Partial CArdiac Denervation to Prevent Postoperative Atrial Fibrillation After Coronary Artery Bypass Grafting (pCAD-POAF): Study Protocol for a Randomized Controlled Trial

Ziang Yang, MD[1], Xieraili Tiemuerniyazi, MD[1], Shengkang Huang, MD[1], Yangwu Song, MD, Fei Xu, MD**, and Wei Feng, MD*

Postoperative atrial fibrillation (POAF) is commonly seen in patients who underwent coronary artery bypass grafting (CABG), increasing the risk of morbidity, mortality, and hospital expenses. This study aimed to evaluate the effect of partial cardiac denervation, which is achieved by cutting off the ligament of Marshall and resecting the fat pad along the Waterston groove, on the prevention of POAF after CABG. Patients planned for CABG at our center were screened for eligibility in this study. A total of 430 patients were randomized into the intervention (partial cardiac denervation) group and control group. Intraoperative high-frequency electrical stimulation and further histologic analysis were performed in a certain number of patients to confirm the existence of ganglia. All patients were continuously monitored for the incidence of POAF through an electrophysiologic device until the sixth day postoperatively, and required to complete a 30-day follow-up (12-lead electrocardiogram and echocardiogram assessment) after discharge. The primary end point is the incidence of POAF, whereas the secondary end points are the cost-effectiveness and safety outcomes. In conclusion, this trial will evaluate whether partial cardiac denervation through cutting off the ligament of Marshall and resecting the fat pad along the Waterston groove can reduce the incidence of POAF after CABG. If this procedure is revealed to be effective and safe, it may provide a potential therapeutic approach to prevent POAF in this group of patients. **(Am J Cardiol 2024;221:120−125)**

Keywords: coronary artery bypass grafting, partial cardiac denervation, postoperative atrial fibrillation

Postoperative atrial fibrillation (POAF) is one of the major complications after cardiac surgery, which occurs mostly within 1 week after the operation, with an incidence of 10% to 50%.[1,2] POAF has been proved to increase the risk of hemodynamic deterioration, heart failure, and stroke, resulting in increased hospital stays and medical expenses.[3] Although the incidence of POAF after coronary artery bypass grafting (CABG) ranges from 5% to 40%,[4] it could result in severe postoperative circulatory fluctuations and expose patients to a high risk of systemic embolism, such as stroke. Therefore, preventing POAF after CABG is essential.

The mechanism of POAF still remains unclear. Existing opinions are as follows: (1) disorder of cardiac autonomic nerve system (CANS), (2) inflammation, (3) oxidative stress, (4) abnormal activation of Ca^+ channels, and (5) other potential mechanisms.[5] Of these possible mechanisms, the activation of CANS plays an important role in the occurrence of POAF. In fact, β blocker, which mainly inhibits cardiac sympathetic excitability, is now the only drug listed as class I recommendation by the present guideline to prevent POAF.[5] However, previous study showed that even after administration of β blockers with a rate up to 80%, the incidence of POAF after CABG is as high as 21.1%.[6]

Zafeiropoulos et al[7] meticulously summarized the potential role of autonomic neuromodulation therapies (ANMTs) in preventing POAF after cardiac surgery. Studies also tried to reduce the incidence of POAF through surgical intervention of CANS during cardiac surgery, including resection of fat pads, ganglionated plexi ablation, and botulinum toxin injection into epicardial fat pads.[8−10] However, these studies differed in several aspects, including population size, eligibility criteria, randomization approach, surgical procedure,

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[1]The authors Ziang Yang, Xieraili Tiemuerniyazi, and Shengkang Huang contributed equally to this manuscript.

See page 124 for Declaration of Competing Interest.

*Corresponding authors: Tel: +86-010-88396771; fax: +86-010 88322355.

**Tel: +86-010-88322265; fax: +86-010-88322355.

E-mail addresses: felix_xufei@126.com (F. Xu), fengwei@fuwai.com (W. Feng).

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and non-optimal electrocardiogram (ECG) monitoring strategies. As a result, they failed to reveal the potential benefit of ANMTs. More recently, Wang et al[11] reported a promising result of POAF reduction by calcium chloride ($CaCl_2$) injection into 4 major ganglionated plexi during off-pump CABG (15% vs 36%, p = 0.001), and the NeurOtoxin for the PreVention of Post-Operative Atrial Fibrillation (NOVA) trial also showed similar outcomes in isolated CABG patients, and in patients with advanced age receiving lower dose of botulinum toxin type A after cardiac surgery.

Partial cardiac denervation by resecting epicardial adipose tissue is also one of the ANMTs. Several previous studies[8,12,13] evaluated the efficacy of ventral cardiac denervation through resecting fat pads surrounding the great vessels of heart for the prevention of POAF. Unfortunately, however, the results were inconsistent because of the heterogeneity of enrolled population, limited sample size and incomplete monitoring timeline.

Therefore, in this study, we focused on reevaluating the effect of partial cardiac denervation on preventing POAF after CABG in a larger population through more complete and longer duration of continuous ECG monitoring. To begin with, previous studies showed that the ligament of Marshall (LOM) is the critical site of CANS participating in the occurrence of atrial fibrillation (AF).[8] Kim et al[14] noticed that the LOM contained sympathetic nerve fibers and had insertions into the myocardium of the left atrium and coronary sinus, providing the essentials for the formation of arrhythmia. Other reports[15−17] clearly implicated the LOM and adjacent atrium as the origins of arrhythmias. In addition, Haemers et al[18] showed that the right atrium was obviously infiltrated by adipose tissue in patients with AF, especially in those with persistent AF. Besides, cutting off the LOM and resecting the fat pad along the Waterston groove is routinely used in maze surgery to treat patients with AF. Lastly, this trial also aimed to seek a safe, simple, and convenient way to prevent POAF after CABG. We believe that choosing 1 site at both right and left atrium namely the LOM and the fat pad along the Waterston groove, exactly meets our purpose.

In conclusion, the present single-center, prospective, randomized, controlled study will focus on the evaluation of the role of partial cardiac denervation, which was achieved by cutting off the LOM and resecting the fat pad along the Waterston groove, in preventing POAF after CABG.

Methods

Figure 1 shows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines[19] instructing the designation of our study.

The Department of Cardiovascular Surgery at Fuwai Hospital, National Center for Cardiovascular Diseases, National Clinical Research Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, and Peking Union Medical College.

At the beginning of designing the study, we invited several patients who submitted to receive CABG to review the original study protocol with the interpretation of our research doctors. Then they gave advice on amending and optimizing the study designation.

We consecutively recruited adult patients who underwent CABG (on-pump/off-pump) and agreed to participate in this clinical trial.

Exclusion criteria are were follows: (1) age <18 years; (2) emergent CABG; (3) history of cardiac surgery; (4) simultaneously underwent any other cardiac surgery (such as Morrow procedure, valvular surgery, ventricular reconstruction because of ventricular aneurysm, or repair of the congenital heart diseases); (5) critical condition requiring hemodynamic support before CABG, such as the need for extracorporeal membrane oxygenation or intra-aortic balloon pump; (6) history of AF; and (7) receiving antiarrhythmic therapies except taking β blockers before surgery (such as taking amiodarone or having cardiac implantable devices).

At the beginning of the trial, high-frequency electrical stimulation was used in 5 patients to test and prove the presence of ganglia in fat pads, which is confirmed by the appearance of vagal responses (bradycardia and hypotension).

In the intervention group, we performed partial cardiac denervation on the both left and right atrium, the procedure was performed by cutting off the LOM and resecting the fat pad along the Waterston groove. Specifically, during the on-pump CABG, the heart was pulled to the right to expose the LOM between the left atrial appendage and the left pulmonary veins under extracorporeal circulation after cardiac arrest, and the LOM was cut off by electrotome. Then, the fat pad along the Waterston groove was exposed between the right pulmonary veins and right atrium and excised completely to the surface of the myocardium, with the upper edge extending beyond the opening of the right upper pulmonary vein and the lower edge to the inferior vena cava. For off-pump CABG, we will cut off the LOM in the same way previously mentioned. Then, if the heart was well-tolerated and hemodynamics were stable, a fixator was used to fix the heart when resecting the fat pad along the Waterston groove. Otherwise, cardiac denervation was performed after CABG was completed. The estimated additional surgery time was 5 to 10 minutes. To achieve satisfactory efficacy, a thorough cardiac denervation of the myocardium surface was emphasized. In addition, the existence of ganglia was further proved through histologic analysis using the fat pad samples collected from 10 pairs of patients with or without POAF, respectively.

After the present clinical practice, patients continued to take β blockers until the time of operation if they were already taking the medicine preoperatively. After conventional CABG, all our patients were prescribed β blockers unless there was a contraindication, such as complication with bradycardia (heart rate less than 65 beats per minute), atrioventricular block, or requiring epicardial pacing. For further evaluation of heart rhythm and function, patients received transthoracic echocardiogram and ECG before discharge and at 30-day follow-up.

The primary outcome was POAF, defined as supraventricular arrhythmia lasting for >30 seconds.[20] Patients were monitored continuously beginning within 1 hour after the surgery to the sixth day postoperatively through the NS-SP-

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		
TIMEPOINT	*Pre Intervention*	T_0	*Surgery*	*Post-operative Hospital stay*	*Follow-up Clinic Visit*
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Control(no intervention)			X		
Cardiac denervation			X		
ASSESSMENTS:					
Preoperative Atrial Fibrillation				X	
Post-operative Atrial Fibrillation				X	X
Time Spent in Atrial Fibrillation				X	
Blood Transfusion			X	X	
Transferring to On-pump			X		
Re-operation				X	
Pericarial Effusion				X	X
Arrhythmia Exclude of AF				X	X
Length of Hospital Stay				X	
All Costs During Hospitalization				X	
All Costs After Surgery				X	

Figure 1. Standard protocol items: recommendations for interventional trials (SPIRIT). AF = atrial fibrillation.

B-01 Attached Dynamic ECG Recording System. In addition, the overall lasting time of supraventricular arrhythmia was also recorded for evaluating AF burden. Heart rates were continuously monitored, including lowest/highest/average heartbeats, premature atrial/ventricular contractions, and so on. Two independent and blinded research doctors will interpret the ECG and determine the existence of POAF.

The secondary outcomes include: (1) safety assessment including the incidence of the need for blood transfusion, transferring to on-pump CABG, re-operation for postoperative bleeding caused by partial cardiac denervation, incidence of pericardial effusion, and arrhythmias other than AF within 30 days after discharge, (2) economics assessment including length of hospital stay, all costs during the hospitalization and total costs after the surgery, and (3) major adverse cardiovascular and cerebrovascular events, defined as the composite of all-cause death, myocardial infarction, stroke and repeat coronary revascularization during the 30-day follow-up.

During the primary screening, patients were evaluated for eligibility into the study, and individual informed consent was signed at the willingness of each patient. Then, participants were randomly allocated to either intervention or control group. After surgery, monitoring for the occurrence of AF lasted until the sixth day postoperatively in all patients. Meanwhile, complications such as pericardial effusion were also assessed. On the day of discharge, participants were investigated by 12-lead standard ECG and echocardiogram. During the 30-day follow-up, information such as the overall health status of participants, medication use, and whether they have experienced any kind of arrhythmia or major adverse cardiovascular and cerebrovascular events, were collected. The participants will also be investigated by ECG and echocardiogram again for further assessment (Figure 2).

Two parallel arms were required. The occurrence of POAF after cardiac surgery was about 23%, according to the previous study.[20] Based on a detailed review of existing studies, cardiac denervation reduces the incidence of POAF

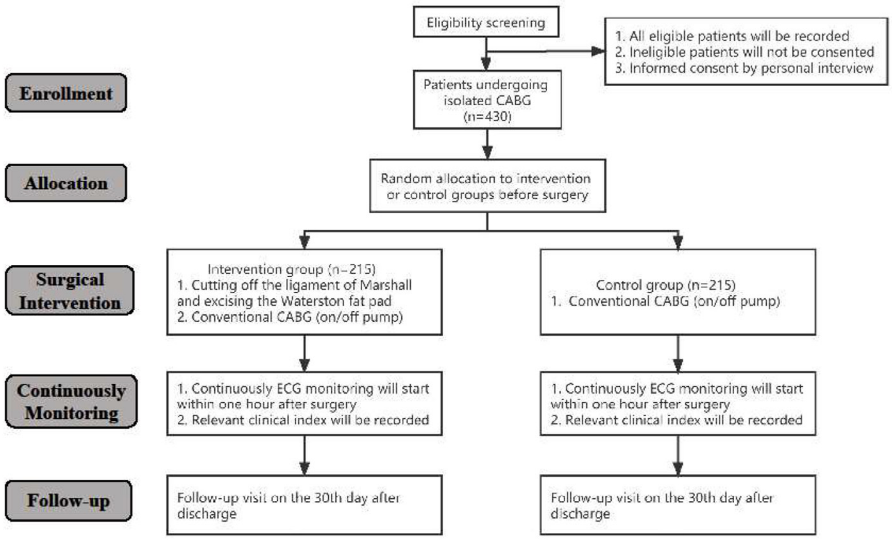

Figure 2. Participant timeline diagram.
CABG = coronary artery bypass grafting; ECG = electrocardiogram.

by 50%.[21] Therefore, with 80% power and 0.05 alpha, 408 participants are needed to detect 23% POAF rate in the control group and a reduction of 50% in the intervention group. Taking into account a 5% protocol violation rate and patient loss/dropout, a population size of 430 (215 in each group) was sufficient for this investigation. As one of the world's largest centers of cardiovascular diseases, Fuwai Hospital completes more than 10,000 cardiac surgeries every year, of which approximately 5,000 are isolated CABG. This trial shall be completed in due course.

A controlled, randomized process was used to assign participants to treatment groups. A computer-generated minimized random allocation technique based on factors including age, gender, history of myocardial infarction, and left ventricular ejection fraction was employed to ensure that the cases were distributed equally. The department research fellow informed the surgeon of the patient group assignment once they were under general anesthesia in the operating room.

As different surgical operations were involved, complete double-blindness cannot be achieved. To reduce the researcher bias, surgeons were not allowed to know the result of patient assignment until surgery, and the third-party supervisor responsible for randomization could inform the surgeons of the results only after general anesthesia and before the surgical procedure started. Patients and data analysts were blinded throughout the process. Unblinding was done under third-party supervision after all data analysis was completed.

By filling out the specific Case Report Form, data collection was completed in a prospective manner throughout the hospital stay. Final data sets were accessible to the primary investigator, statistician, and other researchers. One of the research doctors had access to the database and was required to ensure the accuracy and quality of the data.

Because POAF was influenced by a great deal of aspects, data collection was comprehensive. Postoperative results of high-sensitivity C-reactive protein, interleukin (IL) −4, IL-6, IL-8, tumor necrosis factor-α on the first day and preoperative high-sensitivity C-reactive protein were assessed. Factors such as left atrium size, left ventricular end-diastolic diameter, left ventricular ejection fraction, and mitral regurgitation degree in both baseline, discharge, and follow-up echocardiograms will also be collected.

Continuous variables were tested by Student *t* test if normally distributed; otherwise, by Mann-Whitney *U* test. Chi-square test or Fisher's exact test was applied for categorical variables, as appropriate.

The analysis of the primary outcomes was carried out through an intention-to-treat approach. Meanwhile, as-treated, per-protocol, and/or modified intention-to-treat analysis will also be conducted. Univariable and multivariable logistic regression analyses were used to evaluate the primary outcome analysis. The regression model will incorporate baseline factors for sensitivity analysis. Secondary outcomes including safety and economics will also be analyzed.

Because patient data collection was completed mostly during the hospital stay and only a short-time follow-up was required, we did not expect any missing data. Multiple imputations were performed if missing data existed. Patients who were lost to follow-up were reported and compared.

The Data Monitoring Committee is composed of 1 cardiologist, 1 cardiac surgeon, 1 cardiac anesthesiologist, 1 bioethicist, and 1 statistician who were not involved in this trial. The Institutional Review Board and the Data Monitoring Committee were made aware once there were serious adverse events. If there was a significant difference in mortality or serious adverse events between the 2 groups and it was considered to be a direct result of this cardiac partial denervation approach, the study was stopped.

Data were de-identified and stored in the electronic storage system of our institution. Statistical analyses were performed by R 4.0.2 (R Core Team, Vienna, Austria). All access to data was protected by a personal login password within strict management.

Before the main results of the trial were released, we did not present any blinding break data. We submitted a manuscript reporting the final results to a medical journal once the trial was completed.

In conclusion, the pCAD-POAF trial evaluated the effect of cutting off the LOM and resecting the fat pad along the Waterston groove to prevent POAF after CABG. If the final results show this approach is effective and safe, we may provide cardiac surgeons with a therapy option that can be achieved conveniently to reduce POAF.

The study had several limitations. First, we found it hard to design and conduct this trial to be a multi-center one because COVID-19 was prevalent at the beginning of the study. Second, we mainly focused on the outcome during hospitalization and short-term follow-up because POAF mostly occurs within 1 week after surgery. We would like to keep a long-term investigation on this group of patients in the future. Finally, given that previous studies have proved the existence of ganglia and nerve fibers in both epicardial adipose tissue and the LOM,[22] high-frequency electrical stimulation and pathologic examination will only be done in a minority of patients to further confirm the validity of our intervention.

Trial Status

This trial was registered at *ClinicalTrials.gov* in June 2021 with protocol record NCRC2020003 and identifier NCT05009914.

The date of initial recruitment: August 14, 2022.

The approximate date when recruitment was completed: January 31, 2024.

Declaration of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Ziang Yang: Writing − original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xieraili Tiemuerniyazi:** Writing − original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Shengkang Huang:** Writing − original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yangwu Song:** Validation, Supervision, Data curation. **Fei Xu:** Supervision, Resources. **Wei Feng:** Writing − review & editing, Supervision, Funding acquisition.

Ethical Approval

The Institutional Review Board of Fuwai Hospital approved the study on May 12, 2021 (identification: 2021-1292).

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