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The Effect of Trimetazidine Combined with Cardiac Rehabilitation on the Prognosis of Patients with Acute Myocardial Infarction

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Abstract: ***Objective:*** *To investigate the effects of Trimetazidine (TMZ) combined with Cardiac Rehabilitation (CR) on acute myocardial infarction (AMI). A Acute Myocardial Infarction (AMI) patients who underwent PCI, the effects of ventricular remodeling and quality of life at different times after PCI; to observe the changes in the expression of Nod-Like Receptor Protein 3 (NLRP3) in peripheral blood mononuclear cells at different times after the onset of AMI and the effects of TMZ combined with CR therapy on it.* ***Methods:*** *The study population was selected from 89 AMI patients admitted to the Second Hospital of Dalian Medical University from October 2018 to January 2020. All of them underwent PCI in emergency or within 2 days of admission, and they were all treated with double antibiotics, heparin and statins, and β-receptor antagonists or CCB or RAS system antagonists according to the patients' blood pressure and heart rate. The patients were divided into a control group and a rehabilitation group according to their willingness and adherence to rehabilitation. The control group consisted of 44 patients (n=44), who were treated only with the above treatments and no other treatments. The rehabilitation group consisted of 45 patients (n=45) who were treated with TMZ and CR in combination with the above treatments. In the rehabilitation group, the cardiac rehabilitation program was initiated as appropriate from day 2 after PCI, and trimetazidine hydrochloride treatment (35 mg bid po) was given on day 7 after PCI for a total of 1 year (52±2 weeks). Blood was collected in the morning of the 2nd day of admission for routine blood tests, cTnI, lipids, blood glucose, liver and kidney function, and glycosylated hemoglobin. Cardiac ultrasound was performed at weeks 1, 4, 12, and 52±2, and left ventricular end-diastolic diameter (LVEDd) and left ventricular ejection fraction (LVEF) were measured. The Quality of Life Scale (SF-12) and Generalized Anxiety Disorder Scale (GAD-7) were assessed at week 1 and week 52±2. Cardiopulmonary exercise test was performed at week 1 and week 52±2 of onset, and maximum kilogram oxygen uptake (peakVO_2/kg), kilogram oxygen uptake at anaerobic threshold (VO_2/kg@AT), and metabolic equivalents at anaerobic threshold (Mets@AT) were recorded. The expression of NLRP3 in peripheral blood mononuclear cells of patients at 24-36 hours of onset, week 1, week 4, week 12 and week 52±2 was detected. All the above data were analyzed by SPSS 24.0 software.* ***Results:*** *At 1 year of onset, LVEDd was less in the rehabilitation group than in the control group. At weeks 4 and 12 of onset, LVEF was higher in the rehabilitation group than in the control group. At 1 year after the onset of the disease, the quality of life and anxiety and depression status of the rehabilitation group were significantly improved, the SF-12 score was higher than that of the control group, and the GAD-7 score was lower than that of the control group. And the cardiopulmonary exercise experiment indexes of the two groups were compared, and the peakVO_2/kg, VO_2/kg@AT and Mets@AT of the rehabilitation group were significantly higher than those of the control group. During the 1-year follow-up, peripheral blood mononuclear cell NLRP3 levels tended to decrease in both groups and were at their highest values at 24-36 hours after onset. At weeks 4 and 12, peripheral blood mononuclear cell NLRP3 levels were significantly lower in the rehabilitation group than in the control group.* ***Conclusion:*** *TMZ combined with CR therapy showed significant improvement in ventricular remodeling, exercise tolerance, and quality of life in patients with AMI, and it was most effective and beneficial to patients at 1 year after PCI. TMZ combined with CR therapy significantly reduced peripheral blood mononuclear cell NLRP3 levels in AMI patients, and the effect was most pronounced at 3 months after PCI.*

Keywords: Acute myocardial infarction, Trimetazidine, Cardiac rehabilitation, Left ventricular ejection fraction, NLRP3.

1. Preamble

Due to the current social competition pressure surge and aging population phenomenon aggravation, cardiovascular disease (CVD) death rate in recent years, in developed countries has reached 20%-50% of the total number of diseases, accounting for about one-fifth of the total number of global diseases [1]. In developed countries, CVD accounts for 20%-50% of the total number of diseases in the world, which is about one fifth of the total number of diseases worldwide [2]. Acute myocardial infarction (AcMI) Acute myocardial infarction (AMI) is one of the types of CVD, and now with the rapid development of percutaneous coronary intervention (PCI), its treatment outcome has been improved [3]. However, PCI does not reverse CVD. However, PCI does not reverse or delay the development of coronary artery disease [4]. However, it is difficult to ignore the prognostic problems such as decline in cardiac function, recurrent infarction, and restenosis of coronary artery that occur after AMI, which will cause patients' exercise tolerance to decrease, negative emotions to appear, and difficulty to return to normal social life. Currently, our healthcare system and the general public have come to realize that conventional interventional interventions combined with pharmacological treatments are not sufficient and effective for the long-term rehabilitation program of post-infarction patients, so improving the prognosis of AMI survivors has become a major challenge that needs to be solved [5]. Therefore, improving the prognosis of AMI survivors has become a major challenge to be addressed.

Because the process of post-infarction ventricular remodeling (Ventricular remodeling) is irreversible, the microcirculatory and myocardial energy metabolism disorders caused by it cannot be effectively alleviated. The pharmacological mechanism of Trimetazidine (TMZ) includes the inhibition of free fatty acid β-oxidation, the enhancement of pyruvate

dehydrogenase activity, the inhibition of further reperfusion injury and the generation of oxygen radicals, etc. TMZ optimizes the fatty acid oxidation pathway of myocardial metabolism to the glucose oxidation pathway, maintains ATP in cardiomyocytes, and optimizes myocardial metabolism to the glucose oxidation pathway, and maintains ATP in cardiac cells [6]. TMZ can optimize the fatty acid oxidation pathway of myocardial metabolism to glucose oxidation pathway, maintain the ATP level in myocardial cells, improve myocardial ischemia without affecting the heart rate and blood pressure, and inhibit ventricular remodeling, which has been widely used in clinical work. At present, the concept of cardiac rehabilitation (Cardiac rehabilitation, CR) has also been gradually emphasized [7]. The concept of cardiac rehabilitation (CR) is also gaining attention nowadays. Cardiac rehabilitation, especially exercise rehabilitation, has been shown to reduce the recurrence rate and mortality rate, correct bad mood and improve the quality of life of AMI patients [8]. The concept of cardiac rehabilitation, especially exercise rehabilitation, has been gaining attention. Currently, there are fewer studies on trimetazidine combined with exercise rehabilitation to improve ventricular remodeling and increase exercise endurance in patients with AMI.

Studies have shown that the inflammatory response plays an important role in the development of AMI [9]. The innate immune pattern recognition receptor NLRP3 (Nod-like receptor protein 3 (NLRP3)) can be activated and expressed by a variety of danger signals such as infection, metabolic dysfunction, and oxidative stress [10]-[11]. Nodlike receptor protein 3 (NLRP3) It has been found that [12] strenuous exercise can increase the expression of NLRP3 and lead to cardiomyocyte apoptosis. Moderate exercise can modulate the inflammatory response generated by NLRP3, reduce the production of its downstream inflammatory factors such as IL-1β, IL-8, etc. [13], reducing cardiomyocyte apoptosis and providing some protection to the heart, and long-term moderate exercise is better than short-term [14]. The effect of long-term moderate exercise is better than that of short-term. Existing studies have indicated that [15] TMZ can inhibit the expression of NLRP3 inflammatory vesicles by increasing autophagy activity, and TMZ can also inhibit lipopolysaccharide (LPS)-induced high intracellular expression of NLRP3 and IL-1β [16]. The effect of cardiac rehabilitation on NLRP3 inflammatory vesicle expression after acute myocardial infarction has been less reported.

Therefore, the main objectives of this study were to observe the effects of TMZ combined with CR therapy on ventricular remodeling and quality of life in patients after AMI, and to investigate the effects of TMZ combined with CR therapy on peripheral blood NLRP3 levels in patients with AMI.

2. Materials and Methods

2.1 Research Objectives

2.1.1 Grouping of research subjects

The study population of this study was screened according to the inclusion criteria and exclusion criteria, and a total of 89 patients with AMI were selected, all of whom were admitted to the Second Affiliated Hospital of Dalian Medical University from October 2018 to December 2019, including 79 males and 10 females. All enrolled patients were perfected coronary angiography + PCI in emergency or within the 2nd day of admission. The patients were divided into the control group and the rehabilitation group according to whether they had the willingness and adherence to rehabilitation. 44 cases (n=44) in the control group were taken standard treatment after AMI, of which 36 cases were male and 8 cases were female. Forty-five patients (n=45) in the rehabilitation group were treated with TMZ and CR in combination with standard treatment for AMI patients, of which 39 were male and 6 were female.

2.1.2 Inclusion criteria

(1) Adults aged 18 to 80 years. (2) Patients with the first diagnosis of AMI, whose diagnostic criteria refer to the "Guidelines for the Diagnosis and Treatment of Acute ST-Segment Elevation Myocardial Infarction" in China in 2019. (3) Post-AMI Killip classification of grade I-IV. (4) The patients were informed and agreed to be enrolled.

2.1.3 Exclusion criteria

(1) Pregnant and lactating females and those planning to have children within the experimental period. (2) Previous history of heart failure. (3) Severe hepatic and renal dysfunction. (4) Previous malignant tumors. (5) Myocardial injury due to surgery, trauma, gastrointestinal bleeding and PCI. (6) Previously allergic to trimetazidine. (7) Patients who are participating in other clinical trials.

2.2 Research Methodology

2.2.1 Collect basic information:

Medical history data such as age, gender, BMI, recording of AMI lesion site, vital signs such as heart rate and blood pressure on admission, personal history and past history were collected.

2.2.2 Laboratory tests:

BNP was measured by i2000SR chemiluminescence method. Blood routine, blood lipids, liver and kidney function, blood glucose, glycosylated hemoglobin level, and cTnI were tested in the biochemistry room of the testing department of the Second Hospital of Dalian Medical University.

2.2.3 Flow cytometry

FACS Calibur flow cytometer was applied to analyze the expression of NLRP3 in peripheral blood mononuclear cells.

(a) Reagents used

Buy NLRP3 antibody from Miltenyi Biotec, Germany. Buy CD45 antibody and CD14 antibody from Abcam, USA. Buy Membrane Breaker (A/B) and Hemolysin from Shanghai Xinrui Biotechnology Co.

(b) Instruments used

Benchtop centrifuge, Eppendorf, Germany; Flow cytometer, FACE Calibur, BD, USA; High precision spiker, Eppendorf, Germany.

2.2.4 NLRP3 specimen collection

(a) Before starting the experiment, each experimental reagent was left at room temperature for 20 min.

(b) Add 50ul of patient's whole blood into the EDTA blood collection tube, add 2ul CD45 and CD14 to the wall respectively, shake and mix for 30s away from light, and then leave it at room temperature for 15min.

(c) Add 40ul of Reagent A to the tube, shake it away from light and let it stand for 5min.

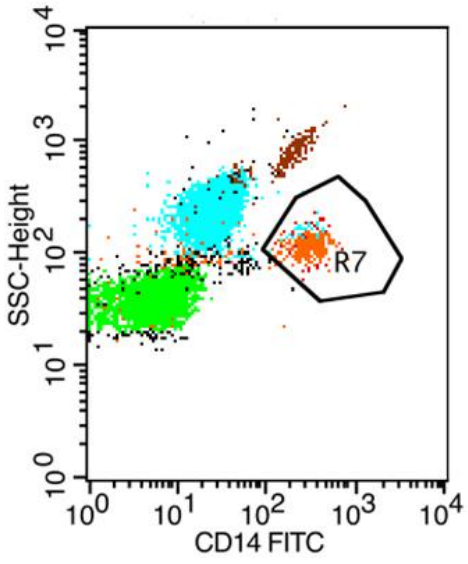
(d) 1ml of hemolysin was added to the tube, followed by shaking and mixing, and again left to stand for 10min at room temperature away from light.

(e) Centrifugation, 2500 rpm for 3 min.

(f) Gently take out the blood collection tube, quickly invert the tube and discard the supernatant, followed by adding 500 ml of saline to the tube, gently blowing and mixing.

(g) Place in a centrifuge and centrifuge, 2500 rpm, continuously for 3 min. subsequently discard the supernatant and add 20ul of liquid B and 2ul of NLRP3 antibody to the experimental groups to be treated, respectively. Mix well away from light and leave at room temperature for 20min.

(h) In each tube, 200 ml of saline was added, gently mixed and put on the machine, and analyzed by specialized personnel of the Department of Laboratory of the Second Affiliated Hospital of Dalian Medical University for flow-through experimental operation.



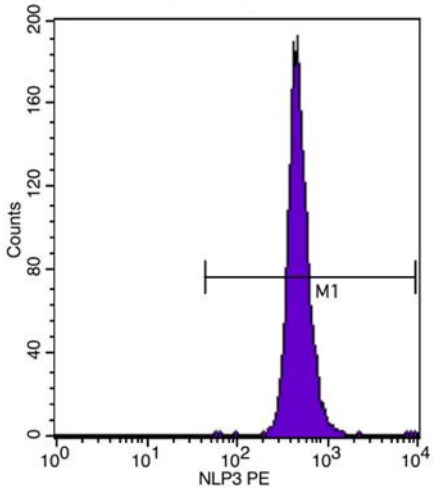


Figure 1: NLRP3 expression level in peripheral blood mononuclear cells

2.2.5 Coronary angiography procedure and instrumentation

Instrumentation: Digital Subtraction Imaging (DSA) machine.

The enrolled patients underwent coronary angiography using transradial artery puncture approach and the report of the angiographic findings was recorded with reference to the international common standards.

2.2.6 Echocardiography

Echocardiography was performed on the patients by the same cardiac sonographer licensed to practice medicine, and left ventricular end-diastolic internal diameter (LVEDd) and ejection fraction (LVEF) were measured.

2.2.7 Treatment

The enrolled patients were treated with dual antibiotics, heparin and statins, and beta receptor antagonists or CCB or RAS system antagonists were given according to the patients' blood pressure and heart rate. The rehabilitation group was treated with trimetazidine hydrochloride, 35 mg twice a day, on top of the above treatment. (Manufacturer: Schweizer Tianjin Pharmaceutical Co., Ltd; Approval No.: H20100077; Specification: 35 mg)

2.2.8 Rehabilitation methods

Patients in the rehabilitation group were eligible for cardiac rehabilitation on day 2 after PCI if they met the following criteria: (1) no recurrence of chest pain in the past 8 hours; (2) no reelevation of myocardial markers; (3) no new onset of cardiac arrhythmia in the past 8 hours; and (4) no obvious symptoms of heart failure such as dyspnea. Patients in the rehabilitation group who met the criteria began cardiac rehabilitation therapy under the guidance of a specialized cardiac rehabilitation physician for a period of 52±2 weeks.

Table 1: Rehabilitation program of 52±2 weeks duration

	commencement date	rehabilitation purpose	rehabilitation program	caveat
Phase I	Carried out 24h after PCI as appropriate.	Improve patients' cardiorespiratory function, shorten hospitalization	Assess the general condition of the patients, educate the patients and their families, supervise smoking cessation, give	(Cardiac monitoring is required, and the amount of exercise is controlled by an increase in heart rate to 20 beats/min over

		period, prevent complications, and prepare for phase II rehabilitation.	instructions on exercise rehabilitation and daily life, complete the 6-MWT before discharge, and formulate rehabilitation prescriptions and follow-up plans.	resting heart rate and a Borg dyspnea score of <12).
Phase II	4-12 weeks after discharge.	Make every effort to restore the patient's ability to exercise in daily life as soon as possible, and urge him or her to return to normal social life as soon as possible.	General clinical evaluation of the patients and refinement of CPET, correction of their bad habits, exercise rehabilitation including aerobic, resistance and flexibility training, guidance on daily life and work ability, and clarification of drug prescription.	Evaluate the individual to assess the need for cardiac monitoring during exercise, recommend moderate-intensity exercise, recommend 25-36 recoveries over 12 weeks, and review cardiorespiratory reserve function after 12 weeks to adjust the exercise program.
Phase III	12-(52±2) weeks after discharge.	Control the recurrence of cardiovascular events and adopt a healthy lifestyle to promote the recovery of psychosocial functioning.	Risk factors were controlled, individualized exercise prescriptions were developed, medication prescriptions were adjusted based on follow-up results, and reviews were performed on a regular basis.	May exercise at home, with or without medical supervision chosen based on risk stratification (medical supervision is generally not required).

2.2.9 Cardiopulmonary exercise test

Using the Swiss-made SCHILLER-CS200 cardiopulmonary exercise machine, a cardiac rehabilitation physician will set the appropriate power load according to the patient's condition and perform a symptom-limited maximum amount of cardiopulmonary exercise test.

2.2.10 Quality of Life Rating Scale and Generalized Anxiety Scale

SF-12 was used as the quality of life scale, with a total score of 100, and a higher score represented a high quality of survival. GAD-7 was used as the generalized anxiety scale to assess the anxiety and depression status of the patients, with a high score representing severe anxiety symptoms.

3. Data Processing

Statistical methods: Statistical software was used with SPSS 24.0. Measurement information was expressed using mean ± standard deviation (X ± S), and t-test was used to compare the measurement information between the two groups. Non-normally distributed measures were expressed in the form of quartiles (Q1-Q3), and the Mann-Whitney U test was used to test the difference in non-normal measures between the two groups. $p < 0.05$ was statistically different.

4. Results

4.1 General Information Analysis

There was no significant difference in the general information of the two groups of patients, as shown in Table 2.

Table 2: Comparison of general information between control group and rehabilitation group

	Control group (n=44)	Rehabilitation group (n=45)	P-value
Age (years)	62.5±10.4	57.4±11.0	0.559
Male patients n (%)	36 (81.8)	39 (86.7)	0.530
Smoking history n (%)	27 (61.4)	31 (68.9)	0.456
History of hypertension n (%)	26 (59.1)	19 (42.2)	0.112
History of diabetes n (%)	12 (27.3)	13 (28.89)	0.865
AMI site n (%)			0.764
Front wall/front side wall	27 (61.4)	29 (64.4)	
Lower wall/lower side wall	17 (38.6)	16 (35.6)	
AMIn (%)			0.724
STEMI	28 (63.6)	27 (60.0)	
NSTEMI	16 (36.4)	18 (40.0)	
Systolic blood pressure (mmHg)	125.66±23.18	122.02±16.18	0.081
Diastolic blood pressure (mmHg)	75.00 (65.00-77.00)	76.00 (69.00-85.00)	0.669
Heart rate (bpm)	68.50 (61.75-77.00)	70.00 (66.00-79.00)	0.278
BMI (kg/m^2)	26.74±4.01	27.14±3.12	0.610
Troponin I (ug/L)	48.34 (5.39-178.47)	76.36 (4.81-357.31)	0.252
White blood cell count ($\times 10^9$ /L)	8.76±2.22	9.80±2.93	0.084
Platelet count ($\times 10^9$ /L)	220.63±47.91	228.78±45.86	0.981
Total cholesterol (mmol/L)	4.63±1.15	5.02±1.18	0.825
High-density lipoprotein (mmol/L)	1.05±0.30	1.04±0.28	0.877
Low-density lipoprotein (mmol/L)	2.43±0.73	2.59±0.95	0.266
Alanine aminotransferase (U/L)	29.46 (21.71-47.50)	37.44 (21.92-63.80)	0.237
Aspartate aminotransferase (U/L)	56.88 (32.32-104.16)	62.99 (27.20-135.57)	0.506
Fasting blood glucose (mmol/L)	5.69 (5.08-7.47)	6.02 (4.69-9.30)	0.912
Glycosylated hemoglobin (%)	6.10 (5.75-7.45)	5.90 (5.60-7.90)	0.475
Creatinine (umol/L)	68.70 (64.23-85.82)	68.39 (63.59-76.46)	0.375

Note: $P < 0.05$ statistically different.

4.2 Effect of TMZ Combined with CR on Left Ventricular End-diastolic Internal Diameter and Ejection Fraction

During the follow-up, there was no significant difference in LVEDd values between the two groups at week 1, week 4, and week 12 of onset ($P>0.05$), and the rehabilitation group was significantly lower than the control group at week 52±2 of onset (45.67±5.32 vs. 46.98±4.44). There was no significant difference ($P>0.05$) in LVEF values between the two groups at week 1 and week 4 of onset, and LVEF values were significantly higher in the rehabilitation group than in the control group at week 12 of onset (59.69±3.13 vs 56.90±4.40) and at week 52±2 of onset (61.42±3.14 vs 59.20±4.65).

Table 3: Effect of TMZ combined with CR on left ventricular end-diastolic internal diameter in AMI patients (mm)

	1st week of illness	4th week of illness	12th week of illness	52±2 weeks of disease onset
control subjects	47.74±3.11	46.95±4.71	47.05±4.36#	46.98±4.44#
rehabilitation group	47.96±3.32	46.78±3.70	46.52±4.34#	45.67±5.32#▲★
P-value	0.682	0.082	0.888	0.042

Note: #: P<0.05 compared with the same group at week 1 of onset; ▲: P<0.05 compared with the same group at week 4 of onset; ★: P<0.05 compared with the same group at week 12 of onset.

Table 4: Effect of TMZ combined with CR on left ventricular ejection fraction in patients with AMI (%)

	1st week of illness	4th week of illness	12th week of illness	52±2 weeks after onset of illness
control subjects	54.57±6.74	55.30±7.46	56.90±4.40#▲	59.20±4.65#▲★
rehabilitation group	52.18±8.06	55.64±6.82	59.69±3.13#▲	61.42±3.14#▲★
P-value	0.085	0.279	0.043	0.040

Note: #: P<0.05 compared with the same group at week 1 of onset; ▲: P<0.05 compared with the same group at week 4 of onset; ★: P<0.05 compared with the same group at week 12 of onset.

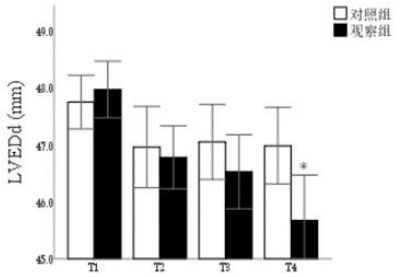


Figure 2: Effect of TMZ combined CR on LVEDd
Note: *: P<0.05 compared to control group.

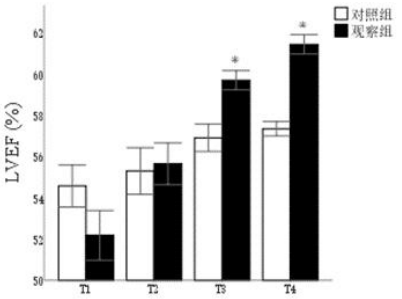


Figure 3: Effect of TMZ combined CR on LVEF
Note: *: P<0.05 compared to control group.

4.3 Effects of TMZ Combined with CR Treatment on SF-12 and GAD-7 Scales

At the 1st week of the disease, the SF-12 scale scores and GAD-7 scale scores of the control group were statistically compared with those of the control group, and the differences were not statistically significant (p > 0.05). At 52±2 weeks of onset, the above scales of the rehabilitation group were again statistically compared with those of the control group, and the results showed that the SF-12 scale scores of the rehabilitation group were higher (85.64±6.84 vs. 80.15±11.24), and the GAD-7 scale scores were lower (0.00 (0.00-1.00) vs. 0.50 (0.00-2.00)), and the differences were statistically significant (P<0.05). was statistically significant (p < 0.5).

Table 5: Comparison of SF-12 scale between two groups of patients

	1st week of illness	52±2 weeks after onset of illness	P-value
control subjects	63.38±18.51	80.15±11.24	0.001
rehabilitation group	69.57±16.33	85.64±6.84	0.000
P-value	0.484	0.006	

Table 6: Comparison of GAD-7 scale between the two groups of patients

	1st week of illness	52±2 weeks after onset of illness	P-value
control subjects	3.00 (1.00-6.75)	0.50 (0.00-2.00)	0.000
rehabilitation group	3.00 (2.00-7.00)	0.00 (0.00-1.00)	0.000
P-value	0.377	0.028	

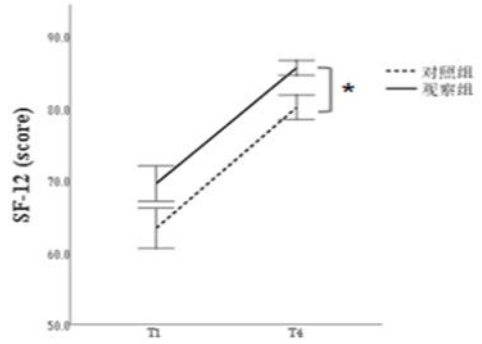


Figure 4: Effect of TMZ combined CR on SF-12
Note: *: P<0.05 compared to control group.

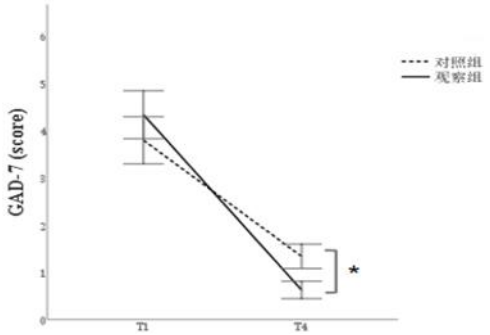


Figure 5: Effect of TMZ combined CR on GAD-7
Note: *: P<0.05 compared to control group.

4.4 Effect of TMZ Combined with CR on Cardiopulmonary Exercise Test Indexes after Treatment

At the 1st week of onset, the relevant cardiopulmonary exercise indices of the rehabilitation group were compared with those of the control group, and the difference was not statistically significant (P > 0.05). At 52±2 weeks of onset, the peak VO_2/kg (9.06±1.53L/kg.min vs. 8.36±2.40L/kg.min), VO_2/kg@AT (7.98±1.71ml/kg.min vs. 6.61±2.72ml/kg.min), and Mets@AT (2.24±0.72) were higher in the rehabilitation group than in the control group. vs 1.68±0.57) were higher than those of the control group, and the differences were statistically significant (p<0.5).

Table 7: Comparison of peak VO_2/kg between the two groups of patients (L/kg.min)

	1st week of illness	52±2 weeks after onset of illness	P-value
control subjects	6.26±2.26	8.36±2.40	0.043
rehabilitation group	6.43±2.00	9.06±1.53	0.027
P-value	0.896	0.013	

Table 8: Comparison of VO_2/kg@AT between the two groups (ml/kg.min)

	1st week of illness	52±2 weeks after onset of illness	P-value
control subjects	5.59±1.69	6.61±2.72	0.011
rehabilitation group	5.02±1.35	7.98±1.71	0.017
P-value	0.216	0.037	

Table 9: Comparison of Mets@AT between the two groups of patients

	1st week of illness	52±2 weeks after onset of illness	P-value
control subjects	1.04±0.38	1.68±0.57	0.013
rehabilitation group	1.22±0.50	2.24±0.72	0.001
P-value	0.135	0.025	

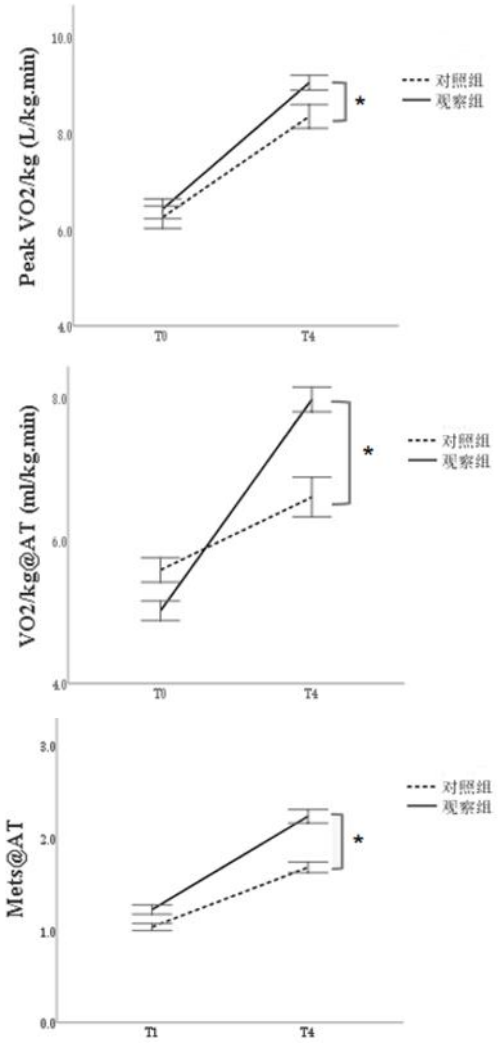


Figure 6: Effect of TMZ combined with CR on cardiopulmonary exercise test related indexes

Note: *: P<0.05 compared to control group.

4.5 Effect of TMZ Combined with CR on NLRP3 Expression in Peripheral Blood Mononuclear Cells

During the follow-up, we found that at 24-36 hours after the onset of the disease, the peripheral blood mononuclear cell NLRP3's of both groups were at the highest level in the same group, but the difference was not statistically significant when comparing the two groups (P > 0.05). During the 52±2-week follow-up, the peripheral blood mononuclear cell NLRP3 levels in both groups showed a decreasing trend, and the levels in the rehabilitation group were even lower at the 4th week of the onset of disease (704.05±183.33 vs. 47.61±246.23) and at the 12th week of the onset of disease (641.61±244.59 vs. 716.73±129.32), with a statistically significant difference (P<0.05). statistically significant (P < 0.05).

Table 10: Effect of TMZ combined with CR therapy on peripheral blood NLRP3 levels in AMI patients

	control subjects	rehabilitation group	P-value
24-36 hours after onset	897.46±132.43	912.02±111.01	0.294
1st week of illness	765.20±231.85•	780.46±279.34•	0.215
4th week of illness	747.61±246.23•	704.05±183.33•	0.042
12th week of illness	716.73±129.32•	641.61±244.59•	0.003
52±2 weeks after onset of illness	522.24±200.26•	510.99±169.51•	0.089

Note: ●: P < 0.05 compared to the same group at 24-36 hours of onset.

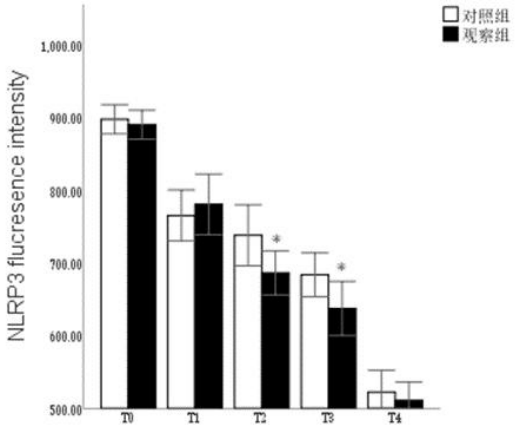


Figure 7: Effect of TMZ combined with CR on peripheral blood NLRP3 levels in AMI patients

Note: *: P<0.05 compared to control group.

5. Discussion

5.1 Effect of TMZ Combined with CR Therapy on Cardiac Function and Ventricular Remodeling after PCI in Patients with AMI

There are two main periods of ventricular remodeling after AMI; the early period refers to further expansion of the infarcted area and further thinning of the ventricular wall, a change that cannot be explained by myocardial infarction alone. The late phase of ventricular remodeling, on the other hand, refers to reactive hypertrophy of residual cardiomyocytes, interstitial fibrosis, and ventricular dilatation [17]. The postinfarction heart undergoes ventricular remodeling through the accumulation of fibrous tissue in both infarcted and noninfarcted myocardium, which alters myocardial tissue structure and ultimately leads to ventricular dysfunction [18] Post-AMI residual myocardial metabolic dysfunction accelerates the process of ventricular remodeling, leading to left ventricular hypofunction [19]. Exercise rehabilitation in cardiac rehabilitation can significantly improve LV dysfunction, thus benefiting myocardial metabolism [20]. Therefore, myocardial metabolizing drugs combined with appropriate exercise rehabilitation can improve the prognosis of patients with AMI.

TMZ optimizes myocardial energy metabolism, reduces oxygen consumption, and also enables the reduction of intracellular acidosis, maintains intracellular ATP levels,

protects mitochondrial function, and avoids meso [21]. Animal experimental studies have shown that the use of TMZ can greatly promote the recovery of cardiac mechanical function after myocardial ischemia [22]. The use of TMZ can greatly promote the recovery of cardiac mechanical function after myocardial ischemia. Relevant clinical trials have also confirmed that TMZ can improve myocardial perfusion levels in AMI patients and reduce myocardial reperfusion injury by inhibiting the opening of the mitochondrial permeability transition pore [21] The reduction of infarct size [23] and significantly improves left ventricular function in patients with AMI. It has also been shown that [24] 6 months of TMZ treatment added to standard treatment after thrombolysis in patients with AMI can inhibit left ventricular remodeling.

Exercise rehabilitation, as a core component of cardiac rehabilitation, is now progressively used in clinical care and is considered an important adjunct to existing pharmacological treatments. Its mechanism includes inhibition of the RAAS system, which in turn inhibits ventricular remodeling. A study of MI patients showed [25]. In a study of patients with MI, plasma levels of angiotensin II (AngII), aldosterone, vasopressin (AVP), and BNP were significantly reduced after 4 months of exercise training, and the reduction of AngII levels could negatively feedback inhibit the progression of myocardial fibrosis and aldosterone secretion, as well as regulate collagen production [26] and also increases cardiac compliance by regulating collagen accumulation [27] AngII also increases cardiac compliance by modulating collagen accumulation, increasing β-adrenergic receptor sensitivity and cyclic adenosine monophosphate (cAMP) levels [28]-[29] and reversing the conversion of cardiac myosin heavy chain α-mRNA (α-MHC) to cardiac myosin heavy chain β-mRNA (β-MHC) [30] which enhances the capacity of antioxidant enzymes, attenuates oxidative stress and increases myocardial contractility. Most clinical and animal experiments have shown [31] that exercise training after AMI not only improves clinical symptoms, but also has a positive effect on myocardial remodeling, including preventing the progression of left ventricular dysfunction, reducing interstitial myocardial fibrosis, improving cardiac function, and enhancing physical fitness, etc. Zhang Y [32] et al. found that long-term exercise rehabilitation (including phase II and phase III rehabilitation) can significantly improve LVEF levels in patients with AMI through clinical observation of patients undergoing interventional therapy for AMI. Yuan Y [33] et al. also confirmed that exercise training after AMI can significantly reduce LVEDV and LVESV levels and increase LVEF levels, and the earlier the start and the longer the duration, the greater the benefit.

The higher the metabolic level of the residual myocardium after infarction in AMI patients, the longer the duration and the better the safety of the patients when they undergo exercise rehabilitation, and it has now been found that TMZ significantly improves the ischemic changes exhibited by AMI patients during exercise [34]. This suggests that TMZ can increase the benefits of exercise rehabilitation by increasing the metabolic level of the residual myocardium, and we therefore propose the conjecture that TMZ in combination with CR may provide even better improvement of cardiac function in patients with AMI.

In this study the results showed that there was no significant difference between the LVEDd values of the two groups at 1 week, 1 month and 3 months of onset, and at 1 year of onset the above indexes were significantly lower in the rehabilitation group than in the control group. There was no significant difference between the LVEF values of the two groups of patients at 1 week and 1 month of the onset of the disease, and the LVEF values of the rehabilitation group were significantly higher than those of the control group at 3 months and 1 year of the onset of the disease. Taken together, these results can preliminarily indicate that TMZ combined with CR therapy can lead to a substantial increase in ejection fraction in AMI patients, play a certain inhibitory role in ventricular remodeling, and have better long-term gains. This is consistent with the findings of Xie Liying [35] Shuo Feng [20] and Hu Xiaohong [36] et al, who concluded that TMZ combined with CR for 1 year after PCI in patients with AMI can significantly improve cardiac function, inhibit ventricular remodeling, and improve the prognosis of patients. Therefore, we tentatively conclude that TMZ combined with CR therapy can improve LV function, and the long-term effect is better than the short-term effect.

5.2 The Effect of TMZ Combined with CR Therapy on the Quality of Life after PCI in AMI Patients

Patients who have experienced AMI near-death sensation will be left with certain psychological problems, such as persistent anxiety, depression, high mental nervousness, etc., which not only cause certain disturbances to the patients' own psychological state, but also bring certain obstacles to the clinical work. The prevalence of depression and anxiety in CAD patients is reported to be 16%, which is significantly higher than that of the general population, and about 16% of CAD patients are suffering from depression and anxiety [37], which is significantly higher than that of the general population, and about 15-20% of patients meet the criteria for severe [38]. Therefore, psychological problems in the prognosis of AMI patients have attracted public attention. Some animal experiments have shown that TMZ can inhibit the anxiety state of highly emotional mice, and its anxiolytic effect is no less than that of benzodiazepine anxiolytic drugs [39]. Exercise training can also improve depression and anxiety states and reduce stress in CAD patients [40]-[41] Olsen et al [42]. A study of 9013 post-PCI patients showed that exercise training resulted in a significant reduction in long-term depression and anxiety levels in these patients. The Quality of Life Scale (SF-12) provides a simple assessment of patients' social well-being, and the Generalized Anxiety Disorder Scale (GAD-7) provides an initial assessment of patients' emotional and psychological status, so in this study we used both scales to assess patients' psychological and life status.

The results of the study showed that at the 1st week of the onset of the disease, the SF-12 scale and the GAD-7 scale were compared between the two groups of patients and there was a difference in the results, but this difference was not significant. At 1 year after the onset of the disease, the above scales were again compared between the two groups of patients and the results showed higher SF-12 scale scores in the rehabilitation group and higher GAD-7 scale scores in the control group. This indicates that TMZ combined with CR

treatment can relieve patients' anxiety after myocardial infarction to a certain extent, improve their depression, restore their quality of life to the pre-morbidity level or even higher as early as possible, and promote their early return to normal family life and social work.

Exercise endurance limitation is common in AMI patients after the onset of the disease, which causes a certain degree of distress and seriously affects their quality of life. Existing studies have found that TMZ can significantly improve exercise tolerance and cardiac function in heart failure patients with ischemic cardiomyopathy [43]. There is also a large body of literature showing that for many patients with coronary artery disease who have had complete PCI, the addition of exercise rehabilitation training can exercise their cardiopulmonary exercise function, which can enable them to return to the normal level of exercise as early as possible [44]-[45]. The effect of long-term exercise training is significantly better than that of short-term exercise training [46]. The effect of long-term exercise training is significantly better than that of short-term exercise training. In this study, we used the Peak VO_2/kg, VO_2/kg@AT, and Mets@AT indexes related to cardiopulmonary exercise test to reflect the recovery of patients' exercise endurance. The results of comparing the cardiopulmonary exercise test-related indexes of the two groups of patients at the 1st week of the onset of the disease were not meaningful. At 1 year after the onset of the disease, the above indexes of the two groups of patients were compared statistically again, and the results were statistically significant. This indicates that TMZ combined with CR has significantly improved the cardiopulmonary function of AMI patients and can significantly improve the exercise endurance of patients.

5.3 Effect of TMZ Combined with CR Therapy on NLRP3 Levels in Peripheral Blood Mononuclear Cells after PCI in Patients with AMI

Inflammatory response plays a key role in the development of acute myocardial infarction (AMI), which not only induces myocardial infarction and determines infarct size, but also participates in adverse left ventricular remodeling after infarction. Therefore, modulation of the persistent excessive inflammatory response after AMI has become an important therapeutic target to improve patient prognosis. Post-AMI

The inflammatory response of the myocardial fibroblasts consists of two main periods, the initial pro-inflammatory period and the inflammatory repair period. Inflammasomes, a multiprotein complex, stimulate the release of IL-1β from cardiac fibroblasts,

Proinflammatory factors such as IL-8, which mediate caspase-1-dependent cellular pyroptosis, play an important role in the initial proinflammatory phase. And a key component of this is the NLRP3 inflammasome, which plays a role in the inflammatory response by stimulating the maturation of IL-1β precursors [47]. The role of NLRP3 in the inflammatory response is to stimulate the maturation of IL-1β precursors. It has been demonstrated in numerous animal studies [48]-[50] that inhibiting the activation of NLRP3 inflammatory vesicle components (including caspase-1, ASC, IL-1β, and NLRP3) reduces the size of myocardial infarction [51] et al. also demonstrated that administration of NLRP3 inhibitors at the initial stage of reperfusion or 1 hour after the start of reperfusion significantly reduced the infarct area 24 hours after reperfusion; therefore, controlling the level of NLRP3 in patients with AMI is of great significance in improving adverse left ventricular remodeling and preventing the development of heart failure. In the present study, we found that during the pathogenesis of AMI, the NLRP3 expression in peripheral blood mononuclear cells of both patients in the recovery group and the control group had certain dynamic changes, which suggests that the changes in peripheral blood mononuclear cell NLRP3 levels of patients with AMI at different time periods after the onset of the disease may be due to the development of the disease itself.

Existing basic studies have shown that TMZ can suppress the expression of NLRP3 inflammatory vesicles in foam cells by inhibiting autophagy [52] TMZ also inhibits cellular damage induced by high expression of NLRP3, IL-1β in human umbilical vein endothelial cells [16]. In addition, TMZ attenuated the inflammatory response and reduced ischemia-reperfusion injury in a rat model of abdominal flap ischemia [53]. There have also been many studies on the reduction of NLRP3 inflammatory vesicle expression by exercise, and in the experiments of Tang Fori [54] et al. found that after a 4-week hypoxic exercise experiment in rats with DM at week 4 of disease onset, serum IL-1β levels and protein levels of NLRP3 and Caspase-1 in myocardial tissues were significantly reduced in exercising rats compared with nonexercising rats. Yubisay Mejías-Peña [55] et al's study evaluated the effects of an 8-week resistance exercise training program on autophagy, NLRP3 inflammatory vesicles, and apoptosis in peripheral blood mononuclear cells from elderly subjects and showed that resistance exercise resulted in a decrease in NLRP3 expression and the caspase-1 / procaspase-1 ratio, thus confirming that an 8-week resistance training program stimulates autophagy, inhibits the activation of NLRP3 inflammatory vesicles, and reduced apoptosis of peripheral blood mononuclear cells in elderly subjects. All of the above studies suggest that both TMZ and appropriate exercise training can directly or indirectly inhibit the activation of NLRP3 and its mediated inflammatory cascade response, which has a positive effect on the prognosis of patients.

In this study, we compared the rehabilitation group with the control group, and the results showed that the peripheral blood mononuclear cell NLRP3 levels of the patients in both groups were at the highest value at 24-36h after the onset of the disease, and were at the lowest value at 1 year after the onset of the disease, and the comparison between the two groups was not meaningful. In addition, the NLRP3 levels in peripheral blood mononuclear cells of both groups showed a gradual decrease during the 1-year follow-up, which is consistent with the dynamic evolution of NLRP3 itself. Moreover, at 1 and 3 months after the onset of the disease, the NLRP3 levels in the rehabilitation group were significantly lower than those in the control group. Indicating that the treatment of AMI patients with TMZ combined with CR can significantly reduce their peripheral blood mononuclear cell NLRP3 levels and accelerate the changes in peripheral blood mononuclear cell NLRP3 levels, which is beneficial to the improvement of anti-inflammatory ability of cardiomyocytes,

tolerance of oxidative stress, and the reduction of myocardial damage.

This experiment has the following 2 drawbacks, one of which is the small sample size, which can be expanded for further research. The second is that because rehabilitation of cardiovascular disease has not been widely popularized in our healthcare system, patients do not have enough knowledge about it, and clinicians have not yet paid attention to it, and patients' participation and cooperation are low.

6. Conclusion

1) TMZ combined with CR therapy showed significant improvement in ventricular remodeling, exercise tolerance, and quality of life in patients with AMI, and it was most effective and beneficial to patients at 1 year after PCI.

2) TMZ combined with CR therapy significantly reduced the level of NLRP3 in peripheral blood mononuclear cells of AMI patients, and the effect was most obvious at 3 months after PCI.

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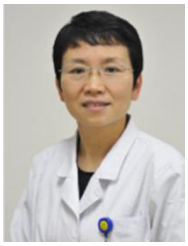

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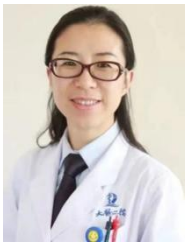

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