Am J Transl Res 2024;16(11):7176-7185
www.ajtr.org /ISSN:1943-8141/AJTR0158270

Original Article

Role of physiological ischemia training in suppressing ventricular remodeling and ventricular arrhythmia in patients after myocardial infarction: a randomized controlled trial

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Received June 4, 2024; Accepted October 30, 2024; Epub November 15, 2024; Published November 30, 2024

Abstract: Objectives: The randomized controlled study explored whether physiological ischemia training (PIT) can inhibit ventricular remodeling and reduce ventricular arrhythmias in the early period of acute myocardial infarction (AMI). Methods: AMI patients with hypotension or bradycardia were randomly divided into PIT (n = 21) and control (n = 20) groups. Meanwhile, patients with normal blood pressure (BP) and heart rate (HR) were randomly divided into PIT+angiotensin-converting enzyme inhibitor (ACEI) and/or β-blocker (AB) (n = 30) and AB (n = 30) groups. PIT was performed in the PIT and PIT+AB groups. Finally, indicators of renin-angiotensin-aldosterone system (RAAS) activity, ventricular remodeling, cardiac function, vascular neovascularization, and ventricular arrhythmias were compared among the groups after 3 months of intervention. Results: Indicators of RAAS activity, ventricular remodeling, left ventricular ejection fraction (LVEF) and QT dispersion (QTd) were improved in the PIT, PIT+AB and AB groups after 3 months of intervention ($P < 0.05$). Improvements in the indicators of RAAS activity, ventricular remodeling, LVEF and QTd in the PIT+AB group were superior to those in the AB group by the end of training ($P < 0.05$). The levels of vascular endothelial growth factor (VEGF) and nitric oxide (NO) in circulating blood were higher significantly in the PIT and PIT+AB groups after 3 months of intervention ($P < 0.05$). The Lown classification in the PIT+AB group decreased more than in other groups, and there was a significant difference compared with the control group ($P < 0.05$). Diastolic BP increased to some extent during PIT, whereas systolic BP or HR showed no significant effects. Conclusions: These findings suggest that PIT can effectively inhibit early ventricular remodeling, thereby reducing the risk of ventricular arrhythmias after myocardial infarction, and patients can further benefit from a combination of PIT and ACEIs/angiotensin receptor blockers and beta-blockers.

Keywords: Acute myocardial infarction, physiological ischemic training, early ventricular remodeling, ventricular arrhythmias, revascularization

Introduction

According to recent epidemiologic evidence, nearly 2.5 million individuals in China are affected by acute myocardial infarction (AMI), which is associated with high morbidity, mortality and disability [1]. A study assessing the effects of timely percutaneous coronary intervention (PCI) and standardized drug therapy showed that the short-term mortality of patients with myocardial infarction was significantly reduced but the incidence of heart failure in surviving patients was 22% and the risk of sudden death was 3% [2]. Ventricular remodeling is the pathological mechanism of heart failure following AMI. It is a process of sustained changes in the heart size, morphology and structure and ventricular function after AMI [3]. Ventricular remodeling eventually results in ventricular enlargement, reduced left ventricular ejection fraction (LVEF) and abnormal ventricular wall activity and is a major determinant of the incidence of cardiac events and long-term prognosis after AMI [4]. In addition, it has been shown

https://doi.org/10.62347/OIUI2017

that 75-80% of patients with AMI experience sudden because of ventricular arrhythmias [5]. Meanwhile, ventricular arrhythmias are the main cause of sudden death in patients with a history of distant infarction [6].

Chinese and international infarction guidelines strongly recommend early treatment with beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs) within 24 hours for patients with AMI (if the patient's blood pressure (BP) and heart rate (HR) are well controlled) to inhibit early ventricular remodeling and prevent the occurrence of ventricular arrhythmias [7, 8]. However, since hypotension is associated with right ventricular infarction and bradycardia with inferior wall infarction, early treatment with beta-blockers and ACEIs is not recommended. Li et al. proposed a rehabilitation training method, and physiological ischemia training (PIT); additionally, a series of animal experiments revealed that PIT increased the expression of vascular endothelial growth factor (VEGF) and nitric oxide (NO) in the blood, promoting the formation of collateral circulation at the site of the ischemic myocardium [9-12]. Chen et al. [13] applied this rehabilitation training method to patients with ischemic cardiomyopathy and found that PIT not only improved coronary flow reserve but also inhibited renin-angiotensin-aldosterone system (RAAS) activity and sympathetic activity, thereby suppressing ventricular remodeling and ultimately improving cardiac function. Lin et al. [14] found that patients' BP and HR increased during PIT, while the mean BP readings and HR of patients were significantly lower after 6 months of long-term training than before. Therefore, the characteristics of changes in BP and HR during PIT show that PIT can be properly applied to patients with AMI and may inhibit RAAS activity and sympathetic activity, suppress ventricular remodeling and reduce ventricular arrhythmias in early AMI. The current study sought to investigate whether PIT can be safely applied to patients with AMI undergoing reperfusion therapy and whether it can effectively inhibit RAAS activity and sympathetic excitability to suppress early ventricular remodeling and reduce ventricular arrhythmias. We also attempted to explore an effective method of rehabilitation training for patients with hypotension and bradycardia after AMI who are intolerant to beta-blockers and ACEIs/ARBs.

Methods

Research subjects

In our hospital between 06/2020 and 06/2021, patients with acute ST-elevation myocardial infarction (STEMI) who had successfully undergone emergency PCI operation and were ultimately transferred to the cardiac care unit for further treatment were enrolled. Inclusion criteria: (1) Patients aged 25-75 years old. (2) Patients with STEMI confirmed by emergency coronary angiography showing that their coronary vessels were acutely occluded. (3) Patients who successfully received emergency PCI reperfusion treatment. (4) Patients with Killip classes I-III. (5) Patients who signed an informed consent form and agreed to participate in the study. Exclusion criteria: (1) Patients who required long-term vasopressor agents to maintain BP due to hemodynamic instability during hospitalization. (2) Patients with recurrent malignant arrhythmias (including sustained ventricular tachycardia, ventricular fibrillation and third-degree atrioventricular block) during hospitalization. (3) Patients with uncontrolled severe hypertension. (4) Patients with disorders of upper limb movement, peripheral vascular lesions and tumors. (5) Patients who changed their treatment plan during the study due to changes in the course of their condition. This prospective randomized controlled study was approved by Suzhou Ninth Hospital Affiliated to Soochow University (Suzhou, China, KY2020-014-01). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

The sample size was obtained through Power Analysis & Sample Size (PASS) software, and the result was calculated using a fixed effect size approach. Patients were divided into two groups based on their BP and HR: hypotension (systolic blood pressure (SBP) < 100 mmHg or 30% decrease from basal values) and/or bradycardia (HR < 60 bpm) groups (n = 70) and non-hypotension and non-bradycardia groups (n = 70). Patients were further randomly divided into four groups: PIT group (n = 35), control group (n = 35), PIT+ACEI and/or β-blocker group (n = 35) and ACEI and/or β-blocker group (n = 35). After 3 months of intervention, 14 patients in the PIT group and 15 patients in the control

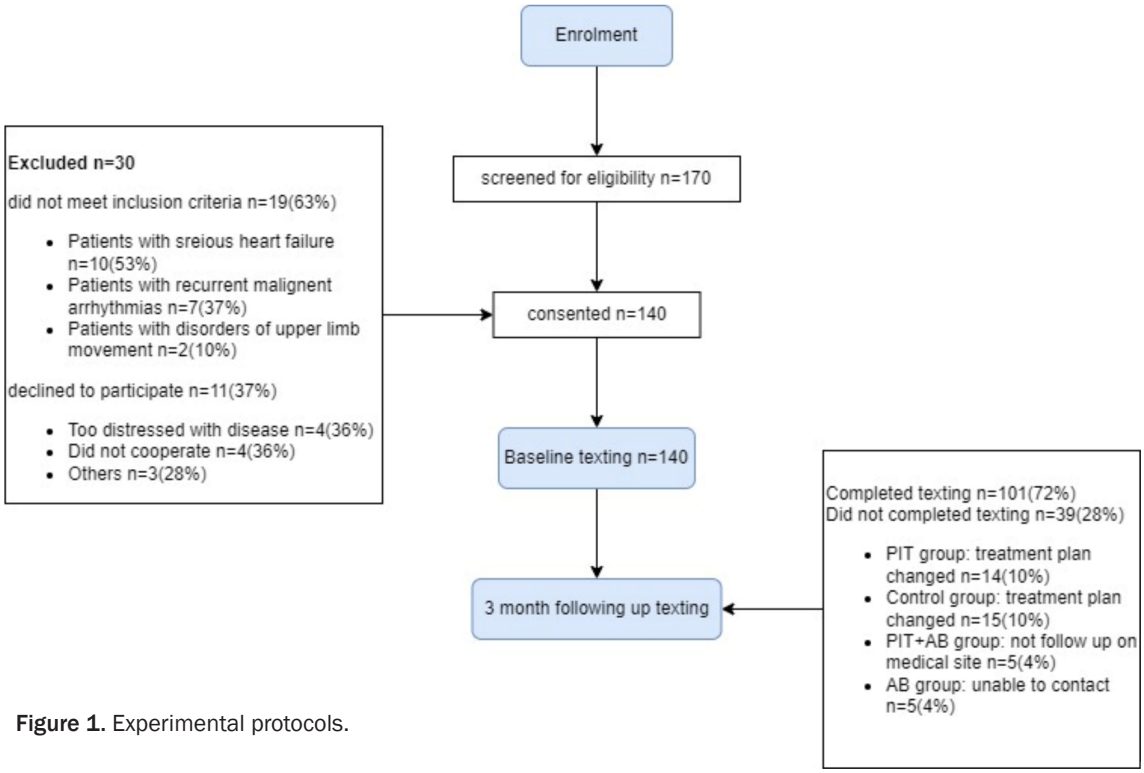

Figure 1. Experimental protocols.

group who received ACEIs and/or β-blockers according to the standardized pharmacologic treatment protocols due to recovery of cardiac function, and those who had a gradual increase in BP or HR during the study were excluded according to the fifth exclusion criterion. Besides, five patients were lost to follow-up in the PIT+AB and AB groups (**Figure 1**).

Research methodology

All patients with STEMI received dual antiplatelet therapy and lipid-lowering therapy according to guideline recommendations after successful reperfusion therapy. Patients in the PIT group performed a handgrip exercise with 40-50% maximum handgrip strength for 1 minute, relaxed for 1 minute, and then repeated the exercise 10 times with the same hand. Meanwhile, the same handgrip exercise was repeated 10 times with the other hand. Performing the exercise 10 times with each hand was defined as a complete session. The whole rehabilitation program was performed daily, 5 days per week, for 3 months. Patients in the control group only received dual antiplatelet therapy and lipid-lowering therapy due to hypotension and bradycardia. Patients in the PIT+AB group were treated with ACEIs/ARBs and/or beta-blockers in the early stages and concomitantly received the same rehabilitation program as patients in the PIT group. Patients in the AB group were treated with ACEIs/ARBs and/or beta-blockers in the early stages to inhibit ventricular remodeling.

Data collection

Serum was obtained from blood samples collected from patients before and after intervention and stored at -80°C until use. Plasma renin activity (PRA) was measured using the radioimmunoassay method. Angiotensin II (Ang II) and aldosterone (ALD) levels were detected by the chemiluminescence method. VEGF, NO and suppression tumorigenicity 2 (ST2) levels were measured by enzyme-linked immunosorbent assay. Doppler echocardiography was used to measure LVEF, left ventricular myocardial mass index (LVMI) and left ventricular posterior wall thickness (LVPWT). Ventricular premature contractions were monitored by 24-hour ambulatory electrocardiography and evaluated according to the Lown grading system. The QT interval was measured by 12-lead electrocardiograms. In addition, BP and HR during the intervention

were measured using an electronic manometer at least three times.

Lown grading

Grade 0: no ventricular premature contraction; Grade 1: frequent and unifocal ventricular premature contractions (< 30/hour); Grade 2: frequent and unifocal ventricular premature contractions (> 30/hour); Grade 3: multifocal ventricular premature contractions; Grade 4A: repetitive paired ventricular premature contractions; Grade 4B: > 3 ventricular premature contractions appear consecutively; and Grade 5: R on T phenomenon.

Statistical analysis

All statistical analyses were performed by SPSS 28.0. All continuous data are expressed as mean ± standard deviation (SD), whereas dichotomous data were expressed as frequencies or percentages (%). Baseline data of patients in the four groups were compared using one-way analysis of variance (ANOVA), and dichotomous count data were analyzed using the χ^2 test. A paired Student's t-test was used to compare intraindividual differences, and intragroup differences after 3 months of intervention among the four groups were compared using the Student's t-test when ANOVA showed a significant difference among the four groups ($P < 0.05$). $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

The baseline characteristics were comparable among the four groups. No differences were found in sex, age, criminal coronary, Killip class, past medical history (hypertension, diabetes, hyperlipidemia, coronary heart disease and smoking), or recent medications taken (aspirin, adenosine-diphosphate receptor antagonist, statins, nitrates, ACEI/ARB, beta-blockers, calcium channel blockers, diuretics, aldosterone receptor antagonist, metformin, sodium-glucose cotransporter-2 (SGLT-2) inhibitor, glucagon-like peptide-1 (GLP1) receptor agonist, insulin, etc.) ($P > 0.05$). However, the differences in HR, SBP, and diastolic blood pressure (DBP) were significant at baseline ($P < 0.05$) (**Table 1**).

Comparison of RAAS activity

PRA, Ang II, and ALD levels were significantly lower in the PIT, PIT+AB and AB groups after 3 months of intervention than before ($P < 0.05$); however, no statistically significant differences were found in the control group ($P > 0.05$). Intergroup comparisons showed that the levels of PRA, Ang II, and ALD were significantly lower in the PIT+AB group than in the AB group after 3 months of intervention ($P < 0.05$) (**Figure 2A**).

Comparison of ventricular remodeling

ST2, LVPWT and LVMI increased in the control group after 3 months of intervention, and the differences were statistically significant ($P < 0.05$). However, ST2, LVPWT and LVMI decreased significantly in the PIT, PIT+AB and AB groups ($P < 0.05$). Intergroup comparison showed that ST2, LVPWT and LVMI in the PIT+AB group decreased more than those in the AB group after 3 months of intervention, and the differences were statistically significant ($P < 0.05$) (**Figure 2B**).

Comparison of cardiac function

Except for the control group, the LVEF in the other 3 groups increased significantly after 3 months of intervention compared with before the intervention ($P < 0.05$). Intergroup comparisons showed that LVEF increased more significantly in the PIT+AB group than in the AB group ($P < 0.05$) (**Figure 2C**).

Comparison of revascularization

VEGF and NO increased significantly in the PIT and PIT+AB groups after 3 months of intervention compared with before the intervention ($P < 0.05$); however, no significant difference was observed in the control and AB groups ($P > 0.05$). VEGF and NO were higher in the PIT and PIT+AB groups than in the control and AB groups after 3 months of intervention ($P < 0.05$); however, no significant differences in VEGF and NO were found between the PIT and PIT+AB groups ($P > 0.05$) (**Figure 3A**).

Comparison of arrhythmia risk

The Lown classification in the four groups was significantly decreased after 3 months of intervention compared with before the intervention ($P < 0.05$). The Lown classification in the PIT+AB

Table 1. Comparison of baseline data among the four groups

	PIT group	Control group	PIT+AB group	AB group	F/χ^2	*P*
Gender (male/female)	14/7	15/5	22/8	20/10	0.666	0.881
Age (year)	64.86±8.66	63.55±8.55	66.20±6.39	66.20±7.05	0.663	0.577
HR (bpm)	55.33±4.00	55.85±3.91	71.00±7.46	74.00±8.06	55.861	0.000*
SBP (mmHg)	95.48±6.29	92.65±7.10	134.70±18.74	130.77±15.34	63.199	0.000*
DBP (mmHg)	55.76±6.16	53.80±4.71	74.83±7.39	72.60±4.66	84.167	0.000*
Criminal coronary (LAD/LCX/RCA)	6/2/13	4/4/12	17/7/6	15/5/10	14.375	0.026*
Killip class (I/II/III/IV)	8/9/4/0	9/9/2/0	20/9/1/0	19/11/0/0	10.824	0.094
Past medical history						
Hypertension	16	14	24	26	1.072	0.784
Diabetes	12	15	21	19	1.769	0.622
Hyperlipidemia	9	8	13	13	0.069	0.995
CHD	13	10	17	19	1.025	0.795
Smoking	8	10	14	16	1.123	0.750
Recent medications taken						
Aspirin	7	5	9	12	1.369	0.713
ADP receptor antagonist	8	8	12	11	0.091	0.993
Statins	15	14	23	21	0.425	0.935
Nitrates	3	5	4	6	1.393	0.707
ACEI/ARB	15	17	19	23	3.130	0.372
Beta-blockers	8	10	15	21	5.532	0.137
CCB	8	5	13	10	1.886	0.596
Diuretics	4	2	6	4	1.205	0.752
Metformin	8	11	17	12	2.883	0.410
SGLT-2 inhibitor	6	4	7	6	0.625	0.891
GLP1 receptor agonist	4	7	3	5	5.048	0.168
Insulin	3	2	4	1	2.300	0.513

LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; RCA: right coronary artery; Killip class: clinical stage of heart failure due to acute myocardial infarction; CHD: coronary heart disease; ADP: adenosine diphosphate; CCB: calcium channel blockers; SGLT-2: sodium-dependent glucose transporters 2; GLP1: glucagon like peptide 1. *The difference was statistically significant ($P < 0.05$).

group decreased more than that in the AB group after 3 months of intervention ($P < 0.05$). No significant change in QT dispersion (QTd) was observed in the control group after 3 months of intervention ($P > 0.05$). However, QTd was significantly decreased in the other three groups ($P < 0.05$). Intergroup comparison showed that QTd decreased more markedly in the PIT+AB group than in the AB group (**Figure 3B**).

Comparison of BP

DBP and HR were significantly increased ($P < 0.05$) and SBP remained unchanged in the PIT group during the intervention ($P > 0.05$). However, no significant changes in SBP, DBP or HR were observed in the control group ($P < 0.05$) (**Figure 3C**).

Discussion

Approximately 30-60% of patients with AMI develop asymptomatic left ventricular systolic dysfunction, and the rate of heart failure development after AMI increases exponentially even after receiving timely and successful reperfusion therapy [15]. This is mainly due to the persistent inflammatory response of myocardial tissues in the infarct areas, which causes changes in cardiomyocyte hypertrophy and myocardial fibrosis, thus affecting the structure and function of the heart. RAAS activation, sympathetic stimulation, neuroendocrine mechanisms such as increased natriuretic peptides, and inflammatory responses are the main pathological mechanisms underlying myocardial remodeling after AMI, which begins within an hour of AMI and lasts for several

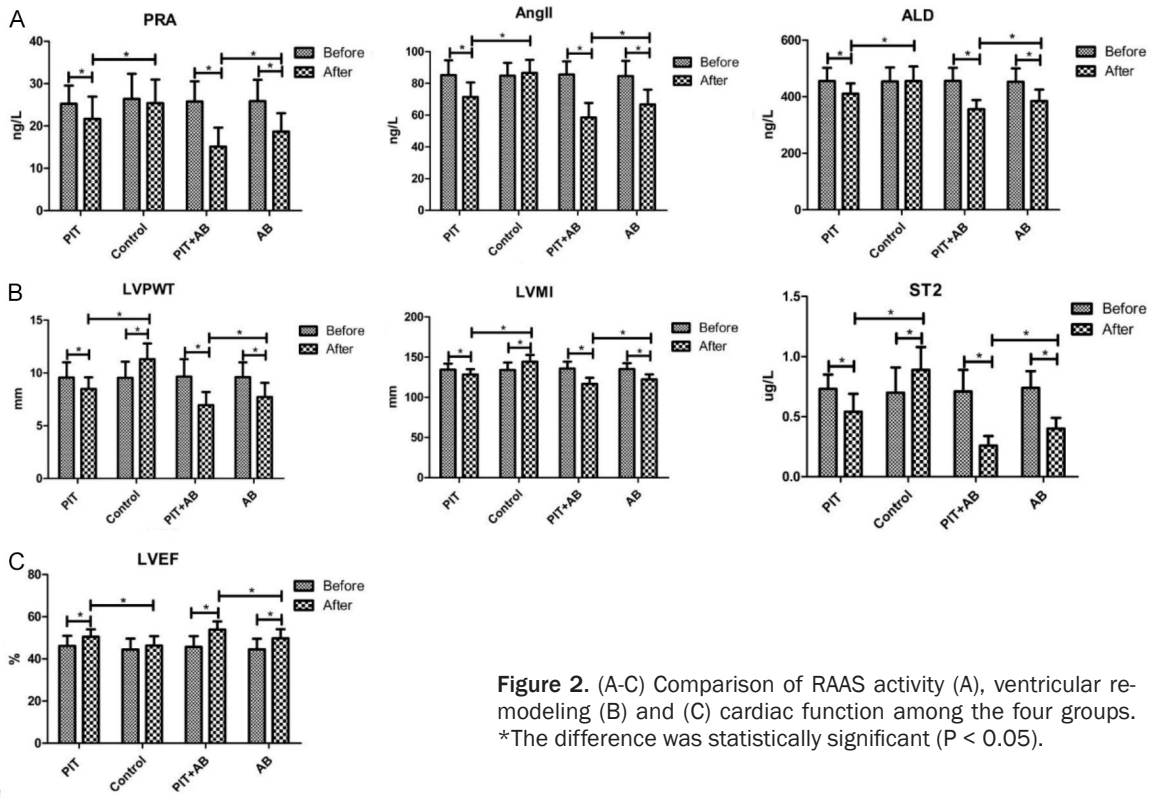

Figure 2. (A-C) Comparison of RAAS activity (A), ventricular remodeling (B) and (C) cardiac function among the four groups. *The difference was statistically significant ($P < 0.05$).

months or even a year [16]. Early ventricular remodeling occurs within 1-3 days after AMI, leading to increased infarct size and ventricular volume, ischemic necrosis and stunning of myocardial cells [17]. Significant individual differences exist in late ventricular remodeling, which persists for months or even years, causing cardiomyocyte hypertrophy, apoptosis and diffuse fibrosis [18]. Increased expression of Ang II induces the effect of the RAAS on adverse ventricular remodeling. Continuous injection of Ang II elevated collagen in perivascular tissue of a rat model [19]. Numerous studies have explored the effect of ST2 on ventricular remodeling in the past few years, revealing that ST2 is implicated in the inflammatory response and myocardial fibrosis, affecting the prognosis of AMI [20, 21]. LVPWT and LVMI are used to assess ventricular remodeling, whereas LVEF is used to evaluate cardiac function. The present study found that PRA, Ang II, ALD and ST2 were significantly decreased in the PIT, PIT+AB and AB groups but markedly increased in the control group. In addition, PRA, Ang II, ALD and ST2 were significantly lower in the PIT+AB group than in the AB group. Improvements in cardiac structure and function were consistent with a decrease in RAAS activation and ST2, as represented by improved LVPWT, LVMI and LVEF in the PIT, PIT+AB and AB groups after the 3-month intervention. Moreover, the cardiac structure and function index improved more significantly in the PIT+AB group than in the AB group. Collectively, these results demonstrate that PIT is effective in inhibiting ventricular remodeling and improving cardiac structure and function, and its combination with ACEIs/ARBs and beta-blockers further inhibits ventricular remodeling and improves cardiac function more significantly.

Coronary collateral circulation is one of the primary factors affecting the clinical prognosis of patients with AMI, which occurs by forming microvascular interatrial pathways during severe stenosis and chronic occlusion of the coronary arteries to provide additional blood supply for the myocardium [22]. Li and colleagues investigated the mechanism of PIT through animal experiments and found that PIT upregulated VEGF and NO expression in the blood and facilitated collateral formation remotely in the ischemic myocardium [23]. Chen et al. found that the expression of endothelial nitric oxide

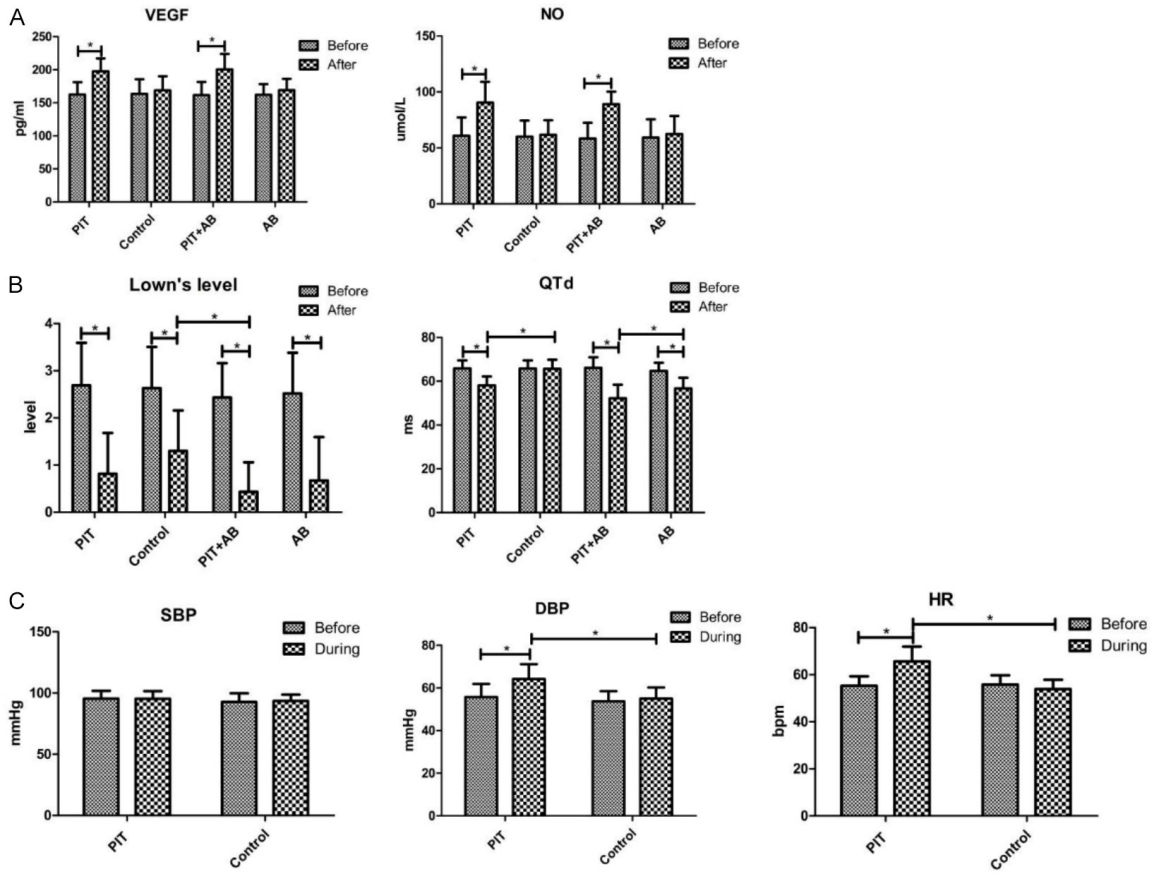

Figure 3. (A, B) Comparison of revascularization (A) and arrhythmia risk (B) among the four groups. (C) Comparison of blood pressure and heart rate between the PIT and control groups during the intervention. *The difference was statistically significant ($P < 0.05$).

synthase was highly related to the levels of VEGF and NO, and these substances were transported by the blood to remote ischemic areas facilitating collateral formation [24]. These findings are consistent with the results of the present study in which VEGF and NO levels in blood were significantly increased in the PIT and PIT+AB groups after 3 months of intervention. Combined with previous experiments, these findings indicate that PIT can increase VEGF and NO levels in the blood and act distally in the coronary vessels, facilitating collateral formation.

The overall survival and even the quality of life of patients with AMI have improved significantly with the rapid development of percutaneous coronary intervention and the increasing number of standardized treatments for AMI. However, ventricular arrhythmias, especially persistent ventricular tachycardia or ventricular fibrillation, are frequent in most postoperative surgical patients, leading to disturbance of hemodynamics, which seriously threatens patient survival and prognosis. Hitherto, ventricular arrhythmia phenomena after AMI have not been fully elucidated. It is believed that cardiac reperfusion after AMI often causes myocardial reperfusion injury, especially reperfusion arrhythmias, such as tachyarrhythmias, ventricular fibrillation and premature ventricular complexes [25]. The mechanisms of reperfusion arrhythmia are summarized as follows: (1) oxygen-free radical accumulation causes myocardial injury; (2) calcium overload of cardiomyocytes affects the stability of ions inside and outside the cell membrane; (3) overdose of catecholamine causes cardiomyocyte calcium overload, eventually leading to arrhythmogenesis; and (4) synthesis of NO is reduced after endothelial cell injury, and the regulation of cardiomyocyte ion channels is weakened, ultimately increasing the risk of arrhythmia. QTd is the difference between the maximum and minimum

values of corrected QT (QTc) in the 12-lead electrocardiogram, and prolonged ventricular repolarization or action potential duration is consistent with prolonged QTd [26]. Changes in potential differences in cardiomyocytes and charge instability occurring after myocardial injury, which result in the repolarization of asynchronous cardiomyocytes, QTc shortening or even shocking, eventually increase QTd [27]. Ion channels of cardiomyocytes are more active in patients with prolonged QTd, and the charge inside and outside the cell membrane is unstable, which increases abnormal electrical charge flow, leading to the development of ventricular arrhythmias [28]. The Lown classification is one of the methods used to evaluate the risk of ventricular arrhythmias. It is well-established that a Lown classification grade ≥ III reflects pathological significance. The current study assessed the risk of ventricular arrhythmias using the Lown classification. It was found that the Lown classification decreased significantly in all four groups after 3 months of intervention, and QTd decreased significantly in the PIT, PIT+AB and AB groups. In addition, the Lown classification and QTd decreased more significantly in the PIT+AB group than in the AB group ($P < 0.05$). Overall, these results suggest that PIT further reduces the risk of ventricular arrhythmias based on the received conventional drug treatment.

BP is the primary determinant of coronary blood flow, and DBP affects coronary bloodstream perfusion directly. BP in patients with coronary artery disease should be controlled not only for declining myocardial oxygen consumption but also for enhancing coronary bloodstream perfusion. Studies have demonstrated that the prevalence of cardiovascular events increases with reductions in DBP [29]. The International Verapamil SR/Trandolapril (INVEST) study showed that the "J" point of DBP was 70 mmHg, and the incidence of angina increased due to decreased coronary bloodstream perfusion when DBP was < 70 mmHg [30]. The present study found that DBP and HR increased substantially during PIT compared with the control group, whereas SBP showed no effect. Taken together, these data confirmed that PIT may enhance coronary bloodstream perfusion by increasing DBP without any effect on myocardial oxygen consumption due to the lack of a significant change in SBP.

As a safe, simple, cost-effective mode of rehabilitation training, PIT can be used as an adjuvant therapy in patients with AMI and hypotension or bradycardia. Our findings suggest that PIT can further inhibit early ventricular remodeling and improve cardiac function by depressing RAAS activity, and it has a positive effect on promoting coronary collateral circulation by increasing VEGF and NO levels while acting in the remote ischemic myocardium. In addition, the risk of ventricular arrhythmias in patients with AMI decreased significantly. Intriguingly, DBP and HR increased and SBP remained unchanged during PIT, which had a positive effect on coronary bloodstream perfusion. However, the effects of the small sample size and the convenience sampling may have an unfavorable influence on the results of the study. Finally, the specific mechanism by which PIT inhibits ventricular remodeling and decreases the risk of ventricular arrhythmias remains elusive, warranting further investigation to confirm these findings.

Acknowledgements

This work was supported by the Technology Development Program of Suzhou (SYSD2019-202) and Science and Technology Development Program of Suzhou Ninth People's Hospital (YK202104). The authors gratefully acknowledge easy editing Ltd. for the English language editing.

Disclosure of conflict of interest

None.

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