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Research Article

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Comparison of the clinical outcomes of two physiological ischemic training methods in patients with coronary heart disease

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Abstract: The aim of the present study was to verify the effectiveness of physiological ischemic training (PIT) in patients with coronary heart disease (CHD) and compare differences in clinical outcomes between isometric exercise training (IET) and cuff inflation training (CIT).

Fifty-five CHD patients were randomized into three groups: IET group (n=19), CIT group (n=18), and no-exercise group (n=18). PIT was practiced in the IET and CIT groups. Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded. The cardiac structure and function were evaluated and vascular endothelial growth factor (VEGF) measured.

SBP and DBP decreased significantly in both PIT groups after 3-month training (P<0.01). Cardiac function and structure were significantly improved in both PIT groups after 3-month training (P<0.01). Cardiac structure and function in the IET group were both superior to those in the CIT group by the end of training (P<0.01). The VEGF level in both PIT groups increased significantly after 3-month training (P<0.01).

PIT was safe and feasible when performed in CHD patients. An appropriate period of PIT helped improve blood pressure and the cardiac structure and function, with the outcome more positive in the IET group.

Keywords: Coronary heart disease; Physiological ischemia training; Isometric exercise training; Cuff inflation training

1 Introduction

Ischemic heart disease, such as angina and myocardial infarction, has become a huge medical challenge because of it's high morbidity and mortality [1]. The establishment of coronary collateral circulation (CCC) is known to help improve the ischemic myocardium [2–4]. A meta-analysis on 12 clinical trials involving 6,529 patients [5] showed that the mortality decreased by 36% in coronary heart disease (CHD) patients with established CCC. Therefore, finding a convenient and effective approach to promote the establishment of CCC is clinically meaningful. Studies [6] have shown that moderate-intensity aerobic exercises causing 50%–60% maximum oxygen consumption (VO_{2max}) can facilitate the establishment of CCC. However, aerobic exercises can also increase oxygen consumption of the ischemic myocardium, which may lead to serious consequences or even cardiovascular accidents. Previous studies [7–9] showed that transient ischemic stimulation of remote organs such as the kidney, mesentery, and skeletal muscle could induce cardiac protection when myocardial ischemia occurred. Physiological ischemic training (PIT) is reported to induce ischemic stimulation on normal skeletal muscles, thus triggering a physiological or functional non-pathological process to improve angi-

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ogenesis in the remote ischemic myocardium [10]. Isometric exercise training (IET) and cuff inflation training (CIT) are the two most commonly used methods to induce controllable physiological ischemia [11–15]. Cuff inflation above 200 mmHg is known to induce ischemia in normal muscles, and IET can also induce local ischemia in the contractile muscle caused by a rise in intramuscular pressure. However, no study has reported whether there is any difference in clinical outcomes between the two methods. Previous studies [16–19] demonstrated that the level of vascular endothelial growth factor (VEGF) increased in circulating blood after PIT, which could promote the establishment of CCC in the ischemic myocardium. However, all of these studies were performed in animals. The aim of the present study was to determine whether PIT was beneficial to CHD patients, and compare differences in clinical outcomes between IET and CIT.

2 Methods

2.1 Study design

Thistrial was a clinically randomized controlled trial (RCT), in which patients were randomly assigned to an IET group, a CIT group, and a no-exercise (NE) group using a random number table. This single-center research was approved by the ethics committee of Nantong Elderly Rehabilitation Hospital (Nantong, China).

2.2 Participants

Included in this study were 100 CHD patients who received treatment in Nantong Elderly Rehabilitation Hospital between November 2015 and February 2016. The inclusion criteria were: (i) patients aged between 50 and 70 years; (ii) patients with a single-vessel lesion (diameter reduction between 50% and 100%) as confirmed by coronary angiography who did not receive PCI treatment; (iii) patients with a history of CHD for more than 3 months as confirmed by coronary angiography; (iv) patients with left ventricular ejection fraction (LVEF) >40% and New York Heart Association class I–II; and (v) patients who participated in the study voluntarily and signed informed consent. The exclusion criteria were: (i) patients with congenital heart disease, ventricular aneurysm, and/or valvular heart disease; (ii) patients with acute myocardial infarction in the previous 3 months; (iii) patients with severe arrhythmia, cardiac insufficiency, or tumors; (iv) patients with uncontrolled hypertension; and (v) patients with upper limb motor dysfunction. Of the initial recruit of 100 CHD patients, 40 were excluded from the study: 33 because they did not meet the inclusion criteria and 7 because they refused to participate. All of the 60 finally included patients completed the baseline assessment, 55 of whom completed the 3-month assessment. The reasons for 5 patients missing the 3-month assessment were disease progression in 1 patient, loss of contact in 2 patients, and loss to follow-up in the remaining 2 patients (Figure 1).

2.3 Exercise intervention

All patients received conventional drug treatment for 3 months. Patients in the IET group did a voluntary isometric handgrip exercise with a 40%–50% maximum contraction force for 1 min in one hand and repeated this exercise 10 times with a 1-min interval of rest; the same exercise was done with the other hand alternatively. Completion of the whole exercise was regarded as one session, and two sessions were performed daily for 5 days per week, for a period of 3 months [20]. Patients in the CIT group received 3-min cuff inflation-induced ischemia and 5-min deflation in both upper limbs alternatively, 3 times daily for 5 days in a week over 3 months [11, 12]. Patients in the NE group received conventional drug treatment only.

As shown in Figure 2, both IET and CIT reduced blood flow in the radial artery, causing physiological ischemia.

2.4 Data collection

Blood samples obtained from each patient before and after training were stored at −80°C for use. VEGF level was measured with an ELISA kit according to the manufacturer's instructions. All patients underwent cardiopulmonary exercise testing (CPET) before and after training to obtain data about anaerobic threshold (AT) and VO_{2max}. Color Doppler echocardiography was used to record the cardiac structure and function of the patients, including LVEF, left ventricular end-diastolic dimension (LVEDD), and left ventricular end-systolic dimension (LVESD). In addition, blood pressure (BP) was measured in triplicate and repeated at least three times by using an electronic manometer.

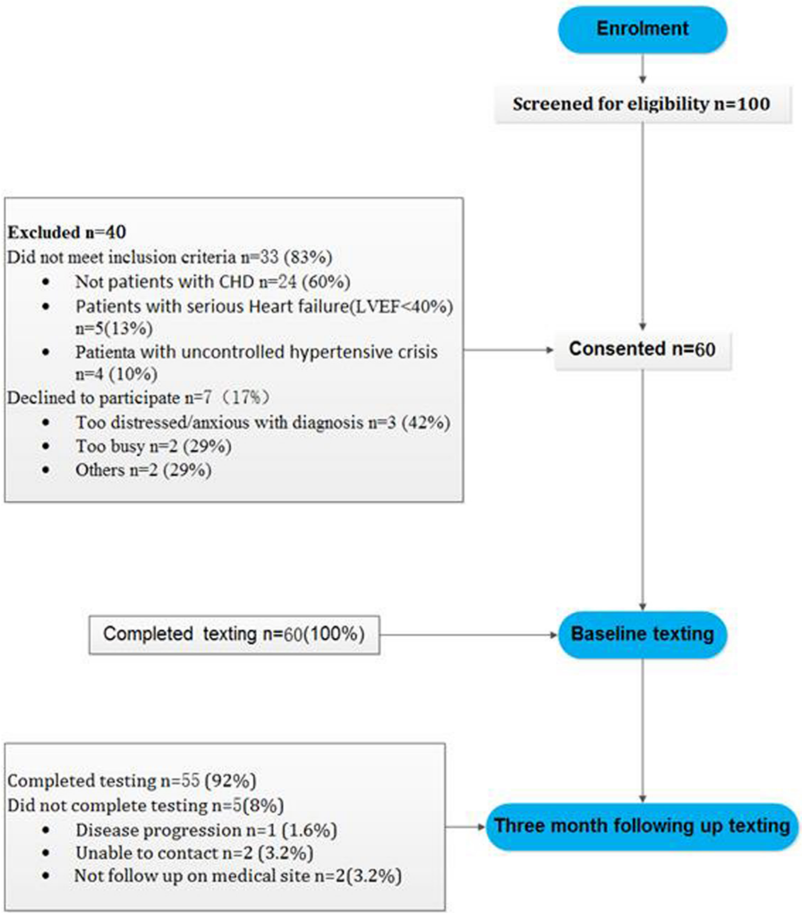

Figure 1: Experimental protocols

2.5 Statistical analysis

All statistical analyses were performed by SPSS 21.0 (SPSS, Chicago, IL, USA). All continuous data were presented as means±standard deviation (SD) and dichotomous data were shown as counts. Intra-individual differences between the baseline data and those obtained at the end of training were compared using a paired Student's *t* test, and intra-group differences among the three groups were compared by ANOVA. *q* test was used when a significant ANOVA was observed ($P<0.05$) to determine differences between different groups. *P* values of less than 0.05 were considered statistically significant.

3 Results

3.1 Baseline data

As shown in Table 1, there was no significant difference in baseline data there was no significant difference in baseline data there was no significant difference in baseline data .

3.2 BP comparison

In IET and CIT groups, there was a statistically significant improvement in SBP and DBP after 3-month training as compared with those before training ($P<0.01$), and there was no significant difference in SBP and DBP before and after 3 months in patients of the NE group ($P>0.05$). There was no significant difference in SBP and DBP among the three groups before training ($P>0.05$). After 3 months of training, a statistically significant difference in BP was observed among the three groups ($P<0.01$). There was a more significant decrease in SBP and DBP in the IET group than in the CIT group ($P<0.01$), and BP in both IET and CIT groups was lower than that in the NE group ($P<0.01$) (Figure 3).

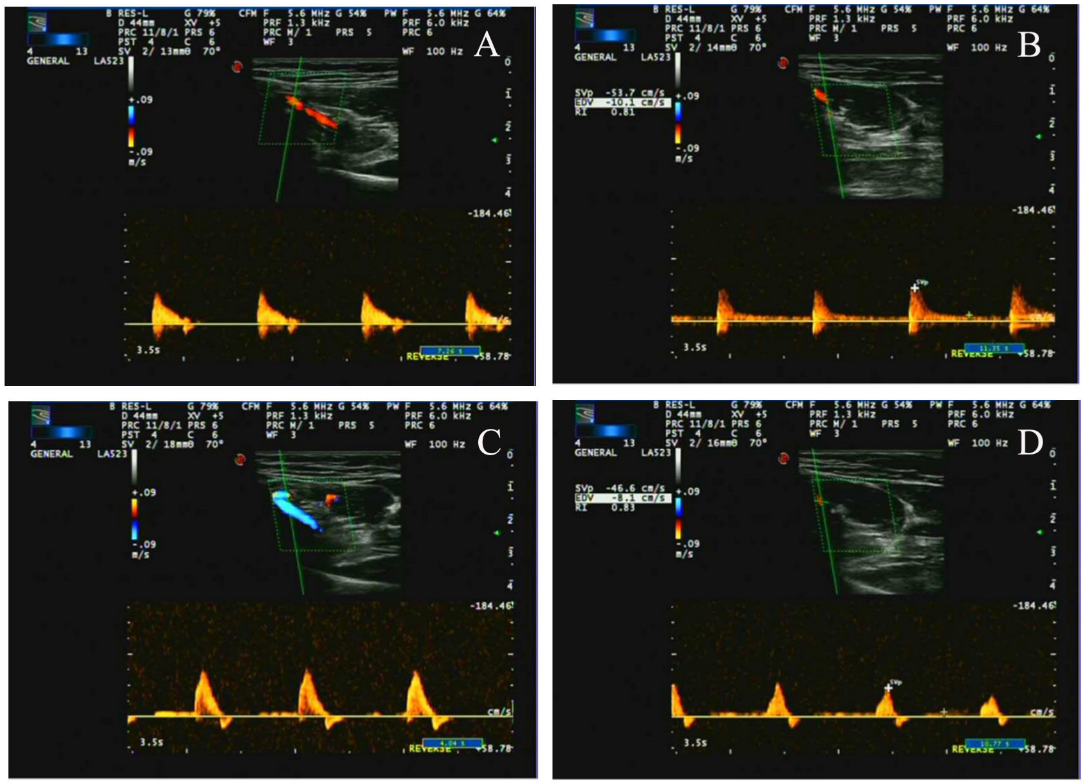

Figure 2: Radial artery blood flow before and after isometric exercise training (A,B); Radial artery blood flow before and after cuff inflation training (C,D)

3.3 Comparison of the cardiac structure and function

Within-group comparison showed that LVEDD and LVESD decreased, and LVEF, AT, and VO_{2max} were in the IET and CIT groups after 3-month training (P<0.01). However, the difference was insignificant in the NE group (P>0.05). There was no significant difference in LVEDD, LVESD, LVEF, AT, and VO_{2max} among the three groups before training (P>0.05). Inter-group comparison showed that LVEDD and LVESD were reduced, and LVEF, AT, and VO_{2max} increased more markedly in the IET group than in the CIT group (P<0.01). All the parameters investigated were improved in both IET and CIT groups as compared with the NE group (P<0.01) (Figure 4).

3.4 Comparison of VEGF and NO levels

In the IET and CIT groups, the VEGF level was significantly increased after 3-month training compared with that before training (P<0.01). The VEGF level remained unchanged before and after the 3-month interval in the NE group (P>0.05). There was no significant difference in VEGF level among the three groups before training (P>0.05). After 3 months of intervention, there was still no statistically significant difference regarding VEGF levels in the IET and CIT groups (P>0.05). However, the VEGF level in both PIT groups was higher than that in the NE group (P<0.01) (Figure 5).

3.5 Analysis of correlation between VEGF level and cardiac function in terms of VO2max and LVEF

As shown in Figure 6, there was a significant correlation between the VEGF level and the cardiac function in terms of VO_{2max} and LVEF (R=0.342, P=0.011; R=0.288, P=0.033, respectively)

3.6 Safety of PIT

No significant change in SBP and DBP was observed in the CIT group during training (P>0.05). In the IET group, DBP increased significantly during training (P<0.01) and recovered after training, while SBP increased insignificantly (P>0.05). Moreover, no myocardial ischemic ECG and

Table 1: Comparisons of baseline data among the three groups

Characteristic	IET group(19)	CIT group(18)	NE group(18)	F(X2)	P
Gender（male/female）	11/8	9/9	11/7	0.479	0.787
Age(years)	62.84±5.54	64.44±8.28	65.89±5.51	1.000	0.375
BMI(kg/m²)	24.59±2.72	23.29±1.58	24.51±3.61	1.236	0.291
HR(beats/min)	79.53±5.69	79.11±8.48	76.78±5.89	0.870	0.425
SBP(mmHg)	143.32±7.48	143.94±9.55	145.78±7.73	0.436	0.649
DBP(mmHg)	82.63±7.65	83.50±7.12	83.22±6.53	0.072	0.931
NYHA（I/II/III/IV）	5/14/0/0	3/15/0/0	4/14/0/0	0.507	0.776
LVEF(%)	54.21±7.38	53.39±7.41	51.44±7.60	0.664	0.519
LVEDD(mm)	47.53±7.31	48.44±8.46	50.89±7.45	0.923	0.404
LVESD(mm)	35.68±6.54	36.22±6.81	38.11±7.11	0.639	0.532
VEGF(pg/ml)	130.0±32.27	139.88±28.47	138.0±23.83	0.624	0.540
AH(ml/kg/min)	11.15±2.64	11.26±3.16	11.86±2.57	0.340	0.714
VO2max((ml/kg/min))	33.50±4.28	32.18±5.39	32.76±5.92	0.299	0.743
History：	-	-	-	-	-
Hypertension	11	9	11	0.479	0.787
Diabetes	8	8	9	0.243	0.885
Hyperlipidemia	9	8	8	0.043	0.979
Smoking	8	7	10	1.140	0.566
SA/UA/AMI	2/14/3	2/15/1	3/14/1	1.872	0.759
Drug use：	-	-	-	-	-
Aspirin	18	17	16	0.586	0.746
Clopidogrel	16	14	16	0.819	0.664
Atatins	19	18	17	2.094	0.351
Aitrate	12	13	13	0.478	0.787
ACEI/ARB	13	15	12	1.532	0.465
βBlocking	5	8	4	2.368	0.306
CCB	7	4	6	0.999	0.607
Diuretics	3	4	3	0.298	0.861

Notes: ACEI means angiotensin converting enzyme inhibitor, SA means stable angina, UA means unstable angina, AMI means acute myocardial infarction, CCB means Calcium Channel Blockers.

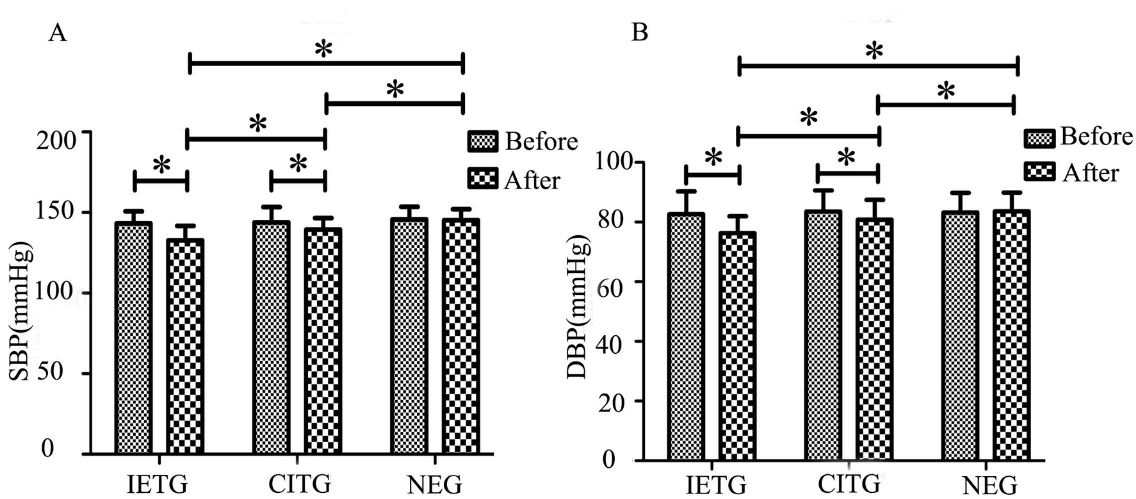

Figure 3: Comparison of BP between the three groups

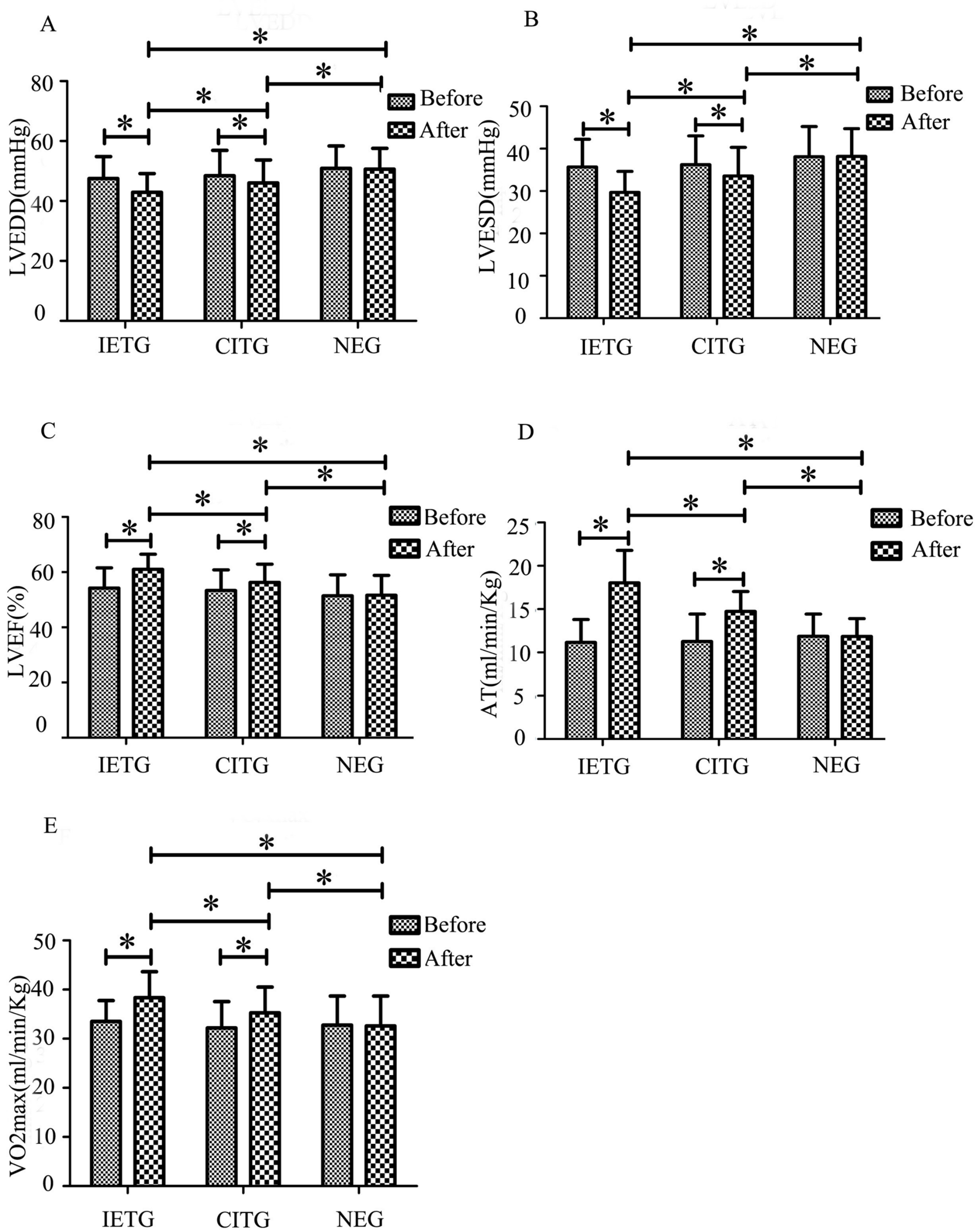

Figure 4: Comparison of the cardiac structure (A,B); Comparison of the cardiac function (C,D,E)

cardiac events occurred throughout the course of training (Figure 7).

4 Discussion

4.1 The concept and intervention of PIT

From the pathological point of view, if the blood supply for tissues and organs cannot meet the need of their metabolism, pathological ischemia develops. Physiological ischemia is defined as repeated intermittent short-term ischemia that causes no significant pathological change in tissues and organs due to the body's ability to compensate [12]. Previous clinical studies [21–23] showed that patients with a history of angina had lower probabilities of developing acute myocardial infarction and mortality compared with those without a history of angina. In addition, radiographic assessment showed that CCC was enriched in patients with a history of angina. These results indicate that stable angina can facilitate CCC establishment and protect the residual myocardium. The pathogenesis of angina involves repeated intermittent short-termrepeated intermittent short-termrepeated intermittent short-termrepeated intermittent short-termrepeated intermittent short-term without eliciting myocardial necrosis [24, 25], which is similar to physiological ischemia. However, it is unwise to induce repeated intermittent short-term myocardial ischemia blindly because irreversible myocardial injury may occur when myocardial ischemia is frequently induced. Therefore, some researchers proposed the concept of PIT, which is defined as induction of repeated intermittent short-term ischemia in distant tissues or organs such as the skeletal muscles of the limbs in order to induce a protective effect on the heart [11, 12]. IET and CIT are common methods used in previous studies to induce physiological ischemia. During IET, the accompanying vessels are occluded by increased intramuscular pressure leading to varying degrees of reversible limb ischemia [26]. In CIT, reversible limb ischemia is induced by using the BP cuff to apply pressure directly on the blood vessels.

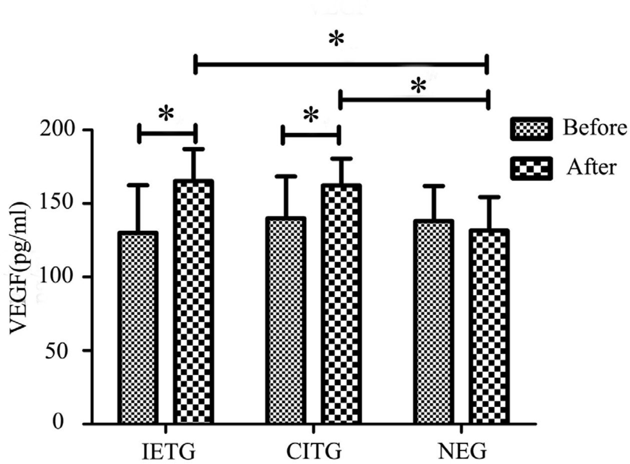

Figure 5: Comparison of VEGF level between the three groups

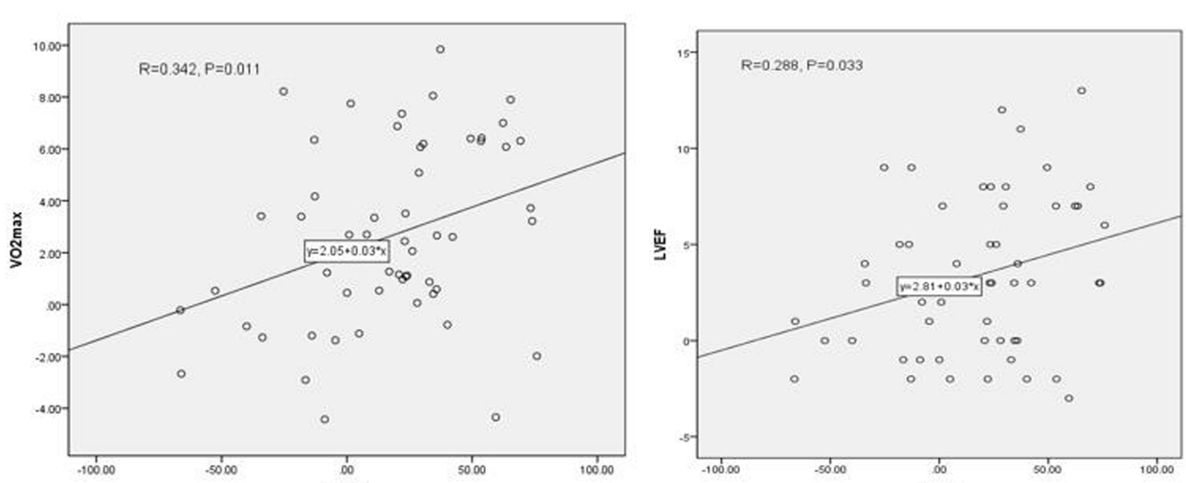

Figure 6: Correlation analysis of VEGF level and the cardiac function

4.2 Effects of PIT on hemodynamics

PIT used to be contraindicated in clinical practice because of its possible adverse effects of raising the BP and inducing myocardial ischemia during training. However, previous studies demonstrated that IET improved cardiac exercise tolerance and function without inducing a single case of angina in CHD patients [27]. Lin et al. showed that BP and heart rate (HR) were moderately raised during IET, and recovered to the usual resting state promptly after termination of the training [20]. They also found that changes in BP and HR gradually showed a negligible rise during PIT after 3-month intervention, indicating that the cardiac exercise tolerance and function were improved. However, limited studies could not corroborate the safety of PIT. It was found in our study that BP was not affected significantly during CIT ($P>0.05$), but SBP was moderately elevated during IET ($P<0.01$) and returned to the normal state after termination of the training, while DBP underwent insignificant change ($P>0.05$). After 3 months of training, it was incidentally found in the IET and CIT groups that SBP and DBP had decreased significantly compared with values from 3 months previously ($P<0.01$), while no significant change was observed in the NE group ($P>0.05$). The BP-lowering effect was more pronounced in the IET group than in the CIT group ($P<0.01$).

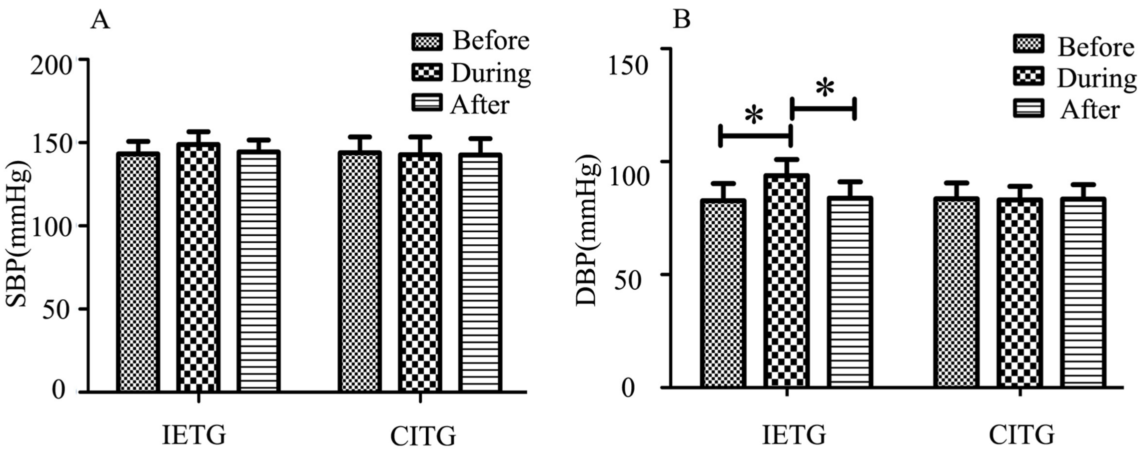

Figure 7: Comparison of BP changes during intervention

4.3 Effects of PIT on structure and function

It is generally recognized that cardiac function is consistently associated with cardiac structure. CPET is a noninvasive method extensively used to evaluate cardiac insufficiency in clinical practice [28]. In this study, we used CPET combined with echocardiographic LVEF to evaluate the outcomes of AT and VO_{2max}, knowing that they can evaluate the cardiac function effectively. Adverse ventricular remodeling is known to occur frequently after myocardial infarction, resulting in ventricular motion dysfunction or even heart failure if no intervention is undertaken. LVEDD and LVESD obtained from echocardiography are valid, reliable, and widely used as a measure of ventricular remodeling in the clinical setting. Previous animal experiments [10, 29] showed that blood supply improved, infarction size decreased, and residuary myocardial contractility strengthened after a period of PIT, and as a result the cardiac function improved. LVEDD and LVESD of both of both while no improvement was noted in patients in the NE group (P>0.05). In addition, LVEDD and LVESD decreased less markedly in the CIT group in comparison with the IET group. In terms of cardiac structure change, cardiac function improvement was consistent with cardiac structure improvement, as represented by improved AT and VO_{2max} in patients of both IET and CIT groups after 3 months of intervention (P<0.01), while there was no significant improvement in the NE group (P>0.05). In addition, the cardiac function index improved more significantly in the IET group than in the CIT group (P<0.01). All these results demonstrated that an appropriate period of PIT appears to be effective for CHD patients in improving the cardiac structure and function, although the precise mechanism remains to be further explored.

4.4 Possible mechanisms underlying the effect of PIT in improving the cardiac function

VEGF is generally accepted as one of the most important growth factors for angiogenesis. Animal experiments [30] showed that increased VEGF was highly correlated with ischemia and could facilitate the establishment of CCC, thus improving the blood supply for the ischemic myocardium. Upregulation of VEGF expression in blood facilitates collateral formation in remote ischemic organs [16]. Other studies showed that the expression of endothelial nitric oxide synthase (eNOS) was highly related to the level of VEGF [17] and that VEGF level, eNOS level, and endothelial progenitor cells increased in the remote ischemic myocardium. These findings are coincident with the results of the present study. We found that the serum expression of VEGF was increased after 3 months in IET or CIT patients (P<0.01), while no such change was observed in the NE group (P>0.05). However, intergroup comparison showed no significant difference in VEGF level between IET and CIT groups after 3-month training (P>0.05). In addition, we found a significant positive correlation between VEGF level and cardiac function in terms of VO_{2max} and LVEF (R=0.342, P=0.011; R=0.288, P=0.033, respectively). These results combined with previous animal experiments indicate that PIT in CHD patients could facilitate collateral formation in the remote ischemic myocardium by upregulating the expression of VEGF and improving blood supply to the at risk areas, thus improving the residual myocardial contractility and cardiac function. Moreover, decreased BP induced by an appropriate period of PIT could improve the cardiac function by relieving cardiac stress.

4.5 Comparisons of the two forms of PIT

The principal finding of this study is the beneficial effect of PIT on CHD patients. Surprisingly, the results demonstrated a more obvious improvement in hemodynamics, hemodynamics, hemodynamics, hemodynamics, hemodynamics, hemodynamics, in the IET group in comparison with the CIT group. However, given that IET is an active movement and CIT is a passive movement, and active movement is usually contraindicated in comatose or paralytic patients, CIT is preferred in such patients. In conclusion, the two methods of PIT have their own advantages and disadvantages and should be recommended according to individualized patients and clinical settings.

4.6 Significance and limitations of this study

Physiological ischemia can be induced by IET and CIT. After a period of PIT, hemodynamics and the cardiac structure and function in CHD patients demonstrated obvious improvement, and the outcome of IET appeared to be better than that of CIT. Based on the findings of previous animal experiments and the present clinical trial, we tend to conclude that PIT in remote normal limbs could increase the expression of VEGF and facilitate the establishment of CCC in the ischemic myocardium, as well as improving the hemodynamics and cardiac structure and function. Taken together, our data show that PIT is a safe, effective, economical, and simple rehabilitation training method for CHD patients. However, patient selection in the present study was based on convenience sampling, which might have had some impact on the results of the study. Therefore multi-center, larger-sample RCTs are required to verify the conclusion of the present study. In fact the conclusion that VEGF facilitates the establishment of CCC in the ischemic myocardium was drawn from previous animal experiments, as it was not appropriate for patients to undergo coronary angiography at 3-month intervals from a financial point of view. Therefore, further clinical studies are required to gain insights into action mechanisms before they can be used in routine clinical practice.

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Conflict of interests: No authors report any conflict of interest.

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