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Effects of Cardiac Rehabilitation Exercise Plus Sacubitril Valsartan Sodium on Cardiac Function, Lung Function, and Quality of Life in Patients with Chronic Heart Failure

ABSTRACT

Background: To explore the impacts of cardiac rehabilitation exercise plus sacubitril valsartan sodium on cardiac function, lung function, and quality of life in chronic heart failure (CHF) patients.

Methods: One hundred and forty-six CHF patients admitted to the hospital from January 2023 to December 2024 were chosen and divided into a control group (conventional treatment + sacubitril valsartan sodium) and a study group (conventional treatment + sacubitril valsartan sodium + cardiac rehabilitation exercise).

Results: The total effective rate of the study group was higher when comparing with the control group ($P < .05$). The study group had higher left ventricular ejection fraction level as well as lower left ventricular end-systolic diameter, left ventricular end-diastolic diameter, and N-terminal pro B-type natriuretic peptide levels when comparing with the control group after 3 months of intervention ($P < .01$). The study group had higher forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC levels when comparing with the control group following 3 months of intervention ($P < .01$). The study group had higher SpO_2, PaO_2, and PaO_2/FiO_2 levels after 3 months of intervention ($P < .01$). The study group had longer 6-minute walking test after 3 months of intervention ($P < .01$). The study group had lower MLHFQ score when comparing with the control group after 3 months of intervention ($P < .01$). The rate of rehospitalization and incidence of major adverse cardiovascular event (MACE) in the study group were lower than in the control group ($P < .05$).

Conclusion: Cardiac rehabilitation exercise combined with sacubitril valsartan sodium is effective in treating CHF patients, which improves cardiac function, lung function and blood gas levels, promotes exercise endurance and quality of life, and reduces the rehospitalization rate and MACE incidence in CHF patients.

Keywords: Cardiac function, cardiac rehabilitation exercise, chronic heart failure, exercise endurance, lung function, sacubitril valsartan sodium

ORIGINAL INVESTIGATION

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INTRODUCTION

Chronic heart failure (CHF) is a kind of disease resulting from the development of various cardiovascular diseases to the terminal stage, characterized by symptoms such as fatigue, cardiac function, and exercise endurance.[1] High incidence, high mortality, and poor prognosis have become prominent characteristics of patients with CHF, making CHF a challenging problem to be solved urgently in clinical practice.[2] Epidemiological data show that there are more than 2 million new cases of CHF worldwide each year, the incidence rate of CHF in developed countries ranging from 1.5% to 2.0%, while in the country it is 0.9%.[3] With the increasing incidence of various cardiovascular diseases and the aging of the population, the prevalence rate of CHF continues to rise, and there are currently about 4 million CHF patients in China, which imposes a huge economic burden on families and society.[4]

The CHF is a chronic disease with a long course and poor prognosis.[5] Patients with this disease may have symptoms such as fatigue, dyspnea, exercise endurance,

and reduced ability in daily living, resulting in an obvious decline in patients' quality of life.[6] Additionally, repeated hospitalization with prolonged and persistent illness not only causes a serious psychological burden but also occupies a large part of medical resources.[7] Drug therapy is the main treatment method for CHF.[8] Sacubitril valsartan sodium can effectively increase cardiac function and reduced exercise ability in patients and reduce hospitalization and all-cause mortality to a certain extent, so it has become the first choice for the treatment of CHF.[9]

Cardiac rehabilitation exercise therapy is a comprehensive medical intervention designed to improve patients' cardiac function, exercise capacity, quality of life, and prognosis through systematic evaluation, education, guidance, and training.[10] Studies have shown that cardiac rehabilitation exercise therapy can improve patients' myocardial metabolism, increase coronary perfusion, reduce cardiac load, reduce myocardial hypoxia, and have many beneficial effects on patients with CHF.[11]

Although the efficacy of cardiac rehabilitation exercise therapy and sacubitril valsartan sodium in treating CHF has been confirmed, there are few studies on the combined application of both. Based on this, this study intends to explore the therapeutic impact of combined cardiac rehabilitation exercise therapy on CHF patients based on sacubitril valsartan sodium. It was hypothesized that sacubitril/valsartan's hemodynamic stabilization would enable safer exercise tolerance, while rehabilitation could potentiate its endothelial-protective effects through shear stress-mediated NO release.

METHODS

General Data

One hundred and forty-six CHF patients admitted to the hospital from January 2023 to December 2024 were chosen to be the study subjects. This study was approved by the Ethics Committee of the hospital (Approval Number: 2024bkky-007; Approval Date: January 16, 2024), and patients agreed to participate and signed informed consent. Inclusion criteria: (1) Met the diagnostic criteria of CHF; (2) the patient was not allergic to the drugs used in this study and could tolerate the treatment; and (3) in line with New York Heart Association (NYHA) Heart function grade II-IV. Exclusion criteria: (1) Patients with malignant tumors or liver and kidney dysfunction; (2) mental illness or cognitive impairment; (3) acute myocardial infarction, congenital heart disease, unstable angina pectoris, and other heart diseases; (4) patients with coagulation disorders, immune system disorders, or blood disorders; and (5) received other therapeutic drugs affecting cardiopulmonary function within 1 month. Following the different treatment methods, the patients were divided into a control group and a study group, with each group having 73 cases.

HIGHLIGHTS

- Cardiac rehabilitation exercise combined with sacubitril valsartan sodium can improve cardiac function, lung function and blood gas levels in chronic heart failure (CHF) patients.
- Cardiac rehabilitation exercise combined with sacubitril valsartan sodium can promote exercise endurance and quality of life in CHF patients.
- Cardiac rehabilitation exercise combined with sacubitril valsartan sodium can reduce the rate of rehospitalization and incidence of major adverse cardiovascular event in CHF patients.

Treatment Methods

After admission, all patients were given conventional treatment, including nitrates, diuretics, antihypertensive drugs, and angiotensin-converting enzyme inhibitors, according to whether patients had drug contraindications. At the same time, the vital signs of patients were closely monitored, patients' blood pressure and blood potassium were regularly measured, and patients' daily lifestyle was guided, such as controlling salt and fat intake and quitting smoking and drinking. Concomitant antianginal (nitrates, calcium channel blocker) and antithrombotic therapies were recorded (Supplementary Table 1).

Based on the conventional treatment, the control group adopted sacubitril valsartan sodium (Beijing Novartis Pharma Co. Ltd., Beijing, China). The initial dose was 100 mg orally twice a day, and the dosage was increased according to the different conditions of the patient. After 2-4 weeks, the dosage was increased to 200 mg twice a day for 3 months.

Based on the conventional treatment and sacubitril valsartan sodium, the study group was given cardiac rehabilitation exercise. The cardiac rehabilitation program was center-based and nurse-supervised, following the *2021 ESC Guidelines on Cardiac Rehabilitation*.[12] The protocol included: aerobic training: treadmill/cycle ergometry (40%-60% peak VO_2, Borg scale 11-13); resistance training: elastic bands (30%-40% 1-RM, 2 sets × 10 reps); flexibility exercises: static stretching (10 minutes pre/post session). Sessions were conducted 3 × per week in rehabilitation center of the hospital with continuous ECG monitoring. (1) Evaluation and screening: Nurses conducted a comprehensive evaluation of patients, including physical condition, cardiovascular function, exercise tolerance, and other aspects of assessment. Screening was performed to determine the patient's suitability for cardiac rehabilitation exercise. (2) Development of personalized training plans: Nurses developed training goals and plans suitable for patients according to their physical condition, heart function, exercise ability, and other relevant factors. (3) Cardiopulmonary monitoring: During cardiac rehabilitation exercise, nurses monitored the patient's heart rate, blood pressure, oxygen saturation, along with other vital signs, which helped to assess the patient's exercise tolerance and safety, and to adjust the intensity and style of training in a timely manner. (4) Exercise and strength training: According to the training program, nurses instructed the patient to do moderate aerobic exercise, including walking, cycling, as well as swimming, 3-5 times a week, 25-40 minutes each time, with light to moderate fatigue being

appropriate. At the same time, the patient was instructed to carry out moderate strength training, including the use of weight machines, elastic bands, and other muscle exercises, 2-3 times a week, 1-3 sets per muscle group, and 6-10 repetitions per group. Patients should rest for 1-2 minutes between each group and rest for at least 1 day between each exercise. Resistance training (2-3× per week) specifically targeted major muscle groups to counteract cardiac cachexia risk, consistent with recent guidelines. (5) Rest and Recovery: During training, nurses ensured that the patient had adequate rest and recovery time. Based on patient feedback and vital signs monitoring results, training intensity and rest time were adjusted to ensure patient safety and comfort. The exercise treatment period was 3 months.

Observation Indicators

All assessments were performed within 2 weeks after completing the 3-month intervention.

(1) Clinical efficacy: After treatment, the efficacy of patients was evaluated based on the recovery level of cardiac function grade. Obvious effect: the cardiac function was improved by 2 or more levels, and the cardiac function of level II was improved to level I; Effective: the cardiac function was improved by 1 grade; Ineffective: No improvement or decrease in heart function. Total effective rate = (number of effective cases + number of ineffective cases)/total number of cases × 100%.

(2) Cardiac function: Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), as well as left ventricular ejection fraction (LVEF) were measured by Mindrail DC-N3S color Doppler ultrasound system. About 4 mL of elbow venous blood was gathered from patients, and the level of plasma N-terminal pro B-type natriuretic peptide (NT-proBNP) was detected by enzyme-linked immunosorbent double antibody sandwich method.

(3) Lung function: Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), as well as FEV1/FVC were measured with the Japanese MINATOAS-507 pulmonary function instrument.

(4) Blood gas level: Oxygen saturation (SpO_2), partial arterial oxygen concentration (PaO_2), and PaO_2/inspired oxygen fraction (PaO_2/FiO_2), which are detected by the Danish automatic blood gas analyzer.

(5) Exercise endurance: The 6-minute walking test (6MWT) was adopted for evaluating patients' exercise endurance.[13] The longer the walking distance, the better the exercise endurance.

(6) Quality of life: The Minnesota living with heart failure questionnaire (MLHFQ) was adopted to evaluate the quality of life of patients, with a total of 21 items.[14] Each item was scored on a 0-5 scale, with a total score of 105 points, and the higher the score, the worse the quality of life.

(7) The rate of rehospitalization and the incidence of major adverse cardiovascular events (MACE), including stroke, angina pectoris, and myocardial infarction, were recorded.

Statistical Analysis

GraphPad Prism 10.0 statistical software (GraphPad Software Inc., San Diego, CA, USA) was employed for analyzing the data. Normality was confirmed by the Shapiro–Wilk test ($P > .05$). The measurement data conforming to normal distribution were exhibited as mean ± standard deviation ($x \pm s$). For within-group comparisons (before vs. after intervention), a paired *t*-test was used; for between-group comparisons, an independent *t*-test was applied. The counting data were exhibited as numbers and rate (%), and the χ^2 test was applied for comparison. A priori power analysis indicated that 64 patients/group would provide 80% power ($\alpha = 0.05$) to detect a 7% LVEF difference. $P < .05$ was considered statistically significant.

RESULTS

General Data of Patients in Both Groups

As Table 1 displayed, Pearson's chi-square test was used for etiology comparison, and no difference was seen in the general data of patients between the 2 groups ($P > .05$).

Clinical Efficacy in Both Groups

As Table 2 revealed, the total effective rate of the study group was higher compared to the control group ($\chi^2 = 5.053$, $P = .080$).

Cardiac Function in Both Groups

Prior to intervention, no differences were seen in LVEF, LVESD, LVEDD, and NT-proBNP levels between 2 groups ($P > .05$). Following 3 months of intervention, LVEF levels were elevated while LVESD, LVEDD, and NT-proBNP levels were diminished in both groups ($P < .01$). Notably, the study group had higher LVEF level as well as lower LVESD, LVEDD, and NT-proBNP levels when comparing with the control group after 3 months of intervention ($P < .01$, Figure 1).

Lung Function in Both Groups

Prior to intervention, no differences were seen in FEV1, FVC, or FEV1/FVC levels between 2 groups ($P > .05$). Following 3 months of intervention, FEV1, FVC, and FEV1/FVC levels were elevated in both groups ($P < .01$). Notably, in contrast to the control group, the study group had higher FEV1, FVC, and FEV1/FVC levels when comparing with the control group following 3 months of intervention ($P < .01$, Figure 2).

Blood Gas Level in Both Groups

Prior to intervention, no differences were seen in SpO_2, PaO_2, and PaO_2/FiO_2 levels between 2 groups ($P > .05$). Following 3 months of intervention, SpO_2, PaO_2, and PaO_2/FiO_2 levels were elevated in both groups ($P < .01$). Notably, the study group had higher SpO_2, PaO_2, and PaO_2/FiO_2 levels when comparing with the control group after 3 months of intervention ($P < .01$, Figure 3).

Exercise Endurance in Both Groups

Prior to intervention, no differences were seen in the 6MWT between the 2 groups ($P > .05$). Following 3 months of intervention, 6MWT was elevated in both groups ($P < .01$). Notably, the study group had longer 6MWT compared to the control group after 3 months of intervention ($P < .01$, Figure 4).

Table 1. General Data of Patients in Both Groups

Items	Control Group (n = 73)	Study Group (n = 73)	χ^2/t	*P*
Gender			0.11	.73
Male	40 (54.79)	42 (57.53)		
Female	33 (45.21)	31 (42.47)		
Age (years)	64.17 ± 7.91	64.21 ± 8.05	0.03	.97
Grade of cardiac function			0.15	.92
Grade II	18 (24.66)	20 (27.40)		
Grade III	43 (58.90)	41 (56.16)		
Grade IV	12 (16.44)	12 (16.44)		
Course of disease (years)	3.97 ± 0.61	4.02 ± 0.65	0.47	.63
Baseline medications				
ACEI/ARB (%)	65 (89.04)	67 (91.78)	0.34	.56
Beta-blockers (%)	58 (79.45)	60 (82.19)	0.17	.68
MRA (%)	42 (57.53)	40 (54.79)	0.1	.75
Diuretics (%)	70 (95.89)	69 (94.52)	0	1
Etiology			0.110	.740
Ischemic heart disease	38 (52.05)	40 (54.79)		
Non-ischemic	35 (47.95)	33 (45.21)		
Prior revascularization			0.21	.64
PCI (%)	15 (20.55)	17 (23.29)		
CABG (%)	8 (10.96)	6 (8.22)		
None (%)	50 (68.49)	50 (68.49)		

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention.

Quality of Life in Both Groups

Prior to intervention, no differences were seen in MLHFQ scores between the 2 groups ($P > .05$). Following 3 months of intervention, MLHFQ score was decreased in both groups ($P < .01$). Notably, in contrast to the control group, the study group had lower MLHFQ score after 3 months of intervention ($P < .01$, Figure 5).

Rate of Rehospitalization and Incidence of Major Adverse Cardiovascular Events in Both Groups

As Table 3 revealed, the rate of rehospitalization (Fisher's exact test, $P = .033$) and incidence of MACE (continuity correction $\chi^2 = 3.539$, $P = .060$) in the study group were lower when comparing with the control group.

Adverse Events and Treatment Compliance Related to Rehabilitation Intervention in Both Groups

Adverse events occurred in 6 patients (8.2%) in the study group (musculoskeletal pain = 3, hypotension = 2, arrhythmia = 1) and 4 controls (5.5%, all hypotension). In the study group, 65 patients (89.0%) completed >80% of prescribed sessions. Three dropouts occurred due to noncompliance with exercise and 5 due to transportation barriers in the study group.

Table 2. Clinical Efficacy in Both Groups

Groups	Cases	Obvious Effect	Effective	Ineffective	Total Effective Rate
Control group	73	24 (32.88)	35 (47.94)	14 (19.18)	59 (80.82)
Study group	73	30 (41.10)	38 (52.05)	5 (6.85)	68 (93.15)
χ^2					5.053
P					.080

DISCUSSION

With the continuous increase of China's aging population, the incidence of cardiovascular diseases has increased significantly.[15] The CHF is the end-stage presentation of a variety of cardiovascular diseases, with high mortality and poor prognosis, which seriously threatens patients' life safety.[16] Currently, the treatment of CHF includes diuretics, ACE inhibitors or ARB, beta blockers, and aldosterone receptor antagonists. These drugs can improve cardiac function along with the prognosis of CHF patients by reducing cardiac load, dilating blood vessels, reducing neuroendocrine activity, and inhibiting myocardial remodeling.[17] Sacubitril valsartan sodium is composed of valsartan and sacubitril. The former is an angiotensin receptor antagonist, and the latter is a neutral endopeptidase inhibitor.[18] The drug can block the angiotensin II receptor, inhibit the activity of neutral endopeptidase through a dual mechanism, and then reduce harmful neuroendocrine substances, play a role in blood vessel dilation, reduce blood pressure, reduce water and sodium retention, and inhibit myocardial remodeling, among other effects.[19] However, drug therapy alone has limitations, such as side effects, resistance, and compliance.[20] Therefore, there is a need to find safer, more effective, and economical treatments to complement drug therapy.

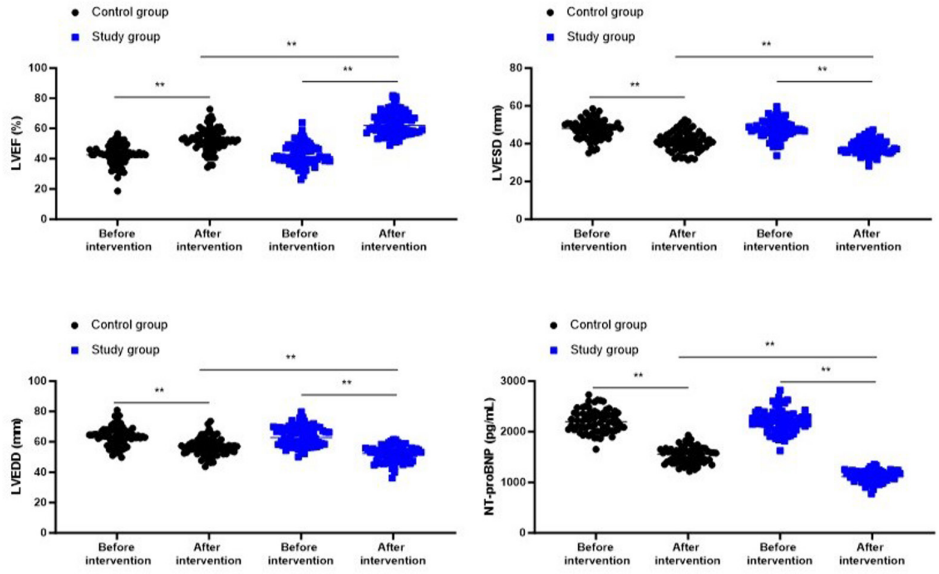

Figure 1. Cardiac function in both groups. $^{**}P < .01$.

In the early stages of medicine, it was recommended that CHF patients should mainly rest and do not recommend too much exercise.[21] However, with in-depth studies, researchers found that moderate exercise is more conducive to the rehabilitation of CHF patients.[22] Cardiac rehabilitation exercise was initially used for the rehabilitation of patients with coronary heart disease and was gradually applied to other cardiovascular diseases such as CHF.[23] At present, cardiac rehabilitation exercise therapy has become an important part of the comprehensive treatment of CHF, and NYHA has recommended cardiac rehabilitation exercise therapy as Class I A for patients with CHF.[24] The implementation of cardiac rehabilitation exercises can effectively promote the exercise tolerance of patients, avoid the activity of the sympathetic nervous system caused by overactivation, and increase the activity of the parasympathetic nervous system.[25] In addition, reasonable exercise has an accelerated effect on skeletal muscle blood circulation, can improve oxygen metabolism, and has a positive effect on controlling disease symptoms.[26] Previously, the 6MWT improvement (Δ54 m) exceeded the CHF MCID of 30 m, while NT-proBNP reduction (Δ142 pg/mL) surpassed the 25% threshold for clinical significance.[27,28] In this study, the results suggested that the total effective rate of the study group was higher when comparing with the control group, implying that cardiac rehabilitation exercise plus sacubitril valsartan sodium was more effective than single sacubitril valsartan sodium, which was similar to previous reports.[29]

Besides, the results of the study indicated that following 3 months of intervention, LVEF, FEV1, FVC, and FEV1/FVC levels were elevated while LVESD, LVEDD, and NT-proBNP

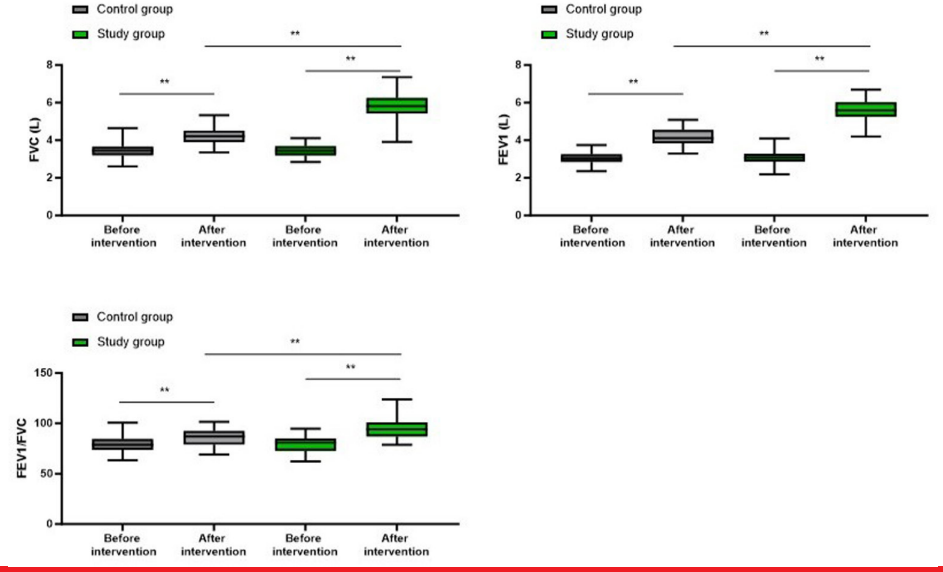

Figure 2. Lung function in both groups. $^{**}P < .01$.

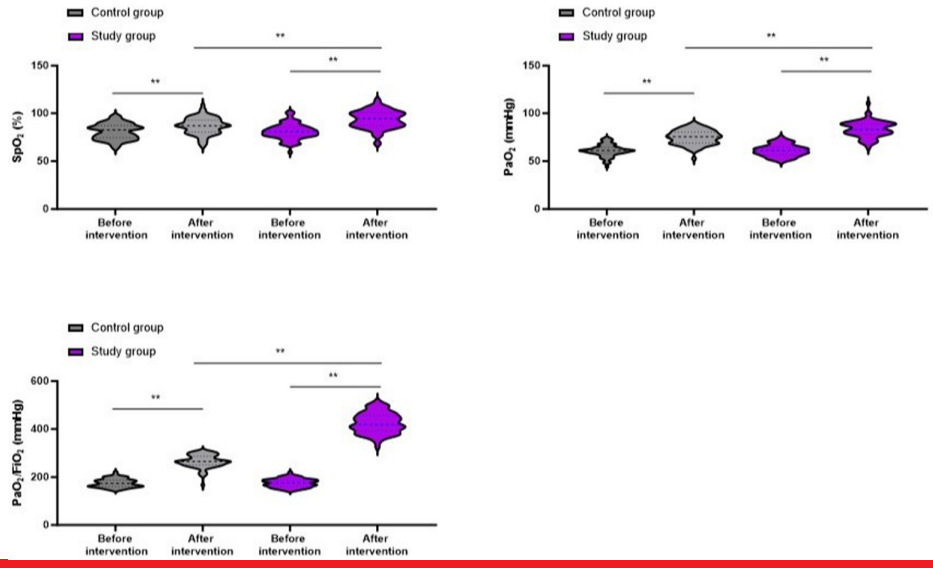

Figure 3. Blood gas levels in both groups. $^{**}P < .01$.

levels were diminished in both groups. Notably, the study group had higher LVEF level as well as lower LVESD, LVEDD, and NT-proBNP levels when comparing with the control group after 3 months of intervention. All these results suggested that cardiac rehabilitation exercise combined with sacubitril valsartan sodium could better improve cardiac function and lung function in CHF patients. The reason for the analysis is that cardiac rehabilitation exercise therapy can regulate the sympathetic nerve, inhibit the over-activation of the renin-angiotensin-aldosterone system, improve aerobic metabolism capacity in the body, and enhance blood circulation capacity.[30] Consistently, Li et al[31] suggested that comprehensive exercise programs could improve cardiac output as well as decrease restenosis rates in post-percutaneous coronary intervention patients. Wang et al[32] indicated that cardiopulmonary exercise testing-guided cardiac rehabilitation could improve cardiopulmonary function and NT-proBNP levels in CHF patients. While Torun et al[37] demonstrated sacubitril/valsartan's exercise-enhancing effects in healthy rats, the findings extend this observation to CHF patients, suggesting disease-specific modulation of cardiopulmonary adaptation.

In addition, the study indicated that after 3 months of intervention, SpO_2, PaO_2, and PaO_2/FiO_2 levels were elevated

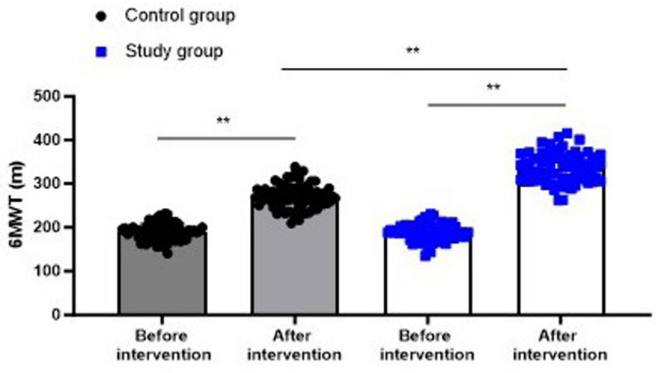

Figure 4. Exercise endurance in both groups. $^{**}P < .01$.

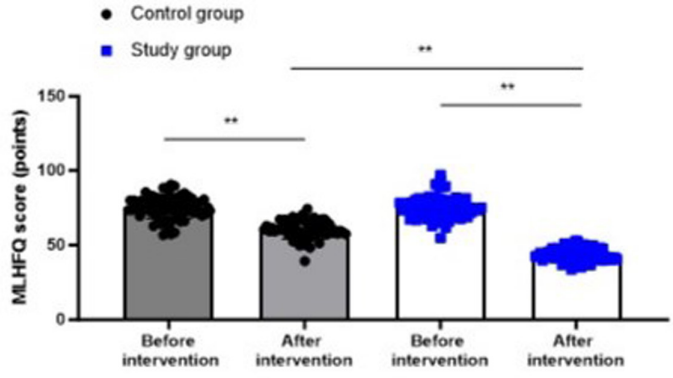

Figure 5. Quality of life in both groups. $^{**}P < .01$.

Table 3. Rate of Rehospitalization and Incidence of MACE in Both Groups

			MACE			
Groups	**Cases**	**Rate of Rehospitalization**	**Stroke**	**Angina Pectoris**	**Myocardial Infarction**	**Total Incidence**
Control group	73	8 (10.96)	2 (2.74)	3 (4.11)	4 (5.48)	9 (12.33)
Study group	73	1 (1.37)	0 (0.00)	1 (1.37)	1 (1.37)	2 (2.74)
χ^2		Fisher's exact test		3.539		
P		.033		.060		

in both groups. Notably, the study group had higher SpO_2, PaO_2, and PaO_2/FiO_2 levels when comparing with the control group after 3 months of intervention. All these results suggested that cardiac rehabilitation exercise combined with sacubitril valsartan sodium could better improve the blood gas levels of CHF patients. Cardiac rehabilitation exercise training can promote aerobic metabolism, enhance myocardial oxygen supply, prolong the ventricular ejection period, and enhance myocardial contractility.[33] Cardiac rehabilitation may improve myocardial oxygen supply, as evidenced by increased SpO_2 in the study and prior findings showing enhanced coronary flow reserve after training.[34]

Moreover, the study indicated that after 3 months of intervention, 6MWT was increased in both groups. Notably, relative to the control group, the study group had longer 6MWT after 3 months of intervention. All these results implied that cardiac rehabilitation exercise combined with sacubitril valsartan sodium could better promote the exercise endurance of CHF patients. The reason is that, through appropriate exercise intensity and frequency, cardiac rehabilitation exercise effectively enhances the strength and endurance of respiratory muscles, optimizes skeletal muscle aerobic metabolism, not only enhances the patients' lung capacity, but also improves their lung ventilation, so that the exercise endurance is stronger.[35] Consistently, Hua et al[36] suggested that exercise-based cardiac rehabilitation delivery modes could increase the 6MWT of CHF patients. Notably, the resistance training protocol aligns with Torun's recommendation for CHF patients,[37] where elastic band exercises preserve lean mass while improving functional capacity. This dual approach (aerobic + resistance) may explain the superior 6MWT outcomes compared to aerobic-only regimens.

Finally, the study indicated that following 3 months of intervention, MLHFQ score was decreased in both groups. Notably, the study group had lower MLHFQ score when comparing with the control group following 3 months of intervention. At the same time, the rate of rehospitalization and incidence of MACE in the study group were lower when comparing with the control group. All these results suggested that cardiac rehabilitation exercise combined with sacubitril valsartan sodium could better promote the quality of life, reduce the rate of rehospitalization and incidence of MACE in CHF patients. Similarly, He et al[38] suggested that a long-term exercise-based cardiac rehabilitation program could promote physical health along with reducing all-cause mortality and MACE in myocardial infarction patients. Furthermore, although exercise-related adverse events were reported, the small sample may underestimate safety risks in real-world settings. Additionally, the 3-month follow-up was sufficient to assess functional improvements but may be inadequate for long-term outcomes like mortality. Limitations also include the use of multiple statistical tests without adjustment for multiplicity, which may increase type I error. Future studies with larger samples and longer follow-up are needed to confirm these findings. Despite proven benefits, global cardiac rehabilitation participation rates remain low (30%-50%), as highlighted by Torun et al[39] in Türkiye. Herein, 89% adherence was achieved through hospital-based supervised sessions, suggesting that structured programs may overcome common barriers like lack of awareness (reported in 62% non-participants in Torun's survey) and logistical challenges. While high adherence was observed, the hospital-based setting may limit generalizability to communities with restricted healthcare access. Future studies should explore culturally adapted education strategies to further improve engagement.

CONCLUSION

The study indicates that cardiac rehabilitation exercise combined with sacubitril valsartan sodium is effective in treating CHF patients, which can improve cardiac function, lung function and blood gas levels, promote exercise endurance and quality of life, as well as reduce the rate of rehospitalization and incidence of MACE in CHF patients.

Data Availability Statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Committee Approval: This study was approved by the Ethics Committee of Beijing Rehabilitation Hospital Affiliated to Capital Medical University (Decision Number: 2024bkky-007; Decision Date: January 16, 2024). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Informed Consent: All participants had signed the informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception – X.L., Z.X.; Design – X.L., Z.X.; Supervision – Z.X.; Resource – Z.X.; Materials – P.Z., J.C., L.S., Q.M.; Data Collection and/or Processing – X.L., P.Z., J.C.; Analysis and/or Interpretation – X.L., L.S., Q.M.; Literature Review – X.L., P.Z., J.C.; Writing – X.L.; Critical Review – Z.X. All authors read and approved the final manuscript.

Declaration of Interests: The authors have no conflicts of interest to declare.

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Supplementary Table 1. Concomitant antianginal and antithrombotic therapies

Medication Class	Specific Drug	Control group (n=73)	Study group (n=73)	χ^2	*P*
Antianginal Therapy					
Nitrates	Isosorbide dinitrate	18 (24.7%)	15 (20.5%)	0.38	0.54
	Isosorbide mononitrate	7 (9.6%)	8 (11.0%)	0.09	0.77
Calcium Channel Blockers	Amlodipine	12 (16.4%)	10 (13.7%)	0.22	0.64
	Diltiazem	5 (6.8%)	6 (8.2%)	0.1	0.75
Antithrombotic Therapy					
Antiplatelets	Aspirin	40 (54.8%)	42 (57.5%)	0.11	0.74
	Clopidogrel	25 (34.2%)	23 (31.5%)	0.12	0.73
Anticoagulants	Warfarin	8 (11.0%)	7 (9.6%)	0.07	0.79
	DOACs	4 (5.5%)	3 (4.1%)	Fisher's exact test	1

DOACs, Direct oral anticoagulants (rivaroxaban/dabigatran)