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Effect of mild hypothermia vs normothermia cardiopulmonary bypass on postoperative bleeding in patients undergoing coronary artery bypass grafting: protocol of a multi-center, randomized, controlled trial

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Abstract

Background Coronary artery bypass grafting (CABG) is often performed with hypothermic cardiopulmonary bypass (CPB) to reduce metabolic demands and protect the myocardium. However, hypothermia can increase bleeding risks and other complications.

Methods This is a prospective, multi-center, randomized controlled trial. From September 2023 to December 2024, a total of 336 eligible patients planning to undergo on-pump CABG will be enrolled. All participants will be randomly divided into mild hypothermia CPB group (target oxygenator arterial outlet blood temperature at 32–33℃) or normothermia CPB group (target oxygenator arterial outlet blood temperature at 35–36℃). The primary endpoint is Universal Definition of Perioperative Bleeding (UDPB) class 2–4. Secondary endpoints are class of UDPB, levels of coagulation and inflammatory factors, in-hospital mortality, perioperative related complications, ICU length of stay, and hospital length of stay.

Discussion This clinical trial aims to compare the effects of different target temperature during CPB on postoperative bleeding and to explore optimal temperature strategy to provide new clinical evidence.

Trial registration Chictr.org.cn: ChiCTR2300075405. The trial was prospectively registered on 4 September 2023.

Keywords Coronary artery bypass grafting, Targeted temperature management, Cardiopulmonary bypass, Bleeding, Coagulation

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Background

Coronary artery bypass grafting (CABG) is a well-established treatment for complex coronary artery disease. In clinical practice, CABG surgery is often performed using hypothermic cardiopulmonary bypass (CPB) to lower the metabolic demand and oxygen consumption of vital tissues, such as the myocardium and brain, thereby enhancing their tolerance to ischemia [1]. However, it is important to recognize that lowering the temperature can disrupt the balance of coagulation, suppress coagulation enzyme activity, and increase the risks of both bleeding and thrombosis [2]. Patients undergoing hypothermia during CPB may also face an increased risk of postoperative renal failure, neurocognitive dysfunction, and prolonged stays in the intensive care unit (ICU) [3].

Given the advancements in cardiac surgery techniques and the growing expertise of surgical teams, adopting temperature management strategies closer to the body temperature could reduce unnecessary prolongation of surgical time associated with cooling and rewarming processes. Normothermia may mitigate the increased metabolic demand during rewarming. Additionally, it may reduce the risk of postoperative ischemia induced by hypothermia, which can affect multiple organs, including the heart and brain. Recent studies have demonstrated that normothermic CPB does not increase the risks of neurological complications or mortality in cardiac surgery patients [4, 5]. Nevertheless, there remains a lack of contemporary evidence from randomized controlled trials (RCTs) evaluating the effects of temperature management during on-pump CABG on patient outcomes.

This study aims to conduct an RCT to compare the effects of different target temperatures during CPB on postoperative bleeding in CABG patients and to explore the optimal temperature strategy.

Methods

Trial design

A multi-center, prospective, single-blinded, randomized controlled trial will be conducted. From September 2023 to December 2024, patients undergoing on-pump CABG and meet the eligibility criteria will be enrolled in this study (Fig. 1). Participating institutions include 10 hospitals in China. All the selected individuals will

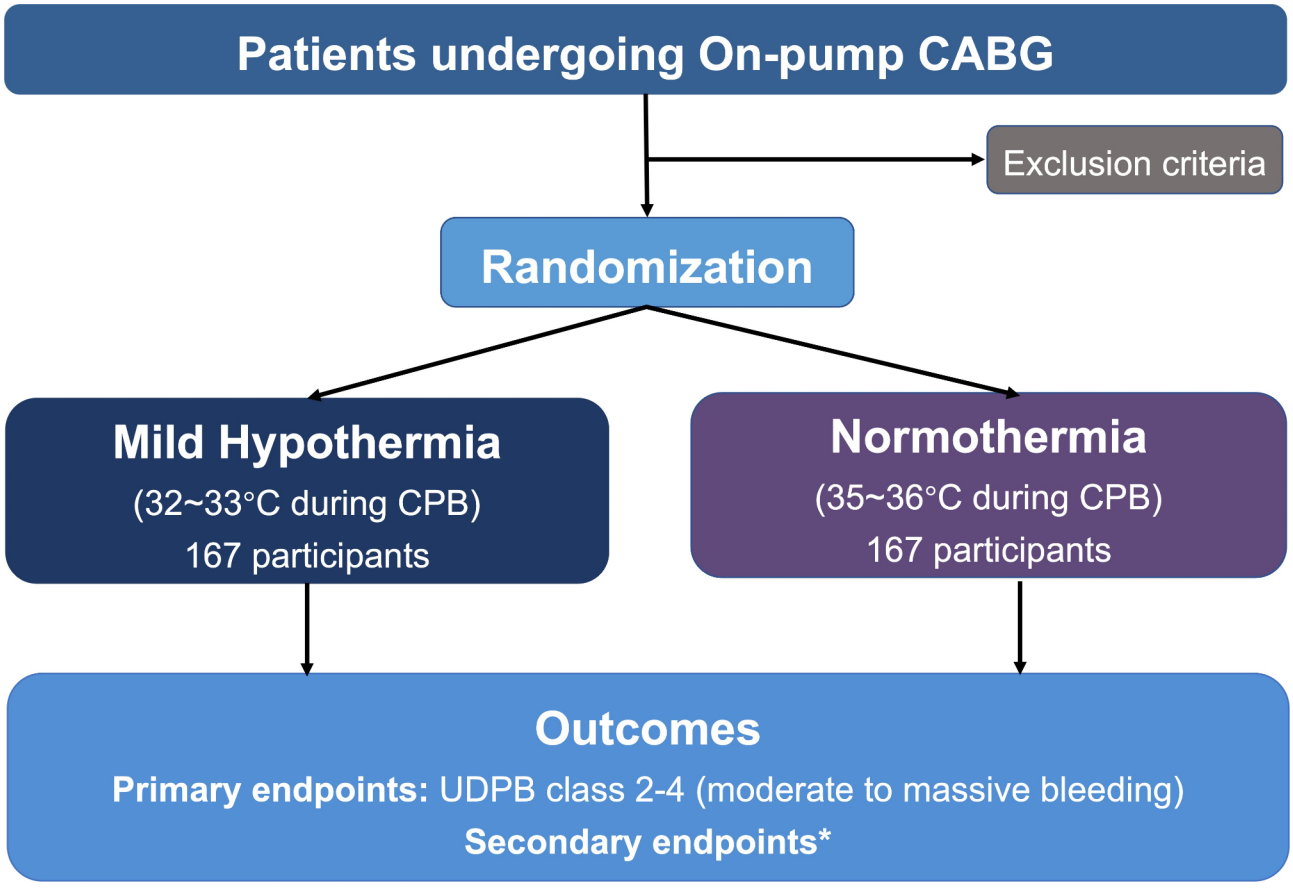

Fig. 1 Flow diagram of enrolment, intervention, and assessment
*Secondary endpoints include efficacy endpoints, safety endpoints and other endpoints. CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; UDPB, Universal Definition of Perioperative Bleeding

be randomly stratified by different temperature management during CPB: mild hypothermia and normothermia. Data collection will start from the accumulation of basic data until the end of follow-up (Table 1). All participants will provide written informed consent. This study was approved by the Ethics Committee of Fuwai Hospital (Ethics number: 2023–2073).

Participants

Inclusion criteria

(1) Aged ≥ 18 years.
(2) Undergoing on-pump isolated CABG.
(3) Able to sign the informed consent.

Exclusion criteria

(1) Emergency surgery.
(2) Undergoing CABG combined with other procedures.
(3) Preoperative hemoglobin < 90 g/L.
(4) Reoperation.
(5) Use of antiplatelet drugs (e.g., clopidogrel, aspirin) or dual antiplatelet therapy within 5 days before surgery.
(6) Participation in other interventional studies within the past month, with assessed significant impact on this study.
(7) Patient considered unsuitable for enrolment in the present trial due to the surgeon's clinical judgment, the perfusionist's preoperative assessment of inability to maintain the target temperature, severe comorbidities, or refusal to participate in the study.

Intervention

The intervention involved maintaining different oxygenator arterial outlet blood temperature during CPB. Patients will be divided into two groups based on different temperature management during CPB. In the mild hypothermia group, the target oxygenator arterial outlet blood temperature during CPB is maintained at 32–33 °C, while in the normothermia group, the target oxygenator arterial outlet blood temperature during CPB is maintained at 35–36 °C. Detailed temperature management strategies during CPB are listed as Table 2.

Randomization and blinding

This is a single-blind study. Group randomization will be performed by a computer-generated randomization sequence with a block of 10. One researcher will be responsible for maintaining the random sequence, concealing group sizes, and communicating with the assigned researchers. After researchers confirming the participants meet the inclusion criteria and obtaining their informed consent, participants will be randomly assigned to the mild hypothermia group or the normothermia group at 1:1. If a participant is unable to undergo surgery after randomization for any reason, their trial number and randomization status will be retained. Participants and their families are not informed about the assigned group to maintain blinding throughout the study.

Outcomes

Primary endpoint

The primary endpoint is Universal Definition of Perioperative Bleeding (UDPB) class 2–4 (moderate to massive bleeding) [6], defined as the occurrence of one or more of the following indexes: (1) delayed sternal closure; (2)

Table 1 Assessment schedule

Assessment	STUDY PERIOD				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Baseline 7 days to 0 days	CPB initiation	Rewarming	Within 48 h after surgery	Surgery to discharge
Informed consent	√				
Inclusion/exclusion criteria	√				
Randomization	√				
Basic medical history	√				
Blood laboratory test	√	√	√	√	√
Blood gas analysis	√	√	√	√	√
Coagulation function		√	√	√	
Coagulation factors		√	√		
Inflammatory factors		√	√		
Chest tube output				√	√
Blood product transfusion		√	√	√	√
UDPB				√	
AE, SAE, and endpoints		√	√	√	√

AE, adverse events; CPB, cardiopulmonary bypass; SAE, severe adverse events; UDPB, Universal Definition of Perioperative Bleeding

Table 2 Temperature management strategies during CPB

Phase	Mild hypothermia group			Normothermia group		
	Water temperature setting	Target oxygenator arterial outlet blood temperature	Target core temperature	Water temperature setting	Target oxygenator arterial outlet blood temperature	Target core temperature
Initiation of CPB	NA	NA	NA	NA	NA	NA
Cooling	32–33℃*	32–33℃	32–33℃	35–36℃	35–36℃	35–36℃
Aortic cross-clamping	32–33℃	32–33℃	32–33℃	35–36℃	35–36℃	35–36℃
Rewarming	Gradually adjusting to > 36℃	> 36℃	> 36℃	Gradually adjusting to > 36℃	> 36℃	> 36℃
Opening of the ascending aorta	> 36℃	> 36℃	> 36℃	> 36℃	> 36℃	> 36℃
Cessation of CPB	NA	NA	> 36℃	NA	NA	> 36℃

CPB, cardiopulmonary bypass; NA, not applicable

*In the mild hypothermia group, the water tank temperature is actively adjusted to 32–33 °C, and a gradual decrease in the patient's core temperature can be observed

chest tube output exceeding 800 mL within 12 h postoperatively; (3) 2 or greater units of red blood cells or fresh frozen plasma (FFP) transfusions within 24 h postoperatively; (4) any of platelets, cryoprecipitate, prothrombin complex concentrate transfusion or recombinant activated factor VII use within 24 h postoperatively; (5) surgical re-exploration for bleeding.

Secondary endpoints

Efficacy endpoints include class of UDPB, rate of perioperative blood products transfusion, including red blood cells, FFP, platelets, cryoprecipitate, prothrombin complex concentrate and rFVIIa, postoperative chest tube output, levels of coagulation factors (FII, FV, FVII, FX, FVIII, FIX, FXI, FXII), levels of inflammatory factors (IL-1ß, IL-2, IL-4, IL-5,113 IL-6, IL-8, IL-10, IL-12p70, IL-17, TNF-α, IFN-α, IFN-γ), surgery time, cooling and rewarming time, aortic cross clamping time, mechanical ventilation time, ICU length of stay, and hospital length of stay.

Safety endpoints

Safety endpoints include in-hospital mortality, perioperative cerebrovascular events (including stroke and cerebral hemorrhage) and cognitive dysfunction, myocardial infarction, acute kidney injury, hepatic dysfunction, infection, postoperative low cardiac output syndrome, significant bleeding events such as heparin resistance, hemolysis, and re-exploration for bleeding.

Sample size calculation

A retrospective analysis of patients who underwent isolated CABG at our center found that the incidence of UDPB class 2–4 was approximately 40%. With the incidence of UDPB class 2–4 as the main endpoint event, we assumed that a 15% reduction of the incidence of UDPB class 2–4 in the normothermic CPB group compared to the hypothermic CPB group. A test for equivalence method was used with a two-sided significance level (α) of 0.05 and a test power (β) of 80%, according to the ratio of 1:1 between the hypothermic group or the normothermic group. Both groups will require 150 participants. Considering a 10% dropout rate (early termination due to other reasons and random assignment), a total of 334 participants were planned to be enrolled in the study, with 167 participants in each group. The sample size was calculated by PASS 2019 (provided by NCSS, LLC.).

Statistical analysis

The primary analysis of all endpoints will be conducted using intention to treat principle, wherein participants will be analyzed according to the initial randomization, irrespective of the final assignment received. For patients who have been randomized into the trial but ultimately do not undergo CABG at the target temperature, they will be excluded from the analysis.

Continuous variables with normal distribution are expressed as mean ± standard deviation, and those with non-normal distribution are expressed as median (interquartile range). The intergroup comparisons are conducted using Student's t-test or Mann-Whitney U tests according to the normality of the data. Categorical variables are expressed as frequencies and percentages, and intergroup comparisons are conducted using chi-square tests or Fisher's exact tests. For the primary endpoint indicators, differences in endpoint occurrence rates between the two groups and 95% confidence interval estimates will be provided. Per-protocol analysis was performed excluding patients for whom there were major protocol deviation. All statistical tests are two-sided, and $p < 0.05$ will be considered statistically significant. SPSS V.26.0 software (IBM, New York, USA) will be used for statistical analyses.

Data safety and monitoring

To ensure the accuracy and authenticity of data collection quality, the research team conducts comprehensive training on data quality control. The data for this study are sourced from Electronic Medical Record System and follow-up data are collected by the researchers. An independent electronic database is created using Epidata software (Version 3.1) and stored on a computer disconnected from external networks. Data entry is conducted by two researchers simultaneously, employing double-entry verification to ensure consistency and quality control. The database adhered to confidentiality principles, with all personal information anonymized. Researchers will collect and retain the informed consent forms, case report forms (CRFs) and other research documents.

Adverse events

Adverse event (AE) or serious adverse event (SAE) will be assessed during the entire study period. SAE were characterized as any adverse medical event or unintended symptom linked to the study intervention, resulting in one or more of the following complications: life-threatening conditions, cerebrovascular events, severe disability, or death. If patients occur AE or SAE, researchers should document the AE record form truthfully and in detail. AE record form should be reported to the ethics committee as part of the annual review.

Discussion

Temperature management during CPB has long been a controversial issue. Hypothermia is commonly utilized in cardiac surgery to reduce metabolic demand and provide organ protection. However, the effects of hypothermia can be significant, potentially leading to the suppression of thrombin activity and impaired coagulation function [7]. Previous studies suggested that hypothermia was associated with adverse perioperative outcomes, including increased bleeding and transfusion requirements [8]. Normothermic CPB has gained attention in recent years for its potential to mitigate these risks. Maintaining normothermia may alleviate the detrimental effects on coagulation, thereby reducing the need for blood transfusions. While some studies have demonstrated the safety of normothermic CPB [3, 4], there is still a lack of definitive evidence regarding its benefits on clinical outcomes [9].

It is important to acknowledge that normothermia may unavoidably result in elevated brain temperatures and increased metabolic demands, particularly in patients with carotid artery stenosis. These patients may face additional neurological challenges. While prior meta-analyses have suggested that normothermia may not adversely affect postoperative cognitive outcomes [4], high-risk patients may require intraoperative assessment by surgeons, anesthesiologists, and perfusionists, potentially leading to a decision to switch to hypothermic CPB. This scenario may contribute to patient crossover into the hypothermia group during future clinical trials, leading to a certain dropout rate. We have accounted for this eventuality in our sample size calculation and will undertake a detailed analysis of the clinical data from these patients in future discussions.

Through a review of the data from our center, we found that patients who previously underwent hypothermic CABG procedures exhibited elevated rates of perioperative blood transfusions. Blood transfusion was associated with an increased risk of adverse postoperative outcomes, such as acute kidney injury and mortality [10, 11]. However, it remains unclear whether hypothermia is the cause of the increased bleeding and transfusion needs. Since 2018, our center has actively engaged in quality control efforts aimed at optimizing blood management, leading to a significant reduction in transfusion rates [12]. As a result of ongoing improvements in blood management practices, the rate of blood product transfusions has stabilized, highlighting the urgent need for more precise and effective management strategies.

Temperature management during CPB is also an important task. Consequently, investigating the optimal temperature management strategy during CPB is imperative for reducing patient bleeding and transfusion. Our clinical trial aims to evaluate the effects of normothermia versus hypothermia CPB on patients undergoing CABG, with a specific focus on perioperative bleeding and transfusion requirements. It also aims to provide high-quality evidence comparing the clinical outcomes of these two temperature management strategies. We have selected UDPB as the primary outcome for our study. UDPB serves as a composite indicator, which provides a comprehensive evaluation of patients' transfusion status, perioperative bleeding events, and bleeding-related adverse outcomes.

This study has some limitations. First, the absence of long-term follow-up restricts the assessment of neurological function. Second, due to the study design, blinding of researchers and clinicians is not feasible.

This trial will provide objective evidence on temperature management during CPB and may help shape guidelines and recommendations for the temperature management during CABG and other cardiac surgeries.

Abbreviations

AE	Adverse event
CABG	Coronary artery bypass grafting
CPB	Cardiopulmonary bypass
CRFs	Case report forms
FFP	Fresh frozen plasma
RCTs	Randomized controlled trials
SAE	Serious adverse event
UDPB	Universal Definition of Perioperative Bleeding

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12893-024-02634-6.

Supplementary Material 1

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Author contributions
Jing Wang drafted the manuscript. Tianlong Wang, Han Zhang, Qiaoni Zhang made substantial contributions to the design of the study. Gang Liu, Shujie Yan, Qian Wang, Yuan Teng, Jian Wang, Qiang Hu made substantial contributions to the conception and design of the study and provided details of the trial status. Bingyang Ji obtained funding, provided critical revision of the manuscript for important intellectual content, and approved the final version of the manuscript. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Fuwai Hospital (2023–2073). Informed consent will be obtained from all participants before enrollment, ensuring they understand the study's purpose, procedures, risks, and benefits. Participants will be informed of their right to withdraw from the study at any time, and confidentiality of their data will be strictly protected.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Current trial status
The current protocol version is Version 4.0 (May 2024). The current informed consent version is Version 3.0 (May 2024). The first patient was enrolled on September 21, 2023. One hundered patients have been enrolled in this study so far. We expect to complete recruitment by December 2024. The results of primary and secondary outcomes will be published after the follow-up.

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References

1. Habibi V, Habibi MR, Habibi A, Emami Zeydi A. The protective effect of hypothermia on postoperative cognitive deficit may be attenuated by prolonged coronary artery bypass time: Meta-analysis and meta-regression. Adv Clin Exp Med. 2020;29(10):1211–9.
2. Jeppesen AN, Duez C, Kirkegaard H, Grejs AM, Hvas AM. Fibrinolysis in Cardiac arrest patients treated with hypothermia. Ther Hypothermia Temp Manag; 2022;13(3):112-9.
3. Bianco V, Kilic A, Aranda-Michel E, Dunn-Lewis C, Serna-Gallegos D, Chen S, et al. Mild hypothermia versus normothermia in patients undergoing cardiac surgery. JTCVS Open. 2021;7:230–42.
4. Linassi F, Maran E, De Laurenzis A, Tellaroli P, Kreuzer M, Schneider G, et al. Targeted temperature management in cardiac surgery: a systematic review and meta-analysis on postoperative cognitive outcomes. Br J Anaesth. 2022;128(1):11–25.
5. Abbasciano RG, Koulouroudias M, Chad T, Mohamed W, Leeman I, Pellowe C, et al. Role of hypothermia in adult cardiac surgery patients: a systematic review and Meta-analysis. J Cardiothorac Vasc Anesth. 2022;36(7):1883–90.
6. Dyke C, Aronson S, Dietrich W, Hofmann A, Karkouti K, Levi M, et al. Universal definition of perioperative bleeding in adult cardiac surgery. J Thorac Cardiovasc Surg. 2014;147(5):1458–e631.
7. Ho KM, Tan JA. Benefits and risks of maintaining normothermia during cardiopulmonary bypass in adult cardiac surgery: a systematic review. Cardiovasc Ther. 2011;29(4):260–79.
8. Lopes CT, Dos Santos TR, Brunori EH, Moorhead SA, Lopes Jde L, Barros AL. Excessive bleeding predictors after cardiac surgery in adults: integrative review. J Clin Nurs. 2015;24(21–22):3046–62.
9. Engelman R, Baker RA, Likosky DS, Grigore A, Dickinson TA, Shore-Lesserson L, et al. The Society of thoracic surgeons, the Society of Cardiovascular Anesthesiologists, and the American Society of ExtraCorporeal Technology: clinical practice guidelines for cardiopulmonary bypass–temperature management during cardiopulmonary bypass. Ann Thorac Surg. 2015;100(2):748–57.
10. Hosseini M, Griffeth EM, Schaff HV, Klompas AM, Warner MA, Stulak JM et al. Analysis of Anemia, transfusions, and CABG outcomes in the Society of thoracic surgeons National Database. Ann Thorac Surg. 2024; 117(5):1053-60.
11. Mazzeffi MA, Holmes SD, Taylor B, Ghoreishi M, McNeil JS, Kertai MD, et al. Red blood cell transfusion and postoperative infection in patients having coronary artery bypass grafting surgery: an analysis of the Society of thoracic surgeons adult cardiac surgery database. Anesth Analg. 2022;135(3):558–66.
12. Zhang Q, Zhao W, Gao S, Yan S, Diao X, Wang Y, et al. Quality Management of a Comprehensive Blood Conservation Program during Cardiopulmonary Bypass. Ann Thorac Surg. 2022;114(1):142–50.

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