Trials

STUDY PROTOCOL

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Effect of perioperative remote ischemic conditioning on myocardial injury in patients with unstable angina undergoing percutaneous coronary intervention: protocol of a multicenter, randomized, double-blind clinical trial

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Abstract

Background Cardiovascular disease is a leading cause of death, with ischemic heart disease being a significant contributor. While percutaneous coronary intervention (PCI) effectively reduces mortality in myocardial infarction patients, its efficacy for unstable angina (UA) patients is controversial. Complications associated with PCI further limit application in UA. RIC is hypothesized to be an effective co-intervention that reduces PCI-related complications and may potentially enhance the efficacy of the PCI procedure itself.

Methods This is a pragmatic, prospective, dual-center, double-blind, randomized controlled clinical trial assessing the effect of remote ischemic conditioning (RIC) during percutaneous coronary intervention (PCI) on injury in unstable angina patients aged ≥ 18 years undergoing coronary angiography. Participants will be randomized to receive either RIC or Sham RIC, in addition to standard pharmacotherapy. Primary outcome includes periprocedural myocardial injury measured by hs-cTnT levels, while secondary outcomes encompass major adverse cardiovascular events, coronary artery lesions Gensini Score, arrhythmia, angina incidence, SAQ scores, ECG changes, and cardiac function assessed by two-dimensional echocardiography. The trial aims to recruit 574 participants and is scheduled to be initiated on 15 January 2024. We will conduct the primary statistical analysis using the intention-to-treat principle. Results from the trial will be presented as comparative summary statistics following the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

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Trial registration ChiCTR2400079855, 15 January 2024.

Keywords Cardiovascular disease, Myocardial ischemia, Percutaneous coronary intervention (PCI), Unstable angina (UA), Ischemic preconditioning, Ischemic postconditioning, Myocardial infarction (MI), Reperfusion injury

Strengths and limitations of this study

Strengths

- This study uses a pragmatic, dual-center, randomized controlled trial design, ensuring a robust methodological approach.
- The implementation of a perioperative RIC program is designed to encompass the protective windows of RIC, increasing the likelihood of capturing its benefits.
- The trial employs blinding and a sham RIC group to minimize bias, enhancing the validity of the findings.

Limitations

- The intervention's specificity is not completely clear, as the study's design does not allow for identification of the specific phase of RIC responsible for any observed effects.
- Conducted across two centers, the findings may have limited generalizability.

Introduction

Cardiovascular disease is the leading cause of mortality in China, with nearly half of the deaths being caused by ischemic heart disease [1]. Consequently, the burden of disease is heavy. Percutaneous coronary intervention (PCI) is an effective treatment method, significantly reducing mortality in myocardial infarction patients and improving prognosis [2, 3]. However, its efficacy in patients with unstable angina (UA) is controversial. Compared to drug therapy, PCI can improve UA symptoms in the short term (3–6 months), but long-term prognosis (12 months and above) shows no difference [4–7]. Moreover, complications associated with PCI further limit its application in patients with UA. Complications due to surgical procedures, such as distal embolization and side branch occlusion (SBO), leading to perioperative myocardial infarction (Type 4a myocardial infarction) and myocardial injury, are most common and correlate with patient prognosis [8–10]. Previous research has shown that the incidence of perioperative myocardial infarction and myocardial injury can reach 20–30% among elective surgery patients with UA [9, 11, 12]. Therefore, co-interventions that can reduce PCI-related complications and possibly facilitate the PCI itself, thus making PCI more broadly applicable in patients with UA, are needed.

Remote ischemic conditioning (RIC) is a candidate co-intervention. It involves a repeated brief interruption of the blood flow of a remote organ or tissue followed by its restoration. In this fashion, it is supposed to stimulate an endogenous physiological response with cardioprotective impact, and thereby improve endothelial as well as cardiac function and reduce the risk of further myocardial injury [13, 14]. RIC is clinically viable and easy-to-implement. There is some previous evidence that RIC may improve angiogenesis [15, 16], stimulate vagus nerve activation [17, 18], decrease atherosclerosis [19, 20], improve coronary blood flow [21–23], and prevent endothelial ischemia–reperfusion injury in ST-elevation myocardial infarction (STEMI) patients [24–28]. A meta-analysis also showed that RIC can improve prognosis in terms of survival and subsequent cardiac events in STEMI patients.

In UA however, there are only two studies evaluating effects of RIC (see Table S1). One study applied RIC preoperatively finding no differences to sham in biomarkers such as hs-CRP and endothelial progenitor cells [29]. Another study used postoperative RIC, reporting no difference in troponin T but a higher incidence of postoperative MI in the subpopulation of patients with diabetes who received RIC versus sham. No differences were found in patients without diabetes [30]. Other studies have been conducted in mixed populations with elective PCI including patients with UA (see Table S1). While a meta-analysis concluded that RIC effectively reduces incidence of post-op MI in this population, subgroup analysis in patients with UA was not performed and specific effects in this population remain unclear. Other clinically relevant outcomes such as coronary artery lesions, arrhythmia, subjective angina after PCI, or cardiac function have not been analyzed to date. Importantly, while it would be especially beneficial if pre-operative RIC could actually reduce the stenosis underlying the angina and so facilitate the insertion of the stent during PCI, no study in populations with UA (or MI) has investigated this outcome.

Based on the above rationale, we propose a dual-center randomized controlled trial (RCT) to answer whether a RIC program is superior over sham control in reducing

the incidence of perioperative myocardial infarction/injury (PMI) and other complications in patients with UA undergoing PCI, decreasing stenosis pre- and postoperatively, and improving subjective angina and cardiac function. Moreover, adverse effects of the intervention in the target population will be evaluated.

Methods/design

Trial design

This is a pragmatic, prospective, dual-center, double-blind, parallel, randomized controlled clinical trial. Table 1 shows the overview of the trial registration information. This trial protocol has been developed according to SPIRIT for pragmatic trials and non-pharmacological treatment interventions [31].

Trial objectives

The primary objective is to evaluate the effect of remote ischemic conditioning (RIC) during the perioperative period of percutaneous coronary intervention (PCI) in reducing periprocedural myocardial injury caused by ischemia and reperfusion in patients with unstable angina (UA). Secondary objectives are to evaluate the effects of RIC during the perioperative period of PCI on other postoperative complications including postoperative arrhythmia, ischemia of the myocardium, pre- and postoperative stenosis, postoperative subjective angina,

Table 1 World Health Organization (WHO) Trial Registration Data Set for trial

Data category	Information
Primary registry and trial identifying number	Chinese Clinical Trial Registry number: ChiCTR2400079855
Date of registration in primary registry	15 January 2024
Secondary identifying numbers	N/A
Trial protocol version	Version 1.2
Source(s) of monetary or material support	N/A
Primary sponsor	N/A
Secondary sponsor	N/A
Contact for public queries	XL, luxiao1972@163.com
Contact for scientific queries	XL, luxiao1972@163.com
Public title	Effect of perioperative remote ischemic conditioning on myocardial injury in patients with unstable angina undergoing percutaneous coronary intervention: a multicenter randomized controlled clinical trial
Scientific title	Effect of perioperative remote ischemic conditioning on myocardial injury in patients with unstable angina undergoing percutaneous coronary intervention: a pragmatic multicenter randomized controlled clinical trial
Countries of recruitment	China
Health condition(s) or problem(s) studied	Periprocedural myocardial infarction and myocardial injury, cardiovascular event rate, coronary artery lesions, SAQ, cardiac function
Intervention(s)	Active comparator: usual care, PCI and RIC program (pre-, per-, and post-operative RIC) Placebo comparator: usual care, PCI and Sham RIC program
Key inclusion and exclusion criteria	Ages eligible for study: aged >18 yr Sexes eligible for study: both Accepts health volunteers: no Inclusion criteria: see Table 2 Exclusion criteria: see Table 2
Study type	Type: Pragmatic, multicenter, randomized controlled, parallel group, clinical trial Allocation: Simple randomization, concealed central allocation by study center Intervention model: parallel assignment Masking: Assessor, surgeon, data analyst, and statistician blinded Primary purpose: prevention and improvement Phase: phase III
Date of first enrollment	Not yet started
Target sample size	574
Recruitment status	Not yet started
Primary outcome(s)	Periprocedural myocardial injury
Key secondary outcomes	Periprocedural myocardial infarction, MACE rate, all-cause mortality, cardiac mortality, myocardial infarction rate, readmission rate for heart failure, unplanned revascularization rate, arrhythmias rate, angina rate, Gensini Score, cardiac function, SAQ

PCI percutaneous coronary intervention, *RIC* remote ischemic conditioning, *MACE* major adverse cardiovascular events, *SAQ* Seattle Angina Questionnaire

and cardiac function in patients with UA. Moreover, adverse event (AE) according to AE scale including pain, local skin breakdown, subcutaneous bleeding, and thrombosis will be evaluated.

Ethics statement

This trial has been prospectively registered at the Chinese Clinical Trial Registry (http://www.chictr.org.cn): ChiCTR2400079855, 15 January 2024. The trial protocol has been reviewed and approved by the Research Ethics Committee at the First Affiliated Hospital of Nanjing Medical University (Reference number: 2023-SR-161, 05 December 2023). In accordance with the Declaration of Helsinki of 1964 as revised in 2013, the International Conference of Harmonization Guidelines for Good Clinical Practice and the requirement of the local ethics committees, written informed consent will be obtained from all enrolled participants [32].

Trial setting

This trial will be conducted in two tertiary-care hospitals in Jiangsu Province: (1) Jiangsu Province Hospital/First Affiliated Hospital of Nanjing Medical University; (2) the Affiliated Nanjing First Hospital of Nanjing Medical University. The hospitals were selected based on their capacity to treat the target patient population, the availability of specialized medical staff, and their experience in conducting clinical trials. The participating hospitals have a combined catchment area of approximately 80 million people, ensuring adequate patient recruitment potential for the study. Each hospital will have a designated principal investigator responsible for overseeing the trial at their respective site.

Trial status

The current version of this clinical trial protocol, designated as version 1.2, was finalized on 5 December 2023. The initiation of the trial is scheduled for 15 January 2024, with an aim to complete the enrollment of all participants by February 2025.

Eligibility and withdrawal criteria

The target population for this trial encompasses those who meet the consolidated eligibility and withdrawal criteria as listed in Table 2.

Recruitment, random sequence generation and allocation concealment

Patients will be selected from candidates diagnosed with unstable angina and awaiting CAG. Patients who meet the eligibility criteria at the participating centers will receive a detailed explanation of the trial purpose and procedures. The randomization procedure will be performed by the Clinical Research Board from the School of Public Health of Nanjing Medical University (the allocation center) with SAS (Version 8.2). Balanced intervention assignments will be achieved using block randomization, with alternating block sizes (8–16), stratified by participating centers. Random sequences for the two hospitals will be generated by an independent statistician and concealed centrally with revelation through phone call to study center upon signature. Once the informed consent form has been signed by the eligible patient, the trial assistants at each participating center will enter the patient's demographic and general clinical data into a secured, remote, web-based electronic case report form, and then receive the group allocation automatically generated by the computer [33]. Figure 1 demonstrates the overview of the trial.

Interventions

Refer to TIDieR checklist (Table 3):

Brief name: Remote Ischemic Conditioning (RIC) to reduce periprocedural myocardial injury in patients with unstable angina undergoing PCI.
Why: The intervention aims to evaluate the effects of RIC on reducing periprocedural myocardial injury and other postoperative complications including postoperative arrhythmia, ischemia of the myocardium, pre- and postoperative stenosis, postoperative subjective angina, and cardiac function in patients with unstable angina undergoing PCI.
What (Materials): Each group will receive usual pharmacotherapy before PCI (300 mg aspirin and 300 mg clopidogrel orally). In addition, RIC with an automated cuff inflation/deflation device is implemented with intervention parameters varying between sham and actual RIC as explained below.
What (Procedure): The RIC program consists of three parts. (1) Three cycles of remote ischemic pre-conditioning are delivered after the eligibility check and informed consent form signature within the preparation period before PCI (usually 1 h before start of surgical procedures). Each cycle involves 3 min of upper limb ischemia (cuff inflation to 20 mmHg above systolic blood pressure on the arm that is opposite to the PCI side) followed by 3 min of reperfusion. (2) One cycle of remote ischemic per-conditioning is delivered during PCI. It will begin when the balloon reaches the target vessel, followed immediately by balloon inflation and stent placement. (3) Three cycles of remote ischemic post-conditioning are delivered within 10 min after PCI. The Sham RIC program follows the same protocol but inflates the cuff to only 60 mmHg.

Table 2 Trial inclusive, exclusive, and withdrawal criteria

Inclusion criteria	Rationale for inclusion
1. Patients diagnosed with unstable angina (New angina: new onset of severe angina; Worsening angina: angina is increasing in frequency, longer in duration, or lower in threshold; Rest angina: prolonged (> 20 min) angina at rest; Variant angina: angina occurs during rest, often at night with ST-segment elevation during the attack) according to 2020 European Society of Cardiology (ESC) Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation	Population of interest
2. Patients are scheduled for coronary angiography	Population of interest
3. Age ≥ 18 years	Population of interest
4. Normal cognitive function, with MMSE score greater than 16, and capable of complying with rehabilitation therapy	Cognitive requirement
5. Agree to participate in the study and sign an informed consent form	Ethical requirement
Exclusion criteria	Rationale for exclusion
1. Elevation of hs-cTnT above two times the upper limit of normal (99th percentile reference value) with other evidence of myocardial injury	Ineligible for diagnostic criteria
2. Patients with severe arrhythmias	Confounding factors
3. Myocardial infarction or stroke within 30 days	Confounding factors
4. Cardiogenic shock	Confounding factors
5. Participation in another clinical trial simultaneously	Confounding factors
6. Diseases that cause elevated hs-cTnT levels, such as myocarditis, severe arrhythmias, sepsis, or systemic inflammatory response syndrome	Competing risk
7. Uncontrolled hypertension: systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg	Compliance
8. Patients with contraindications for remote ischemic conditioning, such as vascular injury, soft tissue injury, orthopedic injury, or arm infection	Contraindications
9. Thrombolytic treatment within 30 days	Potential harm
10. Patients with a bleeding disorder	Potential harm
11. Presence of peripheral neuropathy, peripheral arterial disease, thrombophlebitis, or acute deep vein thrombosis	Potential harm
12. Emergency surgery is required due to severe complications such as interventricular septal rupture, free wall rupture, or acute severe mitral regurgitation	Potential harm
13. With diabetes mellitus	Potential harm
Withdrawal criteria	Rationale for withdrawal
1. The patient evaluated by coronary angiography does not require PCI treatment;	Population of interest
2. Adverse events or serious adverse events occur and the investigator considers it inappropriate to continue the study;	Severe adverse event
3. Poor compliance, affecting the validity or safety of the evaluation	Negative physical condition
4. The patient makes such a request	Personal desire

MMSE mini-mental state examination, *hs-cTnT* high-sensitivity cardiac troponin T

Who provides: The intervention is delivered by four part-time therapists who have received specific training for the trial from an experienced RIC therapist and trainer and undergo weekly supervision at each center. The therapists are employed within the hospital.

How: The RIC and Sham RIC are both performed by the trained therapists.

Where: The remote ischemic pre-conditioning and post-conditioning take place in the ward of the hospital. The remote ischemic per-conditioning is carried out in the operating room during the PCI procedure.

When and how much: The RIC program is implemented as three separate parts: pre-conditioning before PCI, per-conditioning during PCI, and post-conditioning after PCI. Each conditioning phase consists of three 3-min cycles of upper limb ischemia (cuff inflation to 20 mmHg above systolic blood pressure) separated by 3 min intervals of reperfusion. The exception is the per-conditioning phase, which involves only a single 3-min cycle.

Tailoring: No personalization or adaptation is implemented in this study.

How well (planned): Adherence to the intervention will be assessed by RIC therapists, who will document whether the preoperative, perioperative, and postoperative interventions are completed in full, partially, or none. Before initiating the intervention, the RIC therapist will reiterate the benefits of the treatment to the patient and address any discom-

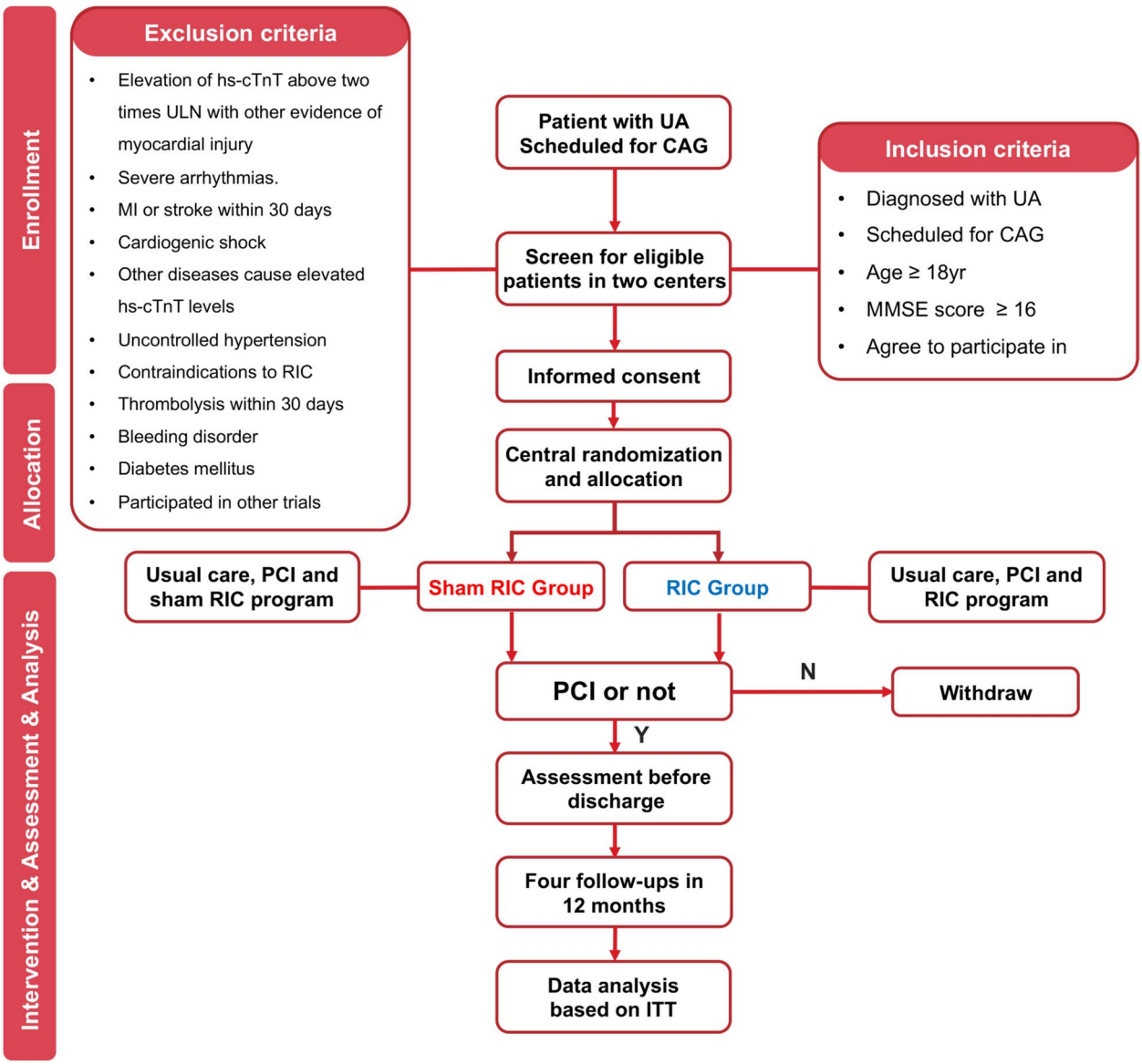

Fig. 1 Flow chart of trial. UA, unstable angina; CAG, coronary angiography; RIC, remote ischemic conditioning; PCI, percutaneous coronary intervention; MACE, major adverse cardiac events; SAQ, Seattle Angina Questionnaire; ULN, upper limit of normal; MI, myocardial infarction; MMSE, Mini-Mental State Examination

fort they may experience during the procedure. The therapist will accompany the patient throughout the intervention, aiming to enhance patient compliance. Patients who do not complete any of the pre-, per-, or post- interventions will be withdrawn from the study.

Outcomes measures

Primary outcome

Primary endpoint of this study is the occurrence of periprocedural myocardial injury, within 48 h after PCI (or earlier censoring if the patient is discharged before 48 h). Periprocedural myocardial injury is defined as the manifestation of an ischemic conditions that result in an increase of high-sensitivity troponin T (hs-cTnT) levels to above 14 ng/L but below 70 ng/L according to the 2018 ESC/ACC/AHA/WHF Fourth Universal Definition of MI [34]. Additionally, patients whose hs-cTnT levels are elevated prior to surgery and continue to increase by more than 20% within 48 h post-surgery, will also be considered to present periprocedural myocardial injury. hs-cTnT will be measured at admission and the morning following PCI.

Table 3 TIDieR checklist

TIDieR Item	RIC Group	Sham RIC Group
Why	• Reduce periprocedural myocardial injury • Minimize postoperative complications	
What (Materials)	• 300 mg aspirin and 300 mg clopidogrel before PCI • RIC with automated cuff inflation/deflation device	
What (Procedure)	An automatic cuff is applied to the arm, inflated to target pressure (either 60 mmHg or 20 mmHg above SBP), inducing upper limb ischemia for 3 min, followed by 3 min of reperfusion	
Who provides	Four trained therapists from the hospital	
How	Performed by therapists with automated cuff device during perioperative period	
Where	• Pre-conditioning: Hospital ward • Per-conditioning: Operating room • Post-conditioning: Hospital ward	
When and how much	Each cycle: 3 min upper limb ischemia and 3 min reperfusion • Pre: 3 cycles before PCI • Per: 1 cycle during PCI • Post: 3 cycles after PCI	
	Cuff inflation to 20 mmHg above SBP	Cuff inflation to only 60 mmHg
Tailoring	No personalization/adaptation	
How well (planned)	• Adherence assessed by RIC therapists • Explanation and accompaniment to improve adherence	

TIDieR template for intervention description and replication, *RIC* remote ischemic conditioning, *PCI* percutaneous coronary intervention, *SBP* systolic blood pressure

Secondary outcomes

Secondary outcomes are as follows:

(1) Periprocedural myocardial infarction is defined as an elevation of hs-cTnT above 70 ng/L after PCI according to the 2018 ESC/ACC/AHA/WHF Fourth Universal Definition of MI [34]. This elevation must be accompanied by at least one of the following criteria: emergence of ischemic electrocardiogram (ECG) changes (ST-elevation/depression or T wave changes in 2 contiguous leads) or pathological Q waves, the loss of viable myocardium as evidenced by imaging, or angiographic findings indicative of myocardial infarction.

(2) Major adverse cardiac events (MACE) are defined as either cardiac death, myocardial infarction, rehospitalization for heart failure, or unplanned revascularization [25, 35, 36].

(3) All-cause mortality is defined as death due to any cause occurring after the enrollment. Causes of death are divided into cardiac (e.g., malignant arrhythmia, myocardial infarction) and non-cardiac (e.g., newly developed cancers or severe systemic diseases) [37]

(4) Myocardial infarction across index hospitalization and follow-up period is diagnosed according to existing guidelines of the 2018 ESC/ACC/AHA/WHF Fourth Universal Definition of MI [34]: Detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and with at least 1 of the following: (a) symptoms of acute myocardial ischemia; (b) new ischemic ECG changes (ST-elevation/depression or T wave changes in 2 contiguous leads); (c) development of pathological Q waves; (d) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; (e) identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.

(5) Rehospitalization for heart failure is defined as rehospitalization for any heart failure category across index hospitalization and follow-up period. Heart failure will be confirmed based on at least one of the following symptoms or signs: new or worsening dyspnea, orthopnea, paroxysmal nocturnal dyspnea, increasing fatigue/worsening exercise tolerance, echocardiography (left ventricular ejection fraction < 45%), new pulmonary edema seen on chest X-ray in the absence of a non-cardiac cause, crepitations due to pulmonary edema, and use of loop diuretics to treat presumed pulmonary congestion [38].

(6) Unplanned revascularization refers to repeated episodes of coronary revascularization, defined as CABG (coronary artery bypass graft) and PCI (percutaneous coronary intervention), with PCI across index hospitalization and follow-up period [39].

(7) The Gensini Score for coronary artery lesions is used to assess the degree of stenosis of the affected vessels [40]. The specific steps are as follows:

Firstly, based on coronary angiography, a quantitative assessment of the maximum stenosis in each branch artery is made. Degrees of stenosis is scored by a cardiologist as ≤25%, 26%~50%, 51%~75%, 76%~90%, 91%~99%, and 100% and respectively scored as 1, 2, 4, 8, 16, and 32 points.

Then, according to different coronary branches, the above scores are multiplied with corresponding weights as below:

(1) Left main (LM) × 5.0.
(2) Left anterior descending (LAD): proximal LAD × 2.5, mid LAD × 1.5, distal LAD × 1.0.
(3) First diagonal branch (D1) × 1.0, second diagonal branch (D2) × 0.5.
(4) Left circumflex (LCX): proximal LCX × 2.5, mid LCX × 1.5, distal LCX × 1.0.
(5) Obtuse marginal branch (OM) × 1.0.
(6) Left posterolateral branch (PL) × 0.5.
(7) Right coronary artery (RCA) × 1.0.
(8) Posterior descending artery (PDA) × 1.0.

Finally, the total scores for each lesion are added together to yield the patient's Gensini Score for coronary artery disease.

(8) The incidence of arrhythmia detected through ECG monitoring is prespecified as an episode of ventricular tachycardia for at least 3 beats in length, any supraventricular tachycardia > 120 bpm lasting at least 4 beats, new-onset atrial fibrillation, an episode of bradycardia of < 45 bpm lasting at least 4 beats, complete heart block, or a ventricular pause ≥ 2.5 s. Ventricular tachycardia is subsequently categorized according to current guidelines [41] for (at least 4 beats, at least 8 beats, and sustained [> 30 s]), as well as by morphology for episodes lasting ≥ 8 beats (monomorphic versus polymorphic). Ventricular pauses were subsequently categorized by length (lasting ≥ 3 s) and by the principal mechanism of action (sinus node dysfunction, atrioventricular node dysfunction, or other mechanism). Any arrhythmias with unstable hemodynamics will be considered as malignant arrhythmia [42].
(9) Angina-related quality of life will be evaluated with the Seattle Angina Questionnaire (SAQ) [43].
(10) Presence of angina is assessed by the physician (hospitalization phase) or telephone survey (follow-up) using SAQ.
(11) An electrocardiogram will be used to provide evidence for arrhythmia and ischemia (with at least ST segment elevation or decline ≥ 0.1 mV or peaked or inverted T waves in two leads).
(12) Cardiac function will be measured with two-dimensional echocardiography and reflected in abnormal wall motion, impaired left ventricular diastolic function, left ventricular ejection fraction (LVEF), fractional shortening (FS), E/A, and E/e'[44, 45].
(13) Hemodynamics indicates heart rate, systolic blood pressure, diastolic blood pressure, or others will be monitored by the automated cuff inflation/deflation device before and after remote ischemic conditioning.

Data collection

During the initial hospitalization and follow-up periods, data will be collected regarding baseline information, adverse events, and surgical procedures. Baseline data will include patients' demographic information (such as age, gender, body mass index), medical history (such as hypertension, diabetes, smoking history), comorbidities (such as chronic kidney disease, heart failure), and biochemical markers (such as lipid profiles, cardiac enzymes, NT-proBNP). These data will be collected through patient self-report and medical records and will be entered into the electronic case report forms (eCRF). In addition, data related to the surgical procedure will be comprehensively collected, including any adjunctive medications used during surgery, surgical techniques (such as stent placement), and any special interventions or complications that occurred during the procedure. All surgical-related data will be recorded by the research team and uploaded to the cloud database to ensure the integrity and accuracy of the data.

Perioperative data collection will help us analyze the potential impact of different baseline characteristics and surgical interventions on trial outcomes. All time-to-event outcomes, including the date and type of the event, will be uploaded to the cloud database by research assistants based on information provided by the patients or their caregivers. Patient-reported events will be reviewed and confirmed by the treating physician. The rates of major adverse cardiac events (MACE) and the Short Form-36 (SAQ) health-related quality of life questionnaires will be measured at all follow-up time points to assess the long-term impact of the trial intervention on patients' cardiac health and quality of life. A detailed data collection plan is shown in Fig. 2.

Blinding

In this study, participants, surgeons, physicians, nurses, data analysts, statisticians, and investigators responsible

		ELIGIBILITY	ALLOCATION	HOSPITALIZATION					FOLLOW UP			
	TIMEPOINT	Diagnosed as UA	Admission	After Randomization	During PCI	After PCI	1 day after PCI	Before Discharge	1 month after PCI	3 months after PCI	6 months after PCI	12 months after PCI
ENROLLMENT	Eligiblilty screen	X										
	Informed consent	X										
	Randomziation		X									
ASSIGNMENT	RIC gorup		X									
	Sham RIC group		X									
VARIABLES	Demographics			X								
	Clinical characteristics			X								
	hs-cTnT	X					X					
	SAQ			X					←	—	—	→
	Angina				X		←	—	—	—	—	→
	MACE							←	—	—	—	→
	Cardiac death							←	—	—	—	→
	Myocardial reinfarction							←	—	—	—	→
	Readmission for heart failure							←	—	—	—	→
	Unplanned revascularization							←	—	—	—	→
	Echocardiogram	X							X			
	ECG	X			X	X			X			
	Arrhythmias	X			X	X		X	X			
	Adverse events			←	—	—	—	—	—	—	—	→

Fig. 2 Scheduled events and timeline of trial. PCI, Percutaneous coronary intervention; MACE, Major adverse cardiovascular events; SAQ, Seattle Angina Questionnaire; ECG, Electrocardiogram; hs-cTnT, High-sensitivity cardiac troponin T

for patient enrollment, follow-up, and assessment of treatment outcomes will be blinded to group assignment. The only exceptions are therapists who administer the RIC or sham RIC treatment.

The appearance of the device for RIC or sham RIC is identical, and the interventions in both groups are presented in a manner that appears consistent to third parties, helping to maintain blinding throughout the study.

In addition, after each participant receives the intervention, a questionnaire will be administered to inquire about their guess regarding the group assignment (RIC or sham RIC), and their answers will be recorded. The same guessing survey will be conducted for the healthcare professionals and evaluators involved in the participants' treatment, to assess their perception of the assigned intervention. The effectiveness of blinding will be evaluated by comparing the guesses with the actual group assignments, using statistical measures such as the Kappa statistic. If significant deviations from the expected blinding occur, improvements to the blinding implementation process or enhanced blinding management strategies will be considered.

In the case of emergencies where unblinding is necessary, the therapists can reveal the assigned intervention. To prevent accidental unblinding, intervention codes are stored on a password-secured server. In addition, a security system has been established to track who has accessed the intervention codes and when. Only a limited number of persons who are all not otherwise involved in the study have access to this system.

Composition of the coordinating center and trial steering committee

The coordinating center for this trial will be composed of the principal investigator (PI), project leader, data management team, and recruitment team, responsible for the overall management and coordination of the trial. The primary duties of the coordinating center include monitoring trial progress, participant recruitment, data collection and entry, and ensuring the quality and compliance of the study. Weekly meetings will be held to discuss recruitment status, data management, and study progress. Trial data will be entered into standardized electronic case report forms (eCRF) and stored in a dedicated trial cloud database. Two trial assistants at each participating center will independently perform, date, and sign the data entry, ensuring the accuracy of the data. All data will undergo automated checks for typographical errors and missing information, and discrepancies will be resolved through raw data verification, patient interviews, or discussion. To ensure data confidentiality, access to the database will be strictly controlled, and only authorized researchers, including members of the Data Safety Monitoring Board (DSMB), will have access to the data.

Composition, role, and reporting structure of the data monitoring committee

This trial has established a Data Safety Monitoring Board (DSMB) to oversee the safety and data integrity of the trial. The DSMB is composed of independent clinical experts and statisticians, who will regularly assess adverse events (AE) and serious adverse events (SAE) during the trial [46]. The committee will meet quarterly to evaluate data quality and make recommendations regarding whether the trial should continue or if any modifications to the protocol are necessary based on monitoring results. The DSMB will particularly focus on events that could impact patient safety, such as those resulting in death, persistent disability, or requiring

hospitalization. When the incidence of serious adverse events in the intervention group is significantly higher than in the control group (more than twice the risk), the trial will be terminated, and the ethics committee as well as all participants will be informed. A comprehensive safety review will be conducted to ensure the safety of the participants. All meeting records and decisions will be promptly reported to the research team, and relevant regulatory bodies and ethics committees will be notified to ensure the safety and compliance of the trial.

Adverse event reporting and harms

All adverse events occurring during the trial will be recorded in the eCRF according to the protocol. For each AE (including adverse device effects, ADE), details such as description, onset and end dates, severity, assessment of device-relatedness, involvement of other potential causes, and actions taken will be documented. The resolution of any AE will be monitored until the event is resolved or stabilized. If an AE leads to participant withdrawal or remains unresolved at the end of the study, it will continue to be followed until a satisfactory outcome is achieved. All AE and SAE will be promptly reported to relevant regulatory bodies, including the trial ethics committee, to ensure appropriate management of all events.

Frequency and plans for auditing trial conduct

The implementation and oversight of the trial will be jointly managed by the coordinating center and the trial steering committee. The principal investigator will assume overall leadership and oversee protocol implementation, participant recruitment, data collection, and analysis. To ensure the trial is conducted according to plan and in compliance with ethical and regulatory requirements, regular meetings will be held to discuss trial progress and potential challenges, with project management meetings taking place monthly to ensure all trial activities are on track and issues are promptly addressed. The Trial Steering Committee will review the trial's progress quarterly, evaluating the overall execution and data quality, providing necessary recommendations for adjustments. The DSMB will regularly review the trial data, focusing on patient safety and data integrity, and will recommend any necessary adjustments or trial termination if deemed necessary.

Plans for communicating important protocol amendments

Any amendments to the trial protocol will be submitted for approval by the relevant ethics committees. Following approval, the principal investigator will notify all participating centers and ensure that the updated protocol is added to the Investigator Site File. All protocol changes will be registered in the trial registry, and participants will be informed of the changes prior to randomization and required to sign an updated informed consent form. Any protocol deviations will be fully documented and tracked using breach report forms to ensure transparency and integrity of the study protocol.

Role of sponsor

This is an investigator-initiated trial. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The investigators retain full control over all study-related decisions.

Dissemination plans

All study findings will be published in peer-reviewed scientific journals. Authorship will follow the Vancouver guidelines to ensure proper recognition of all contributing authors. We will notify all participants of the trial results by preparing a lay summary.

Sample size calculation

This study is a parallel-design RCT. According to previous literature reports, the incidence of the composite event of PCI-related myocardial infarction and myocardial injury is approximately 30% [9, 11, 12]. We assumed that an absolute event rate reduction of 10% [47] was a minimal important difference and estimated the sample size for this trial for a one-sided chi-squared test of independence (superiority test) comparing the hypothesized event rates of the two groups. With $\alpha = 0.05$ (one-sided), $1\text{-}\beta = 80\%$, and a 1:1 allocation ratio of patients, the minimum sample size is estimated as $n = 458$, i.e., 229 per group. Accounting for 20% attrition, recruitment target is 287 patients per group, requiring a total of 574 patients to be enrolled.

Statistical methods

All statistical analyses will be conducted using R (version 4.1.0). Descriptive statistics will be calculated for all study variables. For continuous variables, this will include means, standard deviations, medians, and interquartile ranges. Categorical variables will be presented as frequencies and percentages.

Two sets of analyses will be conducted: the intention-to-treat (ITT) analysis, which includes all participants who were randomly assigned, regardless of whether they adhered to the intervention protocol, and the per-protocol (PP) analysis, which includes only those participants who completed the trial according to the protocol with no major deviations. Major deviations are defined as missing any part of the RIC protocol or failure to complete the primary outcome assessments.

Primary and secondary outcomes will be compared between the treatment groups using logistic regression models, for binary outcomes, and mixed-effects linear regression models, for continuous outcomes. Covariates such as gender, age, BMI, comorbidities, past medical history, and family history will be included in the models to adjust for potential confounding.

Predefined subgroup analyses will be conducted to assess the consistency of treatment effects across different patient subgroups, such as age (≥ 75 years), sex, baseline myocardial injury severity (normal or more than double the upper limit of normal), and presence of comorbidities (whether participants have any comorbidities including hypertension, hyperlipidemia, etc.).

Missing data will be handled using the Multiple Imputation by Chained Equations (MICE) approach. Outliers, identified using standard statistical methods, will be excluded from the analysis. Five imputed datasets will be created, and statistical analyses will be performed separately on each dataset. The results from each imputed dataset will be pooled using Rubin's rules to obtain the final estimates. Given the nature of the study's outcomes, no sensitivity analyses or interim analyses will be conducted, and no adjustments for multiple comparisons will be made.

The results from the trial will be reported as point estimates, with corresponding 95% confidence intervals and *p*-values, where appropriate. All analyses will be documented in a finalized statistical analysis plan, to be completed before database lock and unblinding of the data.

Patient and public involvement

This study did not directly involve patients or the public in the design phase of the trial. However, the research team has carefully considered the safety and rights of patients throughout the study design and implementation, strictly adhering to the review and approval requirements of the ethics committees.

Discussion

Over the past several decades, numerous studies have investigated the effectiveness of RIC in offering cardiac protection during the perioperative period [48–51]. The focus of most studies has been on myocardial ischemia–reperfusion injury during PCI in MI patients, demonstrating effectiveness in numerous animal experiments and a few clinical trials [3, 19, 20, 24, 25, 28, 36]. Some research suggests that pre-RIC (before ischemia occurs) may provide better protection than RIC before reperfusion [52–54], but implementing RIC prior to myocardial infarction is challenging and ethically questionable due unclear risk profiles. In patients with unstable angina, myocardial infarction has not yet occurred, but during or after PCI perioperative myocardial infarction and myocardial injury, similar to myocardial infarction, occurs in approximately 30% of cases [9, 11, 12]. This patient population thus permits a deeper investigation into possible protective effects of ischemic preconditioning, preventing perioperative myocardial injury.

Effects of RIC have been inconsistent across multicenter RIC trials that included populations undergoing PCI [20, 24, 26–28, 36]. This could be due to a relatively short protection window afforded by RIC, with an early protective window occurring within 24 h, and a, less stable, delayed protective window occurring 12–72 h after the conditioning stimulus is given [55–57]. A perioperative RIC program could thus also ensure that patients do not miss these narrow protection windows.

The following considerations were taken into account in preparing the trial. First, the RIC program varies in different studies, with 3 to 4 RIC cycles, 4 to 5 min of ischemia, 4 to 5 min of reperfusion intervals, and inflation pressure higher than systolic pressure by 20 to 50 mmHg, while most trials use 200 mmHg [20, 25, 36, 58–73]. Based on our clinical experience, even a single cycle of cuff inflation for 5 min and pressurizing to 200 mmHg is extremely uncomfortable for patients. Considering effectiveness, tolerance, and feasibility, we recommend performing 3 upper limb ischemia pressurized to 20 mmHg above systolic pressure, with 3-min reperfusion intervals in between [60]. Second, to reduce bias, the study uses blinding with a sham RIC group, ensuring that surgeons, anesthesiologists, and other staff members remain unaware of groupings [74]. Third, perioperative myocardial infarction and myocardial injury have been found to be closely related to patient prognosis [8–10], and RIC may improve patient prognosis by reducing the incidence of these complications. For this reason, we introduce major cardiovascular adverse events and maintain follow-up for up to 12 months. Additionally, the Seattle Angina Questionnaire (SAQ) scale is used to assess the impact of postoperative angina on the quality of life [43].

Our study may face potential limitations in terms of the specificity of the intervention and the generalizability of the results. While we will utilize a perioperative intervention protocol, which is anticipated to provide a comprehensive protective window, the protocol does not enable us to discern the specific phase of RIC that plays a critical role. This ambiguity is a limitation of our study. Future research comparing perioperative intervention protocols with single period (pre-, per-, or post-) protocols will provide further insights. Moreover, an earlier start of preoperative RIC may be worth investigating (1 day before surgery), but is difficult to realize at involves hospitalization of patients a day in advance. Another potential

limitation is that our study is conducted across two centers only, which might pose a challenge to the generalizability of our findings. However, the rigorous study design and protocol should help to maintain consistency and reliability, mitigating this concern. While there are different types of unstable angina such as new angina, worsening angina, rest angina, variant angina, and this may have an effect on intervention effectiveness, these types are difficult to differentiate on the one hand and the trial is not powered for a corresponding subgroup analysis on the other.

In conclusion, if this trial shows significant improvements in primary and secondary outcomes, this could be of great importance to further improve PCI procedures in patients with unstable angina. It would not only make the procedure safer but also broaden surgical indications, provide innovative treatment options, and generate new research perspectives for RIC-related studies.

Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
CAG	Coronary angiography
DSMB	Data safety monitoring board
ECG	Electrocardiogram
ESC	European Society of Cardiology
hs-cTnT	High-sensitivity cardiac troponin T
ITT	Intention-to-treat
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MMSE	Mini-Mental State Examination
PCI	Percutaneous coronary intervention
PMI	Perioperative myocardial infarction/injury
PP	Per-protocol
RIC	Remote ischemic conditioning
SAQ	Seattle Angina Questionnaire
SBP	Systolic blood pressure
SBO	Side branch occlusion
STEMI	ST-elevation myocardial infarction
UA	Unstable angina
WHF	World Heart Federation

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions
XL, YZ, and LX conceived the design of the trial, prepared and drafted the study protocol and statistical analysis plan. XL, SL, LC, and JDR contributed to critical revision of the protocol, training of medical staff, and are coordinating the trial. SL and LC will conduct two-dimensional echocardiography and ensure its harmonized application across the consortium of participating institutions. QY will regularly track adverse events and ask for the SAQ. LJ will perform laboratory biomarker analysis and coordinate it across each participating center. YZ and LX bear the mantle for data stewardship and liaison with the DSMC. JDR, as our senior statistical savant, has designed the statistical strategy. LJ and LX and trial assistants are responsible for data acquisition, protocol adherence, and trial coordination assistance. All authors read and contributed intellectually important content and approved the final manuscript.

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Data Availability
The datasets to be used and/or analyzed are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The Institutional Review Board of the First Affiliated Hospital of Nanjing Medical University has sanctioned the trial protocol (Reference No. 2023-SR-161). Any substantive modifications pertaining to the study protocol, be it eligibility criteria, intervention methodologies, outcome measures, or analytical approaches, will be executed under the vigilant oversight and endorsement of the respective review board. All endeavors undertaken in this trial with human participants shall align scrupulously with the rigorous ethical tenets set forth by both the institutional/national research committees and the 1964 Helsinki Declaration, inclusive of subsequent amendments or analogous ethical benchmarks. Prior to their enrolment and allocation, explicit written consents shall be procured from all participating individuals.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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