

STUDY PROTOCOL

Protocol for a Single-Center Randomized Controlled Trial of Percutaneous Coronary Intervention Via Distal Transradial Access Versus Transradial Access

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Abstract

Background: Although transradial access (TRA) has become the main vascular access for coronary intervention, its high radial artery occlusion rate limits its application in some patients. Studies have shown that compared with TRA, distal transradial access (dTRA) with the snuffbox area or the Hegu acupoint area as the puncture point significantly decreases the incidence of radial artery occlusion. However, no randomized controlled study has confirmed the safety and efficacy of coronary artery intervention via dTRA in China.

Methods and analyses: This single-center, prospective, randomized controlled, superiority open-label study will enroll 428 consecutive patients with coronary heart disease undergoing percutaneous coronary intervention as the study population. After preoperative evaluation, the participants will be randomly divided into a study group (dTRA) and control group (TRA) in a 1:1 ratio. The primary endpoint (radial artery occlusion at 24 hours after operation) and secondary endpoint events will be evaluated and recorded.

Study registration: This study has been registered in the Chinese Clinical Trial Registry (registration number: ChiCTR2300073902).

Keywords: distal transradial access; transradial access; coronary intervention; radial artery occlusion

Introduction

Transradial access (TRA) has become the main vascular approach for coronary angiography and percutaneous coronary intervention (PCI) [1]. According to Chinese quality control data, 1,293,932 coronary heart disease interventions were performed in China in 2022, of which TRA accounted for 96.93%. Compared with transfemoral access, TRA has fewer complications and a lower incidence of puncture related bleeding events. Patients are not required to stay in bed, thus improving their comfort. The most common complication of TRA is radial artery occlusion (RAO). The reported incidence of RAO in the first 24 hours after coronary operation (including coronary angiography and coronary intervention) via TRA is 8%, and the reported incidence of RAO in the first 30 days is 5.5% [2]. The occurrence of RAO affects re-operation via the ipsilateral radial artery, coronary artery bypass grafting with the radial artery as the graft, and arteriovenous fistula in patients undergoing dialysis. Therefore, new interventional approaches must be explored to meet clinical needs and decrease the incidence of RAO.

The distal transradial access (dTRA) technique was first introduced by Babunashvili for recanalization of the occluded radial artery [3]. The first coronary intervention study using dTRA was reported by Kiemeneij in 2017 [4]. In dTRA, the distal radial artery at the snuffbox [2] or Hegu acupoint [5] serves as the puncture site. The fixed anatomical position and clear location enable high success rates of puncture by skilled physicians. A 6 F artery sheath can be safely inserted within the distal radial artery diameter, and a thin-walled 7 F artery sheath can be used in some patients, thus meeting the requirements of diagnostic coronary angiography and coronary intervention [6]. The substantially shorter compression time with dTRA than TRA increases patient comfort. Clinical studies have shown that dTRA, compared with TRA,

significantly decreases the incidence of RAO 24 hours and 30 days after coronary operation. Subgroup analysis has suggested that dTRA is feasible for PCI of single-vessel, double-vessel, and left main coronary artery disease, and that dTRA is also feasible for coronary artery disease intervention [2, 7–10]. Although some retrospective studies have been conducted, the safety and effectiveness of dTRA for coronary artery disease intervention in China have not been further confirmed in randomized controlled trials.

Study Aims and Hypothesis

Objectives

The study objective is to evaluate the safety and feasibility of dTRA versus TRA for PCI.

Hypothesis

Compared with TRA, dTRA is hypothesized to significantly decrease the occlusion rate of the radial artery at 24 hours and 30 days after PCI, and the effectiveness of coronary intervention is hypothesized not to be inferior to that of TRA.

Methods

Study Design and Setting

This study is designed as a single-center, prospective, randomized controlled, superiority, open-label study. Consecutive patients with coronary heart disease who are scheduled to undergo PCI will be enrolled at Fuwai Hospital. In this study, coronary intervention will be defined as procedures including coronary physiology examination, endovascular imaging examination, coronary balloon dilatation, stent implantation, in which a guide catheter is sent into the coronary ostium via vascular access, and the operation is completed along the guide wire. After preoperative evaluation and provision of informed consent, participants will be randomly divided into a study group (dTRA group) and control group (TRA group) in a 1:1 ratio. Participant enrollment began after approval was granted by the ethics committee on July 11,

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2023. All participants will be enrolled and visited at 1 month by September 30, 2024.

Inclusion Criteria

The inclusion criteria are age ≥ 18 to ≤ 80 years; height ≤ 180 cm; undergoing coronary angiography and PCI; no radial artery intervention or radial artery surgery on the operated side; existing radial artery pulse, according to palpation of the radial artery, snuffbox, and Hegu acupoint before operation; unobstructed radial artery blood flow, as confirmed by ultrasound, and inner diameter of the distal radial artery ≥ 1.7 mm; positive Allen test; and patient provision of consent to participate in the study.

Exclusion Criteria

The exclusion criteria are planned transfemoral (transbrachial) artery approach; existing variation in the radial artery not suitable for transradial intervention; previous treatment via bilateral TRA/dTRA or radial artery surgery; direct PCI planned for acute myocardial infarction; occlusion of the radial artery on the operated side, as confirmed by ultrasound; negative Allen test; no further intervention performed after coronary angiography; renal insufficiency, with eGFR < 30 mL/min; allergy to aspirin and inability to tolerate other antiplatelet drugs; and patient refusal of consent to participate in the study.

Informed Consent

All patients meeting the requirements after screening will be included in the study. After receiving an oral and written introduction, patients are provided with detailed information including the study content, randomization process, probability of assignment to each group, intervention methods, relevant examinations, follow-up, benefits, and risks of the study, and emergency contacts; they then sign the informed consent form approved by the ethics committee without any interference. Only patients who have clearly provided written informed consent are considered study participants and proceed to the next step of randomization and intervention. Participants will be entitled to their rights as specified on the informed consent form.

Withdrawal Criteria

Participants may withdraw from the study at any time before the end of the study, or without further intervention after coronary angiography according to the study protocol. If a participant contacts the study physician before withdrawal and provides written withdrawal instructions, the investigator will stop collecting the participant's data, record the time of withdrawal, and delete the non-desensitized data. However, data that have already been desensitized cannot be identified for deletion.

Assessment and Procedures

(Flowchart in Figure 1).

Preoperative Evaluation

After medical history taking, physical examination, laboratory testing, echocardiography, and radial artery ultrasound, participants who meet the criteria and provide written informed consent are randomly assigned to a study group (dTRA group) or a control group (TRA group) by the investigator through a central randomization system, stratified according to whether the patient has diabetes and whether the patient is taking ticagrelor. Participants and operators will be notified of the randomization results. For all patients, wrist and hand function on the operation side will be evaluated by the research nurse at baseline before the procedure, according to the Fugl-Meyer motor function scale [11]. In particular, the vessel diameters of the distal radial artery, and the distal (5 cm from the styloid process), middle (10 cm from the styloid process), and proximal (15 cm from the styloid process, approximately the tip of the sheath) radial artery, will be measured through ultrasonography, and the recommended puncture sites will be located through ultrasonography according to group assignment. For the study group, the puncture point is located at the snuffbox (a triangular area surrounded by the extensor pollicis longus tendon, extensor pollicis brevis tendon, and radial styloid process) or the Hegu acupoint (the midpoint of the radial side of the second metacarpal on the dorsal side of the hand). For the control group, the puncture point is

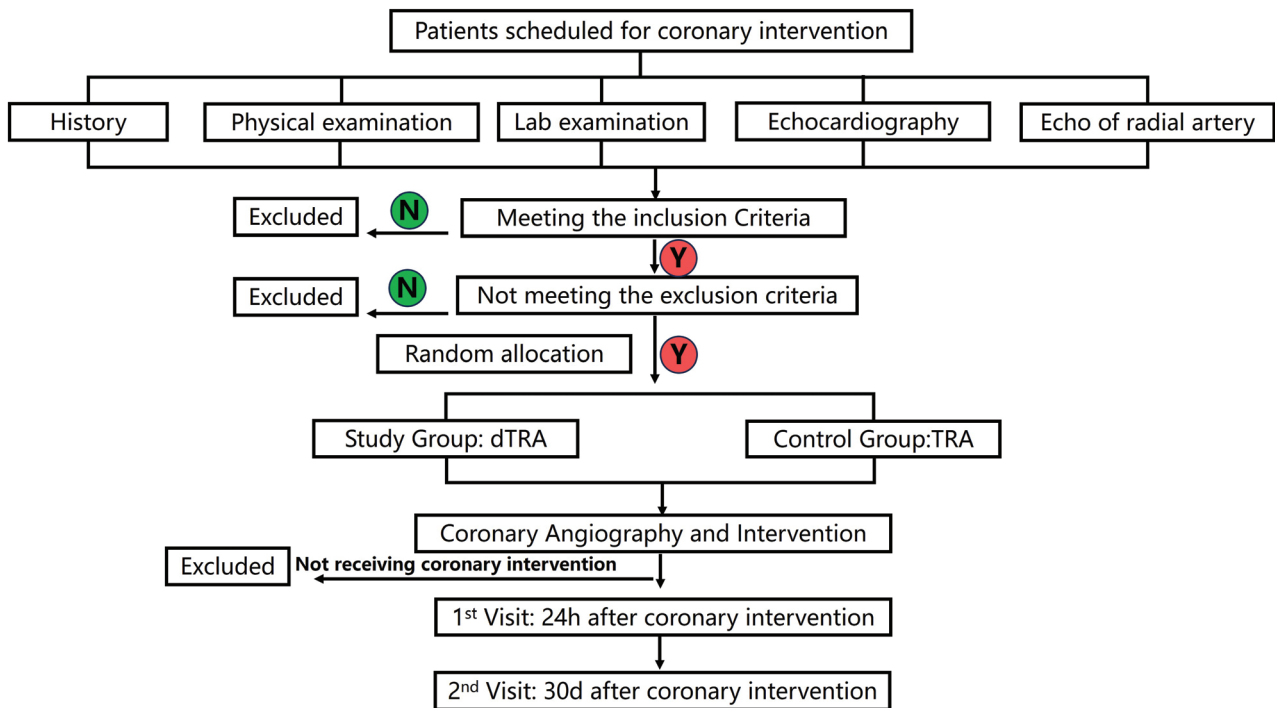


Figure 1 Flowchart of the Study.

Y = yes, N = no, TRA = transradial access, dTRA = distal transradial access.

located at the point of the strongest arterial pulse 2–3 cm from the wrist joint (Figure 2A and B).

Performing Puncture and Catheterization

The study physician will perform the arterial puncture process according to the recommended puncture point of ultrasound localization and the study group. To exclude confounding factors due to the vascular sheath and ensure safe implementation of the coronary intervention, all participants in this study will be implanted with a 6 F arterial sheath in the upper limb (Abbott, USA) after successful arterial puncture. When a 7 F vascular sheath must be inserted because of the requirements of the interventional procedure, a 6 F vascular sheath should be successfully inserted first into the upper limb artery, and the 7 F vascular sheath (APT Medical, China) should be inserted through guide-wire exchange. The puncture time, catheterization time, sheath size, and number of punctures will be recorded. After successful catheterization, 25 mg unfractionated heparin sodium will be administered through the vascular sheath before coronary angiography.

Conducting Coronary Intervention

Heparin will be supplemented at a total amount of 1 mg/kg before coronary intervention. (The maximum total dose of heparin for the first supplement is 90 mg. If the procedure lasts longer than 1 hour, an additional 10 mg heparin will be administered intravenously. If the procedure lasts longer than 2 hours, heparin will be supplemented according to the ACT results.). The procedure will be completed according to the international and Chinese guidelines for the diagnosis and treatment of coronary heart disease. Patients without percutaneous coronary intervention after coronary angiography will be excluded from the study. After the treatment, the type of guiding catheter, specific intervention procedure, type of balloon/stent, total heparin dose, total contrast dose, total fluoroscopy dose, and total fluoroscopy time will be recorded.

Compression and Bandaging

After percutaneous coronary intervention, compression, bandaging, and hemostasis will be performed according to the different puncture sites.

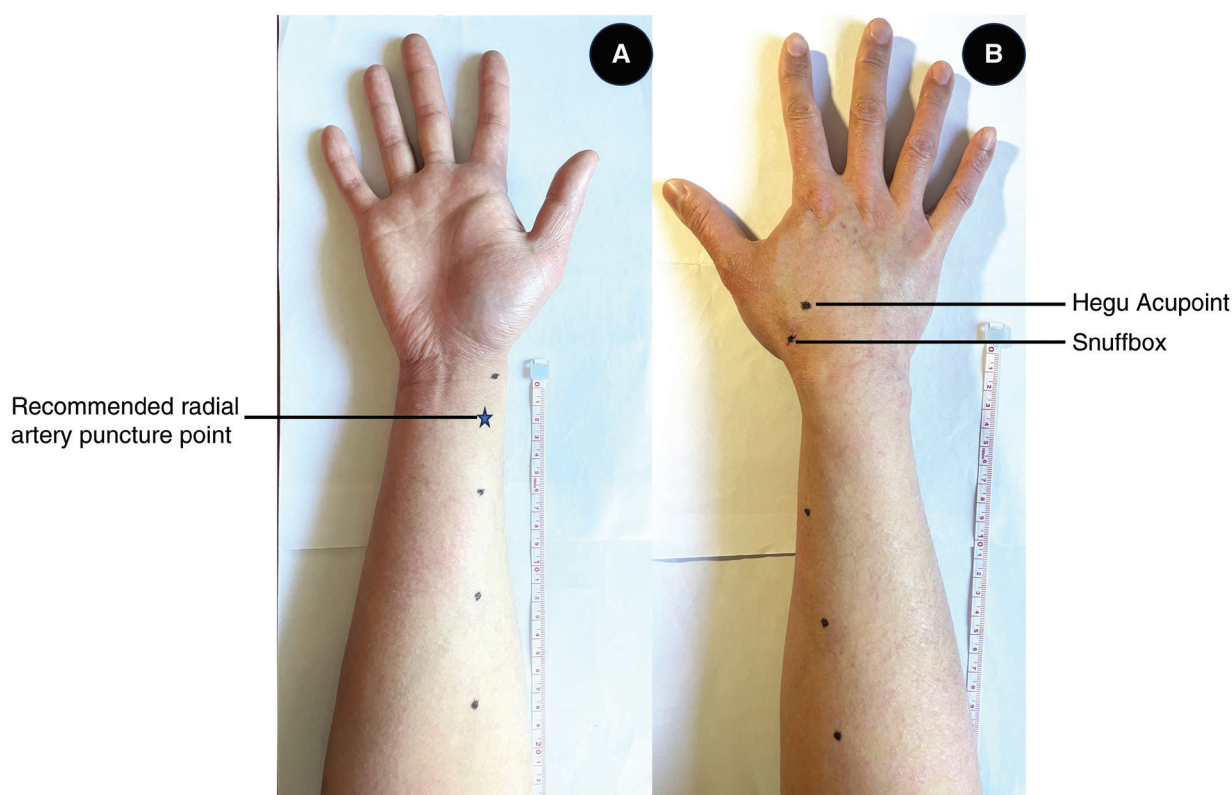


Figure 2 Schematic Diagram of the Radial Artery and Distal Radial Artery Ultrasound Assessment and Puncture Site Location. The internal diameters of the distal (5 cm from the styloid process), middle (10 cm from the styloid process), and proximal (15 cm from the styloid process, near the tip of the sheath) radial artery, and the location of the puncture point of the radial artery, were measured on the extension side (A) of the forearm by vascular ultrasound, and the distal radial artery was measured on the flexion side of the forearm (B). The locations of the Hegu acupoint and snuffbox are shown in (B).

For participants in the study group (dTRA), the puncture wound will be “crossed” with an elastic bandage, which will be removed 3 hours after the procedure and covered with sterile dressing. For participants in the control group (TRA), a spiral-artery hemostat will be applied to the puncture wound, with release every 2 hours and removal of the tourniquet after 6–8 hours, according to routine clinical procedures. In both groups, if bleeding occurs at the puncture site, the compression will be relieved after 1 hour. If bivalirudin or glycoprotein IIb/IIIa receptor antagonist (such as tirofiban) must be maintained after the procedure, the bandage will be removed 1 hour after discontinuation. If bleeding occurs, the compression time should be extended according to the above principles. For all participants, the research nurse will be required to clearly record the start time of compression, the end time of compression, and the presence or absence of abnormalities at the puncture site after compression relieved.

Postoperative Visits

Two postoperative visits will be scheduled, at 24 hours and 30 days after the procedure. Visits will include physical examination of the radial artery (radial artery pulsation), the presence and grade of swelling of the anterior wall on the operation side, bleeding from the puncture wound, and local neurologic complications. Fugl-Meyer motor function assessment, daily living ability score, and radial artery ultrasound examination on the operative side will be completed postoperatively.

Data Analysis Plan

Data Collection

The collected data and collection times are shown in Table 1. The study data will be collated and managed with a dedicated electronic data capture system based on a secure, web-based platform designed to support study data capture. This

Table 1 Data Collected and Collection Times.

Time	Baseline	During intervention	First visit: 24 h after operation	Second visit: 30 d after operation
Sex, age	√			
Physical examination	√		√	√
Laboratory examination	√		√	√
Echocardiography	√			
Radial artery ultrasound examination	√		√	√
Puncture site		√		
Puncture time		√		
Catheterization time		√		
Number of punctures		√		
Type of vascular sheath		√		
Coronary target lesions		√		
Type of guiding catheter		√		
Change in vascular sheath		√		
Specific intervention procedure		√		
Type of balloon/stent		√		
Total heparin dose		√		
Total contrast dose		√		
Total fluoroscopy dose		√		
Total fluoroscopy time		√		
Compression time			√	
Hand and wrist function*	√		√	√
Daily living ability score			√	√

*Hand and wrist function will be evaluated according to the Fugl-Meyer motor function scale.

system provides limited user rights to protect identifiable data, including audit trails for tracking data processing and export. The randomization process can be implemented within the electronic data capture system according to the blinding code provided by the Medical Statistics Center of Fuwai Hospital.

Endpoint Events

Efficacy assessment

The primary endpoint is the rate of radial artery and distal RAO at 24 hours after operation, on the basis of the undetectable flow spectrum of the radial artery under ultrasound.

The secondary endpoints are (1) radial artery and distal RAO rate at 30 days after surgery; (2) access crossing or procedure cessation; (3) Fugl-Meyer motor function assessment score and daily living ability score; (4) duration of hospital stay, number of interventions, and hospitalization cost.

Safety Evaluation

Forearm swelling grading (EASY grading), BARC defined major bleeding (types 2, 3, and 5), arteriovenous fistula formation and pseudoaneurysm formation confirmed by ultrasound, local neurological complications, shock due to puncture or local anesthesia, and major adverse cardiovascular events (including non-fatal stroke, non-fatal myocardial infarction, and cardiovascular death) will be recorded.

Sample Size Calculation

On the basis of previous international expert consensus [12], published randomized controlled clinical studies [2], and our team's previous data [8], the expected incidence of RAO within 24 hours (the primary endpoint) in the dTRA group and the TRA group was estimated to be 1.2% and 8.8%, respectively. The sample size was calculated accordingly.

with the assistance of a statistician. The ratio of the two groups was 1:1, and the significance level was set to 5% (two-sided) with a power of 0.90 and expected dropout rate of 0.2. At least 214 patients in each group were found to be required, and a total of 428 patients in the two groups were found to be required to complete the procedure.

Statistical Analysis

The study will focus on the primary endpoint (incidence of RAO within 24 hours after the procedure). According to the intention-to-treat principle, the difference between groups in the intention-to-treat set and the per-protocol set will be evaluated to determine whether the superiority hypothesis is met. Count data will be described as the rate/constituent ratio, and the chi-square test will be used for comparisons between groups. Measurement data will be described as mean \pm standard deviation, and non-normally distributed measurement data will be described as median and interquartile range. Student's t test, analysis of variance, or Mann-Whitney U test will be used for comparison of measurement data between groups. To adjust for influencing factors, we will perform multivariate analysis by using unconditional logistic regression. SAS9.4 will be used for statistical analysis, and the two-sided alpha will be set to 0.05.

Ethics

This study was first reviewed by the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, on February 8, 2023, and submitted again after revision according to the review opinions. Written approval was obtained on July 11, 2023. Because of the adjustment of the randomization stratification method, the amendment was submitted to the Ethics committee again for review, and written approval was obtained on August 22, 2023 (ethical approval number: 2023-1931).

The dTRA involved in this study has been well developed in our center. Several previous retrospective studies from our center have confirmed that the distal radial artery access is safe for coronary intervention, and the enrolled participants are not expected to have major risks.

Dissemination

Key findings of this study will be disseminated through high-impact peer-reviewed journals, and national and international conferences. The results of this study will also be reported as preliminary results of a future multi-center study of interventional therapy through the distal radial artery in China.

Study Progress

Since the protocol was approved by the ethics committee on August 22, 2023, a total of 325 patients have been screened, and 284 participants have been successfully enrolled, with a 12% dropout rate. A total of 156 participants have completed 30 days of follow-up.

Strengths and Limitations of the Study

Strengths

This is the first randomized clinical trial of distal radial artery coronary intervention in China. Compared with other studies, this study was aimed at evaluating the efficacy and safety of coronary intervention through dTRA, rather than coronary angiography alone, in Chinese patients. In addition to focusing on the important clinical endpoint of RAO, this study focuses on indicators including the compression time, wrist function score, and activities of daily living score to comprehensively evaluate the effects of different vascular access on patient comfort, wrist function, and quality of life. The results will provide more advanced evidence-based medical evidence regarding coronary intervention via dTRA in China.

Limitations

This study is a single-center clinical study, and the conclusions must be confirmed by multi-center studies with larger samples. One limitation of the study is the lack of availability of live ultrasound-guided puncture. We overcome it by locating judgment of the position of blood vessels in puncture by locating the puncture point with ultrasound before the procedure. Differences in compression strategies also

exist among other groups (TRA with a spiral artery compressor and dTRA with bandage compression). Although these differences represent real practice conditions, these confounding factors should be fully considered in the interpretation of future results and should be eliminated to the greatest extent possible in future multicenter clinical studies.

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Contributors

Minghao Liu, Huanhuan Wang, and Lijian Gao were responsible for the design and writing of the research protocol for this project. Xinyue Lang and Minghao Liu were responsible for the statistical design of the study. Lijian Gao, Juechen, Cui Cheng, Ying Song, and Shaodong Ye were responsible for the screening, informed consent, and enrollment of the participants. Lijian Gao, Huanhuan Wang, Minghao Liu, Hao Zhang, Wei Yu, Jue Chen, Cui Cheng, Ying Song, Shaodong Ye, Xiaoning Liu,

and Yong Wang participated in the coronary intervention as skilled interventionalists. Fujian Duan, Hui Li, and Yiying Song were responsible for the preoperative and postoperative radial artery ultrasound examination and the interpretation of the results. Honghui Zhao, Jinwei Zhai, Yana Tong, and Yan Liu were responsible for preoperative and postoperative hand function assessment, postoperative care, and records. Lijian Gao, Huanhuan Wang, Ying Song, Cui Cheng, and Minghao Liu were responsible for patient visits. Minghao Liu and Huanhuan Wang were responsible for the interpretation of abnormal results in participants. Minghao Liu, Huanhuan Wang, Hao Zhang, Wei Yu, Zhan Gao, and Lijian Gao were responsible for the collation of the study data. Xinyue Lang and Zhan Gao were responsible for the statistical analysis of results and the release of the report. Lijian Gao, as a grantee, provided financial support for this study. All authors reviewed and approved the final version of the manuscript for publication.

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Competing Interests

None declared.

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