rehabilitation group was improved by about 200 m, indicating that their cardiopulmonary fitness may be close to normal.[16] Furthermore, the distance change in the CR group was more than the minimal clinically important difference (MCID),[37] explaining that cardiac rehabilitation could improve athletic endurance.

The results of LVEDD and LVEF in our study at baseline and 1 year later showed that LVEDD and LVEF in the two groups were both improved with no statistically significant difference, indicating that cardiac rehabilitation performed on partial revascularization was not inferior to complete revascularization. Chyrchel et al[7] have shown that complete revascularization could improve or maintain similar LVEF in patients with impaired or preserved LVEF. But, in other studies, it has been shown that the beneficial effect of LVEF improvement was only reached with LVEF <45% at baseline.[38]

At the same time, studies have shown complete revascularization among patients with preserved LVEF (>40%) is sufficient in reducing major adverse cardiac events in the long-term (3-year) follow-up.[39] This study found that the incidence of major adverse cardiac events in the cardiac rehabilitation group was not higher than that in the complete revascularization group 1 year later, with no statistical significance. However, the readmission rate in the cardiac rehabilitation group was obviously lower, which could significantly reduce medical expenses and obtain better cost-effectiveness of prevention. Studies have shown that cardiac rehabilitation training from an earlier stage is safe and effective for patients after partial or complete revascularization.[40] Cardiac rehabilitation could not only significantly reduce the mortality after PCI but also reduce the incidence of acute myocardial ischemia events and the hospitalization rate.[41] Moreover, cardiac rehabilitation can benefit patients with CHD and stroke by controlling risk factors of cardiovascular diseases, and play an important role in controlling the occurrence and development of diseases.[42] Of interest, the findings of this study were consistent with the above results, indicating that cardiac rehabilitation was safe and did not increase the incidence of major adverse cardiac events.

Up to now, it has been considered that most patients with CHD have a tendency toward anxiety and depression; exercise training could keep the excitability of the sympathetic nervous system stable and attenuate various clinical symptoms caused by increased sympathetic activation, so that the quality-of-life could be very much improved.[41,43] Moreover, exercise training could improve the mental health status of patients, increase the confidence of cardiac rehabilitation,[44] and further improve the quality-of-life. Our study showed that the scores of PCS and MCS of the patients in the complete revascularization group and cardiac rehabilitation group were significantly improved 1 year later. In the cardiac rehabilitation group, these scores were significantly higher than those in the complete revascularization group, and the difference was statistically significant. It may be because moderate aerobic exercise could eliminate the low mood and feelings of patients with CHD and be conducive to peace of mind, improving their athletic endurance, physical and psychological condition so as to promote their ability to care for life and social functions, thus forming a positive cycle.[13,30,45] Therefore, the researchers further detected the levels of serum NO, NOS, SOD, and VEGF before and after training to explore the possible mechanism.

In recent years, it has been continuously proved that lipid peroxides and their catabolites could cause CHD via damaging the walls of the coronary arteries. SOD, as one of the most important antioxidant enzymes in vivo, can scavenge free radicals and maintain the stability and integrity of cell membranes to prevent CHD by eliminating oxygen free radicals. NO, synthesized by the catalysis of NO synthase, a key rate-limiting enzyme, going through the development of many cardiovascular diseases, is an independent physiological regulatory factor, with the effect of vasodilation, eliminating oxygen free radicals, inhibiting the aggregation and adhesion of platelets, maintaining normal cardiac output, and protecting cells. To a certain extent, a very high NO concentration reflects high vascular activity.[46] When NOS is insufficient, the synthesis of NO will be reduced, causing vasoconstriction, increasing vascular smooth muscle cell proliferation, promoting atherosclerosis, leading to microcirculation disturbance, and consequently result in aggravation

of coronary artery stenosis, myocardial ischemia and hypoxia, and even myocardial infarction.[47] Meanwhile, NO imbalance can stimulate and release endothelin, which could not only induce the proliferation of vascular endothelial cells but also promote the synthesis and secretion of VEGF directly or indirectly.[48] So far, it has been known that VEGF, the content of which is generally low in the body normally but enjoys rapid growth in hypoxia, is the most powerful cytokine in promoting vascular growth. Also, VEGF can build new blood vessels and promote the formation of a collateral circulation and the proliferation and division of endothelial cells.[49,50] The level of VEGF could reflect the degree of myocardial ischemia.[51] Therefore, the level of VEGF can not only be used to evaluate the degree of myocardial ischemia and reperfusion injury in clinical settings but also to evaluate the effect of post-PCI.[52] This study found no significant difference in the levels of NO, NOS, SOD, and VEGF between two groups before training, while a significant improvement in two groups was found 1 year later, more obviously in the cardiac rehabilitation group, with a significant difference. It is possible that long-term cardiac rehabilitation training could increase the levels of NO and SOD in coronary artery endothelial cells, improve the endothelium-dependent vasodilatory function, promote vascular remodeling and angiogenesis, improve autonomic balance, and increase the blood flow perfusion of skeletal muscle via increasing oxygen extraction capacity,[53] which could improve myocardial ischemia-reperfusion injury, myocardioprotection, and reduce the level of VEGF. In addition, local release of NO can restrain intimal hyperplasia, down-regulate the levels of interleukin-6 and c-reactive protein significantly, reduce inflammation, and inhibit the development of in-stent restenosis. The results of NO, NOS, SOD, and VEGF in two groups at baseline and 1 year later showed levels of NO, NOS, and SOD increased more noticeably and the level of VEGF decreased more obviously in the cardiac rehabilitation group with a statistically significant difference, suggesting that cardiac rehabilitation performed on partial revascularization could regulate blood vessel endothelial function.

Strengths and Limitations

This study could provide treatment recommendations for patients with multiple coronary artery lesions who cannot accept complete revascularization, it is not only a simple, safe, and operable approach but is also cost-effective and has improvements in poor cognition. In addition, another strength might be that cardiac rehabilitation could become a part of patients' daily life and gradually improve their lifestyle.

Limitations of this study included it being a single-center study and the relatively short time of observation. Also, this study might overestimate the real effect of cardiac rehabilitation on patients' cardiorespiratory fitness because of some spontaneous recovery after revascularization. Besides, in this study, the researchers did not enroll and observe the patients who underwent cardiac rehabilitation after complete revascularization of multi-vessel coronary artery disease and did not adopt cardiopulmonary exercise testing due to the confinement of objective conditions. The comprehensive effect of cardiac rehabilitation in patients with CHD who underwent partial revascularization performed on multiple coronary artery lesions needs to be corroborated by enlarging the population such as patients with heart failure with a preserved ejection fraction and in multiple centers and verified in a long-term follow-up as well as with cardiopulmonary exercise testing.

Conclusions

Cardiac rehabilitation training is effective, safe, and does not increase the incidence of adverse events after partial revascularization in patients with multiple coronary artery lesions, which has notable clinical advantages in promoting exercise endurance and quality-of-life by improving the nitric oxide synthase system and antioxidant system and reducing the level of VEGF, could significantly reduce medical expenses and obtain a better cost-effectiveness of prevention, providing new ideas and a new basis for the treatment of CHD.

Data Sharing Statement

The data could be obtained from this article.

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