Study Protocol

Seoul National University Bundang Hospital

Far Eastern Memorial Hospital

Effect Of Resuscitative Endovascular Balloon Occlusion of the Aorta in Non-Traumatic Out-of-Hospital Cardiac Arrest (REBOA); A Multinational, Multicenter Randomized Controlled Trial

Trial Registration Number: NCT06031623

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Abstract

Background

Out-of-hospital cardiac arrest (OHCA) is a significant public health issue worldwide and is associated with low survival rates and poor neurological outcomes. The generation of optimal coronary perfusion pressure (CPP) via high-quality chest compressions is a key factor in enhancing survival rates. However, it is often challenging to provide adequate CPP in real-world cardiopulmonary resuscitation (CPR) scenarios. Based on animal studies and human trials on improving CPP in patients with nontraumatic OHCA, resuscitative endovascular balloon occlusion of the aorta (REBOA) is a promising technique in these cases. This study aims to investigate the benefits of REBOA adjunct to CPR compared with conventional CPR for the clinical management of nontraumatic OHCA.

Methods

This is a parallel-group, randomized, controlled, multinational trial that will be conducted at two urban academic tertiary hospitals in Korea and Taiwan. Patients aged 20–80 years presenting with witnessed OHCA will be enrolled in this study. Eligible participants must fulfill the inclusion criteria and written informed consent should be collected from their legal representatives. Patients will be randomly assigned to the intervention (REBOA-CPR) or control (conventional CPR) group. The intervention group will receive REBOA and standard advanced cardiovascular life support (ACLS). Meanwhile, the control group will receive ACLS based on the 2020 American Heart Association guidelines. The primary outcome is return of spontaneous circulation (ROSC). The secondary outcomes include sustained ROSC, survival to admission, survival to discharge, neurological outcome, and hemodynamic changes.

Discussion

Our upcoming trial can provide essential evidence regarding the efficacy of REBOA, a mechanical method for enhancing CPP, in OHCA resuscitation. Our study aims to determine whether REBOA can improve treatment strategies for patients with nontraumatic OHCA based on clinical outcomes, thereby potentially providing valuable insights, and guiding further advancements in this critical public health area.

Trial registration

ClinicalTrials.gov NCT06031623. Registered on September 9, 2023

Keywords

cardiac arrest, cardiopulmonary resuscitation, resuscitative endovascular balloon occlusion of the aorta, REBOA, out-of-hospital cardiac arrest

Administrative information

Title {1}	Effect of resuscitative endovascular balloon occlusion of the aorta in nontraumatic out-of-hospital cardiac arrest: a multinational, multicenter, randomized, controlled trial
Trial registration {2a and 2b}	ClinicalTrials.gov NCT06031623. Registered on September 9, 2023
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Name and contact information for the trial sponsor {5b}	Professor Dong Keon Lee, Principal Investigator Seoul National University College of Medicine Seoul National University Bundang Hospital Goldenegg@snubh.org
Role of sponsor {5c}	This is an investigator initiated trial. The funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Introduction

Background and rationale {6a}

Out-of-hospital cardiac arrest (OHCA) is a medical emergency that remains a public health issue worldwide [1]. The mainstay treatment for cardiac arrest involves immediate attention and treatment, including early recognition, high-quality chest compression, early defibrillation for shockable rhythm, early epinephrine administration, and immediate advanced airway access [2, 3]. With the development of guidelines for the treatment of cardiac arrest, numerous efforts have been made worldwide to increase survival rates and improve prognosis in patients with OHCA. However, despite such measures, the survival rates of patients with OHCA remain <10% in several countries, and the proportion of patients with good neurological prognosis at discharge is even lower [1].

Cardiopulmonary resuscitation (CPR) for OHCA aims to reduce ischemic damage during cardiac arrest via continuous blood flow to the vessels supplying vital organs. In particular, the maintenance of coronary blood flow is directly associated with the possibility of achieving return of spontaneous circulation (ROSC), making it a crucial goal of CPR. However, even with high-quality chest compression, the rate of coronary blood flow usually remains <30% of that before cardiac arrest [4, 5].

Several studies have been conducted on methods that can improve coronary blood flow during CPR. Resuscitative endovascular balloon occlusion of the aorta (REBOA) is a procedure that is traditionally used for temporary hemorrhage control in patients with trauma by occluding the aorta via balloon dilation [6]. In cases of nontraumatic cardiac arrest, REBOA adjunct to CPR can increase coronary perfusion pressure (CPP) by occluding the aorta and rerouting blood circulation to the heart and brain rather than other organs, thereby ultimately help

achieving ROSC [7]. By applying REBOA in cases of nontraumatic cardiac arrest, several animal studies have shown positive results for coronary blood flow in terms of hemodynamics [8]. Further, recent trials have revealed that the application of REBOA in humans has promising outcomes [9, 10]. However, despite such promising results in terms of hemodynamic changes, research on the effect of REBOA on clinical outcomes in patients with nontraumatic OHCA is lacking.

Objectives {7}

The current study aims to compare the clinical outcomes of CPR with REBOA and conventional CPR in patients with nontraumatic adult OHCA in the hospital stage.

Trial design {8}

The REBOA trial was designed as a parallel, randomized, controlled, multinational trial and registered at ClinicalTrials.gov (National Clinical Trial number: NCT06031623). Our study design is based on the SPIRIT 2013 checklist [11]. Figure 1 shows the enrollment schedule, interventions, and study duration. Figure 2 depicts the study algorithm.

			STUDY PERIOD						
	Enroll -ment	Allocation	Post-allocation				Close-out		
TIMEPOINT	*ED arrival*	5 minutes within ED arrival	*Interventi on*	*Hospital Admission*	*PCAS care*	*At discharge*	*1 month after ROSC*	*3 months after ROSC*	*6 months after ROSC*
ENROLLMENT:									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
INTERVENTIONS:									
[REBOA group]			X	X	X				
[Control group]			X	X	X				
ASSESSMENT:									
[Hemodynamic Data]			X						
[ROSC]			X						
[Survival to Admission]				X					
[Survival to Discharge]						X			
[CPC]						X	X	X	X

Fig. 1: Schedule of enrollment, interventions, and assessments according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline

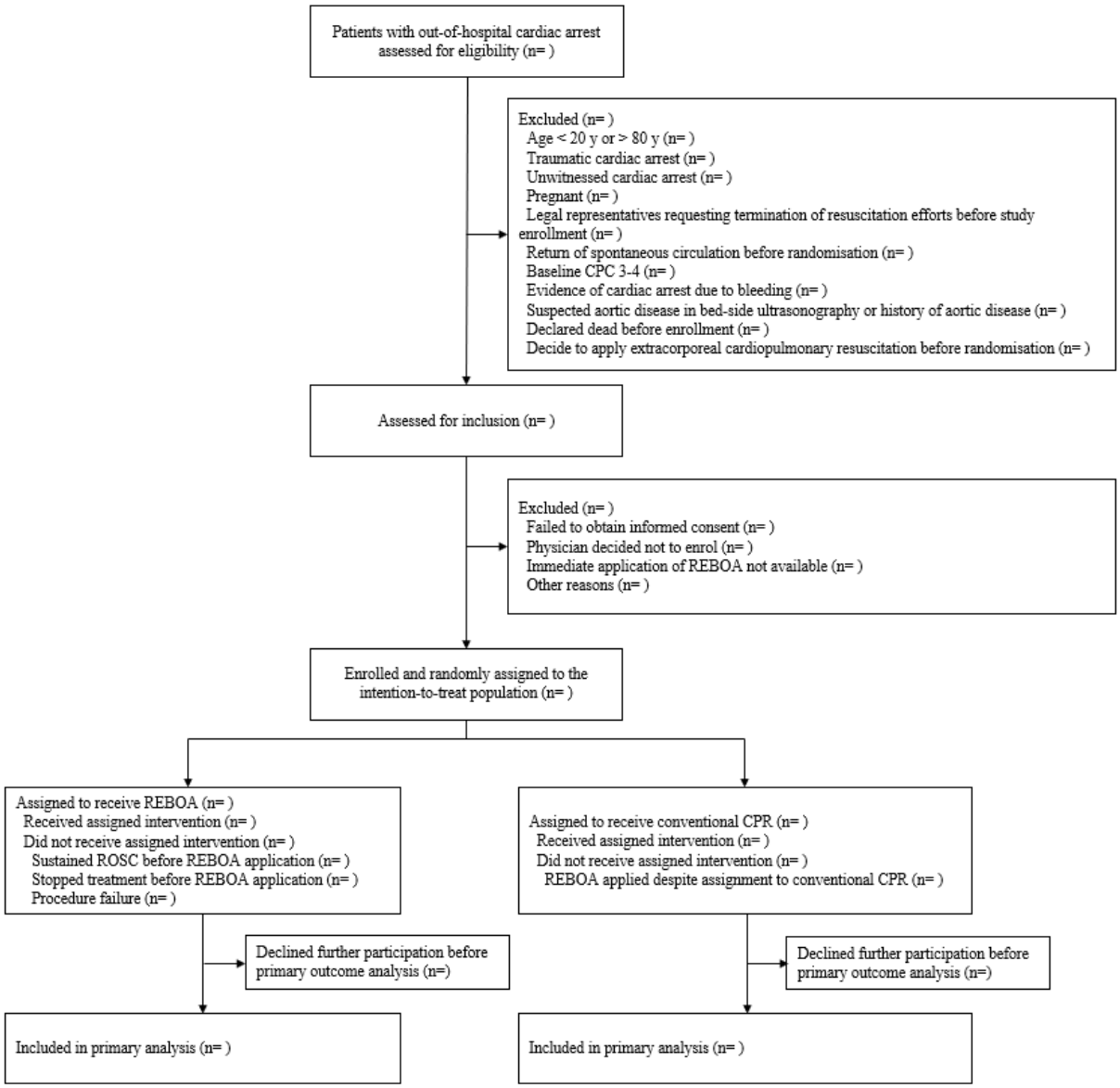

Fig 2. Study flow

Methods: participants, interventions, and outcomes

Study setting {9}

This study will be conducted at two urban academic tertiary hospitals in Korea (Seoul National University Bundang Hospital, SNUBH) and Taiwan (Far Eastern Memorial Hospital, FEMH). SNUBH, a tertiary medical center in Seongnam in the southern Gyeonggi area, has a

population of 3.1 million residents. As a 1,337-bed capacity hospital, SNUBH records 70,000 emergency department (ED) visits annually. FEMH, the only tertiary medical center in New Taipei City, Taiwan, serves over 1.6 million residents in the western area of Greater Taipei. As a 1,415-capacity hospital, FEMH records approximately 10,000 ED visits monthly, which includes approximately 25 cases of nontraumatic OHCA.

The emergency medical system (EMS) in South Korea is government-based and operates on a multi-tiered dispatch system is operated for suspected cardiac arrests. Two teams, each comprising two to three 3 members and located closest to the scene, are dispatched. The first team, upon arrival, initiates basic life support, which includes chest compressions (with a depth of 5cm at a compression rate of 100-120 per minute), bag-mask ventilations, and use of an automated external defibrillator (AED). Upon the second team's arrival, Advanced Life Support (ALS) is initiated if feasible, involving gaining intravenous access, administering epinephrine, and securing an advanced airway (through either a supraglottic airway or endotracheal intubation). ALS, if provided, it is guided by an emergency physician via a video call. If it is determined during CPR at the scene that ROSC is unlikely to be rapidly achieved, preparations for transport immediately commence. Concurrently, upon the decision to initiate transport, notification is sent to the ED of the receiving hospital. This includes the patient's medical history and the details of the arrest circumstances identified thus far. All patients are transported to the hospital for further resuscitation.

In the prehospital setting of Taiwan, when an emergency call is received, the dispatcher initially sends the first ambulance to the scene, equipped with a minimum of two emergency medical technicians (EMTs). If the dispatcher confirms the event as an OHCA during the call, additional ambulances, potentially a second or even a third, are dispatched to the site. Simultaneously, the hospital is notified to commence preparation. Following the protocol of

the New Taipei City Fire Department, these EMTs are required to deliver advanced life support to all patients with OHCA before reaching the ED. This protocol includes mechanical chest compression (using LUCAS® 2, Stryker Medical, Kalamazoo, MI) at the center of the chest, maintaining a rate of 100 compressions per min and a depth of 5 cm. Advanced airway management, involving either endotracheal intubation or a supraglottic airway, defibrillation, and resuscitative medication administration (e.g., epinephrine or amiodarone) through intravenous or intraosseous routes if available, are part of the protocol. Following the initial CPR cycle, unless a prior "Do Not Resuscitate" order is in place, all patients are transported to the hospital for further resuscitation.

Eligibility criteria {10}

Written informed consent should be obtained from the legal representative prior to the research. All patients with witnessed nontraumatic adult OHCA who arrive at the ED from 9 am to 5 pm on working weekdays in each country's time zone will be assessed for eligibility.

Inclusion criteria

Patients aged 20–80 years with nontraumatic witnessed OHCA, arriving at the ED between 9AM and 5PM in Korea, and 8AM to 8PM in Taiwan.

Exclusion criteria

The exclusion criteria include the following: 1) patients aged below 20 years old or over 80 years old, 2) those with traumatic cardiac arrest; 3) those with unwitnessed cardiac arrest; 4) pregnant patients; 5) those who have already achieved ROSC upon arrival at the ED; 6) those with a precardiac arrest cerebral performance category (CPC) score of 3–4; 7) those showing evidence of cardiac arrest caused by bleeding (e.g., gastrointestinal bleeding); 8) those

suspected of aortic disease, such as dissection, intramural hematoma, or aneurysm, using bedside ultrasound performed immediately after ED arrival or have a previous history of aortic disease; 9) those whose legal representatives request termination of resuscitation efforts before study enrollment; 10) those declared dead at scene before enrollment; and 11) those who meet the criteria for extracorporeal CPR (ECPR), and have been decided to receive ECPR. ECPR is applicable when all of the following criteria are met: precardiac arrest CPC score of 1–2; witnessed cardiac arrest with bystander CPR; aged 20–70 years; initial shockable rhythm; ECMO pump-on available within 60 min of cardiac arrest onset; and absence of end-stage diseases, such as cancer, liver cirrhosis, or end-stage renal failure.

Patients will be evaluated for eligibility based on patient history for most items in the exclusion and inclusion criteria. Due to the EMS systems in Korea and Taiwan notifying the ED of incoming cardiac arrests 5–15 min prior to arrival, along with the patient's history and circumstances of the cardiac arrest at the scene, clinicians will be able to reassess whether the patient meets the eligibility criteria to a certain extent.

Need for informed consent {26a}

As per the Declaration of Helsinki, obtaining informed consent is mandatory for any study involving human participants [12]. However, in the context of research on cardiac arrest research, securing informed consent from unconscious patients presents a considerable challenge [13]. Recognizing the necessity for prompt resuscitation, the United States Food and Drug Administration has outlined provisions to exempt the need for informed consent in certain emergency medical research scenarios [14].

At SNUBH, informed consent will be obtained upon ED arrival. Researchers will explain the

purpose of the study, risks and benefits of the intervention, and possible complications. As patients with OHCA are unconscious during enrollment, written informed consent will be obtained from legal representatives; this consent form will include details about the study and provide information on how to reach the study investigator or ethics review board for any questions or concerns related to the research. If the patient regains consciousness and is adequately alert to comprehend the process, the researcher will explain the study protocol to the patient, and informed consent will be obtained.

The current study was approved by the Institutional Review Board (IRB) of FEMH. In accordance with the abovementioned provisions, the IRB of FEMH waived the need for informed consent, irrespective of whether the trial participants were assigned to the intervention (REBOA-CPR) or control (conventional ACLS) group. However, if a participant achieves sustained ROSC, the researchers will then be required to obtain written informed consent from the participant's legally authorized representative.

Need for additional consent for the collection and use of participant data and biological specimens {26b}

Biological specimens will not be collected. All data collected will be deidentified and then stored in an online database, which will only be available to the investigators with pre-authorized ID and password.

Interventions

Explanation regarding the choice of comparators {6b}

This trial aims to examine the clinical impact of REBOA in patients with nontraumatic adult OHCA. Accordingly, patients will be randomly assigned to the intervention or control group with the intention to treat. The intervention group will receive REBOA in addition to conventional ACLS. Conventional ACLS will be provided according to the 2020 American Heart Association (AHA) guidelines [3]. In both study institutions, invasive hemodynamic monitoring using arterial catheterization is a routine practice during ACLS. The control (conventional CPR) group will receive conventional ACLS according to the 2020 AHA guidelines with invasive hemodynamic monitoring.

Intervention description {11a}

In SNUBH, ACLS will be initiated and informed consent will be obtained from legal representatives simultaneously for eligible patients with OHCA upon ED arrival. At FEMH, eligible patients with OHCA will be enrolled in the study starting ACLS as soon as they arrive at the ED, as the IRB waived the acquisition of informed consent. After enrollment, patients will be randomly assigned to the intervention or control group.

REBOA insertion

While performing ACLS, the common femoral artery is accessed using an 8-french sheath catheter (Radifocus Introducer II, Terumo, Tokyo, Japan) based on the Seldinger technique under ultrasound guidance. Arterial catheterization is a routine intervention during ACLS at

both institutions. Hence, an arterial catheter will be inserted, and arterial blood pressure (ABP) levels will be continuously monitored invasively during ACLS in both groups.

In the REBOA-CPR group, the REBOA catheter (Rescue Balloon, Tokai Medical Products, Aichi, Japan) will be inserted through the sheath catheter. To position the REBOA catheter at zone 1, the length from the site of insertion to the site immediately distal to the xiphoid process will be measured, and the REBOA catheter will be placed at the measured length along the presumed pathway of the artery. If possible, an abdominal ultrasonography or portable chest radiography machine will be used to confirm whether the REBOA catheter is placed adequately. After placing the REBOA catheter, the balloon will be cautiously inflated until the balloon diameter reaches 25 millimeter or until the physician experiences resistance. ACLS will be continuously provided with the balloon in an inflated state. After REBOA catheter inflation, ABP levels will be monitored at the tip of the REBOA catheter.

If the femoral artery is accessed via the sheath catheter and the patient is included in the intervention group, the REBOA catheter will be inserted immediately.

Hemodynamic monitoring protocol

ABP levels, central venous pressure (CVP) levels, electrocardiogram, and end-tidal carbon dioxide ($ETCO_2$) levels will be continuously monitored and recorded during ACLS. ABP levels will be continuously monitored using the sheath catheter and REBOA catheter tip before and after balloon inflation, respectively. CVP levels will be measured via a central line placed during ACLS in the right internal jugular vein or subclavian vein under ultrasound guidance. $ETCO_2$ levels will be monitored during ACLS to monitor the quality of chest compression and estimate cardiac output as an adjunct to ABP levels [15].

Postresuscitation care

If the patient achieves ROSC, the REBOA balloon will be gradually deflated based on the discretion of the attending physician, if they judge that the risk of rearrest in a few minutes is low. Patients in both groups who achieved ROSC will receive postcardiac arrest care, including targeted temperature management (TTM), according to the 2020 AHA guideline [3]. If hypotension occurs, intravenous fluid and vasopressors will be administered as necessary.

Criteria for discontinuing or modifying the allocated interventions {11b}

Any participant or legal representatives who want to withdraw from the study will be allowed to do so without any consequences. If the legal representative of the patient chooses to withdraw from the study, the patient will continue to receive conventional CPR, similar to that provided to patients in the control group.

Strategies to improve intervention adherence {11c}

To improve adherence, regular meetings will be conducted to review and ensure protocol adherence. Regarding any protocol violations that are identified after intervention, additional meetings will be conducted to review each case.

Relevant concomitant care permitted or prohibited during the trial {11d}

There are no restrictions regarding concomitant care during the trial. Implementing the intervention will not require alteration to the usual management of cardiac arrest, which follows

the 2020 AHA guidelines and applies to both trial arms.

Provisions for post-trial care {30}

The provisions for post-trial care in this study are within the scope of postcardiac arrest care according to the 2020 AHA guidelines. In addition to TTM, care will be based on the presumed etiology of cardiac arrest for each patient. In patients who achieved ROSC, any subsequent adverse events related to REBOA catheter insertion, such as vessel injury, lower limb ischemia, and hematoma/infection, which occurs at the insertion site of the REBOA catheter, will be monitored. In addition, possible related complications such as acute kidney which requires renal replacement therapy, acute respiratory distress syndrome, bacteremia, pneumonia, sepsis/septic shock, and paraplegia will be monitored.

Outcomes {12}

Primary outcome

The primary outcome will be ROSC in the ED, which is represented by the number of patients who achieved ROSC regardless of sustained time.

Secondary outcomes

The secondary outcomes will be sustained ROSC (defined as ROSC maintained for at least 20 minutes); survival to admission; survival to discharge; neurological outcome at discharge as well as 1, 3, and 6 months after ROSC; and hemodynamic changes at 1, 2, 4, and 10 minute after REBOA inflation. Data regarding complications associated with REBOA catheter

insertion will also be considered as secondary outcomes. Information on neurological outcomes will be obtained using the CPC scale and modified Rankin scale (mRS). If the surviving patients are discharged, the research nurse will conduct phone interviews with them or their legal representatives to determine CPC and mRS scores at each time point. REBOA catheter insertion-related complications include direct or indirect adverse events such as malposition, insertion failure, hematoma/infection, femoral artery injury, lower limb ischemia, and aortic injury.

Participant timeline {13}

Figure 3 shows the participant timeline.

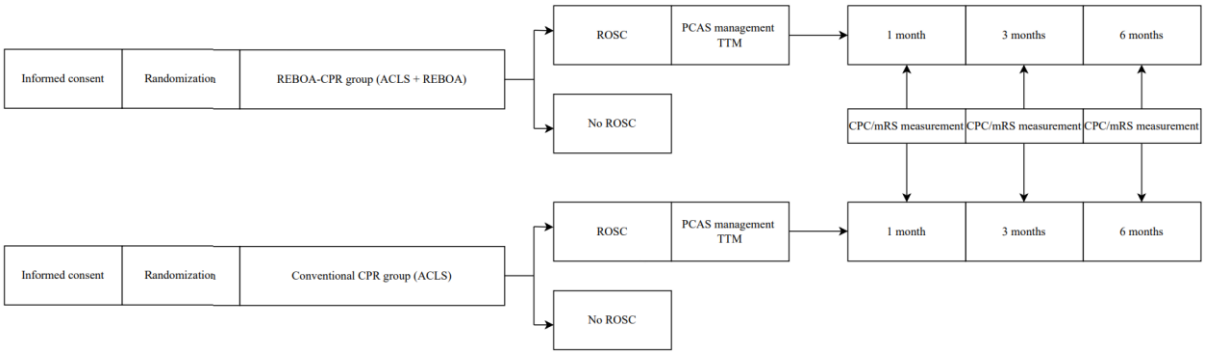

Fig. 3. Participant timeline. ROSC, return of spontaneous circulation; PCAS, postcardiac arrest syndrome; TTM, targeted temperature management; CPC, cerebral performance category; mRS, modified Rankin scale

Sample size {14}

The primary outcome will be ROSC. Current data supporting the sample size of this study are limited. According to a pilot study on the application of REBOA in patients with nontraumatic OHCA, which was performed at one of the two institutions involved in the current study, 40% of patients achieved ROSC in the ED [10]. According to a study on

conventional CPR for patients with OHCA, which was conducted at the same institution, 21.4% of patients achieved ROSC in the ED [13]. We used these differences to estimate the sample size with alpha values of 0.05 and a power of 0.8 and revealed that 212 patients (106 in each group) will be required. Finally, with a dropout rate of 10%, 234 patients should be enrolled, with equal proportions in each arm.

Recruitment {15}

Each hospital will assess all patients with nontraumatic adult OHCA for eligibility and continue to enroll patients until the specific sample size is reached. At least 50 patients will be enrolled competitively at each institution.

Assignment of interventions: allocation

Sequence generation {16a}

The randomization sequence will be generated using R statistical software (version 4.1.3; R Core Team, R Foundation for Statistical Computing, Vienna, Austria). The randomized permuted block design with block sizes of 2, 4, and 6 will be employed. Randomization will be stratified by institution, ensuring that an equal number of participants are assigned to each treatment group in each institution. The sequence will be implemented using electronic case report form (CRF) software (MyECRF, LUNAAIR, Republic of Korea).

Concealment mechanism {16b}

Owing to the nature of the intervention, it will be challenging to blind the participating physicians during the study. Hence, no concealment mechanism will be employed.

Randomization sequences will be concealed from the participating physicians. Group assignments will be blinded to the data analysts. Deidentified CRFs will be used to blind data analysts. Data from each group will be stored in electronic CRF as groups A and B. Thus, the data analyst will be blinded to the actual group.

Implementation {16c}

An independent statistician will generate an allocation sequence. The generated randomization sequence will be stored in electronic CRF (MyECRF, LUNAAIR, South Korea) and will not be released to the research team. If the emergency medical service team notifies the ED of the study institutions regarding incoming OHCA cases, the participating physician on call will assess eligibility and enroll participants. After enrollment, the researcher will disclose the allocation information stored in electronic CRF to the participating physician.

Assignment of interventions: blinding

Who will be blinded {17a}

Owing to the nature of the study, neither the researcher nor the patient or legal representatives will be blinded.

Procedure for unblinding if needed {17b}

The design is an open label study, so unblinding will not occur.

Data collection and management

Plans for the assessment and collection of outcomes {18a}

Demographic characteristics (such as age, sex, underlying medical condition, and CPC score before cardiac arrest), cardiac arrest details (time and place of arrest, witness of the arrest, bystander CPR and AED use, initial rhythm, EMS call time and arrival time, scene departure time, initial cardiac rhythm, established airway, chest compression via EMS, defibrillation energy and attempts, intravenous access, and medication administered), in-hospital information (time of ED arrival, time of central/arterial line insertion, established airway in the ED, medication administration, and ABP levels during ACLS), data regarding REBOA catheter insertion (insertion time and site, number of attempts, balloon inflation volume, and device-related complications), patient outcomes (ROSC; sustained ROSC; time and location of ROSC; survival to admission; survival to discharge; in-hospital mortality; length of hospital/intensive care unit stay; good neurological outcome at hospital discharge as well as 1, 3, and 6 months after ROSC); and adverse events will be collected.

The definition of cardiac arrest data will be recorded based on the Utstein Resuscitation Registry Templates for OHCA [16]. The primary outcome will be ROSC at any point during the resuscitation attempt in the ED. Sustained ROSC will be defined as maintaining the patient's spontaneous circulation without chest compressions for >20 minutes. Further, good neurological outcomes are defined as CPC 1 and 2 [17]. Changes in hemodynamic parameters after REBOA insertion will be analyzed over time by obtaining a continuous blood pressure signal.

Plans to promote participant retention and complete follow up {18b}

Considering that our primary outcome is any ROSC in the ED, no loss to follow up until the primary outcome is checked after enrollment is expected. To assess secondary outcomes, the following plans will be implemented to promote participant retention and complete follow up.

The researcher in charge of each institution will follow up with the patients who achieved ROSC and were discharged from the hospital to collect CPC scores at 1, 3, and 6 months. To reduce loss to follow up as much as possible, the study institution will make every reasonable effort to follow up with patients for the entire study period, including the discussion of their health status when assessing CPC via phone.

Any decisions to withdraw from the study made by the trial participant or their legally authorized representative will be meticulously recorded, along with the reasons and precise timing of such actions. If a participant becomes inaccessible during the follow up period, the corresponding data will be marked as missing in the analysis. Ultimately, these exhaustive details regarding withdrawal will be incorporated into the Consolidated Standards of Reporting Trials flow diagram, thus providing a transparent and integrated overview of participant retention throughout the study.

Data management {19}

Data will be entered into electronic CRF, which will be accessible only to the researcher in charge. Each data item will have a designated range (e.g., 18–150 years for age). If the value for a particular item falls outside this range, an immediate warning will be issued. Furthermore, if the value lies within the appropriate range but does not meet specific conditions (e.g., the recorded time of arterial line insertion precedes the arrival time at the ED), a query will be

forwarded to the researcher in charge for necessary corrections.

Confidentiality {27}

Data will be stored based on the study number assigned to each participant. Paper CRFs will be stored in locked file cabinets in the laboratory. Data will also be transferred to electronic CRFs by the researcher in charge, and only researchers who have been authorized in advance will have access to this system.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

This study will not require biological specimens for genetic or molecular analysis.

Statistical methods

Statistical analysis of the primary and secondary outcomes {20a}

Data analysis will be performed using R statistical software (version 4.1.3; R Core Team, R Foundation for Statistical Computing, Vienna, Austria). The Shapiro–Wilk test will be used to assess data normality. Continuous data that follow a normal distribution will be presented as the mean ± standard deviation and further analyzed using independent *t*-test. In contrast, data not adhering to a normal distribution will be expressed as median and interquartile range and further evaluated using the Mann–Whitney U test. Categorical variables, including ROSC and survival, will be presented as frequencies (percentages) and analyzed using the chi-square test or Fisher's exact test, as appropriate. For variables demonstrating statistically significant

differences between the two groups, the disparity will be reported as either absolute difference or risk difference, depending on the variable type. The analysis of the primary outcome difference between the two groups will use both absolute difference and risk difference. Additionally, when applicable, the risk ratio will be presented as an additional measure, as appropriate. P-values of <0.05 will be considered to indicate statistical significance. In interim analysis, the significance level according to the O'Brien–Fleming approach will be used. A Statistical Analysis Plan will be attached separately.

Interim analysis {21b}

After the enrolment of the first 116 patients, an interim analysis will be performed according to the O'Brien–Fleming rule. A blinded interim analysis will be performed by an independent statistician. Both primary and secondary outcomes will be assessed using interim analysis. If there is a statistically significant difference in ROSC, sustained ROSC, or survival to discharge between the two groups, with a significance level of 0.005, the trial will be considered for termination.

The sample size will be recalculated based on the assumption that the current difference in the primary endpoint between the two groups will persist. (1) If the sample size required to prove a difference exceeds three times the initially planned sample size (with a power of 0.80 and significance level of 0.05), the Trial Steering Committee (TSC) will decide whether to continue the trial. (2) If the recalculated sample size falls within the range of 348–696 (150%–300% of the original sample size), the TSC will discuss whether the study should proceed with the new sample size. (3) If the revised sample size is <348 (150% of the original sample size), the study will proceed with the adjusted sample size.

Methods for additional analysis {20b}

Additional subgroup analysis will aim to investigate factors potentially leading to disparities in treatment outcomes, thereby indicating that these effects may vary based on the distinct clinical characteristics of patients throughout the study. This detailed evaluation will be conducted in various potential subgroups of age, sex, administration of CPR using a bystander, initial rhythm (categorized as shockable or nonshockable), location of the arrest (public vs. nonpublic), presumed cause of arrest, time elapsed from arrest to arrival at the ED, and the institution where the patient received treatment (SNUBH or FEMH).

Analysis method for handling protocol nonadherence and statistical methods for handling missing data {20c}

For statistical analysis, two sets will be utilized: intention-to-treat set and per-protocol set. The intention-to-treat set will analyze patients based on the group they were assigned to after randomization, regardless of the actual randomized treatment received. The per-protocol set will identify patients who received or did not receive REBOA (REBOA or conventional group, respectively) for analysis. In the per-protocol analysis, patients allocated in the REBOA group who achieved ROSC before REBOA insertion are analyzed as part of the conventional group. However, as early ROSC may indicate a more favorable prognosis, this adjustment has the potential to introduce bias. To mitigate this bias and provide a more accurate assessment of treatment effects, such patients will be excluded from the REBOA group. Similarly, patients in the conventional group who achieved ROSC within the corresponding timeframe as those in the REBOA group will also be excluded.

Authors expect no missing data for the primary outcome (any ROSC), which is immediately determined in all patients after the termination of ACLS. When reporting patient clinical characteristics and secondary outcomes, the primary approach to handling missing data will be the direct deletion method. However, in cases where a significant amount of missing data exists for specific clinical characteristics, multiple imputation will be considered as an alternative approach. If multiple imputation is employed for any variable, it will be explicitly stated in the results.

Plans to provide access to the full protocol, participant level data, and statistical code {31c}

The patient-level dataset will not be accessed by the public.

Oversight and monitoring

Composition of the coordinating center and TSC {5d}

Four committees will play roles in the research: Trial Steering Committee, Trial Management Group, Data Monitoring Committee, and the Data Coordinating Center.

Trial Steering Committee (TSC): The TSC, comprising six members, includes an independent chair, an independent statistician, an independent member, and three non-independent members from each participating institution. The TSC oversees patient safety, ensures data integrity, and makes executive decisions, such as modifications to or discontinuation of the study protocol.

Trial Management Group (TMG): The TMG, consisting of two clinicians from each

participating institution, is responsible for overseeing the day-to-day execution of trial performance. Communication within the TMG occurs online as necessary.

Data Monitoring Committee (DMC): The DMC, comprising four members, including one statistician, all independent from the trial, reviews efficacy and safety data, conducts interim analyses, oversees recruitment, assesses data quality, monitors protocol deviations, and addresses safety and adverse events. The DMC meets every 6 months and provides recommendations to the TSC.

Data Coordinating Center (DCC): The DCC, with two members—one from each participating institution—regularly assesses trial data quality using electronic CRF (eCRF) software.

Composition, role, and reporting structure of the DMC {21a}

The trial will be independently monitored by the DMC, which will review the safety and efficacy of the trial and send biannual reports to the TSC.

Reporting of adverse events {22}

Adverse events will be monitored from randomization to hospital discharge. If any adverse events occur, patients will be treated immediately according to routine practice and followed up until resolution or treatment termination. Such adverse events will be reported by the DMC to the TSC and IRB.

All adverse events will be recorded in CRFs for each case. Table 2 presents a list of adverse events that will be recorded. All adverse events and complications associated with REBOA

catheter insertion will be analyzed and reported as secondary outcomes.

Frequency and plans for auditing trial conduct {23}

The DMC will convene every six months to analyze and review trial safety. Basic patient demographic characteristics, adequacy of patient recruitment, protocol deviations, adequacy of follow up, and serious adverse events will be reported. Although the meeting will be conducted independently from the study investigators, any information or issues that are deemed necessary will be reported to the TSC and IRB.

Electronic CRF software employs formulas and conditions to assess data quality. If any input value does not satisfy a condition, an automatic query will be raised, and the DCC will evaluate the patient's original CRF (paper copy) and correct the input value if necessary. If an error occurs despite similar values in paper and electronic CRFs, then the TMG will be informed, and the error will be corrected and reported to the TSC. The DCC will also assess data completeness on a daily basis and may ask the TSC to add/modify/delete formulas and conditions if necessary.

Plans for communicating important protocol amendments to relevant parties {25}

Any modifications to the protocol that may affect the study conduct, potential patient benefits, or patient safety, including changes to the study objectives, study design, patient population, sample size, study procedures, or important administrative aspects, will require notification to the sponsor first. Subsequently, a copy of the revised protocol will be sent to the TSC The revised protocol will undergo review by the TSC, and the final decisions made by the TSC will receive approval from IRB of each participating institution. Following approval, the revised

protocol will be incorporated into the investigator site file, and the trial registration will be updated accordingly. Any deviations from the protocol will be thoroughly documented using a breach report form.

Dissemination plans {31a}

Our findings will be disseminated via journal publications and conference presentations.

Discussion

To achieve ROSC in cardiac arrest, coronary perfusion should be restored [5, 18]. CPP, which is calculated as the difference between aortic and diastolic right atrial pressure levels during the relaxation phase of chest compressions, indicates myocardial perfusion and CPR quality [5, 18].

REBOA, a mechanical technique capable of increasing CPP, serves as an alternative to the currently used method [19]. Demonstrating promising outcomes in animal models and pilot studies, REBOA may offer a feasible alternative or supplementary treatment approach to achieve favorable clinical results in patients with nontraumatic OHCA [20]. A study to observe the utility of REBOA in nontraumatic cardiac arrest is currently underway in Norway [21]. The primary outcome of this study is the proportion of ROSC, with a goal of enrolling 200 patients with a 1:1 allocation. However, this study is focused on the application of REBOA in the prehospital setting. The upcoming parallel-group, randomized controlled trial will be conducted at two academic tertiary hospitals in South Korea and Taiwan, focusing on hospital settings. Further, it will evaluate whether REBOA can significantly improve the current OHCA treatment practices, focusing primarily on achieving ROSC and secondarily on evaluating

sustained ROSC and neurological outcomes in the patient population.

In addition, there has been a recent report regarding the use of REBOA in trauma patients with exsanguinating hemorrhage [22]. The study suggests that in cases of trauma-related exsanguinating hemorrhage, REBOA did not reduce mortality. Since the primary focus of this study is on patients with traumatic hemorrhage, a disease entity distinct from non-traumatic cardiac arrest, interpreting results from this study to non-traumatic cardiac arrest patients may be challenging. Despite the differences in subjects, it is crucial not to overlook the possibility that similar results may emerge in our current study.

By investigating REBOA as a means to enhance CPP during CPR, our study aims to explore alternative treatment protocols that may contribute to more effective outcomes in patients with nontraumatic OHCA. The research results may provide valuable insights and add to the growing body of evidence that may help improve treatment strategies for nontraumatic OHCA. Ultimately, these study findings can be an important step toward further advancements and innovations in this important area of public health.

Trial status

Recruitment will start in October 2023 and end in September 2025. The current version of the protocol is version 1.3 (January 24, 2025).

Abbreviations

Advanced Cardiovascular Life Support (ACLS)

Advanced Life Support (ALS)

American Heart Association (AHA)

Arterial Blood Pressure (ABP)

Automated External Defibrillator (AED)

Cardiopulmonary Resuscitation (CPR)

Case Report Form (CRF)

Central Venous Pressure (CVP)

Cerebral Performance Category (CPC)

Coronary Perfusion Pressure (CPP)

Data Coordinating Center (DCC)

Data Monitoring Committee (DMC)

Emergency Department (ED)

Emergency Medical System (EMS)

End-tidal Carbon Dioxide ($ETCO_2$)

Extracorporeal Cardiopulmonary Resuscitation (ECPR)

Far Eastern Memorial Hospital (FEMH)

Institutional Review Board (IRB)

Modified Rankin Scale (mRS)

Out-of-hospital Cardiac Arrest (OHCA)

Resuscitative Endovascular Balloon Occlusion Of The Aorta (REBOA)

Return of Spontaneous Circulation (ROSC)

Seoul National University Bundang Hospital (SNUBH)

Targeted Temperature Management (TTM)

Trial Management Group (TMG)

Trial Steering Committee (TSC)

Declarations

Acknowledgments

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Funding {4}

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Availability of data and materials {29}

The study results will be published through conferences and scientific publications in medical journals related to emergency medicine or resuscitation. Deidentified data will be available for online provision upon reasonable request.

Patient Public Involvement

There was no patient public involvement in the process of developing this trial protocol.

Plans for seeking research ethics committee/IRB approval {24}

This study protocol and the informed consent forms has been reviewed by the IRB of both institutions (SNUBH IRB no.: B-2302-811-001, FEMH IRB no.: 112075-F).

Consent for publication {32}

Each institution has its own consent form, and all forms have been approved by their respective IRBs. The consent form included the title and purpose of the study, a description of the possible benefits and harms to the patients, the name of the principal investigator, contact information for questions about the study, and details regarding the possible adverse events and their management.

Competing interests {28}

There are no competing interests to declare.

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Title: Effects of Resuscitative Endovascular Balloon Occlusion of the Aorta on Nontraumatic Out-of-hospital Cardiac Arrest (REBOA): A Multinational, Multicenter Randomized Controlled Trial

Trial Registration Number: NCT06031623

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Version History:

V1.01

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Signatures

1. Introduction

1.1. Background and Rationale

Out-of-hospital cardiac arrest (OHCA) is a medical emergency that remains a public health issue worldwide. The primary management approach for cardiac arrest emphasizes immediate attention and treatment, including early recognition, high-quality chest compressions, early defibrillation for shockable rhythms, early epinephrine administration, and advanced airway access as soon as possible. Apart from the development of these guidelines, substantial international efforts have been directed toward increasing survival rates and improving the prognosis of patients with OHCA. However, despite these undertakings, fewer than 10% of OHCA patients in many countries survive, and even fewer show good neurological prognosis at discharge.

Cardiopulmonary resuscitation (CPR) primarily aims to reduce ischemic damage during cardiac arrest by maintaining blood flow to vessels supplying vital organs. Maintaining coronary blood flow, which supplies blood to the heart, is directly associated with the likelihood of achieving return of spontaneous circulation (ROSC). However, even with high-quality chest compressions, coronary blood flow typically remains at less than 30% of the pre-cardiac arrest levels.

Several studies have sought to determine how to improve the coronary blood flow during CPR. Resuscitative endovascular balloon occlusion of the aorta (REBOA) is traditionally used in trauma patients for temporary hemorrhage control by occluding the aorta via balloon dilation. By occluding the aorta and redirecting blood circulation toward the heart and brain rather than other organs during cardiac arrests, REBOA can assist in increasing the coronary perfusion pressure, which consequently helps achieve ROSC. Several animal studies have shown that applying REBOA to nontraumatic cardiac arrest patients promotes positive hemodynamic results in terms of coronary blood flow, and recent trials on its application in humans have also shown promising results (Brede et al. 2019; Jang et al. 2022). However, despite these encouraging findings related to hemodynamic changes, research on the effects of REBOA on clinical outcomes in patients with nontraumatic OHCA remains limited.

1.2. Study Objectives and Hypothesis

This trial primarily aims to evaluate the clinical impact of REBOA in nontraumatic OHCA patients and compare with that of conventional advanced cardiac life support (ACLS). The

hypothesis of this study is that OHCA patients treated with REBOA are more likely to achieve ROSC than those receiving traditional ACLS alone.

2. Study Methods

2.1. Trial Design

This prospective, multicenter, open-label, parallel-group, randomized controlled trial will be conducted in two tertiary hospitals: Seoul National University Bundang Hospital in South Korea and Far Eastern Memorial Hospital in Taiwan. Patients who are transported intra-arrest and satisfy all inclusion criteria without any exclusionary factors will be promptly and randomly assigned on a 1:1 basis to either the REBOA CPR group or the conventional CPR group immediately upon arrival at the emergency department (ED). The primary aim of this study was to compare post-CPR prognosis between the two patient cohorts.

2.2. Randomization

The randomization sequence will be generated using the R statistical software (version 4.2.3; R Core Team, R Foundation for Statistical Computing, Vienna, Austria). A randomized permuted block design with block sizes of 2, 4, and 6 will be used. Randomization will be stratified according to the institution, ensuring an equal number of participants assigned to each treatment group at each institution. The sequence will be implemented in electronic case report form software (MyECRF, LUNAAIR, Republic of Korea).

2.3. Sample Size

2.3.1. Sample Size Calculation

A pilot study on the application of REBOA in nontraumatic OHCA patients at one institution in the present study found that the rate of achieving ROSC in the ED was 40.0%. Another study involving the application of the conventional CPR method for OHCA patients at the same institution showed that the rate of achieving ROSC in the ED was 21.4%.

Using this difference, the sample size was calculated using an alpha of 0.05 and a beta of 0.8, which revealed that a total of 210 patients were required. Assuming a dropout rate of 10%, this study will seek to enroll 232 patients (116 per arm; a minimum of 52 per site for competitive recruitment).

2.3.2. Number of Subjects per Center

Patients will be enrolled competitively with a minimum requirement of 50 at each institution. This has been established to maintain statistical balance and analytical rigor, fostering a reliable and comparative examination of data from these distinct sites. This approach forms a key part of our statistical analysis plan and will aid in achieving meaningful and reliable results.

2.4. Framework

The analytical framework of this study is designed to evaluate the comparability of outcomes between the two CPR strategies: CPR with REBOA and conventional CPR. Consequently, to thoroughly assess the comparability of outcomes, we undertake a two-tailed approach for our hypothesis testing.

2.5. Statistical Interim Analyses and Stopping Guidance

After enrolling the first 116 patients, an interim analysis will be performed according to the O'Brien–Fleming rule. An independent statistician will perform a blinded interim analysis. The primary (ROSC) and secondary outcomes will be assessed in the interim analysis using a significance level of 0.005 following the O'Brien–Fleming approach.

The sample size will be recalculated based on the assumption that the current difference in the primary endpoint between the two groups will persist. (1) If the recalculated sample size needed to demonstrate a difference exceeds three times our initially planned sample size (assuming a power of 0.80 and significance level of 0.05), then the Trial Steering Committee (TSC) will decide whether to continue with the trial. (2) If this recalculated sample size ranges between 348 and 696, which is 150% to 300% of our initial estimate, then the TSC will discuss whether to adjust our study to reflect this new sample size. (3) If this revised calculation falls below 348, which is less than or equal to 150% of our original estimate, then we proceed with this adjusted number for our sample size.

2.6. Timing of Final Analysis

The final analysis for this research study will occur 6 months after the enrollment of the last participant. This timeline was strategically devised to align with the sequential follow-ups planned at the end of the 1st, 3rd, and 6th months after enrollment. Meticulous planning will allow for a comprehensive understanding of the data gathered at these critical time intervals, thereby enhancing the overall credibility and reliability of the study findings.

2.7. Timing of Outcome Assessments

The outcomes of ROSC, including both ROSC and sustained ROSC, and changes in mean arterial blood pressure will be evaluated during resuscitation efforts subsequent to the admission of participating patients to the ED. After achieving ROSC, survival to admission will be assessed based on the patient's transition from ED to inpatient hospitalization. Survival to discharge and neurological prognosis will be evaluated at the time of discharge. Post-discharge follow-up evaluations for survival and neurological functionality will be conducted via telephone interviews at any given time in the week for the 1st, 3rd, and 6th months after ROSC. This comprehensive evaluation strategy aimed to accurately capture and analyze the complete progression and potential recovery trajectories of our study participants. To minimize loss to follow-up as much as possible, staff at each study site will make every reasonable effort to maintain contact with patients throughout the entire study period. This includes discussing their health status when assessing the Cerebral Performance Category (CPC) during phone calls.

3. Statistical Principles

3.1. Confidence Intervals and P-values

All statistical hypotheses in this study will be subjected to rigorous testing at a significance level of 0.05. This standard threshold for significance ensures the robustness of our findings and minimizes the likelihood of false–positive results. Furthermore, we reported our results with 95% confidence intervals for additional validity and precision. This commonly adopted approach

underscores our confidence that the true population parameter lies within this defined range, thereby providing a reliable and comprehensive representation of our study findings.

3.2. Adherence and Protocol Deviations

This study defined adherence to the intervention as the proportion of patients initially assigned to the REBOA CPR group who will have undergone aortic occlusion. This approach reflects real-world circumstances and captures the extent of exposure to the intervention, considering the time-sensitive nature of applying the REBOA upon hospital arrival. Adherence to the intervention will be quantitatively expressed in terms of percentages to depict the proportion of patients who actually received aortic occlusion in the REBOA CPR group.

Protocol deviations will be identified as instances in which patients in the REBOA group did not receive the aortic occlusion as planned. These deviations will be systematically assessed and summarized, focusing on the reasons why aortic occlusion was not achieved in the intervention group. A summary of protocol deviations will provide a detailed breakdown of the reasons for the deviation and their respective proportions within the intervention group.

3.3. Analysis Populations

Two distinct analytical population sets will be used. The first is the intention-to-treat set, which examines patients based on their initial randomized group assignment, irrespective of the ultimately administered treatment. The second is the per-protocol set, which specifically analyzes patients who did (the REBOA group) and did not (the non-REBOA group) undergo the REBOA procedure. In the per-protocol analysis, patients allocated in the REBOA group who achieved ROSC before REBOA insertion are analysed as part of the conventional group. However, as early ROSC may indicate a more favorable prognosis, this adjustment has the potential to introduce bias. To mitigate this bias and provide a more accurate assessment of treatment effects, such patients will be excluded from the REBOA group. Similarly, patients in the conventional group who achieved ROSC within the corresponding timeframe as those in the REBOA group will also be excluded.

The safety analysis for this study will encompass all patients who will have undergone an attempt at REBOA placement, which is characterized by any attempt to puncture the femoral vessels. This indicates regardless of whether the insertion of the REBOA catheter into the target vessel or

accomplishment of aortic occlusion was successful. The purpose of this population was to critically evaluate the safety of implementing REBOA in a CPR scenario. This evaluation guarantees comprehensive accounting of the potential safety considerations associated with the intervention.

4. Trial Population

4.1. Eligibility

4.1.1. Inclusion Criteria

All witnessed OHCA patients will be assessed for eligibility. The inclusion criteria for the study will be nontraumatic, witnessed OHCA patients between the ages of 20 and 80.

4.1.2. Exclusion Criteria

Exclusion criteria for the study are as follows: (1) age below 20 years or over 80 years; (2) traumatic cardiac arrests; (3) unwitnessed cardiac arrests; (4) pregnant patients; (5) patients who already achieved ROSC upon arrival at the ED; (6) pre-cardiac arrest CPC of 3–4; (7) evidence of cardiac arrest due to bleeding (e.g., gastrointestinal bleeding); (8) those suspected of having aortic diseases, such as dissection, intramural hematoma, or aneurysm based on bedside ultrasound performed immediately after ED arrival or those who have a history of aortic disease and whose legal representative had requested termination of resuscitation efforts before study enrollment; and (9) patients who satisfy the criteria for extracorporeal cardiopulmonary resuscitation (ECPR) and who received ECPR. The ECPR criteria are applied when all of the following criteria are satisfied: pre-cardiac arrest CPC of 1–2, witnessed cardiac arrest with bystander CPR, initial shockable rhythm, ECMO pump-on available within 60 min of cardiac arrest onset; and patients without end-stage diseases, such as cancer, liver cirrhosis, or end-stage renal failure.

4.2. Recruitment

Each hospital will assess all OHCA patients for eligibility and will continue until the target number of patients is reached. Enrollment will be continuously monitored to ensure that each hospital can enroll 50% of its total population. A minimum of 50 patients will be enrolled

competitively to minimize racial differences. The Consolidated Standards of Reporting Trials (CONSORT) flowchart is as follows:

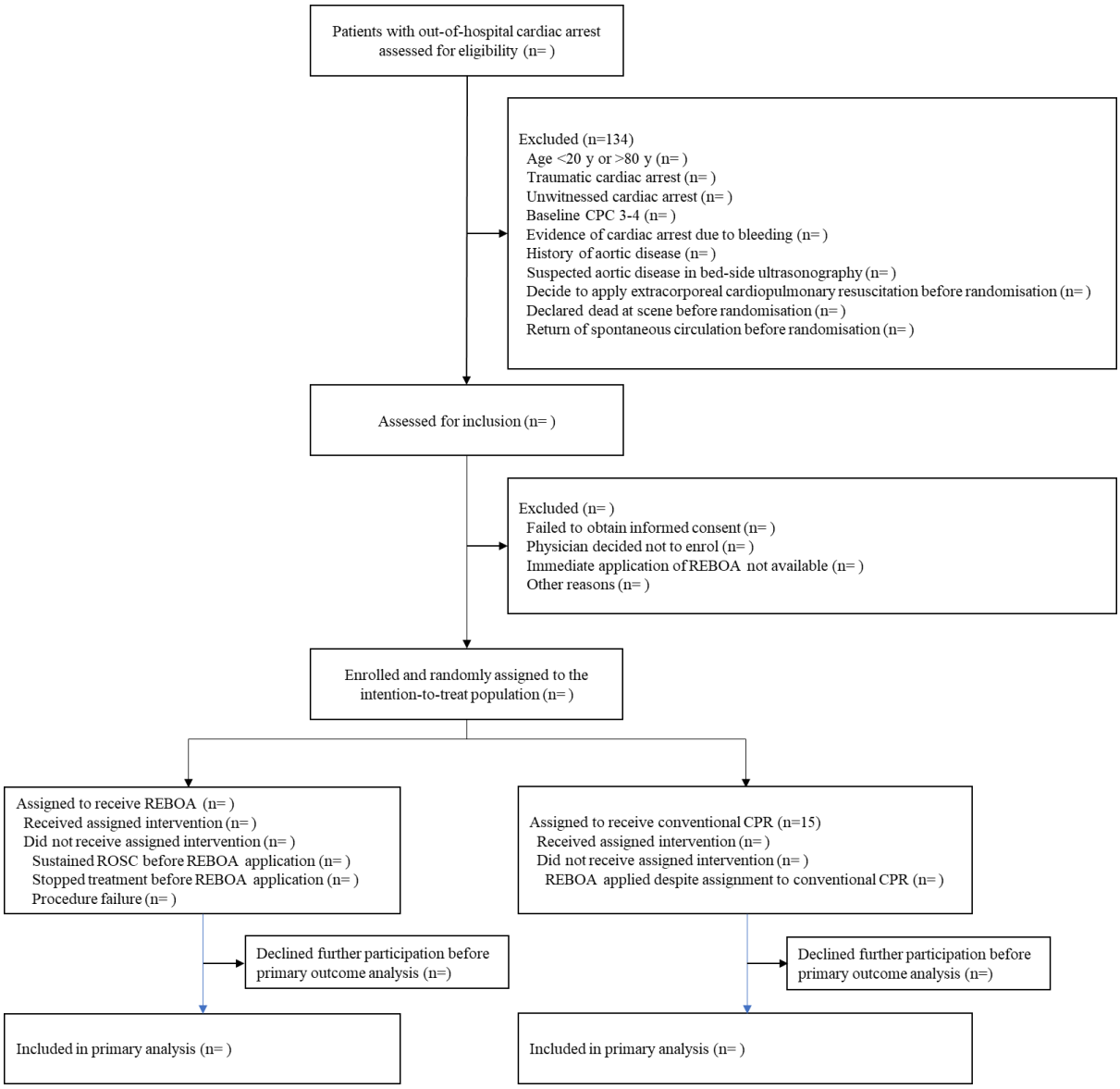


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flowchart

4.3. Withdrawal or Loss Follow-up

The withdrawal level at every stage of the study, whether during the intervention or follow-up phase, will be quantified as a percentage. Any decision to withdraw from the study, made by either the trial participant or their legally authorized representative, will be meticulously recorded,

encapsulating the reasons and precise timing of such actions. If a participant becomes inaccessible during the follow-up period, their data will be considered missing during the analysis. Ultimately, these exhaustive details regarding withdrawal will be incorporated into the CONSORT flow diagram to provide a transparent and integrated overview of participant retention throughout the course of the study.

4.4. Baseline Patient Characteristics

Demographics (age, gender, and underlying disease), arrest data (timing and place of arrest, bystander CPR, initial rhythm, etc.), in-hospital data (arrival time, time of central/arterial line placement, etc.), outcome, and adverse events will be collected and are presented (Table 1).

Table 1: Demographic Characteristics of Patients by Group

	Total (n=)	REBOA group (n=)	Conventional group (n=)
Age			
Sex			
Comorbidity			
HTN			
DM			
CAOD			
HF			
Stroke			
Public place			
Bystander CPR			
Initial rhythm shockable			
Cardiac arrest etiology			
Prehospital no flow time (min)			
Prehospital low flow time (min)			
ED arrival to arterial line insertion interval (min)			
ED arrival to central line insertion interval (min)			

HTN, hypertension; DM, diabetes mellitus; CAOD, coronary artery obstructive disease; HF, heart failure; CPR, cardiopulmonary resuscitation; ED, emergency department

Data related to REBOA placement, including the time of placement, volume of balloon inflation, and depth of placement, will also be meticulously recorded and encapsulated within a table (Table 2) for a comprehensive review and reference.

Table 2: Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) Procedure Data

	Total (n=)	REBOA group (n=)
ED arrival to REBOA inflation interval (sec)		
Insertion depth of REBOA catheter (cm)		
Amount of NS used for ballooning (cc)		
Adverse events		
Device related complications		
Malposition		
Insertion failure		
Insertion site hematoma		
Insertion site infection		
Balloon rupture		
Catheter removal failure		
Vascular access-related complications		
Femoral artery injury		
Lower limb ischemia		
Amputation		
Aorta injury		
Adverse events		
AKI with dialysis		
ARDS		
Pneumonia		
Sepsis/Septic shock		
Stroke/CVA		
Paraplegia		
Myocardial infarction		
Multiorgan failure		
Neurologic deficit secondary to spinal cord ischemia		
Ventilator days		
Length of ICU stay		
Length of hospital stay		
In hospital stay		
Mortality, hours after admission		
Mortality, hospital days		

ED, emergency department; REBOA, resuscitative endovascular balloon occlusion of aorta; NS, normal saline; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CVA, cerebrovascular accident; ICU, intensive care unit

5. Analysis

5.1. Outcome Definitions

5.1.1. Primary Efficacy Endpoints

- Any ROSC, defined as an occurrence in which a post-CPR patient establishes a palpable pulse that endures for a duration exceeding 1 min.

5.1.2. Secondary Efficacy Endpoints

- Change in mean arterial blood pressure 1 min after balloon inflation.
- Sustained ROSC is defined as an occurrence in which a post-CPR patient establishes a palpable pulse that endures for a duration exceeding 20 min.

- Survival to hospital admission.
- Survival to hospital discharge.
- CPC score at the 1st, 3rd, and 6th month after ROSC.

CPC scores were defined as follows:

- CPC 1: Good cerebral performance—The patient is conscious, alert, and able to work. There might be slight neurological or psychological deficit.
- CPC 2: Moderate cerebral disability—The patient is conscious and has sufficient cerebral function for independent activities of daily life. The patient could work in a sheltered environment.
- CPC 3: Severe cerebral disability—The patient is conscious but dependent on others for daily support because of impaired brain function.
- CPC 4: Coma or vegetative state—The patient is unconscious, with no meaningful interaction with the environment.
- CPC 5: Brain death—The patient had no measurable brain function.

5.2. Analysis Methods

The Shapiro–Wilk test will be used to assess the normality of the data. Continuous data that follow a normal distribution will be presented as means and standard deviations and further analyzed using an independent t-test. In contrast, data not adhering to a normal distribution will be expressed as medians coupled with their interquartile ranges (IQRs) and evaluated using the Mann–Whitney U test. Numerical variables, such as the CPC score, will also be presented as medians with IQRs and analyzed using the Mann–Whitney U test. Categorical variables, including ROSC and survival, will be presented as frequencies (percentages) and analyzed using the chi-squared test or Fisher's exact test, as appropriate. Statistical significance was set at p value < 0.05. All the outcome analyses are presented in Table 3.

Table 3: Comparison of Patient Outcomes by Group

	Total (n=)	REBOA group (n=)	Conventional group (n=)
Any ROSC			
Time to the 1st ROSC (min)			
Sustained ROSC			
Time to the 1st sustained ROSC			
The length of time a sustained ROSC has been maintained			
TTM			
CRRT			
CAG			
Length of hospital stay (days)			
Survival to admission			
Good CPC at			
Hospital discharge			
1 month after ED arrival			
3 months after ED arrival			
6 months after ED arrival			

ROSC, return of spontaneous circulation; TTM, targeted temperature management; CRRT, continuous renal replacement treatment; CAG, coronary artery angiography; CPC, cerebral performance category; ED, emergency department

5.3. Missing Data

We expect no missing data for the primary outcome of this study, given that it can be determined immediately when CPR is terminated, either due to ROSC or a determination of death in the EDs. Regarding the reporting of the clinical characteristics of patients and secondary outcomes, the primary approach to handling missing data is the direct deletion method. However, in cases where a significant amount of missing data exists for specific variables among the clinical characteristics, multiple imputation is considered an alternative approach. If multiple imputation is employed for any variable, it is explicitly stated in the reporting of results.

5.4. Additional Analyses

The objective of the additional subgroup analysis is to investigate the factors potentially causing disparities in treatment outcomes, which may vary based on the distinct clinical characteristics of patients throughout the study. This detailed evaluation will be conducted for various potential determinants, including age, gender, whether CPR was administered by a bystander, initial rhythm (categorized as shockable or non-shockable), location of the arrest (public vs. non-public), cause of arrest (cardiogenic vs. non-cardiogenic), time elapsed from arrest to arrival at the ED, and the institution where the treatment was received (Seoul National University Bundang Hospital or Far Eastern Memorial Hospital).

5.5. Harms

Adverse events will be monitored from randomization to hospital discharge. Any adverse events, including malposition, insertion failure, insertion site hematoma/infection, femoral artery injury, lower limb ischemia, aorta injury, and others, will be recorded in the case report form for each case. If any adverse events occur, patients will be treated immediately according to routine practice and will be followed up until complete resolution or termination of treatment. Such adverse events will be reported to the TSC and IRB.

5.6. Statistical Software

Data will be analyzed using the R statistical software (version 4.2.3; R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Seoul National University Bundang Hospital

Informed Consent

Effect Of Resuscitative Endovascular Balloon Occlusion of the Aorta in Non-Traumatic Out-of-Hospital Cardiac Arrest (REBOA); A Multinational, Multicenter Randomized Controlled Trial

Subject Information Sheet

Subject Screening Number: _____

Title of the Study: Effect Of Resuscitative Endovascular Balloon Occlusion of the Aorta in Non-Traumatic Out-of-Hospital Cardiac Arrest (REBOA); A Multinational, Multicenter Randomized Controlled Trial

Principal Investigator: Professor Dong Keon Lee, Department of Emergency Medicine, Bundang Seoul National University Hospital

We kindly request your participation in this study.

Before deciding to participate, it is important for you to fully understand why this study is being conducted and what your involvement will entail.

The following information is provided to explain the details of this study, your role in it, and the process of the research. Please take sufficient time to read this subject information sheet, and if desired, discuss it with your family or others. Additionally, if you have any questions, please ask the exam coordinator or other study personnel, and carefully consider your decision to participate in this study.

1. This study is conducted for research purposes.

This clinical trial is not conducted for therapeutic purposes. It is a research study aimed at investigating the impact of Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) during cardiopulmonary resuscitation on the prognosis of out-of-hospital cardiac arrest patients, with the goal of improving the prognosis of cardiac arrest patients.

2. Background and Purpose of the Clinical Trial

For out-of-hospital cardiac arrest (OHCA), cardiopulmonary resuscitation (CPR) is performed. However, even with high-quality CPR, the rate of return of spontaneous circulation (ROSC) is extremely low. The primary goal of CPR is to maintain sufficient blood flow to the brain and coronary arteries, preventing ischemic damage and correcting the reversible causes of cardiac arrest. However, even with effective chest compressions, only 30% of the pre-arrest blood flow to vital organs is achieved. This study aims to increase the rate of ROSC by using REBOA during CPR, which involves occluding the descending aorta to increase blood flow to major organs during resuscitation.

3. Information on Investigational Drugs/Medical Devices and Randomization Probability

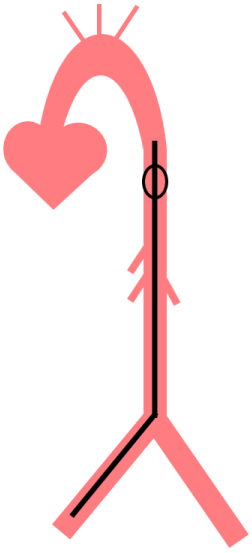
This study will be conducted using randomization. The assignment to either the CPR group or the REBOA group will be determined randomly based on a computer-generated randomization table,

with an equal allocation ratio of 1:1. This study is a multinational study, with a total of 232 patients participating from Taiwan and Korea. If you agree to participate in the study, you will be randomly assigned to either the control or experimental group.

4. Various Tests and Procedures that Subjects will Undergo in the Clinical Trial

Both groups will receive CPR according to the 2020 American Heart Association guidelines for cardiopulmonary resuscitation. This standard CPR includes high-quality chest compressions at a rate of 100-120 per minute, prevention of hyperventilation, early defibrillation, and administration of medications such as epinephrine.

After the randomization process, if assigned to the control group, you will receive standard CPR as described above.



If assigned to the experimental group, in addition to the standard CPR according to the guidelines, femoral arterial access will be obtained, and a REBOA catheter will be inserted through the access. The catheter will be positioned within the aorta. The catheter will be inserted to an adequate length, and the balloon attached to the catheter will be positioned in the chest. Saline solution will be injected into the balloon to inflate it, obstructing the aorta, and preventing unnecessary blood flow to the lower body (Figure 1). Additionally, the catheter, arterial access, and other vital sign monitoring devices will be used to monitor hemodynamic parameters, including blood pressure, during CPR. If a return of spontaneous circulation is achieved, the REBOA will be removed after stabilization.

Figure 1. Schematic diagram of REBOA

The expected participation period for research subjects is one year, and they will be contacted by phone to measure neurological outcomes after treatment completion.

5. Compliance requirements for research subjects

There are no specific compliance requirements for research subjects. They may be contacted by phone to investigate neurological outcomes one year after resuscitation. Contact information for patients and caregivers will be collected for phone calls.

6. The fact that it is an unproven clinical trial

In cardiac arrest patients, conventional CPR is usually performed according to the American Heart Association CPR guidelines. This involves processes such as chest compressions, defibrillation, and administration of medications such as epinephrine. However, even when CPR is performed according to these guidelines, neurological outcomes are often poor due to ischemic brain injury caused by cardiac arrest.

This study is an unproven clinical trial aiming to increase the rate of spontaneous circulation recovery by using REBOA during CPR to block the descending aortic blood flow, which directs blood flow to major organs.

7. Expected side effects, risks, or discomfort for subjects

The following side effects may occur in this study:

Insertion-related vascular damage or aortic injury during the insertion process of the arterial sheath and REBOA may occur. To prevent this, the sheath and catheter will be inserted under ultrasound guidance using the Seldinger technique. REBOA will be inserted in a way that does not overlap with the chest compressions. Direct pressure will be applied to control bleeding if a hematoma occurs at the insertion site.

8. Expected benefits for subjects

REBOA is a procedure already being performed on trauma patients, and multiple animal experiments have shown improvements in hemodynamics in cardiac arrest patients. Considering previous research results, higher survival rates can be expected compared to performing conventional CPR alone. However, this study is an unproven clinical trial, so it is difficult to expect unconditional effectiveness.

9. Alternative treatments (other available alternative treatments outside of the clinical trial)

If not participating in this study, participants will receive standard CPR according to the 2020 American Heart Association guidelines. This includes chest compressions at a rate of 100-120 per minute, defibrillation, prevention of hyperventilation, and the use of medications such as epinephrine.

10. Injury and compensation

During the clinical trial period, the medical staff will make every effort to ensure the safety of the patients and take prompt and appropriate actions to minimize any adverse reactions. In the event of harm occurring during this clinical trial, the principal investigator of the study will assume legal responsibility and provide compensation according to the provisions regarding compensation for harm. In the case of adverse reactions, the best possible treatment will be provided.

11. Financial compensation

No financial compensation is provided for participants.

12. Expected costs

The consumables used in this study, such as the REBOA catheter, will be supported by the research budget. Other than the REBOA, procedures performed are the same as procedures administered during conventional CPR, so there will be no additional costs incurred by participating in the study.

13. Voluntary participation

Participating in the clinical trial is entirely up to you. If you do not agree to participate, it will not be a problem. Even after agreeing to participate in the trial, you can withdraw consent at any time without any disadvantages.

14. Provision of personal information

During and after the completion of the clinical trial, the monitor, inspector, and other authorized personnel may directly access research-related data, including medical records, within the scope prescribed by regulations, to verify the procedural integrity and reliability.

15. Confidentiality:

All records regarding your personal information obtained during this research will be kept confidential and will not be disclosed to anyone else. Even if the research results are published, your personal information will remain confidential.

16. Continuous Provision of Research-related Information:

During this research, if the investigator becomes aware of any new facts or information that might influence your decision to continue participation, they will inform you or your representative of such facts or information.

17. Contact Information:

You or your representative may contact the following individuals for telephone consultations at any time:

Person to consult regarding issues, concerns, or questions arising from the clinical trial:

Principal Investigator: Professor Dong Keon Lee ☎031-787-7579

Co-Investigator: Hee Eun Kim ☎031-787-7579

Contact information for discussing issues, concerns, or questions related to the rights of research participants:

IRB (Institutional Review Board) Support Office ☎031-787-8801~8806

Clinical Research Ethics Center ☎031-787-88118813

18. Termination of the Study:

If any clinically significant adverse events occur during this clinical trial that are believed to be not beneficial to the patient, the patient may be withdrawn from the study.

19. Expected Duration of the Participant's Clinical Trial:

The anticipated duration of the participant's involvement in the clinical trial is one year, and they will be contacted by phone to assess their neurological prognosis after treatment completion.

20. Number of Participants in the Clinical Trial:

This is a multi-country, multi-center study. A total of 232 participants are expected to participate. Our institution plans to enroll 116 participants.

21. Miscellaneous:

If you decide to participate in the clinical trial, please fill in the provided consent form.

Consent Form for Research Participants

Title of the Study: Comparison of REBOA Use and Conventional CPR in Out-of-Hospital Cardiac Arrest Patients

1. I have received a detailed explanation from the responsible physician regarding all information related to this research and have understood it sufficiently.
2. I have also read the participant information sheet and understood its contents adequately, and I am aware that this research is being conducted for research purposes.
3. My decision to participate in the research is voluntary, and I understand that I can refuse to continue participating or withdraw freely during the research period due to personal reasons or other factors, without receiving any medical or other disadvantages as a result.
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5. I understand that I may receive telephone contact for the purpose of investigating neurological prognosis up to one year after resuscitation, and I consent to the research accessing my contact information and personal details for research purposes only.
6. I understand that I can contact the investigator at any time if I have any questions related to the research, and I agree to allow direct access to my medical records for research purposes only.

Accordingly, I voluntarily agree to participate in this research according to my free will.
Please sign and date below in your own handwriting.

	Name	**Signature**	**Signed Date**
Participant			YYYY / MM / DD
Legal Representative			YYYY / MM / DD
	Relationship with the Participant: _____ Reasons for Proxy Signature _____		
Principal investigator			YYYY / MM / DD

If applicable,

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IRB SNUH 분당서울대병원 생명윤리심의위원회

Seoul National University Bundang Hospital Informed Consent

Effect Of Resuscitative Endovascular Balloon Occlusion of the Aorta in Non-Traumatic Out-of-Hospital Cardiac Arrest (REBOA); A Multinational, Multicenter Randomized Controlled Trial

Trial Registration Number: NCT06031623

Current version number: Version 1.0

Last updated date: September 17, 2023

Subject Information Sheet

Subject Screening Number: _____

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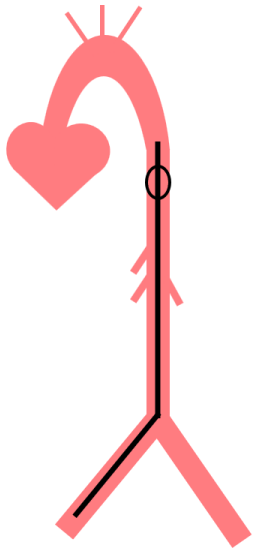

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IRB SNUH 분당서울대병원 생명윤리심의위원회

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	Relationship with the Participant: _____ Reasons for Proxy Signature _____		
Principal investigator			YYYY / MM / DD

If applicable,

	Name	**Signature**	**Signed Date**
Observer			YYYY / MM / DD

Far Eastern Memorial Hospital

Informed Consent

Effect Of Resuscitative Endovascular Balloon Occlusion of the Aorta in Non-Traumatic Out-of-Hospital Cardiac Arrest (REBOA); A Multinational, Multicenter Randomized Controlled Trial

Trial Registration Number: NCT06031623

Current version number: Version 1.0

Last updated date: July 05, 2023

Far Eastern Memorial Hospital

Informed Consent Form for Clinical Trials of Medical Devices

Project Title: Resuscitative Endovascular Balloon occlusion of the Aorta in Patients with Non-Traumatic Out-of-Hospital Cardiac Arrest - An International Multi-center Randomized Clinical Trial

Clinical Trial Institution: Far Eastern Memorial Hospital

Commissioner: Jen-Tang Sun

Project host: Jen-Tang Sun

Position: Director of Surgical and Traumatic Emergency / Tel: 02-77281843

Co-host: Chun-Yen Huang / Position:Attending physician / Tel: 02-77281843

Co-host: Chih-Jung Chang / Position: Attending physician / Tel: 02-77281843

Co-host: Sheng-En Chu / Position: Attending physician / Tel: 02-77281843

Co-host: Yu-Chen Chiu / Position: Attending physician / Tel: 02-77281843

Co-host: Fu-Chieh Hsieh / Position: Attending physician / Tel: 02-77281843

※**24-hour emergency contact:** Jen-Tang Sun **Tel: 0919-388100**

Name:

Gender:

Medical record number:

You are cordially invited to participate in this clinical trial. This document provides you with pertinent information concerning the study. The lead investigator or an authorized representative will thoroughly explain the trial's objectives and address any inquiries you might have. Please ensure that all your questions are answered to your satisfaction before affixing your signature to this consent form. We understand the significance of such a decision, so we encourage you to reflect and deliberate before committing. Your signed consent is a prerequisite for participation in this trial. Should you choose to partake, this document will stand as an official record of your agreement. It's essential to note that even

after giving your consent, you retain the right to withdraw from the study at any point, with no need to furnish a reason.

1. Status of the Medical Device Used in the Trial:

Information on the Medical Device:

The Resuscitative Endovascular Balloon Occlusion of the Aorta (commonly referred to as REBOA) is currently considered suitable for severe hemorrhaging below the diaphragm or even impending traumatic cardiac arrest (ITCA). It offers a minimally invasive, quick, and effective alternative surgery for bleeding control. This technique can halt hemorrhagic shock and prevent the exacerbation of metabolic issues, simultaneously providing patients with vital time, avoiding rushed, potentially unprepared invasive procedures like thoracotomy, laparotomy, or pelvic cavity tamponade in the emergency department. The method involves introducing a catheter into the aorta through a femoral approach and inflating a balloon near the bleeding site to temporarily halt blood flow, thereby increasing afterload to maintain cerebral and cardiac circulation. The aorta can be segmented into three zones: Zone I spans from the left subclavian artery to the celiac trunk, controlling major hemorrhage below the diaphragm; Zone III ranges from the renal arteries to the aortic bifurcation, managing major bleeding at the pelvis or lower limbs; Zone II, which is the region between Zones I and III, presently has limited applicability. Employing this technique can result in ischemia in organs distal to the balloon, potentially leading to complications such as visceral, spinal cord, and lower limb ischemia or reperfusion syndrome. Numerous studies on the use of REBOA in severe trauma patients have shown a 30-day survival rate of 59%. Traumatic cardiac arrest patients using REBOA to restore spontaneous circulation stand at 58.8%, with 40-41% reaching the operating room alive, and a 30-day survival rate between 5-10%. Beyond traumatic shock, REBOA is gradually being used for non-traumatic hemorrhage cases. According to Matsumura's study, common reasons for using REBOA include postoperative hemorrhage, ruptured aneurysm, gastrointestinal bleeding, and major postpartum hemorrhage. Although the mortality rate for these patients matches that of traumatic shock patients, the proportion of deaths due to bleeding is noticeably reduced. Far Eastern Memorial Hospital recorded two cases of aneurysm hemorrhage and two postpartum major hemorrhage cases. Among these, three had cardiac arrest, all of whom were resuscitated. One of the postpartum hemorrhage patients was successfully discharged with full neurological functionality. The team has published a case of ruptured aortic aneurysm treated with

REBOA in the Annals of Emergency Medicine.

Market Status of the Medical Device:

The device has received approval for marketing by the Taiwan Ministry of Health and Welfare and meets the indicated use of temporary vascular occlusion or dilation of artificial vessels (Health Ministry Medical Equipment Import No. 032086).

2. Objective of the Study:

Driven by our expertise in resuscitation for patients with Out-of-Hospital Cardiac Arrest (OHCA), and supported by positive evidence from past literature on the use of REBOA in OHCA patients, along with our team's extensive experience with REBOA, we aim to apply REBOA in the emergency management of OHCA patients. In our study, we explore the potential of using REBOA to assist with Advanced Cardiac Life Support (ACLS) in the hospital setting, an area less emphasized in many Western research studies that often prioritize pre-hospital care. We are proposing a three-year continuous project that will be a randomized controlled study across two international medical centers. Our research hypothesis posits that adult witnessed non-traumatic cardiac arrest patients, when aided with REBOA technique in conjunction with ACLS, as opposed to using ACLS alone, will exhibit better rates of return of spontaneous circulation, improved end-tidal carbon dioxide levels, higher non-invasive cerebral oxygenation levels, and patients will also display superior arterial perfusion, overall survival rates, and neurological prognosis. For this study within our country, we anticipate to include a control group of 58 patients and a REBOA group of 58 patients, totaling 116 participants.

3. Inclusion and Exclusion Criteria:

Inclusion Criteria:

(1) Age between 20 and 80 years.

(2) Non-traumatic and non-hemorrhagic cause of the condition.

(3) Patients who experience witnessed cardiac and respiratory arrest between 9 am and 5 pm from Monday to Friday and are brought to the emergency department.

Exclusion Criteria:

(1)Patients or their representatives who have expressed refusal for resuscitation, either through a signed "Do Not Resuscitate" (DNR) order or an Advanced Care Planning (ACP) that explicitly states an opposition to emergency resuscitation efforts.

(2)Patients who have already achieved ROSC before arrival to the emergency department.

(3)Initiation of extracorporeal cardiopulmonary resuscitation.

(4)Clinical identification of aortic conditions, such as aortic dissections or aneurysms, as evidenced by ultrasound results or a documented history.

(5)Patients who were already severely neurologically impaired or in a vegetative state before the event.

(6)Pregnant women

4. Methodology & Procedures

REBOA Group Procedure:

The on-duty team treats the patient, including ACLS. Study-specific procedures are performed by research team physicians without affecting the original treatment.

(1) The resuscitation process is performed and recorded by the on-duty emergency medical team.

(2) Resuscitation following ACLS guidelines, including LUCAS treatment.

(3) Secure airway establishment (endotracheal intubation) and monitor end-tidal CO2 (EtCO2).

(4) Research team personnel conduct ultrasonography to rule out contraindications.

(5) Research team personnel insert femoral artery and central venous catheters to monitor arterial blood pressure and right atrial pressure.

(6) Non-invasive cerebral oxygenation monitoring is set up by the research team.

(7) Patient grouping (REBOA or Control) is determined using the Redcap system.

(8) If assigned to the REBOA group, the research team places the REBOA between the left subclavian artery and the abdominal aorta main (Zone I), confirmed by transesophageal echocardiography, without interrupting CPR, and arterial pressure is

monitored.

(9) Inflate the REBOA balloon with 20cc saline or until resistance is felt.

(10) Continuous monitoring until the patient achieves Return of Spontaneous Circulation (ROSC) or is declared deceased.

(11) Post-ROSC, the REBOA balloon is gradually deflated and removed. Post-resuscitation care is provided, and a cardiothoracic surgeon is consulted for arterial catheter removal evaluation.

(12) Record patient details, physiological parameters, resuscitation measures, REBOA-related info (attempts, insertion time, complications, CCF, and other ACLS quality indicators).

(13) If the patient achieves sustained ROSC (more than 20 minutes), they sign a consent form. Tracking continues for 30 days post-enrollment or until death. Patient survival status and neurological outcomes are recorded.

Control Group Procedure:

The on-duty team treats the patient, including ACLS. Study-specific procedures are performed by the research team physicians without affecting the original treatment.

(1) to (6) steps are similar to the REBOA group (from emergency procedure to cerebral oxygenation monitoring).

(7) Group assignment is made using the Redcap system.

(8) If assigned to the Control group, REBOA is not inserted.

(9) Monitoring continues until the patient achieves ROSC or is declared deceased.

(10) to (11) steps are consistent with the REBOA group, focusing on ROSC achievement, post-resuscitation care, and consultation with a cardiothoracic surgeon.

(12) to (13) steps. Similarly, record patient details, parameters, resuscitation efforts, and monitor patient's health and neurological outcomes for 30 days post-enrollment or until death.

5. Potential Risks, Occurrence Rates, and Management:

Risks Associated with the Medical Device Used in the Study:

The complications may arise from the REBOA itself or during its placement process. These include but are not limited to: infections at the injury site or the onset of sepsis, allergic reactions, localized bleeding, vasospasms, endothelial injury, air embolism, pain and tenderness at the site of insertion, peripheral vascular ischemia, endocarditis, thrombocytopenia, myocardial infarction, blood clots leading to vascular obstruction, cerebral embolism, arteriovenous fistula, kidney-related complications, vascular complications (dissection, rupture, bleeding, or perforation), respiratory distress, or death.

Risks Related to the Trial Procedure:

The use of REBOA on eligible participants has been optimized to minimize risks, with every case being reviewed by a cardiothoracic surgeon. Despite this, there remains a possibility of participant death even after the standard resuscitation procedure. The primary responsibility of the cardiothoracic surgeon is to assist with the removal of the arterial catheter sheath and to be on standby in cases of difficulty with REBOA removal.

6. Alternative Therapies and Explanation:

Standard Advanced Cardiac Life Support (ACLS) without the placement of REBOA.

7. Anticipated Benefits of the Trial:

The trial aims to increase coronary and cerebral perfusion in participants. In cases where aggressive treatments (such as ECMO) are not applicable, it hopes to enhance the chances of participants achieving return of spontaneous breathing and circulation, as well as improving neurological outcomes.

8. The Contraindications, Limitations, and Requirements for Participants During the Trial:

None

9. Confidentiality of Participants' Personal Information:

The system data is maintained by a dedicated research assistant, ensuring confidentiality

of all relevant information. The project leader takes meticulous steps to protect the collected documents and complies with the "Personal Data Protection Act" and other related regulations. Initially, the data will be labeled with the participant's name and medical record number. The participants will then be coded. Once the subsequent medical record data collection is completed (within 30 days), the names of the participants will be removed, leaving only the code. All case data will be archived on the research computers of both the lead and co-investigators.

After undergoing research coding management, the analyzed data completely omits personal identifiers such as national identification numbers, home phone numbers, addresses, etc., making it impossible to trace the patient's identity, ensuring the privacy of the subjects. Collected hard copies and multimedia data will be stored on the assistant's computer. The lead investigator will personally analyze them, or research members will analyze them on the computer under the supervision of the lead investigator.

10. Withdrawal and Termination of the Trial:

You are free to decide whether to participate in this trial. You can also withdraw your consent and leave the trial at any time, without providing any reason. This decision will not result in any inconvenience and will not affect the future medical care provided to you by your physician. The trial's lead investigator may also choose to terminate the trial if deemed necessary.

11. Medical Care, Compensation, and Insurance:

(1) If you participate in this clinical trial and sustain damage due to an adverse reaction, our hospital will bear the responsibility for compensation. However, anticipated adverse reactions, side effects, or risks noted in this consent form will not be compensated.

(2) If you participate in this clinical trial and experience an adverse reaction or damage, our hospital and the lead investigator are committed to providing professional medical care and consultation. You will not be responsible for the necessary medical expenses associated with treating the adverse reaction or damage.

(3) Aside from the aforementioned compensation and medical care, this trial does not offer any other form of compensation. If you are unwilling to accept these risks,

please refrain from participating in the trial.

(4) Signing this consent form will not deprive you of any legal rights.

(5) This trial does not have liability insurance.

12. Preservation, Use, and Reuse of Participant's Specimens (and their derivatives) and Personal Information:

The collected data will be coded and stored on the computers of the lead and co-investigators, managed by the aforementioned personnel. Only the participant's code will be displayed on the collected data. Additionally, all data gathered during this study, including paper records and video recordings, will be destroyed within 3 years after the conclusion of the study.

13. Rights of the Participant:

(1) There will be no charges related to this study imposed on you, and this trial is not covered under the National Health Insurance scope.

(2) Any significant findings related to your health or illness that may affect your willingness to continue participating in the clinical trial will be promptly communicated to you.

(3) If you have questions about the nature of the trial or concerns about your rights as a participant, or if you suspect any harm as a result of participating in the trial, you can contact the Institutional Review Board (IRB) of our hospital for consultation at 02-89667000, extension 2152. Alternatively, you can contact the Participant Protection Center at 02-89667000, extension 2546.

(4) To proceed with the trial, you must be under the care of the physicians involved in this research. After being admitted to the Intensive Care Unit (ICU), you will be cared for by the ICU physicians. If you have any concerns or issues now or during the trial, please feel free to contact Dr. Sun Ren-Tang from the Emergency Medicine Department at Far Eastern Memorial Hospital, **available 24/7 at 0919-388100**.

(5) Two copies of this consent form have been provided, one of which has been handed to you. The physician has explained the nature and objectives of this trial in full and

has answered all your questions concerning the medical equipment and trial procedures.

14. Signature:

The principal investigator or their authorized personnel has explained in detail the nature, purpose, potential risks, and benefits of the trial method mentioned in this clinical trial.

☐Principal Investigator/☐Co-Investigator/☐Authorized Research Personnel

Signature: _____

Date: ____Year____Month____Day

I have fully understood the aforementioned trial method, its potential risks and benefits. Any questions about this trial have been thoroughly explained by the research team. I voluntarily agree to become a participant in this clinical trial.

Participant's Signature: _____

Date: ____Year____Month____Day

Legal Representative/Person with Consent Authority Signature: _____

Date: ____Year____Month____Day

Relationship to Participant: ☐Spouse, ☐Adult Child, ☐Parent, ☐Sibling, ☐Grandparent

* *If the participant is a teenager aged 7 to 20 with limited legal capacity, both the participant and the legal representative should sign.*
* *The legal representative should also present relevant identification documents for the principal investigator to verify their identity.*
* *Even if the participant is not legally incapacitated or has restricted capacity, should they exhibit signs of confusion, mental, or cognitive impairments that prevent effective communication and sound judgment, a person authorized to provide consent can act on their behalf. When proceeding to sign the consent form, the authorized person must*

present relevant identification documents to allow the principal investigator to validate their identity.

* *For written consents provided by the aforementioned relatives or authorized persons, a single person's signature suffices. In the event of conflicting opinions among these individuals, priority is determined by the predefined sequence, as indicated in the aforementioned order. Within the same category of relationship, closer kinship takes precedence. If kinship level is identical, cohabitating family members are given priority. In the absence of cohabitating relatives, the elder individual's decision takes precedence.*

Witness 1. Signature: _____

Date: ____Year____Month____Day

ID Number:

Address:

Contact Number:

Witness 2. Signature: _____

Date: ____Year____Month____Day

ID Number:

Address:

Contact Number:

* *If the participant, legal representative, or person with the right to consent is illiterate, a witness should be present throughout all discussions related to the consent form. After ensuring that the consent of the participant, legal representative, or person with the right to consent is given voluntarily, they should sign the consent form and record the date. Research-related personnel cannot act as witnesses.*