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ABOUT COVER

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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Clinical Trials Study

Effect of exercise training on left ventricular remodeling in patients with myocardial infarction and possible mechanisms

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Abstract

BACKGROUND

A growing amount of evidence provides support for the hypothesis that acute myocardial infarction (AMI) patients should go through cardiopulmonary exercise testing (CPET) about 3-5 d after AMI is diagnosed, make reasonable exercising prescription, and conduct exercise training under guidance.

AIM

To investigate the effect of exercise training (ET) on left ventricular systolic function and left ventricular remodeling (LVRM) and to study the possible mechanisms of LVRM by the changes of matrix metalloproteinase 9 (MMP-9) and tissue inhibitor of metalloproteinases 1 (TIMP-1) in patients with acute ST-segment elevation myocardial infarction (STEMI).

METHODS

Sixty patients with first STEMI undergoing direct percutaneous coronary intervention from February 2008 to October 2008 were randomly assigned to an exercise group ($n = 30$) and a control group ($n = 30$). The levels of MMP-9 and TIMP-1 were measured in all patients at 1 d, 10-14 d, 30 d, and 6 mo after admission. Two-dimensional echocardiography and cardiopulmonary exercise testing were done in patients at 10-14 d and 6 mo after admission.

RESULTS

There was no significant difference in CPET at baseline between the exercise group and the control group. At 6 mo, the time of exercise, peak and anaerobic threshold values of O_2 uptake, and metabolic equivalents increased in both groups, but markedly increased in the exercise group. At baseline, there were no significant differences in left ventricular ejection fraction (LVEF) between the two

additional unpublished data are available.

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groups. At 6 mo, LVEF increased in the exercise group, but not in the control group. At 6 mo, the percentage of patients with positive result of LVRM was 26.6% in the exercise group and 52.6% in the control group ($P < 0.05$). The levels of plasma MMP-9 and TIMP-1 and the ratio of MMP-9 to TIMP-1 in both groups had no significant difference at 1 d and 10-14 d after AMI, but at 30 d and 6 mo, the levels of plasma MMP-9 and TIMP-1 in the exercise group were significantly lower than those in the control group; the ratio of MMP-9 to TIMP-1 in the exercise group was significantly higher than that in the control group.

CONCLUSION

ET under supervision based on home condition in early and recovery stage of AMI can improve exercise cardiopulmonary function and prevent the LVRM. Therefore, it may reduce unfavorable remodeling response by decreasing the levels of plasma MMP-9 and TIMP-1 and adjusting the ratio of MMP-9 to TIMP-1 hereafter.

Key Words: Myocardial infarction; Rehabilitation; Exercise training; Ventricular remodeling; Matrix metalloproteinase 9; Tissue inhibitor of metalloproteinases 1

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Core Tip: Exercise training under supervision based on home condition in early and recovery stage of acute myocardial infarction can improve exercise cardiopulmonary function and prevent the left ventricular remodeling. And there was no negative effect on left ventricular ejection fraction. Therefore, it may reduce unfavorable remodeling response by decreasing the levels of plasma matrix metalloproteinase 9 (MMP-9) and tissue inhibitor of metalloproteinases 1 (TIMP-1) and adjusting the ratio of MMP-9 to TIMP-1 hereafter.

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INTRODUCTION

Cardiac pulmonary function recovery after acute myocardial infarction (AMI) for a long time has been taking the attention of the vast numbers of medical professionals and patients[1], and the occurrence and development of left ventricular remodeling (LVRM) in patients are vital for AMI prognosis. A growing amount of evidence provides support for the hypothesis that AMI patients should go through cardiopulmonary exercise testing (CPET) about 3-5 d after AMI is diagnosed, make reasonable exercising prescription, and conduct exercise training (ET) under supervision[2,3]. Moreover, it can improve left ventricular systolic function, exercise tolerance, and quality of life, with no adverse impact on cardiac structure[4,5]. Furthermore, previous studies indicated[6,7] that ET can also help slow down the development of LVRM.

Many experiments support that matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinases-1 (TIMP-1) play an important role in LVRM[8,9]. However, so far, no study has been done on the relationship between rehabilitation exercise and changes of MMP-9 and TIMP-1 plasma levels in AMI.

In the present study, we investigated the effect of ET on LVRM in patients with acute ST segment elevation myocardial infarction (STEMI) and explored the possible mechanisms by detecting variations of MMP-9 and TIMP-1.

MATERIALS AND METHODS

Participant

Sixty patients who experienced the first occurrence of STEMI within the period from February to October 2008 at our hospital were recruited. All patients had Killip grade I-II cardiac function and received direct percutaneous coronary intervention (PCI) at the Emergency Department.

Inclusion criteria: The diagnostic criteria for STEMI complied with ACC/AHA Guidelines for the Management of Patients with ST Elevation Myocardial Infarction [10]. The inclusion criteria were: (1) First occurrence of acute STEMI; (2) Age 35-74 years; (3) Grade I-II (Killip's) cardiac function as revealed by LVEF > 40%; (4) Absence of serious cardiac arrhythmia; (5) Absence of serious post-AMI complications; and (6) Willingness to receive CEPT and ET treatment and provide informed consent.

Exclusion criteria: The exclusion criteria were: (1) Suspected diagnosis of AMI that does not meet the above diagnostic criteria; (2) History of AMI and heart valve diseases and pulmonary embolisms; (3) Serious complications of acute AMI (pulmonary edema, serious cardiac arrhythmia, and cardiac shock); (4) Concomitant atrial fibrillation or paced rhythm or preexcitation syndrome; (5) Concomitant serious diseases of other systems (*e.g.*, human immunodeficiency virus infection, malignant tumor, serious primary hepatic or renal diseases, and chronic lung diseases); (6) Inability to exercise and unwillingness to cooperate; (7) Unwillingness or inability to accept PCI; and (8) Unwillingness to provide informed consent.

Standard secondary prevention and treatment of coronary heart disease were administered in all patients according to Guidelines for the Management of Acute Coronary Syndrome.

Study methods

Randomization: Sixty patients were randomized in a 1:1 ratio to either a rehabilitation exercise group (rehabilitation exercise guidance was provided) ($n = 30$) or a control group (no rehabilitation exercise guidance was provided) ($n = 30$). Routine post-AMI secondary prevention medications were given regularly to patients in both groups.

Study protocol: Emergency PCI was performed after admission. Blood samples were drawn immediately, at days 10-14, day 30, and 6 mo after admission, and plasma was separated and stored in a -80 °C freezer for plasma MMP-9 and TIMP-1 tests. Echocardiography was performed at days 10-14 and 6 mo after AMI. CPET was performed at days 10-14 after AMI and again at 6 mo. After discharge, the patients routinely took secondary prevention medications for coronary heart disease. Patients in the rehabilitation exercise group took regular walking exercise. Exercise time, intensity, and frequency depended on the exercise prescription. Family guidance was provided to patients in this group and the exercise prescription was adjusted at week 1. Patients in the control group were not given any exercise prescription and their exercise was not intervened. For patients in both groups, telephone follow-up was performed every 2 wk and outpatient follow-up monthly until the end of 6 mo. Figure 1 and Table 1 show the protocol in detail.

MMP-9 and TIMP-1 assay

Fasting venous blood (3 mL) was drawn in the morning, added into a vacuum blood collection tube containing 10% EDTA, mixed well, and centrifuged at 3000 rpm at 4 °C for 10 min. The supernatant (20 µL) was retained and preserved in a -80 °C freezer. ELISA was carried out by special personnel blinded using kits manufactured by BIOSOURCE.

Evaluation of ventricular remodeling

Evaluation of ventricular remodeling was performed by experienced and professional echocardiography physicians at days 10-14 and month 6 after the AMI onset.

Routine ultrasound and Doppler tissue images were collected in the long and short axis views of the left ventricle, apical four-chamber view, left ventricular two-chamber view, and the apical long axis view using a VIVID-I echocardiography system manufactured by GE (United States).

LVEF was evaluated using Biplane Simpson's method as follows:

$$\text{LVEF} = (\text{LVEDD} - \text{LVESD}) / \text{LVEDV} \times 100\%$$
 (left ventricular end-diastolic dimension as LVEDD, left ventricular end-systolic dimension as LVESD, and left ventricular end-diastolic volume as LVEDV).

Table 1 Follow-up and examination schedule

Item	Immediately	Days 10-14	Follow-up (mo)	
			1	6
Informed consent	√			
Medical history	√			
Physical examination	√		√	√
MMP-9	√	√	√	√
TIMP-1	√	√	√	√
Transthoracic echocardiography		√		√
CPET		√		√
Concomitant medication	√	√	√	√

MMP-9: Matrix metalloproteinase-9; TIMP-1: Tissue inhibitor of metalloproteinases-1; CPET: Cardiopulmonary exercise testing.

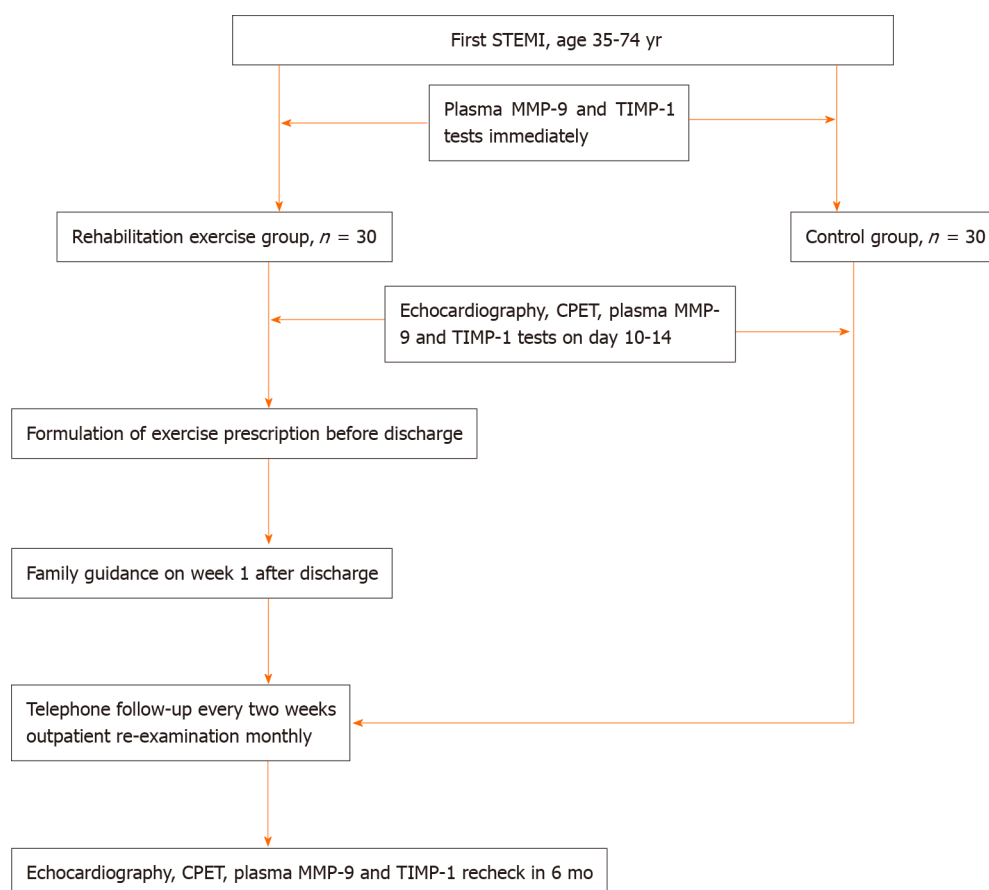


Figure 1 Protocol flow diagram. MMP-9: Matrix metalloproteinase 9; TIMP-1: Tissue inhibitor of metalloproteinases 1; CPET: Cardiopulmonary exercise testing;

Biplane Simpson method was performed to measure LVESV and LVEDV. LVESV and LVEDV were measured at days 10-14 (LVESV₁ and LVEDV₁) and 6 mo (LVESV₂ and LVEDV₂) after AMI. If both LVESV₂/LVESV₁ and LVEDV₂/LVEDV₁ were higher than 1.1 or either one was higher than 1.2 (*i.e.*, increased by 10%-20% as compared to the baseline value), left ventricular dilation would be considered.

Preparation of CPET

The measurement was performed by professional rehabilitation physicians.

CPET was performed using a MAX-II cardiopulmonary exercise device manufactured by PHYSIO DYNE (United States).

Graded treadmill exercise test, 3 min per grade, was carried out using the modified Bruce protocol. The patient's movement electrocardiogram, gaseous metabolism changes, and vital signs were monitored, and the spontaneous symptoms were inquired about any time.

The patient's exercise time, peak oxygen uptake, peak metabolic equivalent, anaerobic threshold, and metabolic equivalent at anaerobic threshold were measured.

The evaluation was terminated in any of the following circumstances: (1) The patient developed instability of gait, weakness of bilateral lower limbs, dizziness, pale complexion, fatigue, short breath, and asthma or the patient asked for rest; (2) The systolic pressure increased by less than 10 mmHg or decreased as compared to the level at rest; the blood pressure increased abnormally, and the systolic pressure was higher than 230 mmHg; (3) Higher than grade II angina (Canadian angina grading); (4) Malignant arrhythmia occurred, including ventricular tachycardia, multifocal premature ventricular contraction or higher than second-degree type II atrio-ventricular block, sinus arrest, *etc.*; (5) Myocardial ischemic changes, *i.e.*, transient ST-segment depression ≥ 0.5 mm in two continuous limb leads or chest leads; or transient ST segment elevation ≥ 1 mm in two continuous leads (NIZ) (or ST segment descent of V1 or V2 ≥ 1 mm); (6) Achievement of the target heart rate, *i.e.*, 70%-80% of the maximum heart rate (maximum heart rate = 220 - age); and (7) Respiration exchange rate ≥ 1.1 .

Preparation of exercise prescription

Individualized exercise prescriptions were prepared for patients in the rehabilitation exercise group by rehabilitation physicians according to CPET results before discharge. The exercise method was walking, and the exercise time, intensity, and frequency were implemented *per* the exercise prescription. In addition to walking rate prepared by the rehabilitation physician, patient's self-felt fatigue was considered for controlling the exercise intensity. Patients were asked to exercise at the anaerobic threshold level or a slightly lower level. Patients in the control group were not given the exercise prescription or any exercise guidance and were allowed to arrange their daily activities themselves.

Statistical analysis

Statistical analyses were performed using SPSS13.0 software. Measurement data are presented as the mean \pm SD. For comparison of continuous variables between two groups, *t* test was carried out. *P* values < 0.05 were considered statistically significant.

RESULTS

Clinical data

A total of 60 male patients (mean age, 56 ± 8 years) were enrolled in this study, 30 in each group.

Tables 2 presents the patients' characteristics at baseline. Patients in the two groups were not statistically different in age, myocardial infarction area, history of smoking, or concomitant diseases ($P > 0.05$). All patients accepted standard secondary prevention and treatment of coronary heart disease using aspirin, clopidogrel, statins, angiotensin-converting enzyme inhibitor (ACEI)/angiotensinreceptorblocker (ARB), β -receptor blocker, *etc.*, with no statistical difference between the two groups ($P > 0.05$). Data of the two groups were comparable (Table 2).

Cardiopulmonary exercise function

No significant difference was found between the two groups with respect to baseline exercise time, anaerobic threshold, metabolic equivalent at anaerobic threshold, peak oxygen uptake, and peak metabolic equivalent at days 10-14 after admission ($P > 0.05$). The above exercise indicators significantly increased at the follow-up visit at month 6 as compared to baseline values ($P < 0.05$ -0.01) (Table 3), with the increase being significantly more pronounced in the rehabilitation group ($P < 0.05$ -0.01) (Table 4).

Echocardiography results

LVRM was considered positive when both LVEDV₂/LVEDV₁ and LVESV₂/LVESV₁ were higher than 1.1 or either one was higher than 1.2[4]. The positive rate in the control group was significantly higher than that in the rehabilitation exercise group (52.6% *vs* 26.6%, $P < 0.01$).

Table 2 Patient characteristics at randomization to intervention and control groups, *n* (%)

	Rehabilitation exercise group	Control group
	<i>n</i> = 30	<i>n</i> = 30
Age (yr)	55 ± 9	58 ± 8
Infarction area, <i>n</i> (%)		
Anterior AMI	18 (60)	15 (50)
Non-anterior AMI	12 (40)	15 (50)
History of smoking, <i>n</i> (%)	28 (93.3)	24 (80)
Concomitant disease, <i>n</i> (%)		
Diabetic mellitus	2 (6.7)	3 (10)
Hypertension	5 (16.6)	4 (13.3)
Hypercholesteremia	3 (10)	4 (13.3)
Drug therapy, <i>n</i> (%)		
Aspirin	30 (100)	30 (100)
Clopidogrel	29 (96.7)	28 (93.3)
β-receptor blocker	25 (83.3)	28 (93.3)
ACEI/ARB	29 (96.7)	27 (90)
Statins	28 (93.3)	29 (96.7)

AMI: Acute myocardial infarction; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

Table 3 Cardiopulmonary exercise testing in rehabilitation exercise and control groups

	Baseline		6 mo after onset of myocardial infarction	
	Control group (<i>n</i> = 30)	Exercise group (<i>n</i> = 30)	Control group (<i>n</i> = 30)	Exercise group (<i>n</i> = 30)
Exercise time (min)	8.19 ± 2.55	8.11 ± 2.69	9.37 ± 2.48 ^a	11.89 ± 2.34 ^b
Anaerobic threshold (mL/min)	958.64 ± 298.65	977.23 ± 288.33	1235.88 ± 347.56 ^b	1388.07 ± 355.67 ^b
Metabolic equivalent at anaerobic threshold	3.76 ± 1.05	3.89 ± 1.01	4.58 ± 1.06 ^b	5.20 ± 1.19 ^b
Peak oxygen uptake (mL/min)	1272.37 ± 346.85	1267.35 ± 322.84	1507.88 ± 398.46 ^b	1664.67 ± 365.35 ^b
Peak metabolic equivalent	4.98 ± 1.03	4.87 ± 0.98	5.62 ± 1.01 ^b	6.38 ± 1.09 ^b

Comparison of the second cardiopulmonary exercise testing (CPET) and the first CPET of the same group.

^a*P* < 0.05.

^b*P* < 0.01. CPET: Cardiopulmonary exercise testing.

Baseline values of LVEF of the two groups were not significantly different. LVEF of the rehabilitation exercise group at the follow-up visit at month 6 was higher than but not statistically significantly different from the baseline value (58.4% ± 8.6% *vs* 57.73% ± 7.89%, *P* > 0.05), and LVEF of the control group at the follow-up visit at month 6 was lower than but not statistically significantly different from the baseline value (53% ± 8.86% *vs* 56.1% ± 7.98%, *P* > 0.05). LVEF of the rehabilitation exercise group at month 6 was significantly higher than that of the control group (58.4% ± 8.6% *vs* 53% ± 8.86%, *P* < 0.01; **Table 5**).

MMP-9 and TIMP-1

Plasma MMP-9 levels of patients in the two groups were not significantly different immediately after AMI and at days 10-14 (*P* > 0.05). It decreased in both groups at day 30 and month 6, with the decrease being more pronounced in the rehabilitation exercise group (*P* < 0.05).

Table 4 Differences of results of the two cardiopulmonary exercise tests of patients in the two groups

	Changes of the two tests	
	Control group (<i>n</i> = 30)	Exercise group (<i>n</i> = 30)
Exercise time (min)	1.13 ± 1.69	3.41 ± 2.88 ^b
Anaerobic threshold (mL/min)	252.13 ± 233.66	405.36 ± 207.89 ^a
Metabolic equivalent at anaerobic threshold	0.82 ± 0.71	1.46 ± 0.82 ^b
Peak oxygen uptake (mL/min)	232.73 ± 254.96	402.88 ± 258.35 ^a
Peak metabolic equivalent	0.77 ± 0.86	1.49 ± 0.93 ^b

Intergroup comparison.

^a*P* < 0.05.^b*P* < 0.01. CPET: Cardiopulmonary exercise testing.**Table 5 Echocardiography results in rehabilitation exercise and control groups**

	Baseline value		6 mo	
	Control group (<i>n</i> = 30)	Rehabilitation exercise group (<i>n</i> = 30)	Control group (<i>n</i> = 30)	Rehabilitation exercise group (<i>n</i> = 30)
LVEF	56.1% ± 7.98%	57.73% ± 7.89%	53% ± 8.86%	58.4% ± 8.6% ^a
LVRM positive results			52.60%	26.6% ^a

Intergroup comparison.

^a*P* < 0.01. LVEF: Left ventricular ejection fraction; LVRM: Left ventricular remodeling.

Plasma TIMP-1 levels of patients in the two groups were not significantly different immediately after AMI and at days 10-14 (*P* > 0.05). It increased in both groups at day 30 and month 6, with the increase being less pronounced in the rehabilitation exercise group (*P* < 0.05).

MMP-9/TIMP-1 ratio of patients in the two groups was not significantly different immediately after AMI and at days 10-14 (*P* > 0.05). The MMP-9/TIMP-1 ratio of the rehabilitation exercise group was significantly higher than that of the control group at day 30 and month 6 (*P* < 0.05; Table 6).

DISCUSSION

Effects of ET on post-AMI LVRM

This study examined the effect of exercise training on LVRM in patients with STEMI. Ultrasonic cardiogram (UCG) showed that LVEF of the ET group was significantly higher than that of the control group, indicating that guided rehabilitation exercise in early stage of AMI could maintain patient's left ventricular systolic function, which is consistent with findings in previous studies[11,12]. In contrast with a decrease of cardiac function in the control group, a slight increase was observed in the ET group, possibly for the following reasons. (1) The patients' LVRM was mild; (2) Exercise increased myocardial elastic recoil, decreased resting heart rate, and prolonged left ventricular filling time in AMI patients, thereby enlarging cardiac output; and (3) Exercise reduced poor wall motion and increased left ventricular systolic synchrony.

Consistent with previous reports[13-19], ET resulted in a significantly lower LVRM positive rate (26.6% in ET group *vs* 52.6% in control group) using LVEDV₂/LVEDV₁ and LVESV₂/LVESV₁ ratio as LVRM positive indicators, suggesting that LVRM was more apparent in the control group than in the ET group and ET may, to a certain extent, limit LVRM.

Effects of ET on plasma MMP-9 and TIMP-1 of patients with AMI

The study results showed that plasma levels of MMP-9 and TIMP-1, and MMP-9/TIMP-1 ratio of patients in the ET group and the control group were not significantly different immediately after AMI and at days 10-14. At day 30 and month

Table 6 Comparison of matrix metalloproteinase-9, tissue inhibitor of metalloproteinases-1, and matrix metalloproteinase-9/tissue inhibitor of metalloproteinases-1 ratio in rehabilitation exercise and control groups at different time points

Items	Time	Rehabilitation exercise group (n = 30)	Control group (n = 30)
MMP-9 (ng/mL)	Immediately	6.7 ± 2.97	6.8 ± 3.12
	Days 10-14	8.2 ± 2.5	8.1 ± 2.55
	Day 30	4.2 ± 1.88	5.0 ± 1.98 ^a
	6 mo	4.0 ± 1.87	5.1 ± 2.02 ^a
TIMP-1 (ng/mL)	Immediately	2.1 ± 0.52	2.1 ± 0.51
	Days 10-14	2.4 ± 0.71	2.5 ± 0.65
	Day 30	2.8 ± 0.67	3.0 ± 0.55 ^a
	6 mo	2.7 ± 0.56	2.98 ± 0.51 ^a
MMP-9/TIMP-1	Immediately	3.05 ± 1.05	2.98 ± 1.03
	Days 10-14	4.21 ± 1.58	4.11 ± 1.44
	Day 30	1.78 ± 0.88	1.25 ± 0.66 ^a
	6 mo	1.58 ± 0.67	1.22 ± 0.58 ^a

Intergroup comparison.

^aP < 0.05. MMP-9: Matrix metalloproteinase-9; TIMP-1: Tissue inhibitor of metalloproteinases-1.

6, compared with control group, plasma MMP-9 and TIMP-1 levels were significantly lower and MMP-9/TIMP-1 ratio was significantly higher in the ET group, in which positive LVRM rate was higher, indicating that high plasma MMP-9 and TIMP-1 levels and low MMP-9/TIMP-1 ratio in post-AMI recovery period all had adverse effects on LVRM.

Extracellular matrix (ECM) remodeling was found in recent studies to lead to myocardial fibrosis and progressive ventricular dilatation and to result in heart failure [20-22]. It is currently believed that the ECM plays a very important role in LVRM and that ECM synthesis-degradation imbalance is associated with development and progression of LVRM. Among the ECM secreted by fibroblasts, collagen, mainly type I and type III collagen, accounts for the major part. About 85% of the collagen is type I, which is responsible for myocardial strength and endurance, and about 11% is type III, which is responsible for myocardial elastic recoil. MMP-9 is a gelatinase, which mainly degrades type I and type III collagen. TIMP-1 is a natural inhibitor of MMP-9 and promotes synthesis and deposition of collagen. MMP-9/TIMP-1 imbalance is thought to be able to further enhance remodeling progression[23]. Kelly *et al*[24] studied variation of post-AMI MMP-9 levels and found that increased MMP-9 level at early stage of AMI was positively correlated with leukocyte and neutrophil levels, suggesting that plaque rupture and increased inflammatory factors promoted the release of MMP-9, which intensified collagen degradation and contributed to the development and progression of early-phase LVRM. At the subsequent 90-d follow-up, MMP-9 curve turned from a high peak in the acute phase into a flat top, which had a protective effect on left ventricular function. According to the analysis, excessively high MMP-9 levels enhanced collagen degradation whereas excessively high TIMP-1 level led to excessive decomposition of collagen. Only when an appropriate ratio is maintained can the normal shape and function of cardiac ventricles be kept.

Plasma MMP-9 and TIMP-1 levels

Significantly more decreased plasma MMP-9 level and less increased plasma TIMP-1 level were observed in ET patients at day 30 and month 6, as compared to control patients, indicating that although collagen synthesis and deposition are inevitable in late stage of AMI, rehabilitation exercise might delay LVRM occurrence and lower positive LVRM rate by inhibiting excessive degradation and reducing excessive synthesis and deposition of collagen.

MMP-9/TIMP-1

Although the mechanism of LVRM is still not completely known, MMP-9/TIMP-1 imbalance is suggested as an important reason for ECM remodeling, as also shown in

the present study[25]. MMP-9/TIMP-1 ratio of the ET group was significantly higher than that of the control group; namely, the proportion of TIMP-1 in plasma of patients in the ET group was lower. Evidence is available that high concentration of TIMP-1 in plasma may increase the activity of fibroblasts and enhance collagen synthesis and deposition[26]. It is thus deduced that ET has decreased the concentration of TIMP-1 in plasma, adjusted the proportions of MMP-9 and TIMP-1, and reduced excessive collagen synthesis and deposition in late stage of AMI. The effect of ET on post-AMI LVRM of patients is possibly related to its action in adjusting the MMP-9/TIMP-1 ratio.

However, this study has the following limitations: (1) Although the principle of randomization was followed as far as possible in design and implementation of the trial, given the relatively small sample size, some artificial factors such as patients' individual exercise habits and working time could not be excluded, leading to randomness reduction and selection bias; (2) Rehabilitation exercise was home based. Although telephone follow-up was performed once every 2 wk and outpatient follow-up once per month, the problem of unfixed exercise intensity of the ET group still could not be avoided, leading to errors in study results; (3) The exercise intensity administered in the study was low and the follow-up duration was short. Therefore, individual exercise habits account for an important part of exercise intensity, which might lead to errors in study results; (4) Regarding exercise indicators, the first UCG examination was performed at days 10-14 after AMI and the result was used as the baseline UCG value. The effect of post-AMI early-stage LVRM on ventricular structure and function was neglected, which may have certain influence on the study results; and (5) Due to limited fund and patients' reasons, cardiac structure and function were not evaluated using heart MRI or ventriculography. UCG evaluation is subject to subjective influence.

CONCLUSION

Early rehabilitation exercise after AMI can, to some extent, inhibit progression of LVRM and maintain left ventricular function. Moreover, the post-AMI LVRM limitation by ET is likely due to its action in lowering MMP-9 and TIMP-1 levels and adjusting MMP-9/TIMP-1 ratio.

ARTICLE HIGHLIGHTS

Research background

A growing amount of evidence provides support for the hypothesis that acute myocardial infarction (AMI) patients should go through cardiopulmonary exercise testing about 3-5 d after AMI is diagnosed, make reasonable exercising prescription, and conduct exercise training under guidance.

Research motivation

To investigate the effect of exercise training on left ventricular systolic function and left ventricular remodeling and to study the possible mechanisms of left ventricular remodeling (LVRM) by the changes of matrix metalloproteinase 9 (MMP-9) and tissue inhibitor of metalloproteinases 1 (TIMP-1) in patients with acute ST-segment elevation myocardial infarction (STEMI).

Research objectives

To investigate the effect of exercise training on left ventricular systolic function and left ventricular remodeling and to study the possible mechanisms of LVRM.

Research methods

Sixty patients with first STEMI undergoing direct percutaneous coronary intervention from February 2008 to October 2008 were randomly assigned to an exercise group ($n = 30$) or a control group ($n = 30$). The levels of MMP-9 and TIMP-1 were measured in all patients at 1 d, 10-14 d, 30 d, and 6 mo after admission. Two-dimensional echocardiography and cardiopulmonary exercise testing were done in patients at 10-14 d and 6 mo after admission.

Research results

In cardiopulmonary exercise testing of the two group, at 6 mo, the time of exercise, peak and anaerobic threshold values of O₂ uptake, and metabolic equivalents increased in both groups, but markedly increased in the exercise group than in the control group. There was no significant differences in LVESV, LVEDV, or left ventricular ejection fraction (LVEF) between the two groups. At 6 mo, LVEF increased in the exercise group, but not in the control group. Change in LVEF in the exercise group was significantly higher than that of the control group. At 6 mo, the percentage of patients with positive result of LVRM was 26.6% in the exercise group and 52.6% in the control group ($P < 0.05$). The levels of plasma MMP-9 and TIMP-1 and the ratio of MMP-9 to TIMP-1 in both groups had no significant difference at 1 d and 10-14 d after AMI, but at 30 d and 6 mo, the levels of plasma MMP-9 and TIMP-1 in the exercise group were significantly lower than those in the control group; the ratio of MMP-9 to TIMP-1 in the exercise group was significantly higher than that in the control group.

Research conclusions

Exercise training under supervision based on home condition in early and recovery stage of AMI can improve exercise cardiopulmonary function and prevent the LVRM. Therefore, it may reduce unfavorable remodeling response by decreasing the levels of plasma MMP-9 and TIMP-1 and adjusting the ratio of MMP-9 to TIMP-1 hereafter.

Research perspectives

Randomized controlled trials are needed to investigate the effect of exercise training on left ventricular systolic function and LVRM and to study the possible mechanisms of LVRM in patients with acute STEMI.

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