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ORIGINAL RESEARCH

Impact of remote ischemic preconditioning on the T-lymphocyte mitochondrial damage index: a randomized clinical trial

Zhenzhou Zhao[1,†], Mingxing Lv[1,†], Xuejie Li[1], Muwei Li[1,*]

[1]Heart Center of Henan Provincial People's Hospital, Central China Fuwai Hospital, Central China Fuwai Hospital of Zhengzhou University, Henan Provincial People's Hospital, 450003 Zhengzhou, Henan, China

***Correspondence**
muweili0207@163.com
(Muwei Li)

[†] These authors contributed equally.

Abstract

Background: The role of remote ischemic preconditioning (RIPC) in coronary heart disease patients remains uncertain. This study was aimed to assess the RIPC influence on T-lymphocyte mitochondrial damage index (MDI), high-sensitivity troponin-T (hs-TnT) concentration, and the perioperative incidence of adverse events in ST-segment elevation myocardial infarction (STEMI) patients having exceeded the window for emergency reperfusion therapy. Furthermore, the goal was to determine myocardial protective effects of RIPC and investigate its underlying mechanisms. **Methods**: STEMI patients having surpassed the reperfusion therapy time window were randomly assigned to RIPC (n = 32) and control (n = 32) groups. RIPC group underwent upper limb RIPC (four cycles of 5-min cuff inflation to 200 mmHg followed by 5-min of deflation). T-lymphocyte MDI and hs-TnT concentrations were determined once on admission, and then 2 hours before the percutaneous coronary intervention (PCI), conducted after 10 days. Perioperative incidence for no-reflow, cardiac rupture and malignant arrhythmias were recorded. **Results**: T-lymphocyte MDI and hs-TnT concentrations upon admission did not differ much in both groups, however, there was a decrease after 10 days, and of greater magnitude in RIPC group. **Conclusions**: RIPC group exhibited lower incidence of no-reflow during PCI compared to that of control (p = 0.03). RIPC has the potential to mitigate perioperative myocardial injuries in STEMI patients by reducing T-lymphocyte MDI, inhibiting myocardial cell death, and lowering no-reflow risk during PCI. **Clinical Trial Registration**: Registered website: https://clinicaltrials.gov/search?cond=NCT04766749. Registered number: NCT04766749. Registered date: 10/02/2021.

Keywords

Acute myocardial infarction; Remote ischemic preconditioning; Mitochondrial damage; T-lymphocytes; Percutaneous coronary intervention

1. Introduction

ST-segment elevation myocardial infarction (STEMI) is the severe form of coronary heart disease caused by the insufficient blood supply to myocardium because of coronary artery occlusion. It is the leading cause of global mortality and disability. Numerous STEMI patients in China seek medical attention beyond the critical time window to undergo emergency revascularization, which may cause complications such as cardiac rupture, cardiogenic shock, and arrhythmia. They are influenced by uneven medical resource distribution and the other factors. Early percutaneous coronary intervention (PCI) reperfusion can improve patient prognosis, however, it may exacerbate myocardial damage. Certain STEMI patients experience inadequate restoration of myocardial blood perfusion even after the coronary artery recanalization which lead to no-reflow condition [1]. The mechanisms of coronary no-reflow or slow flow are complex that involve microvascular dysfunction, embolism, and ischemia-reperfusion injury (IRI) [2]. Optimizing the perioperative management strategies for these patients is thus imperative.

T-lymphocytes have role in STEMI where they respond to IRI through anti-inflammatory or pro-inflammatory activation [3, 4]. Autopsies of myocardial infarction (MI) patients have revealed the T-lymphocyte infiltration in peri-infarct zone, while the activated T-lymphocytes are observed in the walls of infarct- and non-infarct-related arteries [5]. Furthermore, studies have demonstrated the impairment in T-lymphocyte function and mitochondrial dysfunction in acute myocardial infarction (AMI) patients [6]. They accelerate inflammation and facilitate the synthesis and release of large amounts of reactive oxygen species (ROS) into cytoplasm to exacerbate the myocardial injury [7].

Mitochondria are the dynamic organelles with a mechanism of mitophagy which removes the damaged mitochondria caused by mild stress [8]. Severe stress can induce the mitochondrial permeability transition and impair mitophagy [9], which hinders the abnormal mitochondrial elimination and increases mitochondrial mass (MM) [10]. MM then effects the mitochondrial function [11, 12]. Remote ischemic preconditioning (RIPC) involves repeated, transient, and non-invasive ischemic preconditioning of distal organs (mesentery, kidneys and limbs) in reducing the secondary IRI risk of vital organs after the acute ischemia by activating neural and humoral signalling pathways [13]. RIPC effects are the subject of ongoing debate. Some studies indicate that RIPC reduces infarct size and improves the outcomes in MI patients [14, 15], however, others reveal contrasting conclusions [16]. Preliminary studies of our team demonstrate that RIPC enhances coronary microcirculation, reduces IRI, and improves the prognosis in coronary heart disease patients [17, 18]. Current study was aimed to explore the RIPC impact on T-lymphocyte mitochondrial function in STEMI patients and its perioperative myocardial protective effects.

2. Materials and methods

2.1 Patients

STEMI patients were enrolled in this study who had exceeded the window for emergency reperfusion therapy and admitted to our hospital between October 2022 and February 2023. Patients were randomly grouped into RIPC (n = 32) and control (n = 32). Inclusion criteria were as follows: (1) age 18 to 80 years; (2) STEMI onset >12 h with no indication of emergency reperfusion therapy; (3) left ventricular ejection fraction (LVEF) of >40%; (4) availability of clinical and biological data; and (5) provision of written informed consent. Exclusion criteria included: (1) age >80 years; (2) inability towards RIPC treatment (because of the conditions like limb defects or difficulty in ruling out the deep vein thrombosis of lower limbs); (3) structural heart disease; (4) heart failure with ≤40% LVEF; (5) ongoing infection, allergies, autoimmune diseases, or usage of anti-inflammatory, antioxidant, or antiviral medications; (6) poor blood pressure control (systolic >180 mmHg or diastolic >110 mmHg), heart rate (>100 beats/min); (7) aortic valve insufficiency, valvular heart diseases, congenital heart disease along with heart failure, or severe arrhythmia; (8) bleeding, peptic ulcers, coagulopathies, cerebral haemorrhage, or craniotomy in the past six months; (9) poor general condition, liver or kidney insufficiency, or malignant neoplasms; (10) contraindications for aspirin, heparin, clopidogrel, and paclitaxel; and (11) allergy to the contrast agents. Fig. 1 shows study flowchart.

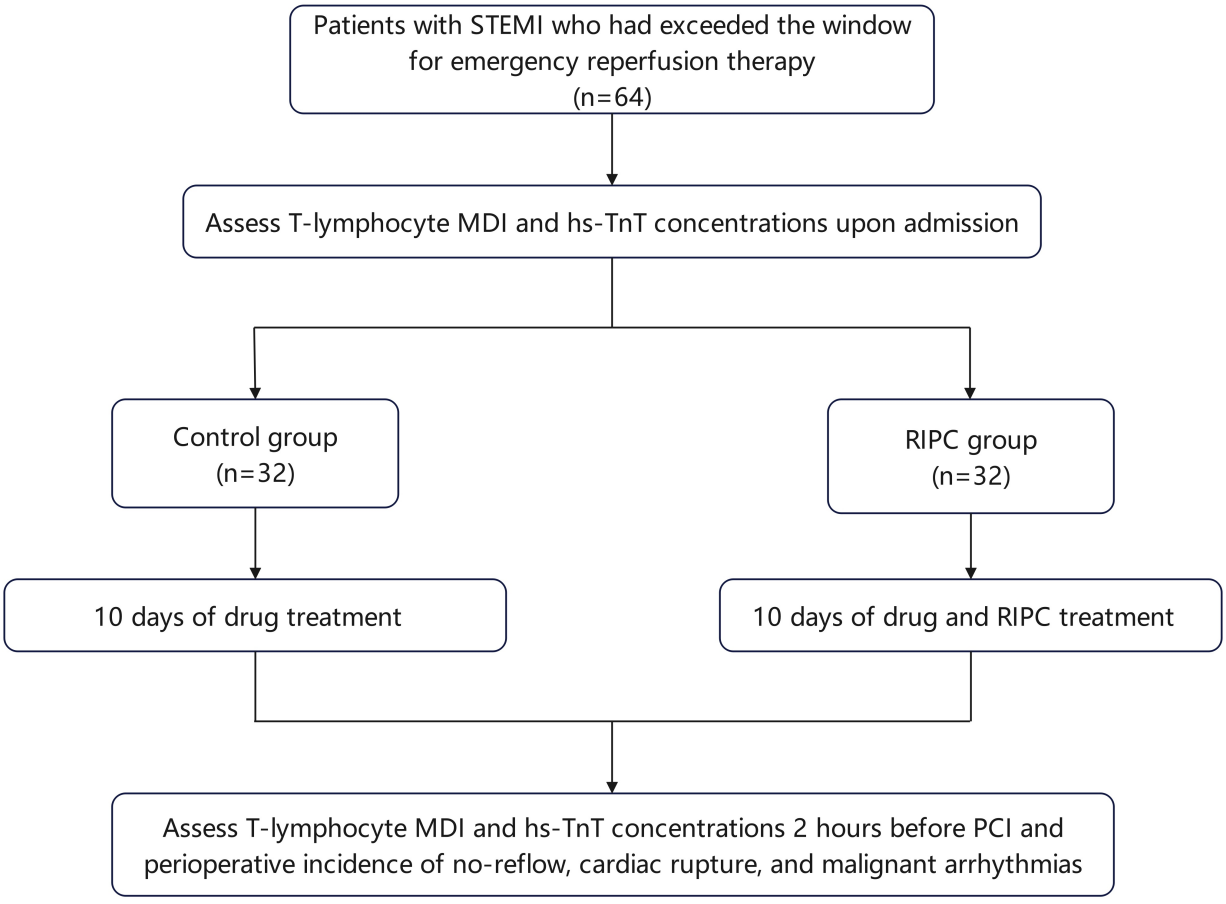

FIGURE 1. Study flowchart. STEMI: ST-segment elevation myocardial infarction; MDI: mitochondrial damage index; hs-TnT: high-sensitivity troponin-T; RIPC: remote ischemic preconditioning; PCI: percutaneous coronary intervention.

2.2 RIPC treatment methods

Patients were laying in the supine position. A cuff was placed on one of the upper limbs and inflated to 200 mmHg which obstructed the arterial blood flow for 5 min followed by 5-min of deflation [19]. The cycle was repeated four times using Jinmaibo ischemic preconditioning therapeutic instrument (L300A, GTHR Medical Technology company, Shenzhen, Guangdong, China). RIPC therapy was given twice a day (morning and evening) for 10 days. It started from the time of admission to the day when PCI was conducted. Furthermore, one RIPC session was carried out 40 min prior to the procedure. Patients in the control group also received cuffs, however, they were not inflated.

2.3 Study measures

The patients' baseline data were recorded pertaining to sex, age, body mass index (BMI), smoking and drinking history, hypertension, diabetes, dyslipidemia, time from onset till presentation, LVEF, malignant arrhythmias during hospitalization, and cardiac rupture. High-sensitivity troponin-T (hs-TnT) concentrations and T-lymphocytes MDI were recorded on admission. After 10 days of drug treatment as per the guidelines, T-lymphocyte MDI and hs-TnT concentrations were reassessed 2 hours before PCI. Interventional physician documented the distribution of culprit vessels, lesion length, diameter, and perioperative incidence of no-reflow, cardiac rupture and malignant arrhythmias.

In this study, thrombolysis in myocardial infarction (TIMI) flow grade classification was employed to evaluate the flow after PCI in culprit coronary artery. No-reflow was defined as the TIMI flow grade <III without the coronary spasm or dissection. Flow cytometry was performed with a mitochondrial dye that selectively binds to mitochondria for determining MM *via* median fluorescence intensity (MFI) [12]. Specific antibodies cluster of differentiation (CD)3, CD4 and CD8) were used to label the lymphocyte subsets for getting respective cell counts. This study derived the mitochondrial damage index (MDI) for lymphocyte subsets using an algorithm based on MFI and subset cell counts (Fig. 2).

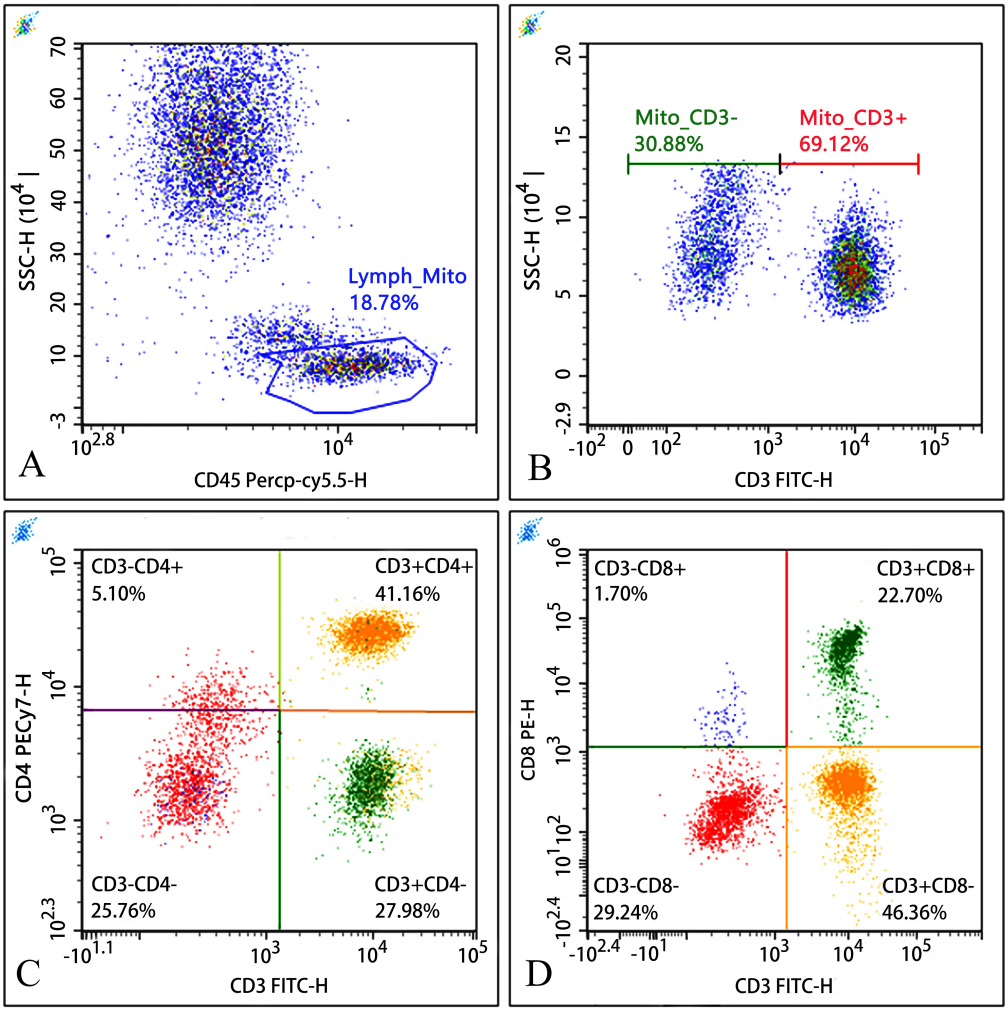

FIGURE 2. Flow cytometry analysis of T cell sub-populations. Note: (A) CD45-PerCP-Cy5.5-H and SSC-H plot identified Lymph cells as CD45 high and SSC low. (B) CD3-FITC-H and SSC-H plot identified CD3+ T cells. (C,D) Quadrant gate defined T cells as CD3+ CD4+, and CD3+ CD8+.

Abbreviations: SSC: side scatter; Percp-cy5.5: peridinin chlorophyll protein-Cyanine5.5; PECy7: phycoerythrin-Cyanine7; FITC: fluorescein isothiocyanate.

2.4 Statistical analysis

Normally distributed continuous variables were expressed as mean ± standard deviation. The inter-group differences were assessed using one-way analysis of variance (ANOVA). Non-normally distributed data were presented as median and quartiles. The between-group comparisons were processed using Mann-Whitney U test. Two-way repeated measures ANOVA analyzed the repeated measures data. Bonferroni correction was employed as the *post hoc* test to adjust *p*-values. Categorical data represented the number of cases and percentages. Inter-group differences were evaluated by the Chi-squared test. All the statistical analyses were conducted as two-tailed tests with statistical significance set at $p < 0.05$. The data were analyzed using SPSS version 22.0 IBM, Armonk, NY, USA).

3. Results

The groups had no statistically significant differences pertaining to patient age, male-to-female ratio, BMI, LVEF, hypertension, hyperlipidemia, diabetes comorbidity ratio, smoking and drinking history ratio, and duration from onset to presentation (Table 1).

No significant differences were found in the characteristics of coronary artery lesions of two groups. Perioperative times to cardiac rupture, mechanical injuries, and malignant arrhythmias did not differ much for the groups (Table 2). However, RIPC group had lower incidence of no-reflow during PCI compared to control ($p = 0.03$).

No significant differences were found in hs-TnT levels, and MDI of CD3+, CD4+ and CD8+ T-lymphocytes between the groups upon admission. Patients in RIPC group exhibited reduced hs-TnT levels and MDI of CD3+, CD4+ and CD8+ T-lymphocytes after 10 days of standard treatment (Table 3).

TABLE 1. The baseline characteristics.

	RIPC (n = 32)	Control (n = 32)	*p*
Age (yr)	55 (53.25, 57.75)	58 (51.00, 65.75)	0.155
Male	20 (62.50)	17 (53.10)	0.448
Hypertension	22 (68.70)	16 (50.00)	0.127
Diabetes mellitus	8 (25.00)	11 (34.30)	0.412
Hyperlipidemia	11 (34.30)	7 (21.80)	0.266
Drinking history	16 (50.00)	14 (43.70)	0.616
Smoking history	15 (46.80)	18 (56.20)	0.453
BMI (kg/m^2)	27.31 (22.80, 29.84)	25.91 (21.80, 30.38)	0.957
LVEF (%)	43.5 (38.25, 48.00)	46.0 (41.00, 53.00)	0.124
Time from onset to presentation (h)	34 (30.00, 41.00)	30 (20.25, 39.75)	0.141

BMI: body mass index; LVEF: left ventricle ejection fraction; RIPC: remote ischemic preconditioning. Smoking defined as >1 piece/day for 6 consecutive or cumulative months; Drinking defined as more than once/week for continuous or cumulative 12 months. Values as the median (interquartile range) or n (%).

TABLE 2. Coronary lesion features.

	RIPC (n = 32)	Control (n = 32)	*p*
Target vessel			
LAD/D	17 (53.10)	14 (43.70)	
LCX/OM	9 (28.10)	7 (21.80)	0.366
RCA/PDA/PLV	6 (18.70)	11 (34.30)	
Lesion length (mm)	26 (20.00, 29.00)	25 (18.25, 28.00)	0.353
Reference vessel diameter (mm)	3.2 (2.83, 3.58)	3.1 (2.93, 3.88)	0.356
Cardiac rupture	1 (3.10)	0	0.313
Malignant arrhythmias	2 (6.30)	2 (6.30)	1.000
No-reflow	3 (9.40)	10 (31.30)	0.030

LAD/D: left anterior descending/diagonal branch; LCX/OM: left circumflex/obtuse marginal branch; RCA/PDA/PLV: right coronary artery/posterior descending artery/posterior lateral vessel; RIPC: remote ischemic preconditioning. Values as the median (interquartile range) or n (%).

TABLE 3. The hs-TnT concentrations and T-lymphocyte MDI on admission and before PCI.

	RIPC (n = 32)	Control (n = 32)	*p*
Pre hs-TnT (pg/mL)	2032.46 (1372.46, 2343.47)	2048.02 (1665.01, 2533.14)	0.175
Post hs-TnT (pg/mL)	226.27 (159.85, 272.07)	270.71 (202.45, 337.14)	0.008
Pre CD3+ TLMDI	5.26 (4.77, 6.09)	5.38 (4.86, 5.67)	0.742
Post CD3+ TLMDI	4.35 (4.10, 4.61)	4.68 (4.36, 4.80)	0.007
Pre CD4+ TLMDI	5.40 (4.72, 6.41)	5.38 (4.73, 5.94)	0.702
Post CD4+ TLMDI	4.71 (4.59, 5.22)	5.05 (4.71, 5.48)	0.045
Pre CD8+ TLMDI	4.30 (3.82, 4.58)	4.17 (3.28, 4.65)	0.347
Post CD8+ TLMDI	2.68 (2.26, 2.99)	2.85 (2.67, 3.25)	0.031

hs-TnT: high-sensitivity troponin-T; TLMDI: T-lymphocytes mitochondrial damage index; RIPC: remote ischemic preconditioning. Values as the median (interquartile range).

4. Discussion

This preliminary study is the first to investigate effect of pre-PCI RIPC on T-lymphocyte mitochondrial function in STEMI patients beyond the reperfusion time window. Results show that: (1) the mitochondrial damage index of CD3+, CD4+ and CD8+ T-lymphocytes, and hs-TnT concentrations in RIPC group are decreased compared to the control; (2) the incidence of no-reflow during PCI in RIPC group is reduced compared to the control.

Evidence suggests T-lymphocytes role in myocardial injury, healing, and remodelling the post myocardial infarction [3, 20]. CD3+ T cells have the central part in immune system and can differentiate into CD4+ and CD8+ T-lymphocytes [21, 22]. CD4+ T-lymphocytes further differentiate into subsets like T helper (Th)1, Th2, Th17 and regulatory (Treg) cells, depending on the cytokines produced and their surface marker expressions [23]. Evidence indicates the CD4+ T-lymphocytes involvement in myocardial injury after the myocardial infarction [24]. Cardiac glucocorticoid-induced leucine zipper (GILZ) protects the mitochondrial membrane potential (ψm) and reduces apoptosis and necrosis. Th17 cells increase after the myocardial infarction which decrease the cardiac GILZ [25]. CD4+ T-lymphocytes infiltrate the myocardium within days of post-myocardial infarction in non-reperfused hearts and shift to Th1 cytokine profile [26, 27] for elevating Th1/Th2 cell ratio in AMI patients and increasing the susceptibility to adverse cardiac events [28]. Animal experiments demonstrate that CD4+ T-lymphocytes promote the myocardial IRI progression. In wild-type and lymphocyte-deficient recombination activating gene 1 (RAG1) knockout mice subjected to transient ischemia-reperfusion, the experimental group shows smaller infarcts. This outcome is reversed by CD4+ T-lymphocyte transplantation [29]. Studies have identified that CD4+ T-lymphocytes secrete interleukin (IL)-17A and IL-21 to promote IRI progression [26]. Some studies report the impaired function of Treg cells derived from CD4+ T-lymphocytes in ischemic cardiomyopathy. This results in suboptimal immunosuppression, transforming from anti-inflammatory to pro-inflammatory phenotype, promoting immune activation, and exacerbating left ventricular remodelling [30]. Treg cells suppress pro-inflammatory changes, reduce inflammatory response after ischemia, and beneficial for left ventricular remodelling in myocardial infarction [31–33]. The imbalance of oxidative phosphorylation in mitochondrial dysfunction affects CD4+ T-lymphocytes differentiation and diminishes the number of Treg cells, which triggers series of inflammatory reactions and exacerbates tissue damage [34, 35]. The potential mechanisms of RIPC thus include improving T-lymphocytes mitochondrial function, influencing T-lymphocytes differentiation, mitigating myocardial damage by enhancing anti-inflammatory effects, and improving IRI.

RIPC has gained attention since its introduction into clinical practice because of its simplicity, ease of use, and high safety profile. Studies have confirmed its cardioprotective effects where RIPC improves coronary artery IRI and reduces PCI-related myocardial infarction incidence [36–38]. RIC-STEMI trial regarding STEMI patients' prognosis has demonstrated that RIPC reduces the combined hard clinical endpoint of cardiac mortality and hospitalization for heart failure [39]. However, CONDI-2/ERIC-PPCI trial reach the opposite conclusion where RIPC does not improve the clinical outcomes of STEMI patients undergoing PCI [40]. Currently, there is no consensus on the optimal strategy for RIPC. Variations in cycle counts, ischemic areas, durations, and degrees of compression may yield diverse outcomes in patients of diverse races. Factors such as age, diabetes, hypertension, and medication can also influence the RIPC efficacy. Anaesthetics in surgery such as propofol may attenuate the cardioprotective effects of RIPC. However, RIPC has demonstrated safety and thus encouraging further explorations into optimal strategies, clinical effects, and underlying mechanisms of RIPC.

Our earlier investigations had confirmed that RIPC improved coronary microcirculation function and alleviated IRI. In this study, RIPC was implemented to STEMI patients surpassing the reperfusion time window. RIPC's capability was demonstrated to improve T-lymphocytes mitochondrial function, mitigate myocardial damage, and reduce the risk of post-PCI no-reflow. These findings were consistent with the outcomes of previous studies [41]. However, this study had certain limitations. Firstly, it was a single-center study with smaller sample size which introduced bias because of insufficient sample representation. Secondly, strict inclusion and

exclusion criteria were ensured. There were no statistical differences in the demographic characteristics, clinical features, and medication used by the RIPC and control groups. Nonetheless, further research involving the participants from diverse ethnicities and regions was imperative in providing geographic clustering and population homogeneity to validate the study's findings.

5. Conclusions

RIPC has the potential to reduce no-reflow incidence during PCI, mitigate the extent of myocardial injury in STEMI patients by decreasing MDI of T-lymphocytes, improving mitochondrial function, and reducing oxidative stress and inflammation.However, the findings need verification through large-scale studies. This pilot study despite the limitations has helped in improving the understanding of remote ischemic preconditioning role in T-lymphocyte mitochondrial damage index regarding STEMI treatment.

ABBREVIATIONS

AMI, acute myocardial infarction; GILZ, glucocorticoid-induced leucine zipper; hs-TnT, high-sensitivity troponin-T; IRI, ischemia-reperfusion injury; LVEF, left ventricular ejection fraction; MDI, mitochondrial damage index; MM, mitochondrial mass; MFI, median fluorescence intensity; PCI, percutaneous coronary intervention; RIPC, remote ischemic preconditioning; STEMI, ST-segment elevation myocardial infarction; RAG1, recombination activating gene 1; IL, interleukin; CD, cluster of differentiation; Th, T helper; ROS, reactive oxygen species; BMI, body mass index; TIMI, thrombolysis in myocardial infarction; ANOVA, one-way analysis of variance; LAD/D, left anterior descending/diagonal branch; LCX/OM, left circumflex/obtuse marginal branch; RCA/PDA/PLV, right coronary artery/posterior descending artery/posterior lateral vessel; TLMDI, T-lymphocytes mitochondrial damage index; Treg, T regulatory; SSC, side scatter; Percp-cy5.5, peridinin chlorophyll protein-Cyanine5.5; PECy7, phycoerythrin-Cyanine7; FITC, fluorescein isothiocyanate.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

ZZZ and MXL—performed the data analyses and wrote the manuscript. XJL—contributed to data collection and funding acquisition. MWL—contributed to the conception of the study and funding acquisition. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted as per the ethical principles of 1975 Declaration of Helsinki and was approved by the Ethics Committee of the Central China Fuwai Hospital of Zhengzhou University with the Approval No: 6-2021 and Date: 24 April 2021. Written informed consent was obtained from all participants. The study was registered at ClinicalTrials.gov with the number NCT04766749, on 10 February 2021.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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