

Randomized clinical trial of physiological ischemic training for patients with coronary heart disease complicated with heart failure: Safety of training, VEGF of peripheral blood and quality of life

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Abstract. Effects of a 12-week physiological ischemic training (PIT) programme on safety of training and quality of life (QOL) in patients with coronary heart disease (CHD) complicated with heart failure were evaluated. A total of 30 patients with CHD complicated with heart failure were randomized to either an intervention group (n=15) or to controls (n=15) after baseline testing. A 12-week, 5 times a week, maximum subjective force group PIT was conducted. Safety of the training was measured with ECG and heart rate and blood pressure, QOL was measured using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and vascular endothelial growth factor (VEGF) was measured with peripheral blood. VEGF and MLHFQ were improved in the intervention group. The finding of the study shows PIT is safe to patients with CHD complicated with heart failure by improving VEGF of peripheral blood and QOL.

Introduction

Recently rehabilitation of heart failure patients has received increased attention in China.

Evidence exists on the effects of exercise training for adults with heart failure (1). According to Psaltis *et al* (2), because of ischemia, coronary heart disease (CHD) can largely damage heart function and cause heart failure. However, in heart failure complicated with CHD, or in older adults, normal aerobic exercise is not possible because of poor physical fitness.

A new physiological ischemic training (PIT) programme for older adults has been described by Ni and co-workers (3). It refers to reversible ischemia training of normal skeletal muscles by using a tourniquet or isometric contraction to cause physiologic ischemia for approximately 4 weeks to trigger molecular and cellular mechanisms to promote angiogenesis and the formation of collateral vessels and protect remote ischemia areas. Physiological ischemia training therapy augments angiogenesis in the ischemic myocardium by inducing the differential expression of proteins involved in energy metabolism, cell migration, protein folding, and generation. The programme can cause vascular endothelial growth factor (VEGF) and endothelial progenitor cells (EPCs) to increase in peripheral blood, and retrohome to heart and promote collateral circulation (4). Our previous study indicated that isometric handgrip exercise-induced physical ischemia training may promote remote collateral growth in CAD patients through EPCs and VEGF release (3), and the segment score of ischemia area of single-photon emission computed tomography (SPECT) reduced significantly.

The aim of the present study was to evaluate the effects of a 12-week PIT programme in older patients with CHD complicated with heart failure, with regards to safety of this training to these patients, VEGF of peripheral blood and quality of life (QOL).

Materials and methods

Patients. This is a prospective, randomized clinical trial with a 12-week follow-up. There were initially 49 subjects included in the study. Of these, 13 did not meet the inclusion criteria; thus, 36 older adults were included in the study. Of these,

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19 subjects were randomized to the PIT group and 17 subjects to the control group. Participants were recruited in the clinic at our Department at Xuzhou Central Hospital (Xuzhou, China). The inclusion criteria were diagnosis of CHD combined with heart failure, diagnostic criteria for heart failure according to American heart failure diagnosis and treatment guidelines (5), clinical symptoms and signs stable for >1 month, New York cardiac function class II-III, and no formal history of exercise training. The exclusion criteria were unstable angina pectoris and acute myocardial infarction, malignant arrhythmia and high atrioventricular block, hemodynamic instability and uncontrolled hypertension; acute pericarditis, severe valvular heart disease; chronic obstructive pulmonary disease, pulmonary heart disease or pulmonary vascular disease; a thrombophlebitis or intracardial thrombus, intermittent claudication, lower limb instability disease. At baseline, testing subjects were randomized to either the intervention or control group by the random number table method.

Eventually, 30 participants followed through with the study. Four of the PIT group were lost to follow-up due to low compliance ($n=2$), and disease exacerbation ($n=2$). Two of the control group were lost to follow-up due to low compliance ($n=2$). The remaining 30 participants were included in the PIT group (mean age, 66.4 ± 12.1 ; male to female ratio, 8/7) and the control group (mean age, 67.1 ± 12.8 ; male to female ratio, 9/6). This study was approved by the Ethics Committee of Xuzhou Central Hospital. Informed consents were signed by the patients that participated in the study.

Method. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) was completed at baseline and at the 12-week follow-up by interviewer-administered, self-assessment.

Test leaders were experienced nurses, and were blinded to group allocation at baseline but not at follow-up.

The intervention study was a 12-week programme of progressive and individually PIT as described in our previous study (3). Training was isometric handgrip exercise-induced physical ischemia training. It was carried out 5 times a week, for 12 weeks; in the course of training, a patient was required to hold a grip and attempt to keep clenching with subjective maximum effort, and each time for 1 min, relaxed 1 min and repeated 10 times for 1 group, prior to repeating the process on the other hand. There were 4 groups every day, in a.m. for 2 groups and p.m. for 2 groups. The exercise required that the patient keep breathing naturally and avoid holding their breath.

Participants in the control group were encouraged to continue living as before (the same activity level).

The participants underwent peripheral blood VEGF test at baseline and at 12-week follow-up. The VEGF was tested using ELISA. The ELISA kits (R&D Systems GmbH, Wiesbaden, Germany) were used to measure serum VEGF level.

Statistical analysis. Statistical analyses were performed using SPSS 10.0 software. Measurement data were expressed as mean \pm standard deviation (SD) and comparisons were performed using t-test. Analysis of variance was used for comparison among multiple groups and the post hoc test was Dunnett test. Enumeration data were expressed as a percentage. $P < 0.05$ was regarded as significant difference.

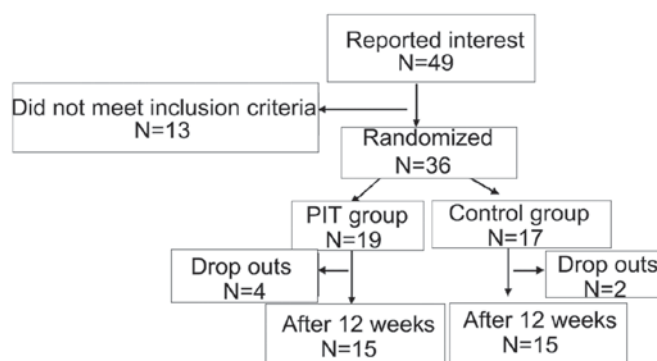


Figure 1. Persons reporting interest in the study, assigned at random to PIT or control group and drop-outs. PIT, physiological ischemic training.

Results

Patient data. There were 49 responses in the clinic. Out of these, 13 did not meet the inclusion criteria, thus, 36 older adults were included in the study. Of these, 19 were randomized to the PIT group and 17 to the control group (Fig. 1). Demographic data of the participants are presented in Table I. There were no differences between the two groups at baseline regarding age, sex, medical history, medication (Table I).

A total of 30 participants followed through with the study. Four of the PIT group were lost to follow-up due to low compliance ($n=2$), and disease exacerbation ($n=2$). Two of the control group were lost to follow-up due to low compliance ($n=2$).

Training programme, VEGF and MLHFQ scores. During PIT training, there was significant increase in SBP and DBP in training group ($P < 0.05$ both); although heart rate increased, there was no significant difference. The above indexes recovered to resting levels after training for 10 min. Results are shown in Table II. During 12-weeks PIT, there were no ECG and clinical manifestations of myocardial ischemia in training group.

There was no significant difference in blood VEGF concentration between two groups before treatment, $P > 0.05$. Compared with baseline level, there was significant increase in VEGF concentration 81.66 ± 17.1 pg/ml after 12-weeks PIT in training group, $P < 0.05$. There was no significant difference in the above index in control group before and after treatment, $P > 0.05$. The 12-week training levels of the above index in training group were significantly higher than that of control group, $P < 0.05$ (Table III).

The MLHFQ scores in PIT and control group had no differences at baseline. After 12-weeks the MLHFQ scores, the emotional, physical, and total scores, were improved in PIT group compared to baseline ($P < 0.05$), with better QOL. But after 12-weeks in control group there was no significant difference compared to baseline ($P > 0.05$) (Table IV).

Discussion

About 23 million individuals suffer from heart failure worldwide, giving rise to heavy global health and economic burdens (6,7). Congestive heart failure (CHF) is among the most common causes of hospital admissions and readmissions in the

Table I. Demographic data of participants in PIT and control group at the time of randomization.

Variables	PIT group (n=19)	Control group (n=17)	P-value
Age (years)	66.4±12.1	67.1±12.8	0.872
Sex (male/female)	8/7	9/6	
Systolic pressure (mmHg)	128.9±16.2	133.5±12.1	0.138
Diastolic pressure (mmHg)	69.73±5.3	73.4±6.1	0.389
LVEF (%)	39.7±3.2	38.7±4.6	0.128
NYHA (1/2/3/4)	4/8/3/0	4/9/2/0	
Medical history (n, %)			
Hypertension	12 (80)	10 (67)	
Diabetes mellitus	5 (33)	4 (27)	
Hyperlipidemia	5 (33)	5 (33)	
Smoke	4 (27)	6 (40)	
Stroke	12 (80)	10 (67)	
Medication (n, %)			
Aspirin	15 (100)	15 (100)	
Clopidogrel	10 (67)	10 (67)	
ACEI/ARB	6 (40)	7 (47)	
CCB	5 (33)	5 (33)	
β blocker	7 (47)	6 (40)	

PIT, physiological ischemic training.

Table II. PIT group before and after isometric handgrip exercise, the changes of heart rate and blood pressure.

	Before PIT	During PIT	10 min after PIT	P-value
Heart rate (bpm)	75.2±14.5	78.9±14.9	74.7±15.3	0.517
Systolic pressure (mmHg)	128.9±16.2	137.4±18.4 ^a	129.6±16.3 ^b	0.005
Diastolic pressure (mmHg)	69.73±5.3	78.9±12.8 ^a	74.4±7.8 ^b	0.003

P-value is the comparison of each indicator at each time point. ^aP<0.05, compared with before PIT (resting); ^bp<0.05, compared with during PIT. PIT, physiological ischemic training.

Western world (8). In the face of high morbidity and mortality, cardiopulmonary rehabilitation, can improve the QOL, increase the effect of exercise endurance (9). Cardiac rehabilitation is an important content of secondary prevention, has become more and more respected by clinicians, exercise rehabilitation is its core content (10,11). Exercise rehabilitation prescription formulation is a key link in the process of rehabilitation, the heart movement in elderly patients with CHD is usually due to a variety of complications, such as muscle mass reducing, myocardial infarction, heart failure, unstable angina and sudden cardiac arrest, malnutrition, mood, sleep disorders, severe osteoporosis, balance coordination fall (12,13), caused the general aerobic and resistance training to have difficulty in implementation.

Table III. Changes of blood VEGF concentration in the two groups before and 12-weeks after treatment (SD).

VEGF (pg/ml)	Before training	After training	P-value
PIT group (n=15)	48.89±15.8	81.66±17.1 ^a	<0.001
Control group (n=15)	48.42±16.3	50.5±16.4	0.860

^aP<0.05, compared with routine treatment group. VEGF, vascular endothelial growth factor.

Table IV. Comparison of the two groups of MLHFQ before and after 12-weeks (SD).

Variable	Before training	After training	P-value
PIT group (n=15)			
Physical	31.2±4.52	23.7±7.58	0.037
Emotional	9.5±4.36	5.92±2.84	0.009
Total	47.5±18.24	39.1±8.57	0.025
Control group (n=15)			
Physical	30.7±5.13	28.4±4.34	0.398
Emotional	9.6±5.27	8.6±4.68	0.614
Total	47.35±17.67	46.6±17.11	0.953

MLHFQ, Minnesota Living with Heart Failure Questionnaire; PIT, physiological ischemic training.

In previous studies, we demonstrated that skeletal muscle ischemia can induce ischemic myocardial collateral circulation (14,15) and reduce the area (16). Previous findings have confirmed that the isometric contractions in 40-50% of the largest independent contraction [maximal voluntary contraction (MVC)] intensity can almost completely block blood flow (17); therefore, the movement form can be used as a peripheral controllable physical model of ischemia. Our task group named this exercise as the PIT. Physiological mechanisms of ischemia training are as follows: peripheral skeletal muscle training in brief, periodic, long cycle of ischemic training, produced by peripheral blood VEGF and vascular EPCs through homing mechanism into the heart, reach the biological bypass, improve the collateral circulation, and improve myocardial blood flow (7,14,16,18-20). In patients with heart failure, vascular endothelial function was impaired and endothelial cell dysfunction provided a potential pathophysiological relationship between normal endothelial function loss and heart failure (21). CHD is the main cause of heart failure. Due to hypoxia of myocardial ischemia, heart failure can be induced, and heart failure can further affect the cardiac blood supply of CHD (2). Based on previous research, this study suggests that PIT training can improve the endothelial function of blood vessels, and provides the possibility to delay the process of ischemic heart failure caused by CHD. The present findings show that, before, during and after PIT training in patients with CHD, VEGF concentrations were significantly higher than before. Furthermore, movement training improved the patient's coronary collateral circulation.

Both of these constitute possible reasons for the movement to promote peripheral blood VEGF concentration increases, homing to the heart, to improve the patient's collateral circulation. These results are in agreement with those of Lin *et al* on physiologic ischemia of CHD training (19), which further improves myocardial ischemia in patients with heart failure.

There is a certain cardiovascular risk in rehabilitation training for patients with heart failure, so it is necessary to assess the risk of rehabilitation training properly. In this study, during PIT training, the systolic pressure, and diastolic blood pressure compared with before PIT training (rest) was increased, and the difference was statistically significant. In addition, PIT training blocked the blood flow to part of the skeletal muscle, causing a change in blood pressure and hemodynamics, and even increased the shear force of blood vessels. This increase in blood pressure was relatively high, and patients could tolerate it, and there were fewer opportunities for ST-T changes and arrhythmias, results that are similar to those of Olher *et al* (22). This change of blood pressure can cause transient ischemia of skeletal muscle and improve the preadaptability of ischemia, as also reported by Lin *et al* (19). During and after PIT training, the change of heart rate was not statistically significant, and the training effect on the heart rate was relatively small, probably because of heart failure patients with widespread use of β blockers, and relative amount was larger, myocardial contraction in patients with heart failure ability was relatively weak, an exercise that is less likely to cause a rapid increase in the heart rate. The results show that PIT training is safe for patients with CHD and heart failure.

In patients with heart failure, the relative activity endurance decreases (23), the heart failure disease restricts its daily life activities, and seriously affects QOL (24). Elderly patients with CHD (ADL) and QOL are the primary target (13). In this study, the effect of PIT training on the QOL was emphasized because of the selection of patients with coronary heart failure. The Minnesota heart failure scale is a recognized indicator of cardiac failure (25). In addition, we found that the Minnesota heart failure scale, the scores of the three aspects are also lower before treatment, and shows that the quality of patient life greatly improved, instructions for the intervention of the heart failure can retard the disease process, improving the QOL.

To sum up, PIT is effective for patients with coronary heart failure and patients with heart failure. The overall patient's motor ability and QOL were improved. This investigation of the CHD with mild or moderate heart failure patients the sample size was small. In future the sample size will be increased in order to observe the changes of peripheral blood in patients with severe heart failure VEGF concentration, and cardiopulmonary exercise testing response, to provide theoretical basis for sports rehabilitation in patients with heart failure.

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Availability of data and materials

The datasets analyzed during the current study are not publicly available due to the protection of patient privacy but are available from the corresponding author on reasonable request.

Authors' contributions

MG and JL were responsible for the Minnesota Living with Heart Failure Questionnaire; XL and WC collected the patient clinical information and follow-up; GHX, YZ and RY performed ELISA. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Xuzhou Central Hospital (Xuzhou, China). Informed consents were signed by the patients that participated in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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