Effects of remote ischaemic preconditioning on myocardial injury after major abdominal surgery in patients at high risk for cardiovascular adverse events in China (RIPC-MAS): protocol for a randomised, sham-controlled, observer-blinded trial

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ABSTRACT
Introduction Myocardial injury after non-cardiac surgery (MINS) caused by an ischaemic mechanism is common and is associated with adverse short-term and long-term prognoses. However, MINS is a recent concept, and few studies have prospectively used it as a primary outcome. Remote ischaemic preconditioning (RIPC) is a non-invasive procedure that induces innate cardioprotection and may reduce MINS.

Methods and analysis This is a multicentre, randomised, sham-controlled, observer-blinded trial. Patients with a high clinical risk of cardiovascular events who are scheduled to undergo major abdominal surgery will be enrolled. A total of 766 participants will be randomised (1:1 ratio) to receive RIPC or control treatment before anaesthesia. RIPC will comprise four cycles of cuff inflation for 5 min to 200 mm Hg and deflation for 5 min. In the controls, an identical-looking cuff will be placed around the arm but will not be actually inflated.

The primary outcome will be MINS, defined as at least one postoperative cardiac troponin (cTn) concentration above the 99th percentile upper reference limit of the cTn assay as a result of a presumed ischaemic mechanism. This trial will test the concentration of high-sensitivity cardiac troponin T (hs-cTnT). The secondary outcomes will be hs-cTnT levels reaching/above the prognostically important thresholds, peak hs-cTnT and total hs-cTnT release during the initial 3 days after surgery, length of hospital stay after surgery, length of stay in the intensive care unit, myocardial infarction, major adverse cardiovascular events, cardiac-related death, all-cause death within 30 days, 6 months, 1 year and 2 years after surgery, and postoperative complications and adverse events within 30 days after surgery.

Ethics and dissemination This study protocol (version 5.0 on 7 April 2023) was approved by the Ethics Committee of Sixth Affiliated Hospital of Sun Yat-sen University. The findings will be published in peer-reviewed journals.

Trial registration number NCT05733208.

STRENGTHS AND LIMITATIONS OF THIS STUDY
⇒ This is a multicentre, randomised, sham-controlled, observer-blinded trial with 766 participants.
⇒ Remote ischaemic preconditioning will be performed before anaesthesia.
⇒ A sham control instead of a blank control will be implemented.
⇒ The participants are awake and may be aware of the intervention.

INTRODUCTION
Over 300 million surgeries are performed annually in the world, and this number is steadily increasing.1 Although the level of surgical technology and anaesthesia management has continuously improved in recent decades,2 postoperative mortality remains far higher than the expectations of patients and doctors, accounting for 7.7% of global mortality.3 Adverse cardiovascular events are the main cause of postoperative mortality. Demographic changes have resulted in an increasing number of older patients with cardiovascular risk factors undergoing surgery who are susceptible to adverse cardiovascular events. Managing these patients is becoming a common challenge in the perioperative period.

Myocardial injury after non-cardiac surgery (MINS) is defined as at least one postoperative cardiac troponin (cTn) concentration above the 99th percentile upper reference limit of the cTn assay as a result of a presumed ischaemic mechanism during or within 30 days after non-cardiac surgery in 2021.4
Historically, these biomarker abnormalities have been ignored, but recent large prospective cohort studies have shown that silent cardiac biomarker elevations after non-cardiac surgery are common and associated with adverse short-term and long-term prognoses. Therefore, strategies to improve prevention, treatment, and outcomes of patients with MINS may provide major medical benefits.

As the diagnostic criteria for MINS were recently established by the American Heart Association in 2021, few studies have prospectively diagnosed MINS using these criteria as a primary outcome to evaluate prevention and management strategies in high-risk population. A Remote ischaemic preconditioning (RIPC) is a phenomenon in which transient non-lethal ischaemia and reperfusion on an organ or tissue remote from the heart protects the myocardium from a lethal ischaemia. RIPC can be induced by inflating and deflating the blood pressure cuff placed on the upper arm. RIPC has been shown to be non-invasive and beneficial in reducing myocardial injury in the settings of cardiac bypass surgery, primary percutaneous coronary intervention and abdominal aortic aneurysm surgery. RIPC has also been shown to have anti-inflammatory and antithrombotic effects as well as endothelial protection. By definition, MINS is caused by ischaemia. Moreover, the pathophysiology of MINS has been demonstrated to involve endothelial dysfunction and increased platelet activation and hypercoagulability which are caused by a surge in inflammatory cytokines during surgery. In addition, perioperative haemodynamic fluctuations may provoke pre-existing plaque disruption or lead to an imbalance between oxygen supply and demand, finally causing myocardial injury. Considering the effects and mechanisms of RIPC and the pathophysiology of MINS, RIPC may potentially reduce the incidence of MINS.

Thus, we planned this multicentre, parallel-group, randomised, sham-controlled, observer-blinded trial to evaluate the efficacy and safety of RIPC for the prevention of MINS after major abdominal surgery.

METHODS AND ANALYSIS
Objective
This study aimed to evaluate the efficacy and safety of RIPC in preventing MINS in patients undergoing major abdominal surgery. This study protocol (version 5.0 on 7 April 2023) was approved by the institutional review board. The trial flow diagram is presented in figure 1.

Study setting
This is a multicentre, parallel-group, randomised, sham-controlled, observer-blinded trial conducted at three centres in China.

Outcomes
Primary outcomes
We will choose the MINS as the primary outcome.

According to the diagnostic criteria established by the American Heart Association, the diagnostic criteria for MINS are the following: (a) elevated postoperative cTn with ≥1 cTn measurement above the 99th percentile of the upper reference limit for the cTn assay, with a rise/fall pattern indicative of acute myocardial injury; (b) occurs in the first 30 days (and typically within 72 hours) after surgery; (c) myocardial injury is caused by a presumed ischaemic mechanism in the absence of an overt precipitating non-ischaemic cause; (d) an ischaemic feature is not required.

Contemporary cTn assays (cardiac troponin T (cTnT) or cardiac troponin I (cTnI)) or high-sensitivity cTn (hs-cTnT or hs-cTnI) assays are all useful for MINS diagnosis. We plan to test the level of hs-cTnT before the first implementation of RIPC or control treatment which is performed approximately 24 hours before anaesthesia, and once a day on postoperative day 1, day 2 and day 3. The level of hs-cTnT will be measured by an Elecsys System using the Cobas e801 (Roche Diagnostics) assay. The lower limit of detection is 3 ng/L and the upper limit of detection is 10 000 ng/L. The upper reference limit of the 99th percentile is 14 ng/L.

In case of patients with normal baseline troponin values, myocardial injury is considered if the level of postoperative hs-cTnT level is above 14 ng/L. In case of patients with abnormal baseline troponin values, myocardial injury is considered acute if there is a ≥20% rise of cTnT after non-cardiac surgery, an absolute increase in hs-cTnT ≥14 ng/L above preoperative values or an increase in hs-cTnT ≥5 ng/L above the prior concentration and with a peak hs-cTnT ≥20 ng/L. MINS will be centrally adjudicated by two independent blinded reviewers in the endpoint adjudication committee (EAC) based on all clinical information obtained during the index hospitalisation, and non-ischaemic causes of elevated troponin levels such as sepsis or pulmonary emboli or stroke, will be excluded. In cases of disagreement between the two reviewers, the EAC adjudicator will provide the authoritative assessment endpoint.

In the document of the Fourth Universal Definition of Myocardial Infarction, non-ischaemic myocardial injury included cardiac conditions such as heart failure, myocarditis, cardiomyopathy (any type), Takotsubo syndrome, coronary revascularisation procedure, cardiac procedure other than revascularisation, catheter ablation, defibrillator shocks, cardiac contusion and systemic conditions such as sepsis, infectious disease, chronic kidney disease, stroke, subarachnoid haemorrhage, pulmonary embolism, pulmonary hypertension, infiltrative diseases (eg, amyloidosis, sarcoidosis), chemotherapeutic agents, critically ill patients and strenuous exercise.

Secondary outcomes
1. Participants with the concentration of hs-cTnT reaching/above the prognostically important thresholds.
   - Prognostically important thresholds are defined as hs-cTnT ≥20 to <65 ng/L with an absolute change
of ≥5 ng/L, any elevation ≥65 ng/L, or any absolute change ≥14 ng/L.4

2. Peak concentration of hs-cTnT within the initial 3 days after surgery.

3. Total hs-cTnT release within the initial 3 days after surgery (area under the curve).

4. Length of postoperative stay.

5. Length of stay in the intensive care unit (ICU).

6. Myocardial infarction within 30 days, 6 months, 1 year and 2 years after surgery.
   - Myocardial infarction is diagnosed according to the Fourth Universal Definition of Myocardial Infarction.18

7. Major adverse cardiovascular events (MACEs) within 30 days, 6 months, 1 year and 2 years after surgery.
   - MACEs are defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.19

8. Cardiac-related deaths within 30 days, 6 months, 1 year and 2 years after surgery.
   - Cardiac-related deaths are defined as all deaths for which there was no clinical or postmortem evidence of non-cardiac aetiology.

9. All deaths within 30 days, 6 months, 1 year or 2 years after surgery.

10. Major postoperative complications within 30 days after surgery.

Figure 1 Trial flow chart. hs-cTnT, high-sensitivity cardiac troponin T; RIPC, remote ischaemic preconditioning.
Inclusion criteria

1. Patients with a high clinical risk of cardiovascular events.
   A high clinical risk of cardiovascular events is defined as ≥65 years of age or ≥45 years of age with a history of coronary artery disease, peripheral arterial disease or stroke. A history of coronary artery disease includes a history of acute myocardial infarction, finding of stenosis on coronary angiogram or positive stress testing. A history of stroke includes a history of acute new focal neurological deficit judged by treating physicians to be of vascular cause lasting more than 24 hours.

2. Patients scheduled to undergo major abdominal surgery.
   Major abdominal surgery is defined as a skin incision, expected operative duration of at least 2 hours, and expected hospital stay of at least 3 days. The operation types of surgery mainly included gastric or small intestinal surgery, hiatal hernia repair, hepatobiliary surgery, pancreatic, colorectal, urological or renal, gynaecological and other surgery performed on multiple abdominal organs.

Exclusion criteria

1. Immediate or urgent surgery or surgery where there is insufficient time to perform RIPC.
2. Abdominal vascular surgery, such as surgery for abdominal aortic aneurysm.
3. Experience of conditions precluding the use of RIPC in both arms.
4. Patients who are being treated with drugs, such as sulphonamide or nicorandil.
5. With contraindications for anaesthetic regime required in this trial.

Recruitment

Participants will be recruited by trained investigators in each participating hospital. Eligible patients will obtain all relevant information about the study in form of oral explanation but also in form of an information sheet. After they give written consent to take part in the study, they will be screened to complete a questionnaire comprising contact details, demographics, detailed medical history and medication listing. The participant has the right to withdraw from the study at any time of the study process without prejudice to their future care.

Randomisation and treatment groups

Eligible patients will randomly (1:1 ratio) be assigned to receive RIPC or no RIPC (control). The random sequence will be generated by an independent statistician using the SAS software (V.9.4), with stratification by participating centre and type of anaesthesia using permuted blocks. Then, the sequence will be implemented securely into the web-based secure electronic module for central randomisation incorporated in the electronic data capture system (Zhejiang Taimei Medical Technology, China). Access to this module and results of randomisation will be strictly controlled and limited to unmasked trained implementer of the RIPC or control. The members involved in participant recruitment, data collection and outcome assessment, and participant care in the perioperative period will be blinded.

RIPC will consist of four cycles of 5 min inflation of a blood pressure cuff on the upper arm to 200 mm Hg, followed by 5 min deflation. For patients with systolic blood pressure (SBP) ≥175 mm Hg, the cuff will be inflated to at least 25 mm Hg above the SBP. In the controls, an identical-looking cuff will be placed around the upper arm. However, unlike in RIPC, the valve of inflation pump is unlocked, such that the cuff cannot be inflated. The operation of the control including cycling number and cycling time are identical to those of the RIPC procedure, except that the blood pressure cuff does not inflate. RIPC or control treatment will be performed two times, one at approximately 24 hours before anaesthesia and the other at approximately 1 hour before anaesthesia.

The anaesthesia regimes will be restricted to either total intravenous anaesthesia containing propofol or volatile anaesthesia without propofol and the anaesthesia regime will be one of the stratification factors. The same goal of
pain regimes will be set, which is a pain score no more than 3 after surgery, to balance the increment of oxygen demand caused by pain. The choice of pain regimes will be left to anaesthesiologist and the patients’ requirement to maintain the generalisability of the results.

**Follow-up**

*Figure 2* provides details of the schedule of enrolment, interventions and assessments. Blood will be collected to test the hs-cTnT concentration before the first implementation of RIPC or control treatment, and once a day on postoperative day 1, day 2 and day 3. The participants will be followed-up at the bedside by investigators every day to record postoperative complications, adverse events, and the length of ICU stay and hospital stay and followed up by telephone at 30 days to investigate the adverse events and the events of myocardial infarction, death and the cause of death. Moreover, they will be followed up by telephone at 6 months, 1 year and 2 years to investigate the events of myocardial infarction, MACEs, death and the cause of death.

**Sample size calculation**

Based on the results of PIXIE trial in 2019 and the VISION study in 2017, 5%–35% of the patients developed MINS according to the diagnostic criteria established by the American Heart Association. We estimated that RIPC would reduce the incidence to 20%. Therefore, assuming an incidence of 31% in the control group and 20% in the RIPC group, we calculated that 650 participants would be required to detect this difference using R software (V.4.2.1), with a 5% type I error and a power of 90% in a two-sided test. The planned number of patients for enrolment was finally set at 766 (383 participants

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*Figure 2* The schedule of enrolment, interventions and assessments. hs-cTnT, high-sensitivity cardiac troponin T; ICU, intensive care unit; MACE, major adverse cardiovascular event; RIPC, remote ischaemic preconditioning.
in each group), considering a 15% dropout rate and non-compliance.

**Statistical analysis**

A detailed statistical analysis plan will be produced prior to unblinding of any data. All continuous, normally distributed or approximately normally distributed variables will be expressed as mean (SD). All continuous, non-normally distributed variables will be expressed as median (IQR). Differences between groups will be investigated using the Student’s t-test for normally distributed or approximately normally distributed continuous variables, the Mann-Whitney U test for non-normally distributed continuous variables, and Pearson’s $\chi^2$ test or Fisher’s exact test for categorical variables. Two-tailed tests will be performed. Risk ratios with 95% CIs will be calculated using log-binomial regression or Poisson regression. HRs and CIs will be calculated using Cox proportional hazards modeling and Kaplan-Meier curves will be produced. Risk difference with 95% CIs will be calculated using binomial regression or Poisson regression. Differences in means (continuous variables) together with 95% CIs will be calculated using linear regression models or generalised estimation equation. Both adjusted analyses and unadjusted analyses will be performed. $P<0.05$ will be considered statistically significant. Analyses will be performed both in the full analysis set and in the per-protocol set. In the intention to treat analysis, the missing data will be imputed by the method of multiple imputation. In the per-protocol analysis, the missing data will not be imputed. Subgroup analyses will be stratified by sex, type of anaesthesia, age group, trial centre, revised cardiac risk index and Duke activity status index. Statistical analyses will be performed using R software (V.4.2.1).

**Data management**

The data will be entered into the electronic data capture database, which has data entry and validation rules to reduce data entry errors, and the management functions to facilitate auditing. Participants’ data will be held securely in line with data protection legislation. Anonymous datasets will be stored in the Research Data storage facility at Sun Yat-sen University. The data management team will be responsible for establishing the module in the electronic data capturing system, designing the case report form, reviewing data blindly, locking database, exporting data and so on.

**Monitoring, safety and audit**

The coordinating centre will be responsible for coordinating the three participating centres, and collecting data from each centre, laboratory and EAC. The Trial Steering Committee (TSC) will be responsible for the protocol design and implementation, drafting the final report and submission for publication. The EAC will be responsible for validating and adjudicating the endpoints independently.

This trial will be overseen and audited by the Clinical Research Centre, Ethics Committee and Data Safety Monitoring Committee (DSMC). The DSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, determining whether there are any unforeseen effects of RIPC, recommending to the TSC whether the trial needs to be changed or terminated based on analysis. The DSMC will first convene prior to trial initiation and will then define frequency of subsequent meetings (at least two times a year). The Clinical Research Centre and Ethics Committee will monitor the trials annually. The investigators at each centre will be responsible for registering and reacting in case of serious adverse event (SAE) and suspected unexpected serious adverse reaction (SUSAR) happened. The investigators at each centre will report the related SAE and SUSAR to the chief investigator, the ethics committees and the DSMC.

**Public and patient involvement**

Public and patient involvement (PPI) representatives have been actively involved in the study design stage, including the development of an intervention protocol and adding outcomes that PPI representatives care about, such as participants with the concentration of hs-cTnT above the prognostically important thresholds. PPI will advise on the communication with participants and report of the findings of this study with a wider audience.

**ETHICS AND DISSEMINATION**

This study was reviewed and approved by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University. Potential participants are required to provide written informed consent before participating in the trial. The results of this study will be presented at national and international meetings and published in peer-reviewed journals. We will work with our PPI contributors to produce study summaries for the patients.

**Trial status**

This trial has started on 6 May 2023. We planned to complete this trial in December 2027.
and XW contributed to design the study and revise the manuscript. All the authors have read and approved the final manuscript.

**Funding** This work was funded by the 1010 Programme of the Sixth Affiliated Hospital of Sun Yat-sen University (No. 1010PY(2022)-21), the Scientific and Technological Planning Project of Guangzhou City (No. 202201011669) and Special Funds for the Cultivation of Guangdong College Students’ Scientific and Technological Innovation (No. pdjh2021b0018).

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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