Future Integrative Medicine **2023** vol. 2(4) | 181–188
DOI: 10.14218/FIM.2023.00034

Original Article

Effects of Remote Ischemic Preconditioning Combined with *Radix salviae* Decoction on Coronary Stenosis and Prognosis: A Prospective Pilot Study

Qingqing Liu[1#], Guangchu Pan[2#], Peizhong Liu[1#], Aimeng Zhang[1], Kaili Wang[1], Rongyuan Yang[1*] and Qing Liu[1*]

[1]*State Key Laboratory of Traditional Chinese Medicine Syndrome, The Second Clinical School of Medicine, Guangzhou University of Chinese Medicine, Guangdong Provincial Hospital of Chinese Medicine-Zhuhai Hospital, Zhuhai, China;* [2]*The Fourth People's Hospital of Zhanjiang, Zhanjiang, China*

Received: June 16, 2023 | **Revised:** July 25, 2023 | **Accepted:** October 10, 2023 | **Published online:** November 21, 2023

Abstract

Background and objectives: Coronary stenosis is responsible for angina attacks in coronary heart disease (CHD). A prospective pilot study was conducted to investigate the effects of combining remote ischemic preconditioning (RIPC) with Radix salviae decoction (RSD).

Methods: A total of 60 patients diagnosed with CHD were enrolled and divided into the control group and the RIPC-RSD treatment group. The primary outcome was the frequency of angina attacks, while the secondary outcomes included Canadian Cardiovascular Society levels, emergency medications, and prognosis indicators.

Results: A total of 57 patients were included in the final analysis. Demographic characteristics and vessel stenosis comparisons showed similar results ($p > 0.05$). There was no significant difference in the frequency of angina attacks before ($\chi^2 = 2.170$, $p = 0.404$) or after ($\chi^2 = 1.509$, $p = 0.662$) treatment. Similarly, there was no significant difference in CCS levels of angina attacks between the two groups before ($\chi^2 = 1.504$, $p = 0.681$) or after ($\chi^2 = 1.392$, $p = 0.707$) treatment. Although there was no significant difference in the use of emergency medications for angina attacks before ($\chi^2 = 1.321$, $p = 0.517$) or after ($\chi^2 = 2.457$, $p = 0.356$) treatment, a significant decrease in the frequency of emergency medications was observed ($Z = -2.188$, $p = 0.029$). However, the RIPC-RSD treatment did not have a significant impact on the prognosis (cardiac death, $\chi^2 = 1.831$, $p = 0.176$; target vessel revascularization, $\chi^2 = 1.111$, $p = 0.292$; rehospitalization, $\chi^2 = 0.495$, $p = 0.482$) of coronary stenosis in CHD patients.

Conclusions: Due to the limitations of a relatively small sample size, this prospective pilot study did not observe a significant effect of RIPC-RSD on angina attacks and prognosis in CHD patients, but it implied potential efficacy in reducing the frequency of emergency medications.

Keywords: Coronary heart disease; Remote ischemic preconditioning; *Radix salviae* decoction; Stenosis; Prognosis.

Abbreviations: ALT, alanine transaminase; AST, alanine transaminase; CCS, Canadian Cardiovascular Society; CHD, coronary heart disease; Cr, creatinine; DM, diabetes mellitus; INR, international normalized ratio; I/R, ischemic/reperfusion; IQR, interquartile range; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; MI, myocardial infarction; RCA, right coronary artery; RIPC, remote ischemic preconditioning; RSD, *Radix salviae* decoction; TCM, traditional Chinese medicine.

[*]**Correspondence to:** Rongyuan Yang and Qing Liu, The Second Clinical School of Medicine, Guangzhou University of Chinese Medicine, Guangdong 510120, China. ORCID: https://orcid.org/0000-0002-8792-8017 (RYY); https://orcid.org/0000-0002-2199-2999 (QL). Tel: 02081887233 (RYY); +86 13631223512 (QL), Fax: 02081887233 (RYY); 0756-3325088 (QL), E-mails: yangrongyuan@163.com (RYY); 851757626@qq.com (QL)

[#]Contributed equally to this work.

How to cite this article: Liu Q, Pan G, Liu P, Zhang A, Wang K, Yang R, *et al*. Effects of Remote Ischemic Preconditioning Combined with *Radix salviae* Decoction on Coronary Stenosis and Prognosis: A Prospective Pilot Study. *Future Integr Med* 2023;2(4):181–188. doi: 10.14218/FIM.2023.00034.

Introduction

Coronary heart disease (CHD) is a global disease characterized by angina attacks. The narrowing or blockage of coronary arteries leads to myocardial ischemia and hypoxia, resulting in abnormal myocardial cell metabolism. This abnormality triggers a response in the nerves and blood vessels associated with the heart muscle, causing angina pain.[1] Resting, sitting down, or ceasing physical activity are common preferences for angina patients, and relief can be achieved within minutes through rest or emergency use of nitroglycerin. Other factors such as emotional stress, overeating, and physical exertion can also trigger or exacerbate angina attacks. Both randomized controlled trials and real-world studies have shown that these factors can increase cardiac workload, intensify myocardial hypoxia, and lead to angina

© 2023 The Author(s). This article has been published under the terms of Creative Commons Attribution-Noncommercial 4.0 International License (CC BY-NC 4.0), which permits noncommercial unrestricted use, distribution, and reproduction in any medium, provided that the following statement is provided. "This article has been published in *Future Integrative Medicine* at https://doi.org/10.14218/FIM.2023.00034 and can also be viewed on the Journal's website at https://www.xiahepublishing.com/journal/fim".

attacks. Psychosocial stress, particularly mental stress ischemia, may play a significant role in daily angina.[2,3] Increased frequency and severity of angina attacks associated with myocardial ischemia and hypoxia often necessitate an increased use of emergency medications. Thus, angina attacks and emergency medications were usually used to evaluate the occurrence and severity of CHD in patients.

In addition to conventional medications in treatment guidelines, physiotherapy in modern cardiac rehabilitation has become increasingly popular in the prevention and treatment of CHD. Remote ischemic preconditioning (RIPC) is a well-established technique in cardiac rehabilitation that involves inducing short periods of remote limb ischemia and reperfusion to enhance the tolerance of organs or tissues to ischemic/reperfusion (I/R) injury. This non-invasive method has shown potential for clinical application in ischemic cardiovascular diseases.[4] RIPC is considered a safe and well-tolerated non-pharmacological therapy. Studies have suggested that RIPC not only benefits myocardial injury in patients undergoing various surgical interventions,[5] but also improves myocardial ischemia,[6,7] potentially reducing angina attacks. In a 2016 study, RIPC was found to reduce systolic blood pressure and improve arterial compliance and heart rate modulation reserve, which may contribute to its antianginal effect.[8] Another study in 2018 demonstrated that RIPC prior to percutaneous coronary intervention prevented periprocedural myocardial damage in patients with complex coronary lesions.[9] However, the role of RIPC remains uncertain, as indicated by a large multicenter study that reported limited clinical outcomes in patients undergoing cardiac surgery.[10] A recent report published in 2023 discussed the challenges and opportunities of RIPC in clinical applications, highlighting promising results in cerebrovascular disease trials that may reignite research prospects for RIPC in cardiovascular diseases.[11] Given the controversial effects of RIPC in clinical settings, we designed and conducted this preliminary clinical trial to investigate the role of RIPC combined with classical Chinese herbal decoction in coronary stenosis and prognosis. We aimed to determine whether the combination of RIPC and herbal medicine could yield improved clinical outcomes in cardiovascular diseases.

Moreover, herbal medicines are widely used in Asian countries to prevent and treat CHD along with physiotherapy. *Radix salviae* decoction (RSD) is an herbal formula consisting of *Radix salviae,* sandalwood, and sand kerne. This formula is known for its ability to activate blood circulation, remove blood stasis, and relieve pain, making it commonly used in the treatment of CHD. Animal experimental studies conducted in the 1990s have demonstrated that *Radix salviae*, the key component of RSD, has negative inotropic effects that can enhance coronary blood flow and effectively protect the heart from I/R injury.[12] Subsequent research has shown that RSD and its active ingredients can prevent various cardiovascular diseases, including I/R-related heart diseases,[13] myocardial infarction, and atherosclerosis.[14] Numerous studies published in Chinese journals have also highlighted the efficacy of RSD in improving myocardial ischemia.[15] The clinical significance of organ protection after I/R is well recognized, and *Radix salviae* root extract has a significant ameliorative effect on microcirculatory impairment and target organ damage caused by I/R.[16] The cardioprotective effect of RSD on acute ischemic myocardial injury in rats may be attributed to its anti-inflammatory and antioxidant properties.[13] Further analysis of the components of RSD has revealed that *Salvia miltiorrhiza* contains lipophilic components (such as tanshinone I, tanshinone IIa, tanshinone IIb, cryptotanshinone, and dihydrotanshinone) and hydrophilic components (such as tanshinin, tanshinolic acid A/B, and protocatechuic aldehyde). These components exert cardioprotective effects through multiple targets and pathways,[17,18] and there may be synergistic effects among them.[19,20] Therefore, RSD offers multiple therapeutic modalities for the treatment of ischemic cardiomyopathy,[21] which forms the foundation for the present study.

This study was designed as a prospective pilot study protocol to investigate the effects of combining RIPC with RSD in the treatment of angina pectoris in patients with CHD. The study aimed to evaluate the impact of RIPC combined with RSD on the frequency and severity of angina attacks, the frequency of emergency medication use, and the prognosis of patients.

Materials and methods

Ethical approval and informed consent

This study has received approval from the Ethics Committee of Guangdong Provincial Hospital of Traditional Chinese Medicine (TCM), with a registration number of BF2021-242. The collection of all samples was conducted in strict accordance with the principles outlined in the Helsinki Declaration and with the informed consent of all participants.

Patient source

Patients were recruited for the study based on specific diagnostic criteria, as well as inclusion and exclusion criteria. Initially, a total of 60 patients who underwent percutaneous coronary intervention and were diagnosed with CHD between 2020 and December 2022 at Guangdong Provincial Hospital of TCM were included. These patients were then divided into two groups, with 30 patients in each group. The first group received basic drug therapy for the prevention and treatment of CHD (*e.g.*, antiplatelet aggregation and lipid-lowering drugs) and served as the control group. The second group received basic drug therapy combined with RIPC and RSD therapy, and was referred to as the RIPC-RSD group.

Group treatment

For the control group, basic drug therapy typically included the administration of antiplatelet medications, lipid-lowering drugs, heart rate control medications, and medications to manage hypertension or hyperglycemia. In the RIPC-RSD group, patients received the same basic drug therapy as the control group, along with RIPC therapy. The RIPC therapy involved inflating the subject's upper arm to 200 mmHg, followed by 5 m of ischemia and 5 m of reperfusion. This procedure was repeated for a total of five rounds to complete the therapy. Additionally, patients in the RIPC-RSD group were prescribed oral RSD granules, which consisted of 15 g of *Radix salviae*, 10 g of sandalwood, and 10 g of sand kernel. These granules were decocted in water and taken twice daily for a period of 5 days. Both groups of patients continued their basic medications after being discharged from the hospital.

Diagnostic criteria

The diagnosis of patients with CHD was based on the 2021 Chinese "Guidelines for the Rational Use of Drugs in Coronary Heart Disease" and the 2022 "Chinese Medicine Treatment Plan and Clinical Pathway" for TCM diagnosis.

Inclusion and exclusion criteria

Inclusion criteria

Firstly, patients who meet the diagnostic criteria for CHD in both modern medicine and TCM. Secondly, patients who can complete the follow-up period. Finally, patients who voluntarily agree to participate and have signed an informed consent form.

Exclusion criteria

Firstly, patients with abnormal mental consciousness or unstable vital signs who are unable to cooperate. Secondly, patients with contraindications or allergies to relevant medications. In addition, patients who have participated in other clinical trials within the past month. Finally, patients who are over 85 years old, pregnant, or planning to become pregnant, nursing women, or infants.

Abscission criteria

Firstly, patients who withdrew from the trial without experiencing adverse effects or poor efficacy. Secondly, patients who were lost to follow-up.

Termination criteria

(1) Medical necessity to terminate the trial in the opinion of the investigator. (2) Patient withdrawal from the trial on his or her own initiative. (3) Those who suffer serious adverse reactions and are unable to adhere to continued treatment. Firstly, the investigator determined that it was medically necessary to terminate the trial for the subject. Secondly, the patient voluntarily withdraws from the trial. Finally, patients who experience serious adverse reactions and are unable to continue treatment.

Primary and secondary outcomes

The frequency of angina episodes was the primary outcome. The severity of angina attacks, the frequency of emergency medications, and the prognosis of coronary stenosis following the criteria of Canadian Cardiovascular Society (CCS) criteria were the secondary outcomes. All outcomes were observed within 18 months after treatment. The frequency of angina episodes was defined as the primary outcome. The severity of angina attacks, the frequency of emergency medication use, and the prognosis of coronary stenosis based on the CCS levels were defined as secondary outcomes. All outcomes were observed within one and a half years after treatment.

Safety index monitoring

During the treatment of patients, utmost attention was given to monitoring and addressing any adverse reactions that may occur. All adverse reactions were carefully observed, and appropriate treatment was provided when necessary. Detailed documentation of these adverse reactions was maintained promptly.

Statistical analysis

Data sets were analyzed with SPSS v26.0, (IBM Corp., Armonk, NY, USA) and R (v3.6.2, http://www.r-project.org). Continuous data were reported as means ± standard deviation and assessed for normal distribution using the Kolmogorov-Smirnov test. If continuous data was normally distributed, Student's *t*-test for two independent samples was used to compare between-group differences. Otherwise, the Mann-Whitney *U* test was used. Categorical variables were reported as frequencies and percentages (%), and group comparisons were conducted with χ^2 tests, with or without continuity correction, or Fisher's exact test, *p*-values < 0.05 were considered statistically significant.

Results

Demographic characteristics of subjects

Demographic characteristics of subjects were determined before analyzing the efficacy of RIPC and RSD combination therapy for CHD. Initially, a total of 60 patients were enrolled based on the specified criteria. Three patients were lost to follow-up. The remaining 57 patients completed follow-up and were included in the final analysis. Demographic characteristics, including sex, age, duration of hospital stay, comorbidities (*e.g.*, hypertension, diabetes, hyperlipidemia), diagnostic subsets, and hematological indicators (*e.g.*, aspartate aminotransferase, alanine aminotransferase, creatinine, and international normalized ratio), were assessed. Differences between the control group ($n = 30$) and the RIPC-RSD group ($n = 24$) were not significant, indicating comparable baseline characteristics between the two groups (Table 1).

Baseline vessel features in stenosis

Given that vessel features, such as stenosis severity, have been identified as predictors of stenosis, we aimed to evaluate the baseline vessel characteristics.[22] Before examining the effect of RIPC-RSD, we compared the baseline stenosis characteristics between the control and RIPC-RSD groups. The degree of stenosis was calculated as the percentage of occluded area, and the severity of stenosis was assessed using the Gensini score. The comparison of stenosis severity revealed no significant difference between the two groups ($p > 0.05$) (Table 2). Additionally, the comparison of the number of stenotic vessels also demonstrated no statistically significant difference ($\chi^2 = 2.953$, $p = 0.399$) (Table 3). The data suggest that the baseline vascular characteristics and severity of stenosis at in the two groups were similar.

Effects of RIPC-RSD on the frequency and severity of angina attacks

The frequency and severity of angina attack as the primary outcome were analyzed to evaluate the efficacy of RIPC-RSD combination treatment for CHD. On one hand, the frequency of angina attacks was stratified into three groups, none, fewer than three episodes per week, and more than three episodes per week. The frequency of angina attacks in the control and RIPC-RSD groups before RIPC-RSD treatment was compared. No significant differences were observed between the two groups ($\chi^2 = 2.170$, $p = 0.404$) (Table 3). A similar comparison was conducted between the control and RIPC-RSD groups after RIPC-RSD treatment, and again, no significant differences were found ($\chi^2 = 1.509$, $p = 0.662$) (Table 3). Furthermore, the reduction in angina attack frequency after treatment was calculated, and the comparison between the two groups did not yield a significant difference ($Z = -1.066$, $p = 0.286$) (Table 4).

On the other hand, the severity of angina attacks was evaluated using the CCS levels, and the number of patients in each level was recorded. The CCS levels of angina attacks in the control and RIPC-RSD groups before RIPC-RSD treatment were compared, and no substantial difference was observed between the two groups ($\chi^2 = 1.504$, $p = 0.681$). Similarly, a comparison of CCS levels in the control and RIPC-RSD groups after RIPC-RSD treatment revealed no significant difference ($\chi^2 = 1.392$, $p = 0.707$) (Table 3). These findings indicate that the combination treatment of RIPC and RSD did not have a significant impact on the frequency and severity of angina attacks in patients with CHD.

Effects of RIPC-RSD on emergency medications

Emergency medications are an important factor in evaluating the severity of angina attacks, so we selected the frequency of emergency medications as the key secondary outcome to evaluate the efficacy of RIPC-RSD combination treatment for CHD. The medicine (*e.g.*, nitroglycerin tablets) used temporarily in addition to

Table 1. Comparison of the baseline characteristics between groups

Variables	Control, *n* = 30	RIPC + RSD, *n* = 27	*p*
Sex			1.000
Female	9 (30.0)	9 (33.3)	
Male	21 (70.0)	18 (66.7)	
Age	62.6 (9.78)	64.2 (11.1)	0.571
Days in hospital	7.00 [5.25;9.00]	7.00 [6.00;8.50]	0.852
Comorbidities			
Hypertension	15 (50.0)	19 (70.4)	0.195
DM	10 (33.3)	10 (37.0)	0.988
Hyperlipidemia	18 (60.0)	14 (51.9)	0.725
Comorbidities			0.800
0	4 (13.3)	4 (14.8)	
1	13 (43.3)	9 (33.3)	
2	9 (30.0)	8 (29.6)	
3	4 (13.3)	6 (22.2)	
Diagnosis			1.000
angina	29 (96.7)	26 (96.3)	
MI	1 (3.33)	1 (3.70)	
Hematological indicators			
AST	20.2 [15.1; 29.1]	18.6 [14.7; 22.3]	0.190
ALT	19.6 [11.7; 25.4]	21.3 [14.8; 27.1]	0.507
Cr	78.0 [63.1; 93.0]	67.7 [55.0; 85.1]	0.152
INR	0.92 [0.87; 0.98]	0.91 [0.88; 0.96]	0.873

Data are presented as *n* (%) or mean [IQR]. ALT, alanine transaminase; AST, alanine transaminase; Cr, creatinine; DM, diabetes mellitus; RSD, Radix salviae Decoction; INR, international normalized ratio; IQR, interquartile range; MI, myocardial infarction; RIPC, remote ischemic preconditioning.

conventional pharmacotherapy (*i.e.*, antiplatelet aggregation and lipid-lowering drugs) during an angina attack was considered as an emergency medication, and the frequency of emergency medications per week was recorded and calculated for each patient. The comparison of emergency medication frequency between the control and RIPC-RSD groups before RIPC-RSD treatment revealed no significant difference ($\chi^2 = 1.321$, $p = 0.517$) (Table 3). Similarly, there was no significant difference in emergency medication frequency between the control and RIPC-RSD groups after treatment ($\chi^2 = 2.457$, $p = 0.356$) (Table 3). However, when comparing the reduction in emergency medication frequency after treatment, a significant difference was observed between the two groups ($Z = -2.188$, $p = 0.029$) (Table 5). These findings suggest that RIPC-RSD treatment may help reduce the frequency of emergency medication administration in patients with CHD.

Effects of RIPC-RSD on the prognosis of coronary stenosis

Both the frequency and severity of angina attacks are indicators of the severity of CHD and can impact prognosis. Thus, the indicators for the prognosis of coronary stenosis were then analyzed. The prognosis of coronary artery stenosis in CHD patients was evaluated using three indicators: cardiac death, target vessel revas-

Table 2. Characteristics of vessels in stenosis between groups

Variables	Control, *n* = 30	RIPC + RSD, *n* = 27	P
Stenosis in vessels, %			
LAD	50.0 [20.0; 80.0]	40.0 [15.0; 80.0]	0.949
LCX	0.00 [0.00; 57.5]	30.0 [0.00; 75.0]	0.210
RCA	30.0 [0.00; 86.0]	50.0 [30.0; 60.0]	0.437
Gensini score	12.0 [4.25; 28.0]	15.0 [4.75; 29.5]	0.660

Data are presented as mean [IQR]. RSD, Radix salviae Decoction; IQR, interquartile range; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; RIPC, remote ischemic preconditioning.

Table 3. Comparisons of the number of vessels in stenosis, frequency of angina attack, CCS levels and medicine administration between groups

Variables	Control, *n* = 30		RIPC + RSD, *n* = 27		Z/χ^2	*p*
Number of vessels in stenosis					2.953	0.399
0	11	36.667	7	25.926		
1	9	30.000	6	22.222		
2	4	13.333	3	11.111		
3	6	20.000	11	40.741		
Frequency of angina attacks per week						
Before treatment					2.170	0.404
0	21	70.000	16	59.259		
1~3	9	30.000	9	33.333		
4~7	0	0.000	2	7.407		
After treatment					1.509	0.662
0	28	93.333	23	85.185		
1	1	3.333	3	11.111		
2	1	3.333	1	3.704		
CCS						
Before treatment					1.504	0.681
0	7	23.333	4	14.815		
1	17	56.667	16	59.259		
2	4	13.333	3	11.111		
3	2	6.667	4	14.815		
After treatment					1.392	0.707
0	7	23.333	4	14.815		
1	17	56.667	16	59.259		
2	3	10.000	5	18.519		
3	3	10.000	2	7.407		
Medicine administration						
Before treatment					1.321	0.517
0	24	80.000	20	74.074		
1	5	16.667	4	14.815		
2	1	3.333	3	11.111		
After treatment					2.457	0.356
0	25	83.333	26	96.296		
1	4	13.333	1	3.704		
2	1	3.333	0	0.000		

Data are presented as *n* (%). CCS, Canadian Cardiovascular Society; RSD, Radix salviae Decoction; RIPC, remote ischemic preconditioning.

cularization, and rehospitalization. Cumulative survival curves for cardiac death were plotted (Fig. 1a), and although the survival rate was higher in the RIPC-RSD group compared to the control group, the difference was not statistically significant ($\chi^2 = 1.831$, $p = 0.176$) (Supplementary Table 1). For target vessel revascularization, the cumulative success rate is shown in Figure 1b, and while the RIPC-RSD group had a slightly lower rate compared to the control group, the difference was not statistically significant ($\chi^2 = 1.111$, $p = 0.292$) (Supplementary Table 1). Regarding rehospitalization rates, the cumulative safety rates are presented in Figure 1c. It was observed that the RIPC-RSD group had slightly lower rates compared to the control group, but the difference was not statistically significant ($\chi^2 = 0.495$, $p = 0.482$) (Supplementary Table 1). These findings suggest that RIPC-RSD treatment did not have a significant impact on the prognosis of coronary artery stenosis in patients with CHD.

Table 4. Comparison of the reduced frequency of angina attack after treatment between groups

Group	*n*	Rank mean	Rank sum	Mann-Whitney *U*	Z	*p*
Control	30	27.15	814.5	349.5	−1.066	0.286
RIPC + RSD	27	31.06	838.5			
Total	57					

RSD, Radix salviae Decoction; RIPC, remote ischemic preconditioning.

Table 5. Comparisons of the reduced frequency of emergency medication after treatment between groups

Group	*n*	Rank mean	Rank sum	Mann-Whitney *U*	Z	*p*
Control	30	26.4	792	327	−2.188	0.029*
RIPC + RSD	27	31.89	861			
Total	57					

*$p < 0.05$. RSD, Radix salviae Decoction; RIPC, remote ischemic preconditioning.

Adverse events

In terms of safety analysis, we recorded and examined the occurrence of adverse events associated with RIPC-RSD treatment. No significant adverse effects were observed or documented in either the control or RIPC-RSD groups, indicating that RIPC-RSD was safe for treating of patients with CHD.

Discussion

Myocardial ischemia in CHD, caused by coronary artery stenosis, is the primary cause of angina pectoris.[23,24] Published literature showed RIPC protected target organs from myocardial ischemia and reperfusion-induced injury by temporarily interrupting and then restoring blood flow to remote organs. Traditional Chinese herbal medicine, such as the RSD formula, has been used for the treatment of various types of chest pain, including angina. Therefore, we aimed to investigate whether the combination treatment of RIPC and RSD could affect the clinical features of angina, including the frequency of angina attacks per week and the severity of angina assessed by CCS levels in this study. Our results did not show a statistically significant effect on the frequency, severity, or prognosis of angina attacks. However, we observed a potential efficacy in reducing the frequency of emergency medication use.

Before analyzing the clinical efficacy of the RIPC-RSD combination treatment, we compared the baseline clinical characteristics between the control and RIPC-RSD groups. We examined demographic factors such as age, sex, and length of hospital stay, as well as disease characteristics including comorbidities and diagnosis. We also assessed hematological indicators. Each of these variables showed comparable results between the two groups. Additionally, we evaluated the vascular characteristics, such as stenosis diameter at baseline, which are known predictors of clinical stenosis.[22] Findings of the control and RIPC-RSD groups were comparable.

In the primary outcome evaluation in this study, we did not observe statistically significant efficacy of RIPC-RSD for the treatment of angina pectoris in patients with CHD. Considering that only the primary outcome may not fully reflect the efficacy of RIPC-RSD treatment for CHD, we searched the literature and

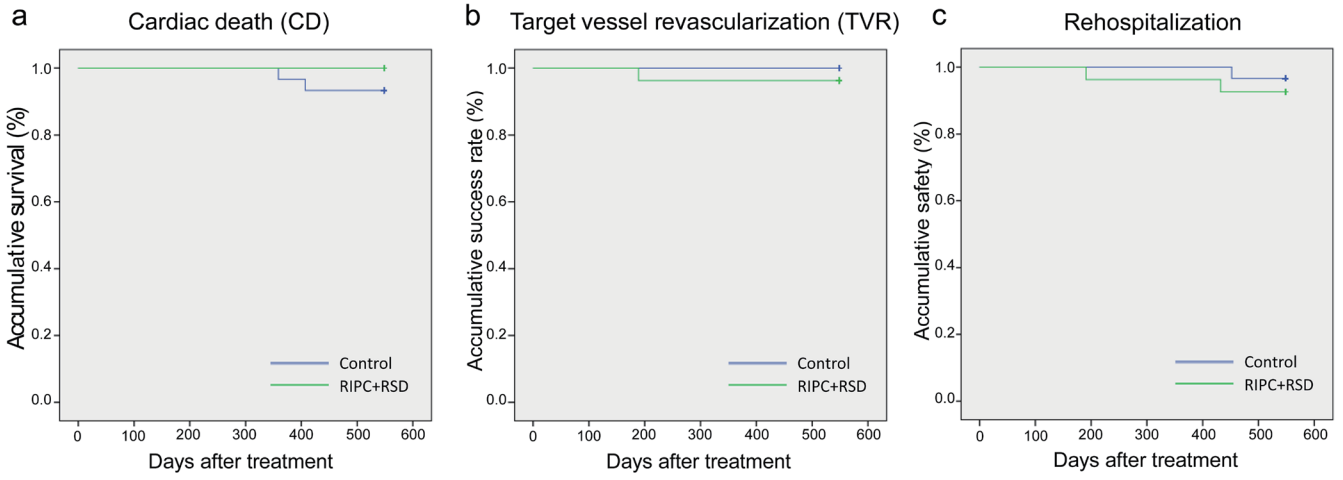

Fig. 1. The survival plots for cumulative rates of cardiac death, target vessel revascularization and rehospitalization. (a) The cumulative survival curves for cardiac death. (b) The cumulative success rates of target vessel revascularization. (c) The cumulative safety rates without rehospitalization. RIPC, remote ischemic preconditioning; RSD, Radix salviae decoction.

found that the frequency of emergency medications, such as sublingual nitroglycerin administration, was also a common indicator of the severity of angina episodes.[25,26] Therefore, we then examined the use of emergency medication between the two groups. Our results demonstrated that the combination treatment of RIPC-RSD reduced the frequency of emergency medication, which may be considered an indicator of the treatment's efficacy in improving angina attacks.

In addition to evaluating the long-term manifestation of angina attacks, we also analyzed the prognosis of myocardial ischemia caused by coronary artery stenosis. We assessed the events of cardiac death, target vessel revascularization, and rehospitalization rates, which are well-established indicators of cardiovascular prognosis. However, our statistical analysis of the cumulative rates between the two groups did not show a significant difference, suggesting that the combination treatment of RIPC-RSD does not have a positive effect on the long-term prognosis of ischemic cardiovascular disease.

Limitations and prospects

In this prospective pilot trial, although the RIPC-RSD treatment did not have a significant impact on the frequency and severity of angina attacks, as well as the prognosis of coronary stenosis, it was observed that the combination treatment reduced the frequency of emergency medication use in patients with CHD. There are several possible reasons for this observation.

Firstly, the pathogenic mechanisms of ischemic heart disease involve abnormalities in the dilation response of coronary microvasculature, coronary microvascular spasm, and extravascular compression forces. Coronary microvascular dysfunction also plays a crucial role in the development of angina pectoris.[27] Various factors, such as physical exertion, emotional stress, overeating, and restricted exercise, can lead to myocardial ischemia and subsequent angina symptoms. The RIPC-RSD combination treatment may influence one or more of these factors, thereby alleviating angina attacks. However, it is important to note that other factors may still contribute to angina attacks despite the medication treatment, which could explain the overall lack of significant results in this relatively small sample size study.

Secondly, RIPC is a short-term adaptation to ischemia and is a clinically applicable, noninvasive method that provides beneficial effects in mitigating myocardial ischemia-reperfusion injury by improving myocardial ischemia and reducing angina attacks.[5] The procedure involves inflating a blood pressure cuff to induce forearm ischemia for 5 m, followed by deflating the cuff for another 5 m. This cycle was typically repeated three to five times consecutively to precondition tissues and improve survival. The mechanisms underlying the effects of RIPC are multifactorial and involve the release of preconditioning inflammatory mediators from the preconditioned organ and circulation, neuronal stimulation, systemic anti-inflammatory and anti-apoptotic responses to transient ischemic episodes, modification of circulating immune cells, and activation of hypoxia-inducible genes.[4,6] These findings suggest that while RIPC may have a mechanical effect in alleviating angina symptoms, its effects may be temporary and may not significantly impact the prognosis of ischemic cardiovascular disease.

Furthermore, the design of this pilot clinical study could be improved. The relatively small sample size may not fully represent the entire population, and a clinical trial with rigorous randomization and blinding would help minimize bias compared to nonrandomized studies. The clinical intervention options for RIPC, including dosing and duration of treatment, may also be factors that affect the endpoint outcomes. Therefore, increasing the dosing and duration of RIPC and/or RSD treatment may enhance the clinical efficacy of this combination treatment for angina attacks.

In summary, our data shows a mild decrease in the frequency and severity of angina attacks after RIPC-RSD treatment, with no significant impact on prognosis. Although statistical significance was not achieved in the changes in angina attack frequency and severity, the reduction in the frequency of emergency medication use may reflect the efficacy of the RIPC-RSD combination treatment from one aspect. This pilot study provides valuable data to guide the design of future clinical studies on this topic.

Conclusion

Owing to a small sample size, we did not observe significant effects of RIPC-RSD on angina attacks and prognosis in patients with CHD. However, it may be effective in reducing the frequency of emergency medication use. Several factors may contribute to these findings. Firstly, the small sample size may not adequately represent the entire population, leading to potential individual variations and sampling errors. Secondly, the intervention of RIPC could be optimized, including the duration of treatment, early initiation in the target population, treatment dosing, and evaluation of biomarkers. These factors may influence the clinical benefits for patients. Thirdly, this prospective pilot study provides valuable information, particularly in terms of sample size estimation, to guide the design of future randomized controlled trials or real-world studies evaluating the combined effect of RIPC-RSD in CHD treatment. Therefore, in future studies, we will increase the sample size, improve the design of clinical trials, optimize the intervention of RIPC, select a more suitable patient population, and employ appropriate statistical analysis methods based on the collected clinical data to enhance the quality of the study.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/FIM.2023.00034.

Supplementary Table 1. Comparison of the events of CD, TVR and rehospitalization after treatment between groups.

Acknowledgments

There is nothing to declare.

Funding

This study was supported by Zhuhai Medical Science and Technology Research Fund Project (No. ZH24013310210002PWC, to QL), National Natural Science Foundation of China (No. 82274279, to QL), Special Funding for Chinese Medicine Science and Technology Research of Guangdong Provincial Hospital of Chinese Medicine (No. YN2020QN10, to QL) and Guangdong Provincial Bureau of Chinese medicine Fund Project (No. 20221360, to QL).

Conflict of interest

The authors declared that there is no conflict of interests in the authorship and publication of this contribution.

Author contributions

Designed the study and finalized the manuscript (QL), collected patient information and constructed the dataset (QQL, AMZ, KLW), wrote the first version of the manuscript (GCP, RYY, QL), and finalized the manuscript revisions (QL). All authors read, revised, and approved the final manuscript.

Ethical statement

This study was approved by the Ethics Committee of Guangdong Provincial Hospital of Traditional Chinese Medicine, with the approval registration number of BF2021-242. The collection of all samples was conducted in strict accordance with the principles outlined in the Helsinki Declaration and with the informed consent of all participants.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

[1] Shao C, Wang J, Tian J, Tang YD. Coronary artery disease: from mechanism to clinical practice. Adv Exp Med Biol 2020;1177:1–36. doi:10.1007/978-981-15-2517-9_1, PMID:32246442.

[2] Pimple P, Shah AJ, Rooks C, Bremner JD, Nye J, Ibeanu I, *et al*. Angina and mental stress-induced myocardial ischemia. J Psychosom Res 2015;78(5):433–437. doi:10.1016/j.jpsychores.2015.02.007, PMID:25727240.

[3] Pimple P, Hammadah M, Wilmot K, Ramadan R, Al Mheid I, Levantsevych O, *et al*. Chest Pain and Mental Stress-Induced Myocardial Ischemia: Sex Differences. Am J Med 2018;131(5):540–547.e1. doi:10.1016/j.amjmed.2017.11.026, PMID:29224740.

[4] Ravingerova T, Farkasova V, Griecsova L, Carnicka S, Murarikova M, Barlaka E, *et al*. Remote preconditioning as a novel "conditioning" approach to repair the broken heart: potential mechanisms and clinical applications. Physiol Res 2016;65(Suppl 1):S55–S64. doi:10.33549/physiolres.933392, PMID:27643940.

[5] Randhawa PK, Bali A, Jaggi AS. RIPC for multiorgan salvage in clinical settings: evolution of concept, evidences and mechanisms. Eur J Pharmacol 2015;746:317–332. doi:10.1016/j.ejphar.2014.08.016, PMID:25176179.

[6] Anttila V, Haapanen H, Yannopoulos F, Herajärvi J, Anttila T, Juvonen T. Review of remote ischemic preconditioning: from laboratory studies to clinical trials. Scand Cardiovasc J 2016;50(5-6):355–361. doi:10.1080/14017431.2016.1233351, PMID:27595164.

[7] Billah M, Ridiandries A, Allahwala U, Mudaliar H, Dona A, Hunyor S, *et al*. Circulating mediators of remote ischemic preconditioning: search for the missing link between non-lethal ischemia and cardioprotection. Oncotarget 2019;10(2):216–244. doi:10.18632/oncotarget.26537, PMID:30719216.

[8] Zagidullin N, Scherbakova E, Safina Y, Zulkarneev R, Zagidullin S. The Impact of Remote Ischemic Preconditioning on Arterial Stiffness and Heart Rate Variability in Patients with Angina Pectoris. J Clin Med 2016;5(7):60. doi:10.3390/jcm5070060, PMID:27348009.

[9] Ejiri K, Miyoshi T, Kohno K, Nakahama M, Doi M, Munemasa M, *et al*. Protective Effect of Remote Ischemic Preconditioning on Myocardial Damage After Percutaneous Coronary Intervention in Stable Angina Patients With Complex Coronary Lesions - Subanalysis of a Randomized Controlled Trial. Circ J 2018;82(7):1788–1796. doi:10.1253/circj.CJ-17-1000, PMID:29669963.

[10] Meybohm P, Bein B, Brosteanu O, Cremer J, Gruenewald M, Stoppe C, *et al*. A Multicenter Trial of Remote Ischemic Preconditioning for Heart Surgery. N Engl J Med 2015;373(15):1397–1407. doi:10.1056/NEJMoa1413579, PMID:26436208.

[11] Zhao W, Hausenloy DJ, Hess DC, Yellon DM, Ji X. Remote Ischemic Conditioning: Challenges and Opportunities. Stroke 2023;54(8):2204–2207. doi:10.1161/STROKEAHA.123.043279, PMID:37417240.

[12] Zhou W, Ruigrok TJ. Protective effect of danshen during myocardial ischemia and reperfusion: an isolated rat heart study. Am J Chin Med 1990;18(1-2):19–24. doi:10.1142/S0192415X90000046, PMID:2239811.

[13] Yan KP, Guo Y, Xing Z, Huang X, Dai S, Duan M, *et al*. Dan-Shen-Yin protects the heart against inflammation and oxidative stress induced by acute ischemic myocardial injury in rats. Exp Ther Med 2012;3(2):314–318. doi:10.3892/etm.2011.404, PMID:22969888.

[14] Hong M, Wu Y, Zhang H, Gu J, Chen J, Guan Y, *et al*. Network pharmacology and experimental analysis to reveal the mechanism of Dan-Shen-Yin against endothelial to mesenchymal transition in atherosclerosis. Front Pharmacol 2022;13:946193. doi:10.3389/fphar.2022.946193, PMID:36091823.

[15] Wang Y, Xiao L, Mu W, Yu HL, Zhang S, Tian GH, *et al*. A summary and evaluation of current evidence for myocardial infarction with Chinese medicine. Chin J Integr Med 2017;23(12):948–955. doi:10.1007/s11655-017-2824-y, PMID:29079906.

[16] Han JY, Fan JY, Horie Y, Miura S, Cui DH, Ishii H, *et al*. Ameliorating effects of compounds derived from Salvia miltiorrhiza root extract on microcirculatory disturbance and target organ injury by ischemia and reperfusion. Pharmacol Ther 2008;117(2):280–295. doi:10.1016/j.pharmthera.2007.09.008, PMID:18048101.

[17] Yang HY, Liu ML, Luo P, Yao XS, Zhou H. Network pharmacology provides a systematic approach to understanding the treatment of ischemic heart diseases with traditional Chinese medicine. Phytomedicine 2022;104:154268. doi:10.1016/j.phymed.2022.154268, PMID:35777118.

[18] Gong D, Yuan T, Wang R, Sun S, Dawuti A, Wang S, *et al*. Network pharmacology approach and experimental verification of Dan-Shen Decoction in the treatment of ischemic heart disease. Pharm Biol 2023;61(1):69–79. doi:10.1080/13880209.2022.2152059, PMID:36546685.

[19] MEIm XD, Cao YF, Che YY, Li J, Shang ZP, Zhao WJ, *et al*. Danshen: a phytochemical and pharmacological overview. Chin J Nat Med 2019;17(1):59–80. doi:10.1016/S1875-5364(19)30010-X, PMID:30704625.

[20] Li ZM, Xu SW, Liu PQ. Salvia miltiorrhizaBurge (Danshen): a golden herbal medicine in cardiovascular therapeutics. Acta Pharmacol Sin 2018;39(5):802–824. doi:10.1038/aps.2017.193, PMID:29698387.

[21] Liu M, Yuan G, Luo G, Guo X, Chen M, Yang H, *et al*. Network Pharmacology Analysis and Experimental Verification Strategies Reveal the Action Mechanism of Danshen Decoction in Treating Ischemic Cardiomyopathy. Evid Based Complement Alternat Med 2022;2022:7578055. doi:10.1155/2022/7578055, PMID:35722148.

[22] Kastrati A, Dibra A, Mehilli J, Mayer S, Pinieck S, Pache J, *et al*. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. Circulation 2006;113(19):2293–2300. doi:10.1161/CIRCULATIONAHA.105.601823, PMID:16682614.

[23] Levy BI, Heusch G, Camici PG. The many faces of myocardial ischaemia and angina. Cardiovasc Res 2019;115(10):1460–1470. doi:10.1093/cvr/cvz160, PMID:31228187.

[24] Luchi RJ, Chahine RA, Raizner AE. Coronary artery spasm. Ann Intern Med 1979;91(3):441–449. doi:10.7326/0003-4819-91-3-441, PMID:382940.

[25] Boden WE, Padala SK, Cabral KP, Buschmann IR, Sidhu MS. Role of short-acting nitroglycerin in the management of ischemic heart disease. Drug Des Devel Ther 2015;9:4793–4805. doi:10.2147/DDDT.S79116, PMID:26316714.

[26] Bray CL, Jain S, Faragher EB, Myers A, Myers P, MacIntyre P, *et al*. A comparison of buccal nitroglycerin and sublingual nitroglycerin in the prophylaxis and treatment of exertional (situation-provoked) angina pectoris. Eur Heart J 1991;12(Suppl A):16–20. PMID:1908385.

[27] Kaski JC, Crea F, Gersh BJ, Camici PG. Reappraisal of Ischemic Heart Disease. Circulation 2018;138(14):1463–1480. doi:10.1161/CIRCULATIONAHA.118.031373, PMID:30354347.