Feasibility study of a novel leukocyte adsorption device during cardiopulmonary bypass: protocol for a first-in-human pilot trial

INTRODUCTION

Cardiopulmonary bypass (CPB) during cardiac surgery triggers systemic inflammatory responses, primarily because of contact between blood and the artificial surfaces of the extracorporeal circuit, non-physiological shear stress during non-pulsatile flow, as well as ischaemia during aortic cross-clamping followed by reperfusion (1-3). During these responses, activated neutrophils adhere to endothelium, where they release proteases, reactive oxygen species, and arachidonic acid metabolites, leading to tissue damage. In parallel, activated neutrophils and other activated leukocytes release large quantities of inflammatory mediators and proteases, which permeabilise the endothelium as well as promote leukocyte activation and proliferation, amplifying the inflammatory cascade (4) (5). These systemic immune responses can compromise recovery and increase risk of postoperative organ dysfunction, which occurs in 15- 66 % of patients (6).

Glucocorticoids such as methylprednisolone can be used to attenuate CPB-induced inflammation, but they increase risk of immunosuppression, infection, and other adverse effects such as peptic ulcers. At the same time, their efficacy is questionable: a randomised trial involving more than 7,500 patients undergoing CPB found that intraoperative methylprednisolone did not significantly improve 30-day mortality or major complications compared to placebo (7).

Another strategy to mitigate CPB-induced inflammation, which draws inspiration from extracorporeal blood purification techniques that have been used to treat sepsis or failure of the liver or kidney, is to filter leukocytes (e.g. LeukoGuard-6) or adsorb inflammatory cytokines (e.g. CytoSorb, oXiris) from the bloodstream during bypass. Several studies have indicated that these techniques during CPB can improve organ function soon after surgery (8-11), yet several

studies have shown that they do not significantly reduce numbers of activated leukocytes or levels of cytokines (12-16), raising questions about their clinical efficacy(17, 18).

Therefore, we investigated leukocyte dynamics during CPB. In our 120-patient cohort, activated leukocytes—particularly neutrophils—increased markedly during rewarming and remained elevated for up to 24 h; greater activation correlated with higher risk of postoperative organ dysfunction, particularly acute kidney injury(19). Concurrently, clustering of Mac-1 (CD11b/CD18) on neutrophil surfaces reflected enhanced adhesiveness, a property that in our preclinical rat CPB models directly contributed to acute lung injury. In these models, inhibition of F-actin reorganisation prevented Mac-1 clustering at the neutrophil leading edge, thereby limiting adhesion and migration, reducing bronchoalveolar cytokine levels, and attenuating lung injury (20). These findings identify rewarming as the peak of leukocyte-mediated injury and provide the rationale for targeting activated leukocytes at this phase of CPB.

Based on this rationale, we developed a novel leukocyte filter, designed for the rewarming phase of CPB, incorporating a polymer membrane engineered with Arg-Gly-Asp tripeptides, manufactured by Chengdu Shangyuantai Biotechnology (Chengdu, China), that strongly adsorbs activated leukocytes through binding to Mac-1 integrins and other adhesion receptors on the leukocyte surface. As a result, the membrane adsorbs activated leukocytes while minimally affecting quiescent leukocytes, red blood cells, or platelets. In our preclinical porcine model of CPB (Large White pigs), the device effectively removed activated neutrophils without significant haemolysis, thrombocytopenia, coagulopathy, or organ dysfunction, and reduced infiltration of inflammatory leukocytes into major organs while increasing levels of the anti-inflammatory cytokines interferon (IFN)-γ and interleukins (IL)-10 and -4 (unpublished data). Nevertheless, the device has not yet been evaluated in humans.

Therefore we have planned a first-in-human trial to assess the feasibility of the device and explore its safety and efficacy in patients undergoing cardiac surgery involving CPB. The findings from this study will inform the feasibility, design, and sample size of a future randomised controlled trial.

METHODS AND ANALYSIS

The trial protocol has been reported in accordance with the CONSORT extension for pilot and feasibility trials.

Setting and design of the study

This trial is designed as a single-centre prospective feasibility study involving a single arm. It will be conducted at the Second Xiangya Hospital of Central South University, a tertiary academic medical centre in Changsha, China. The trial will be conducted in compliance with the 'Regulations on the Supervision and Administration of Medical Devices' (21) and 'Good Clinical Practice for Medical Device Clinical Trials' (22).

The aim is to recruit six patients in this exploratory clinical study; the sample size is not based on formal statistical considerations. All participants will undergo CPB involving the novel leukocyte adsorber and will otherwise receive standard perioperative care. Each patient will be enrolled for a maximum of 30 days after surgery (see Table 2 below).

Neither patients nor clinicians will be blinded in the trial due to the nature of the intervention. The single-arm design means that no randomisation will be performed. Trial progress will be monitored regularly by suitably qualified external experts.

Inclusion and exclusion criteria for participants

Patients will be eligible for enrolment if they are 18-75 years old and are scheduled for elective cardiac surgery requiring CPB. Patients must be able to understand the purpose of the study and provide written informed consent.

Patients will be excluded if they present any of the following: need for emergency surgery or cardiac transplantation, active systemic infection, major organ dysfunction requiring mechanical support or renal replacement therapy, planned circulatory arrest procedure, known allergies to device materials, immune system disorders or immunosuppressive therapy, coagulation abnormalities or severe thrombocytopenia, pregnancy or lactation, severe psychiatric disorders, recent participation in another clinical trial, or any other condition considered unsuitable by the investigator. Full details of exclusion criteria are provided in **Table 1**.

Participants may withdraw from the study at any time, and such withdrawals will be categorised as dropouts. The reasons for withdrawal will be documented on the case report form. Every effort will be made to avoid losses to follow-up.

Involvement of patient and public

Patients and the public will not be involved in the design, conduct, reporting or dissemination of this research.

Primary efficacy outcomes

The primary outcome will be the immediate removal rate of activated leukocytes, defined as the percentage reduction in CD11b+ neutrophils in the blood between immediately before initiation of leukocyte adsorption (timepoint T1) and immediately after device removal (timepoint T2). In other words,

$$\text{Removal Rate} = (\text{Count}_{T1} - \text{Count}_{T2}) / \text{Count}_{T1} \times 100\%.$$

CD11b+ neutrophils in blood will also be quantified by flow cytometry at T0 (baseline, immediately before initiation of CPB), as well as at timepoints T1 and T2 and at 6, 24, and 48 h after surgery.

Secondary efficacy outcomes

The trial will assess numerous secondary outcomes. One is the incidence of acute kidney injury, defined as the percentage of participants who develop acute kidney injury according to the diagnostic criteria of the KDIGO Clinical Practice Guideline for Acute Kidney Injury (23) within one week after surgery or on discharge, whichever occurs first. To determine this outcome, blood biochemistry will be measured before surgery; at 6, 24 and 48 h after surgery; on discharge from the intensive care unit; and on postoperative day 7 or discharge, whichever occurs first. Urine output will be recorded before urinary catheter removal according to standard protocols.

Another secondary outcome is the incidence of respiratory dysfunction, defined as the percentage of participants who develop respiratory dysfunction as previously defined (24) within one week after surgery or until discharge, whichever occurs first. To determine this outcome, arterial blood gases and clinical symptoms will be analysed at 6 and 24 h after surgery. SpO_2 and FiO_2 will be recorded at 6, 24 and 48 h after surgery, discharge from intensive care unit, and on postoperative day 7 or discharge, whichever occurs first. If respiratory dysfunction is suspected, then echocardiography and/or X-ray or computed

tomography of the chest will be performed. The time of extubation and any instances of reintubation, tracheostomy, or mechanical ventilation will be documented.

Stroke incidence is defined as the percentage of participants who develop new stroke within 30 days after surgery, with stroke defined as acute focal neurological deficits of vascular origin that persist for at least 24 h, are confirmed by a neurologist based on computed tomography or magnetic resonance imaging, and are consistent with ischaemic or haemorrhagic stroke (25). Potential stroke symptoms will be assessed at 6, 24 and 48 h after surgery, discharge from the intensive care unit; on postoperative day 7 or discharge, whichever occurs first; and at 30 days after surgery. If stroke is suspected based on sudden onset of headache, disturbed consciousness, seizures, pupil changes, motor/sensory deficits, or speech disturbance, neuroimaging will be performed to confirm the diagnosis.

The incidence of cardiovascular complications refers to the percentage of participants who develop new cardiovascular complications, as previously defined (26-28), within 30 days after surgery. Such complications include low cardiac output syndrome; myocardial infarction; and malignant arrhythmia, defined as ventricular tachycardia, ventricular fibrillation, or cardiac arrest. To determine this outcome, patients will undergo continuous postoperative electrocardiographic monitoring with bedside monitors. Within the first 48 h after surgery, the use of inotropic agents will be recorded; during hospitalisation, the use of extracorporeal membrane oxygenation, a left ventricular assist device or an intra-aortic balloon pump will be recorded. High-sensitivity cardiac troponin T (hs-cTnT) will be measured at 6, 24 and 48 h after surgery; if elevated hs-cTnT levels or clinical symptoms suggest myocardial ischaemia, additional diagnostic tests will be performed, which may include 12-lead electrocardiography, transthoracic echocardiography, coronary computed tomography angiography, cardiac magnetic resonance imaging, or invasive coronary angiography.

The relative change in total white blood cell count is defined as the percentage difference between the count at timepoint T1 and the counts at timepoint T0, T2, and at 6, 24 and 48 h after surgery. Analogously, relative change in the levels of several inflammatory markers, including IL-6, IL-8, IL-10, tumour necrosis factor-α, myeloperoxidase, granulocyte colony-stimulating factor, C-reactive protein and procalcitonin will be determined between screening period and 6, 24 and 48 h after surgery.

The duration of postoperative mechanical ventilation will be recorded from the initial admission to the intensive care unit, excluding any subsequent episodes of reintubation. If a tracheostomy is required due to prolonged mechanical ventilation, the end time for this parameter will be the time of ventilator withdrawal after tracheostomy.

Other secondary outcomes are all-cause mortality within 30 days after surgery; use of circulatory support medications during hospitalisation, which are defined as positive inotropic and vasopressor drugs continuously administered *via* intravenous infusion; score on the Sequential Organ Failure Assessment (29) before surgery and 24 h later; duration of the first admission to the intensive care unit after surgery; and duration of hospitalisation after surgery, defined as the interval between the end of surgery and discharge.

Rationale for efficacy outcomes

The primary and secondary efficacy outcomes, and the timing of their measurement, reflect the fact that the levels of inflammatory cytokines during CPB-induced inflammation peak typically within 6 h after the start of bypass and return to baseline within 24-48 h (30). Many of the secondary efficacy

outcomes assess dysfunction of the brain, heart, lungs, and kidneys that typically results from CPB-induced inflammation (5, 30) (31). To provide a more comprehensive picture of the leukocyte adsorber's clinical effects, the trial will also assess the use of circulatory support medications, changes in SOFA score, and postoperative durations of mechanical ventilation, stay in the intensive care unit, and hospitalisation.

Safety outcomes

Numerous safety outcomes will be determined for this first-in-human study. Changes in serum levels of haptoglobin as well as counts of red blood cells and platelets, will be measured at timepoints T0, T1, and T2 and at 6, 24 and 48 h after surgery. Various coagulation parameters, including activated partial thromboplastin time, prothrombin time and levels of fibrinogen, fibrin degradation products and D-dimer will also be compared between screening period and at 6, 24 and 48 h after surgery.

Volumes of allogeneic blood products (red blood cells, platelets, plasma, cryoprecipitate) transfused from the start of surgery until discharge will be recorded. Total volumes drained from the chest tube will be measured at 24 and 48 h after surgery. Incidence of infection within 30 days after surgery will be recorded, where infection may include sepsis, deep sternal wound infection, catheter-related infection, and pneumonia. Infection events will be diagnosed as described (32) based on clinical symptoms and relevant diagnostic tests involving culture or imaging.

Any device malfunction or defect observed during the trial will also be documented as a safety outcome. Such defects may include leaks, breakage, abnormal pressure, or failure to function properly.

All adverse events, regardless of cause, will be recorded from enrolment through the end of follow-up. Events will be categorised and graded by severity, and their potential relationship to the device will be assessed. Serious adverse events, including life-threatening events and death, will be reported immediately to the Ethics Committee and relevant authorities.

Rationale for safety outcomes

Safety endpoints include both biological effects and device performance. The extensive contact between blood and the investigational device may lead to loss of blood components or their activity during CPB. Therefore levels of haptoglobin as an index of intravascular haemolysis will be measured, as well as counts of red blood cell and platelets and various coagulation parameters. To ensure comprehensive assessment of device safety, we will also monitor transfusion requirements, chest tube drainage volume, infection incidence, as well as postoperative durations of mechanical ventilation, stay in the intensive care unit, and postoperative hospitalisation.

Sample size

This is an exploratory first-in-human feasibility study; the sample size is not based on formal statistical considerations(33). A sample of six is considered sufficient for exploratory assessment of device feasibility, efficacy and safety in order to justify and guide future randomised trials. This sample size is based on exploratory trials of other devices for cardiovascular uses(34, 35), rather than formal power calculation.

Assessments

Six assessments will be performed as follows (**Table 2**). At *Visit 1* (-7 to 0 days), patients will be screened for enrolment according to the inclusion and exclusion criteria, and informed consent will be obtained from the patient or a legal guardian. Data will be collected on demographic characteristics (age, sex, height, weight, ethnicity), clinical history (including New York Heart Association functional class), comorbidities, surgical history, allergies, and lifestyle habits (smoking, alcohol and substance use). Data will also be collected on heart rate, invasive or non-invasive blood pressure, SpO_2, FiO_2, respiratory rate (mechanical, assisted or spontaneous) and body temperature. Laboratory testing will comprise complete blood counts, blood biochemistry, the coagulation indices mentioned above, hs-cTnT and the inflammatory markers mentioned above. All patients will undergo 12-lead electrocardiography and transthoracic echocardiography to determine the left ventricular ejection fraction. Premenopausal women will undergo pregnancy testing. If equivalent results are available from within the previous 7 days, those results may be used.

At *Visit 2* (day of surgery), arterial blood gases (PaO_2, $PaCO_2$, PaO_2/FiO_2) will be measured and the SOFA score will be calculated before anaesthesia induction. Routine cardiovascular surgery will be performed, and the investigational device will be used for leukocyte adsorption during CPB rewarming according to the manufacturer's recommendations (Appendix S1). Blood will be sampled at timepoints T0, T1 and T2, and routine indices of blood composition and liver function as well as haptoglobin level and abundance of CD11b+ neutrophils will be determined. Data will be collected about surgical approach (eg, median sternotomy or thoracoscopy); surgery type (eg, coronary artery bypass grafting or valve surgery); timing of anaesthesia induction; durations of surgery, aortic cross-clamping and CPB; timing of rewarming; intraoperative transfusion; ultrafiltration use and duration of device use; adverse events; and concomitant treatments.

During *Visit 3* (spanning 6-48 h after surgery), postoperative hour 0 is defined as intensive care unit admission. Vital signs will be measured at 6, 24 and 48 h after surgery, as will routine blood composition and biochemistry and levels of coagulation markers, hs-cTnT and inflammatory markers. Blood gases will be analysed at 6 and 24 h, while chest tube drainage volumes will be determined at 24 and 48 h. Adverse events and concomitant treatments will be documented.

At both *Visit 4* (discharge from intensive care unit) and *Visit 5* (postoperative day 7 or discharge, whichever occurs first), the time of intensive care unit discharge will be recorded, vital signs will be measured and routine blood counts and biochemistry will be determined. Adverse events and any concomitant treatments will be recorded.

At *Visit 6* (postoperative day 30), inpatients will be assessed exactly as during Visits 4 and 5, while outpatients will be followed up by telephone; if necessary, outpatients will be asked to return to hospital for evaluation and treatment. Adverse events and concomitant treatments will be recorded, as will data about other postoperative factors, including extubation time, reintubation, tracheostomy, mechanical ventilation, repeat admission to the intensive care unit, urine output, time of urinary catheter removal (hours after surgery), transfusion types and amounts, and discharge time. Additional diagnostic tests, such as transthoracic echocardiography, 12-lead electrocardiography, chest X-ray or computed tomography, and brain computed tomography or magnetic resonance imaging, will be performed as clinically indicated.

Collection and management of trial data

All study data will be collected prospectively using standardised case report forms, in accordance with Good Clinical Practice for medical device clinical trials (21). Each participant will be assigned a unique identification number under which all data will be recorded to ensure anonymity. To safeguard data

quality, external monitors will conduct routine logical checks of the database. Any incomplete, inconsistent, or implausible entries will be raised as queries with the investigators and subsequently verified or corrected by the research team. The study team will retain overall responsibility for data verification to ensure completeness, accuracy, and timeliness of data collection.

Statistical analysis

Statistical analysis will be minimised given the small sample. Continuous data will be reported as mean ± standard deviation if normally distributed, or as median (interquartile range) if skewed. Categorical data will be reported as n (%). All statistical analyses will be conducted using SPSS version 29.0 (IBM Corp., Armonk, NY, USA).

For exploratory purposes, we may assess the significance of changes in certain outcomes, such as neutrophil counts before or after adsorption, or cytokine levels before or after surgery. These statistical tests will be interpreted with caution and without formal inferential claims because of the limited statistical power of the trial. For the same reason, missing data will not be imputed but simply omitted.

ETHICS AND DISSEMINATION

This study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University (Approval No. 2025 Ethics Review 208) and was prospectively registered at the Chinese Clinical Trial Registry (ChiCTR; Registration No. ChiCTR2500109580). Written informed consent was obtained from all participants or their legal representatives prior to enrolment. The consent process included an explanation of the study objectives, procedures,

potential risks and benefits, and the voluntary nature of participation. Participants were informed of their right to withdraw from the study at any time without any impact on their medical care.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and applicable Chinese regulations governing medical device clinical trials. Participant confidentiality was strictly protected, and all data were anonymised prior to analysis and publication. The study was monitored by the trial sponsor or a designated monitor to ensure compliance with this protocol, good clinical practice, and relevant regulatory requirements.

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Tables

Table 1 Criteria for exclusion from the trial.

Criterion	Description
Emergency surgery or cardiac transplantation	Requirement for urgent surgery or cardiac transplantation
Systemic infection	Documented systemic infection confirmed by preoperative microbiological testing, such as culture or PCR assay
Major organ dysfunction	Preoperative dysfunction of heart, lungs, or kidneys requiring mechanical ventilatory support, mechanical circulatory assistance (e.g. intra-aortic balloon pump, extracorporeal membrane oxygenation, left ventricular assist device), or renal replacement therapy
Planned circulatory arrest	Intended circulatory arrest procedure during surgery
Allergies	Known allergy to device materials, including polyester or silicone
Immune disorders	Concomitant immune system disorders, such as autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus) or immunodeficiency-related diseases (e.g., HIV/AIDS, haematologic malignancies)
Immunosuppressive therapy	Ongoing immunosuppressive or corticosteroid therapy (e.g., prednisone >0.5 mg/kg/day or equivalent dose)
Heparin-induced thrombocytopenia	History of heparin-induced thrombocytopenia
Coagulopathy	Preoperative coagulopathy with activated partial thromboplastin time or prothrombin time > 1.5 × upper normal limit
Thrombocytopenia	Preoperative platelet count < 75×10^9 /L
Pregnancy or lactation	Current pregnancy or breastfeeding
Psychiatric disorder	Severe psychiatric disorder impairing the patient's ability to understand the study or comply with the trial protocol
Clinical trial participation	Participation in another interventional clinical trial during the three months before enrolment
Investigator judgement	Any other condition that the investigators deem inappropriate for participation

291 **Table 2.** Assessments and their timing during the trial

Characteristic of visit	Visit 1	Visit 2	Visit 3¶¶	Visit 4¶¶	Visit 5¶¶	Visit 6¶¶
Timing	Screening	T0, T1, T2	6, 24, 48 h after surgery	Discharge from intensive care unit	Day 7 or discharge from hospital	Day 30 or discharge from hospital
Informed consent	X					
Medical history and demographics	X					
Vital signs*	X		X	X	X	
Pregnancy test	X					
Complete blood count †, Serum biochemistry ‡	X	X	X	X	X	
Coagulation §, hs-cTnT	X		X			
Echocardiography, electrocardiography	X					
Eligibility check, Enrolment	X					
Cytokines ¶	X		X			
CD11b+ neutrophils and haptoglobin		X	X			
Arterial blood gases #		X	X (6, 24 h)			
Sequential Organ Failure Assessment score #		X	X (24 h)			
Surgical data **		X				
Chest drainage volume			X (24, 48 h)			
Post-operative care †† and additional tests §§			X	X	X	X
Telephone follow-up						X
Device defects and malfunctions		X (T1, T2)				

Adverse events and adjuvant therapy	X	X	X	X	X	X

* Heart rate, invasive or non-invasive blood pressure, SpO_2, FiO_2, respiratory rate, and temperature.

† Counts of red blood cells, white blood cells, platelets; relative percentages of neutrophils, lymphocytes, monocytes; level of haemoglobin and haematocrit.

‡ Aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, albumin, globulin, creatinine, urea/blood urea nitrogen, at Visit 2, liver function only.

§ Activated partial thromboplastin time, prothrombin time, fibrinogen, fibrin degradation products, and D-dimer.

¶ Interleukin-6, -8 and -10; tumour necrosis factor-α; myeloperoxidase; granulocyte colony-stimulating factor; C-reactive protein; procalcitonin.

PaO_2, $PaCO_2$, PaO_2/FiO_2 and Sequential Organ Failure Assessment score (measured at Visit 2, before anaesthesia induction).

** Type of surgery, anaesthesia, transfusion volumes, requirement for ultrafiltration, and durations of cardiopulmonary bypass, overall surgery, cross-clamping, rewarming, and use of novel leukocyte adsorber.

†† Extubation, reintubation/tracheostomy/ventilation, readmission to intensive care unit, urine output, transfusion volumes.

§§ As indicated, electrocardiography, transesophageal echocardiography, X-ray or computed tomography of the chest or computed tomography/magnetic resonance imaging of the head.

¶¶ Postoperative hour 0 is ICU admission. Visits 3 and 4 (if ICU discharge ≤48 h after surgery) will be merged without duplication. Visit 4 and 5 (if within 24 h of ICU discharge) will be merged without duplication. Day 30 follows Visit 5 if hospitalised.