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Effect of the oXiris membrane on microcirculation after cardiac surgery under cardiopulmonary bypass: study protocol for a randomised controlled trial (OXICARD Study)

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ABSTRACT

Introduction Cytokine storm and endotoxin release during cardiac surgery with cardiopulmonary bypass (CPB) have been related to vasoplegic shock and organ dysfunction. We hypothesised that early (during CPB) cytokine adsorption with oXiris membrane for patients at high risk of inflammatory syndrome following cardiac surgery may improve microcirculation, endothelial function and outcomes.

Methods and analysis The Oxicard trial is a prospective, monocentric trial, randomising 70 patients scheduled for cardiac surgery. The inclusion criterion is patients aged more than 18 years old undergoing elective cardiac surgery under CPB with an expected CPB time >90 min (double valve replacement or valve replacement plus coronary arterial bypass graft). Patients will be allocated to the intervention group (n=35) or the control group (n=35). In the intervention group, oXiris membrane will be used on the Prismaflex device (Baxter) at blood pump flow of 450 mL/min during cardiac surgery under CPB. In the control group, cardiac surgery under CPB will be conducted as usual without oXiris membrane. An intention-to-treat analysis will be performed. The primary endpoint will be the microcirculatory flow index measured by sublingual microcirculation device at day 1 following cardiac surgery. The secondary endpoints will be other microcirculation variables at CPB end, 6 hours after CPB, at day 1 and at day 2. We also aim to evaluate the occurrence of major cardiovascular and cerebral events (eg, myocardial infarction, stroke, ischaemic mesenteric, resuscitated cardiac arrest, acute kidney injury) within the first 30 days. Cumulative catecholamine use, intensive care unit length of stay, endothelium glycocalyx shedding parameters (syndecan-1, heparan-sulfate and hyaluronic acid), inflammatory cytokines (tumour necrosis factor (TNF) alpha, interleukin 1 (IL1) beta, IL 10, IL 6, lipopolysaccharide, endothelin) and endothelial permeability biomarkers (angiopoietin 1, angiopoietin 2, Tie2 soluble receptor and Vascular Endothelial Growth Factor (VEGF) will also be evaluated.

Ethics and dissemination Ethical approval has been obtained from the Institutional Review Board of the University Hospital of Amiens (registration number ID RDB: 2019-A02437-50 in February 2020). Results of the study will be disseminated via peer-reviewed publications and presentations at national and international conferences.

Trial registration number NCT04201119.

Strengths and limitations of this study

- The trial will be a prospective, monocentric, randomised trial and will include 70 patients scheduled for cardiac surgery.
- We will include patients undergoing elective cardiac surgery under cardiopulmonary bypass (CPB) with an expected CPB time >90 min.
- The intervention that is being investigated is oXiris membrane use during cardiac surgery under CPB.
- The primary endpoint will be the microcirculatory flow index measured by sublingual microcirculation device at day 1 following cardiac surgery.
- The secondary endpoints will include major outcomes within the first 30 days, endothelium glycocalyx shedding variables, inflammatory cytokines and endothelial permeability biomarkers.

INTRODUCTION

A 'sepsis-like syndrome' is often observed in postoperative cardiac surgery under cardiopulmonary bypass (CPB), especially when CPB is over 90 min (double valve replacement or valve replacement plus coronary arterial bypass graft (CABG)).

This condition is due to microcirculation disturbances induced by endothelial dysfunction. Indeed, extracorporeal circulation, associated with aortic clamping, induces changes in the blood circulation with a so-called continuous circulation (unlike the usual pulsed circulation), leading to a heterogeneity of organ perfusion. The associated vasoplegic syndrome in postoperative cardiac surgery is due to acute circulatory failure,

defined by persistent low blood pressure, requiring treatment with vasopressors.[1–3] From a pathophysiological point of view, SV is the result of a complex inflammatory cascade whose origin is multifactorial. This proinflammatory state activates complement, platelets and leucocytes which release vasoactive substances. Following CPB, impaired microcirculation is still common and can lead to true organ failure by decreasing oxygen delivery to tissues. Impaired microcirculation after bypass surgery has been well demonstrated with a decrease in microcirculatory flow to the lateral margin of the tongue. The use of sidestream or incident dark field/orthogonal polarised microscopy remains the reference method to clinically assess microcirculation.[4 5] The most easily accessible site at the patient's bedside is the microcirculation of the sublingual mucosa.[6–8] This proinflammatory state can be modulated with the removal of cytokines. The oXiris (Baxter, Illinois, USA) membrane is an AN-69 membrane, surface-treated with polyethylenimine and grafted with heparin. This property allows the adsorption of inflammatory cytokines and lipopolysaccharide (LPS).[9 10] The accepted indication is sepsis or septic shock requiring renal replacement therapy (RRT).[11 12] In cardiac surgery, there are no sufficient clinical data to recommend the use of the oXiris membrane to reduce postoperative inflammatory syndrome. Some studies have demonstrated the feasibility of using the oXiris membrane during cardiac surgery with CPB with effective removal of inflammatory cytokines.[11 12] However, to date, no studies have established the beneficial effect of cytokine removal on microcirculatory variables.

We hypothesised that the early use (during CPB) of cytokine adsorption with the oXiris membrane in patients at high risk of inflammatory syndrome following cardiac surgery may improve microcirculation and, hence, clinical outcomes.

METHODS AND ANALYSIS

Study design

This is a monocentric, prospective, randomised study.

Study population

The inclusion criteria are as follows:

- Patients aged more than 18 years old.
- Elective cardiac surgery under CPB with an expected CPB time >90 min (double valve replacement or valve replacement plus coronary arterial bypass graft (CABG)).
- Written informed consent from patient or next of kin.

The non-inclusion criteria are as follows:

- Missing informed consent.
- Patient under 18 years old.
- Planned hypothermia <32°C during CPB.
- Emergency surgery.
- Acute infective endocarditis.
- Immunosuppressive treatment or steroids (prednisone >0.5 mg/kg/day or equivalent).
- AIDS with a CD4 count of <200/mm^3.
- Autoimmune disorder.
- Transplant recipient
- Advances chronic kidney disease (CKD 4 or 5).
- RRT in the last 90 days.
- Known allergy to study device.
- History of confirmed or suspected heparin-induced thrombocytopenia.
- Inclusion in other study within the last 30 days.
- Pregnancy.
- Coexisting illness with a high probability of death (inferior to 6 months).

Study protocol

Randomisation

Patients will be randomised into two parallel open-label group. Randomisation will be carried out using Clinsight software, implemented by a data manager. The result of randomisation will be displayed as 'standard group' or 'intervention group' (figure 1).

Intervention

In the intervention group, cardiac surgery will be conducted with the use of the oXiris membrane connected to the CPB device.

The oXiris membrane will be fitted to a dedicated Prismaflex machine (Baxter, Illinois, USA) at the maximum flow rate recommended by the pharmaceutical laboratory at a blood flow rate of 450 mL/min (figure 2). The inflow of the Prismaflex (and the Oxiris membrane) will be positioned between the venous line of CPB and the reservoir, and the outflow between the venous reservoir and the head of the CPB pump. In the standard group, cardiac surgery with CPB without the use of the oXiris membrane. The conditions for performing CPB are those usually used for this type of surgery in the Anesthesia Department of the Amiens University Hospital, and do not differ from those that would be used outside the scope of this study.

For both arms, monitoring of sublingual microcirculation, primary and second endpoints will be assessed as defined in the Data collection and outcome definitions section.

There is no provision for ancillary and post-trial care.

Standard procedures

Patients will undergo cardiac surgery as usual and usual postoperative care will be provided. CPB circuit will be primed (1000 mL crystalloid and 500 mL colloid solution together with 5000 IE heparin) in accordance with institutional guidelines. CPB will be performed by using non-pulsatile flow at 2.5 L/min/m^2, a non-heparin-coated circuit, and a membrane oxygenator (QuadroxTM, Maquet, Hirrlingen, Germany, or Capiox, Terumo, Eschborn, Germany). Blood transfusion will be performed in accordance with the Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists (STS-SCA) transfusion guidelines and administration

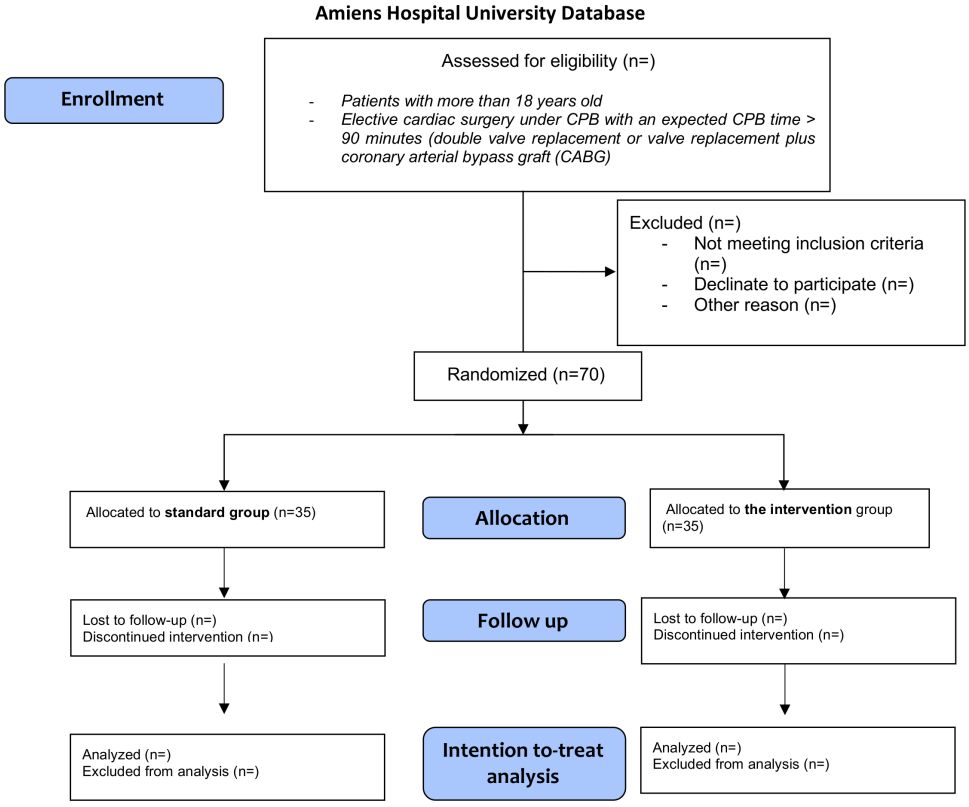

Figure 1 Consort diagram. CABG, coronary arterial bypass graft; CPB, cardiopulmonary bypass.

of coagulation factors will be based on blood samples.[13] Blood samples and all variables will be equally collected and registered in the control group with no modifications from CPB standard practice. The conduct of CPB will be standardised for the study with normothermia, haematocrit more than 20%, mean arterial pressure over 50 mm Hg using vasopressor if required.

Standard of care will be given in the ICU after cardiac surgery to all study subjects.

Especially for mechanical ventilation, nutrition, sedation, anticoagulation and blood glucose control, therapy is based on local treatment protocols. In the intensive care unit (ICU), treatment with vasopressors, inotropes and fluids is guided by haemodynamic monitoring using echocardiography to achieve a mean arterial pressure of 65 mm Hg, a cardiac index over 2.5 mL/min/m^2 and a diuresis >0.5 mL/kg/hour. All patient will have a continuous cardiac output monitoring with a transpulmonary thermodilution device (Picco, Drager). Haemodynamics timepoint assessment will be performed at ICU admission, 6 hours after, at day 1 and at day 2 after surgery.

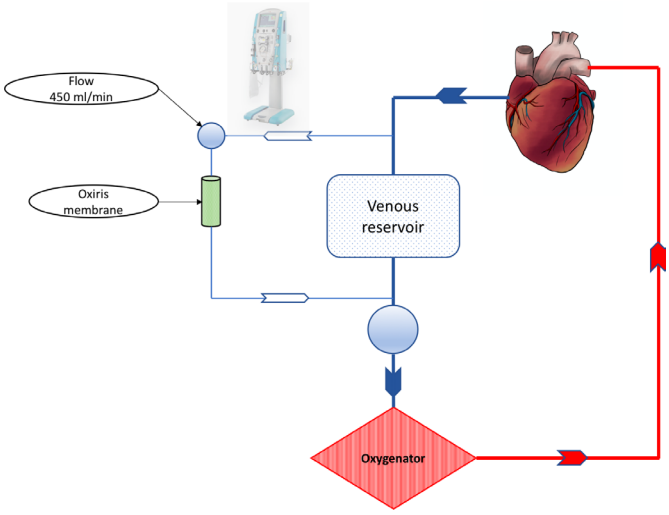

Figure 2 Insertion of the Oxiris membrane within the cardiopulmonary bypass (CPB).The Oxiris membrane will be connected to the Prismaflex.The inflow of the Prismaflex (and the Oxiris membrane) will be positioned betweenthe venous line of CPB and the reservoir, and the outflow between the venousreservoir and the head of the pump. Appendices: Informed consent given to participant and authorised surrogates.

Outcome measures

Primary endpoint

The endpoints and definitions are presented in table 1.

The primary endpoint will be the microcirculatory flow using the MFI measured by sublingual microcirculation device at day 1 following cardiac surgery.

Sublingual microcirculation will be visualised and measured using an incident dark field imaging device (Cytocam, Breadius, Amsterdam, The Netherlands) derived from the orthogonal polarised spectral imaging. Five sequences of 20 s each from different adjacent sublingual areas will be recorded. Video sequences will be analysed offline by a single rater blinded to the timepoint of

Table 1 Endpoints and definitions

Endpoints	Definitions
Primary endpoint at day 1 after cardiac surgery	
Microcirculatory flow index	Microcirculatory flow index (MFI) measured by sublingual microcirculation device (Cytocam, Braedius Medical) at day 1 following cardiac surgery. A 20 s video sequence is recorded. A grid (four quadrants) of the measurement area is made and the predominant type of flow is analysed. The flux is noted from 0 (no flow) to 3 (continuous). The MFI is the average value of each the four quadrants, giving a total score from 0 to 3. The measurement is repeated for four sublingual areas.
Secondary endpoints	
Microcirculatory flow	Before CPB, at the end of CPB and at 6, 24 and 48 hours postoperatively with the following items: ► MFI (microcirculatory flow index) ► PPV (proportion of perfused vessels) ► PVD (perfused vessel density) ► HI (heterogeneity index)
Major cardiovascular and cerebral event (MACE)	One of the following criterion (definitions above): ► Stroke ► Myocardial infarction ► Acute kidney injury ► Mesenteric ischaemia ► Successful resuscitated cardiac arrest
Stroke	An embolic, thrombotic or haemorrhagic cerebral event with persistent residual motor, sensory or cognitive dysfunction (eg, hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory) diagnosed on a cerebral scanner
Myocardial infarction	Myocardial infarction was diagnosed by the characteristics presentation, serial changes on 12-lead electrocardiographic suggesting infarction, and arise in cardiac markers, preferably cardiac troponins, with at least one value above the 99th percentile of the upper reference limit
Acute kidney injury	KDIGO guidelines Increase in serum creatinine of over 27 µmol/L within 48 hours or diuresis lower than 0.5 mL/kg/hour
Mesenteric ischaemia	Mesenteric ischaemia confirmed by imaging or exploratory laparotomy and/or ischaemic colitis confirmed by gastrointestinal endoscopy or exploratory laparotomy
Resuscitated cardiac arrest	Cessation of mechanical cardiac activity confirmed by the absence of clinical signs of blood flow
In-hospital mortality	Mortality from surgery to hospital discharge
1-month hospital mortality	Mortality after surgery until 1-month follow-up
Cumulative catecholamine use	Cumulative dose of norepinephrine and dobutamine in resuscitation during stay in mg
SOFA score	Sepsis Organ Failure Assessment
SAPS II	Simplified Acute Physiologic Score Assessment
Biomarkers of glycocalyx degradation	Before CPB, at the end of CPB then at 6, 24 and 48 hours postoperatively. ► Syndecan-1 ► Heparan-sulfate ► Hyaluronic acid Biomarkers will be assessed by ELISA test with dedicated kits.
Biomarkers of endothelial permeability	Before CPB, at the end of CPB then at 6, 24 and 48 hours postoperatively ► Angiopoietin 1 ► Angiopoietin 2 ► Soluble Tie2 receptor ► Vascular Endothelial Growth Factor (VEGF) Biomarkers will be assessed by ELISA test with dedicated kits.
Pro and anti-inflammatory cytokine	Before CPB, at the end of CPB then at 6, 24 and 48 hours postoperatively ► TNF alpha ► IL1 beta ► IL-10 ► IL-6 ► LPS ► Endothelin Biomarkers will be assessed by ELISA test with dedicated kits.

CPB, cardiopulmonary bypass; IL, interleukin; KDIGO, Kidney Disease Improving Global Outcomes; LPS, lipopolysaccharide; SAPS, Simplified Acute Physiologic Score; SOFA, Sepsis Organ Failure Assessment; TNF, tumour necrosis factor.

recording, to the study protocol, the surgical procedure and the clinical status of the patient.

MFI will be assessed manually after dividing the screen in four quadrants. According to the classification of Boerma and colleagues,[4] MFI values will be notified as follows: 0=no flow, 1=intermittent flow, 2=sluggish flow, 3=continuous flow. MFI value is the average value of the four quadrants.

Secondary endpoint

The secondary endpoints will be other microcirculatory flow variables: the perfused vessel density (PVD), the proportion of perfused vessels (PPV), the total vessel density and the De Backer score recorded by the sublingual microcirculation device (Cytocam, Breadius, Amsterdam, The Netherlands) and automatically calculated via a dedicated software (CytoCamtools software (Braedius Medical, Huizen, the Netherlands) at different timepoints: prior to CPB, at the end of CPB, 6 hours after CPB, at day 1 and at day 2.

We also aim to evaluate the occurrence within the first 30 days of major cardiovascular and cerebral events (MACE) defined as the occurrence of at least one outcome among the following: successfully resuscitated cardiac arrest, stroke, acute kidney injury, myocardial infarction, mesenteric ischaemia. Other outcomes will be in-hospital mortality and at 1 month, cumulative catecholamine use, ICU stay (days), hospital stay (days), Sepsis Organ Failure Assessment (SOFA) score and Simplified Acute Physiologic Score (SAPS) II. Several biomarkers will be measured on blood sample. Endothelium glycocalyx shedding markers (syndecan-1, heparan-sulfate and hyaluronic acid), inflammatory cytokines (tumour necrosis factor (TNF) alpha, interleukin 1 (IL1) beta, IL 10, IL 6, LPS) and endothelial permeability biomarkers (angiopoietin 1, angiopoietin 2, Tie2 soluble receptor, endothelin-1 and Vascular Endothelial Growth Factor (VEGF)) will be also evaluated.

Data collection and outcome definitions

The following data will be collected: age (years), gender, body mass index (kg/m^2), medical history (coronary disease, peripheral vascular disease, stroke, smoking, diabetes, dyslipidaemia, chronic obstructive pulmonary disease, logistic EuroSCORE,[14] hypertension, chronic kidney disease, usual medication, surgery type (valve replacement, coronary bypass graft or combined surgery), preoperative left ventricular ejection fraction, baseline haemoglobin, duration of CPB and aortic clamp, intraoperative transfusion, and cumulative dose of vasoactive drugs (dobutamine, norepinephrine, ephedrine, phenylephrine).

Before and after CPB until day 2, the following data will be collected: systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, heart rate, arterial blood gas variables (pH, PaO_2, $PaCO_2$, lactate, HCO_3), $ScVO_2$ (%), SOFA score, SAPS II score, vasoactive drug dose and biological variables (creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin time (PT), platelet, cardiac troponin, myoglobin). ICU and hospital stays (days) will be recorded. Endothelium glycocalyx shedding (syndecan-1, heparan-sulfate and hyaluronic acid), inflammatory cytokine dosage (TNF alpha, IL1 beta, IL 10, IL 6, LPS, endothelin), and endothelial permeability biomarkers (angiopoietin 1, angiopoietin 2, Tie2 soluble receptor and VEGF) will be collected before CPB, at the end of CPB, 6 hours after ending CPB, then at day 1 and day 2 after CPB.

Endpoints will be assessed after cardiac surgery. Adverse events will be declared and notified in the electronic case report forms (eCRFs).

Some secondary endpoints cannot be measured blindly and may be influenced by the treatment group. An independent observer blinded from the treatment group will be in charge of collecting data. The primary outcome and biological data will be collected blinded to the treatment group.

Standard definitions of postoperative outcomes established by the European Society of Anaesthesia were used.[15] Cardiac arrest is defined as the cessation of cardiac mechanical activity, as confirmed by the absence of circulation signs. Stroke is defined as an embolic, thrombotic or haemorrhagic cerebral event with persistent residual motor, sensory or cognitive dysfunction (eg, hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory) diagnosed on a cerebral scanner. Acute kidney injury is defined according to Kidney Disease Improving Global Outcomes (KDIGO) criteria as an increase in serum creatinine of over 27 µmol/L within 48 hours or diuresis lower than 0.5 mL/kg/hour.[16] Myocardial injury is diagnosed by the characteristics presentation, serial changes on 12-lead electrocardiographic suggesting infarction, and arise in cardiac troponin, with at least one value above the 99th percentile of the upper reference limit.[17] Mesenteric ischaemia will be confirmed by imaging or exploratory laparotomy and ischaemic colitis will be confirmed by gastrointestinal endoscopy or exploratory laparotomy.

Intention-to-treat analysis

Patients with serious adverse events will be analysed according to their assigned group following the intention-to-treat principle.

Statistical method and sample size calculation

According to a recent study, we predict a baseline mean MFI of 2.8 with an SD of 0.5.[5]

Admitting that the SD of MFI at D1 is 0.5 in both groups, we calculated a sample size of 70 patients to show a difference in MFI of 0.4 at D1 after surgery in a two-sided test with a type 1 error of 0.05 and a power of 90%. Approximately 450 cardiac surgery procedures with bypass surgery are performed per year at Amiens University Hospital. If we consider that 30% of patients will be eligible, this represents a potential inclusion of 130 patients per year. Taking into account possible non-inclusions due to

vacations and operating room closures, a total inclusion time of 7 months is expected for a total of 70 patients. Thirty-five patients in each group (standard and interventional groups).

Primary endpoint will be compared by a Student's test or Wilcoxon-Mann-Whitney test as appropriate. Secondary endpoints will be assessed using an analysis of variance test for repeated measures. MACE and mortality rate will be compared with a χ^2 test. ICU and hospital stay will be compared using a Student's test. Cumulative event curves will be estimated with the Kaplan-Meier procedure (censored at 30 days). Variables or parameters between usual and intervention groups will be compared with a Student's test, a Wilcoxon-Mann-Whitney test, a χ^2 or a Fisher's exact test as appropriate. A p value of 0.05 will be considered as significant. No intermediate analysis is planned in the trial.

Data management and monitoring

Registration

Data will be collected and registered using eCRFs by a dedicated local research technician. A research coordinator will centralise and verify the data.

Record keeping

Consent forms and eCRFs will be retained for 15 years at the University Hospital of Amiens in accordance with French law.

Study organisation

The study promotion is performed by the University Hospital of Amiens, France.

Duration and timeline

Patients from the Amiens University Hospital can be included during a 2-year period beginning from July 2020.

The processes of developing the protocol, obtaining approval from the ethical committee, obtaining financial support and developing the eCRFs occurred in 2019. The database should be closed after all participants have been included, followed by data analysis, manuscript writing and submission for publication.

Ethics and dissemination

The Institutional Review Board (IRB) of the University Hospital of Amiens (Comité de Protection des Personnes Nord-Ouest III, 80 054 Amiens, France) approved the study (Registration number ID RDB: 2019-A02437-50 in February 2020). The Oxicard study will be conducted in accordance with the Declaration of Helsinki and French law on clinical research[18] and was registered on 17 December 2019 on the ClinicalTrials.gov website with the trial identification number NCT04201119. Oxicard trial follows CONSORT (Consolidated Standards of Reporting Trials) statement—CONSORT diagram is given in figure 1.[19] Written informed consent will be obtained from all participants or next of kin.

Authors will be involved in disseminating research findings (through attending conferences and coauthoring results' papers).

Patients or public involvement

Patients or the public will not be involved in the design, or conduct, or reporting or dissemination plans of our research. Written informed consent will be obtained from all participants or next of kin.

DISCUSSION

The hypothesis is that early use (during CPB) of cytokine adsorption with the oXiris membrane in patients at high risk of vasoplegic syndrome following cardiac surgery may improve microcirculation and endothelial function.

Postoperative period following cardiac surgery is associated with an inflammatory state leading to side effects such as vasoplegia and major adverse events.[20] Clinical and experimental data support a link between inflammation with cytokine production and endothelial cell injury.[21] Microcirculatory impairment has also been observed after cardiac surgery.[8 22 23]

Despite normal macrocirculatory variables, microcirculatory dysfunction resulting in functional oxygen shunting can lead to impairment in oxygen delivery and thus to organ dysfunction and mortality.[24]

Several studies have investigated cytokine adsorption in vitro. Moreover, it has been shown that oXiris membrane reduces the concentration of cytokines after CPB and during sepsis.[9 10] However, to date, no studies have been performed on the effect of cytokine adsorption on endothelial function and microcirculation.

We hypothesise that systemic microcirculation, assessed by sublingual microcirculation, may be improved when an adsorbent membrane is used to reduce the amount of circulating cytokines.

A pilot study to evaluate the cytokine adsorption effect is an important step before carrying out a larger prospective randomised study with clinical endpoints.

Nevertheless, we will also assess MACE (stroke, acute kidney injury and myocardial infarction) in order to evaluate the impact of improved microcirculation on organ dysfunction. In the event of a positive effect, a multicentre randomised trial will be conducted using morbidity and mortality as primary endpoints.

We have privileged sublingual microcirculatory measurement at day 1 as a primary endpoint. Measurement at H6 may be difficult when the patient is awakening. Six hours after the end of CPB, some patients may still be under sedation and some may not. We will adjust the results on the patient's state of awakening in order to avoid measurement bias.

Trial status

The trial is not yet recruiting.

Acknowledgements The Oxiris trial is sponsored by Amiens Hospital University.

Contributors OA-A and PH participated in the design of the study and helped to write the manuscript. GH, GT, CB, MD, YM and MG participated in the design of the study. MD will perform the statistical analysis. HD and YM helped to write the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Shaefi S, Mittel A, Klick J, *et al*. Vasoplegia after cardiovascular Procedures-Pathophysiology and targeted therapy. *J Cardiothorac Vasc Anesth* 2018;32:1013–22.
2 Guinot P-G, Abou-Arab O, Guilbart M, *et al*. Monitoring dynamic arterial elastance as a means of decreasing the duration of norepinephrine treatment in vasoplegic syndrome following cardiac surgery: a prospective, randomized trial. *Intensive Care Med* 2017;43:643–51.
3 Laffey JG, Boylan JF, Cheng DCH. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. *Anesthesiology* 2002;97:215–52.
4 Boerma EC, Mathura KR, van der Voort PHJ, *et al*. Quantifying bedside-derived imaging of microcirculatory abnormalities in septic patients: a prospective validation study. *Crit Care* 2005;9:R601–6.
5 Bauer A, Kofler S, Thiel M, *et al*. Monitoring of the sublingual microcirculation in cardiac surgery using orthogonal polarization spectral imaging: preliminary results. *Anesthesiology* 2007;107:939–45.
6 Tanaka S, Escudier E, Hamada S, *et al*. Effect of RBC transfusion on sublingual microcirculation in hemorrhagic shock patients: a pilot study. *Crit Care Med* 2017;45:e154–60.
7 Dekker NAM, van Meurs M, van Leeuwen ALI, *et al*. Vasculotide, an angiopoietin-1 mimetic, reduces pulmonary vascular leakage and preserves microcirculatory perfusion during cardiopulmonary bypass in rats. *Br J Anaesth* 2018;121:1041–51.
8 Koning NJ, Simon LE, Asfar P, *et al*. Systemic microvascular shunting through hyperdynamic capillaries after acute physiological disturbances following cardiopulmonary bypass. *Am J Physiol Heart Circ Physiol* 2014;307:H967–75.
9 Träger K, Fritzler D, Fischer G, *et al*. Treatment of post-cardiopulmonary bypass SIRS by hemoadsorption: a case series. *Int J Artif Organs* 2016;39:141–6.
10 Turani F, Barchetta R, Falco M, *et al*. Continuous renal replacement therapy with the Adsorbing filter oXiris in septic patients: a case series. *Blood Purif* 2019;47 Suppl 3:54–8.
11 Malard B, Lambert C, Kellum JA. In vitro comparison of the adsorption of inflammatory mediators by blood purification devices. *Intensive Care Med Exp* 2018;6:12.
12 Bernardi MH, Rinoesl H, Dragosits K, *et al*. Effect of hemoadsorption during cardiopulmonary bypass surgery - a blinded, randomized, controlled pilot study using a novel adsorbent. *Crit Care* 2016;20:96.
13 Pagano D, Milojevic M, Meesters MI. EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. *Eur J Cardiothorac Surg* 2017;2018:79–111.
14 Nashef SAM, Roques F, Sharples LD, *et al*. EuroSCORE II. *Eur J Cardiothorac Surg* 2012;41:734–45.
15 Jammer I, Wickboldt N, Sander M, *et al*. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European perioperative clinical outcome (EPCO) definitions: a statement from the ESA-ESICM joint Taskforce on perioperative outcome measures. *Eur J Anaesthesiol* 2015;32:88–105.
16 Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012;120:c179–84.
17 Thygesen K, Alpert JS, Jaffe AS, *et al*. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;40:237–69.
18 Toulouse E, Masseguin C, Lafont B, *et al*. French legal approach to clinical research. *Anaesth Crit Care Pain Med* 2018;37:607–14.
19 Schulz KF, Altman DG, CONSORT MD. Statement: updated guidelines for reporting parallel group randomised trials. *J Pharmacol Pharmacother* 2010;2010:100–7.
20 Ortoleva J, Shapeton A, Vanneman M, *et al*. Vasoplegia during cardiopulmonary bypass: current literature and rescue therapy options. *J Cardiothorac Vasc Anesth* 2020;34:2766–75.
21 Pober JS, Sessa WC. Evolving functions of endothelial cells in inflammation. *Nat Rev Immunol* 2007;7:803–15.
22 Dekker NAM, Veerhoek D, Koning NJ, *et al*. Postoperative microcirculatory perfusion and endothelial glycocalyx shedding following cardiac surgery with cardiopulmonary bypass. *Anaesthesia* 2019;74:609–18.
23 De Backer D, Dubois M-J, Schmartz D, *et al*. Microcirculatory alterations in cardiac surgery: effects of cardiopulmonary bypass and anesthesia. *Ann Thorac Surg* 2009;88:1396–403.
24 Guven G, Hilty MP, Ince C. Microcirculation: physiology, pathophysiology, and clinical application. *Blood Purif* 2020;49:143–50.