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Cytokine Hemoadsorption *versus* Standard Care in Cardiac Surgery Using the Oxiris Membrane: The OXICARD Single-center Randomized Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Cardiac surgery is associated with a proinflammatory state that can lead to adverse outcomes. Hemadsorption using the AN-69 membrane (Oxiris, Baxter, USA) has been proposed to reduce inflammation and improve outcomes by chelating inflammatory cytokines.

What This Article Tells Us That Is New

- This study was a randomized trial to evaluate the Oxiris membrane during cardiopulmonary bypass in cardiac surgery patients at high risk of inflammation. Despite the theoretical benefits of the membrane, the study found no significant improvement in microcirculation, major cardiovascular events, or inflammatory biomarkers compared to standard care.

ABSTRACT

Background: Cardiac surgery can lead to dysregulation with a proinflammatory state, resulting in adverse outcomes. Hemadsorption using the AN-69 membrane (Oxiris membrane, Baxter, USA) has the properties to chelate inflammatory cytokines. The authors hypothesized that in patients at high risk of inflammation, the use of the Oxiris membrane could decrease inflammation, preserve endothelial function, and improve postoperative outcomes.

Methods: The authors conducted a randomized single-center study at Amiens University Hospital (Amiens, France). The study population consisted of adult patients admitted for scheduled cardiac surgery with an expected cardiopulmonary bypass (CPB) time greater than 90 min. The patients were allocated to either the standard group or the Oxiris group. The intervention consisted of using the Oxiris membrane on a Prismaflex device (Baxter, USA) at a blood flow rate of 450 ml/min during CPB. The primary outcome was the assessment of microcirculation on day 1 after surgery by measuring sublingual microcirculation using the microvascular flow index. Microvascular flow index reflects the microcirculation flow type and is graded from 0 to 3 as follows: 0, no flow; 1, intermittent flow; 2, sluggish flow; 3, continuous flow. The secondary outcome was a composite adverse outcome within 30 days after surgery. Cytokines and endothelial biomarkers were measured in all patients at different time points. An intention-to-treat analysis was performed.

Results: From October 2019 to November 2022, the study included 70 patients. Two patients were excluded from the Oxiris group: one patient did not undergo surgery, and one procedure was performed under deep hypothermia. The microvascular flow index did not differ between groups on day 1 from baseline: difference (95% CI) Oxiris minus standard at –0.17 (–0.44 to 0.10); $P = 0.2$. The occurrence of a composite adverse outcome did not significantly differ between groups (14 [42%] for the Oxiris group *vs.* 12 [35%] for the standard group; $P = 0.7$). The overall variation in cytokines and angiopoietins did not significantly differ between groups.

Conclusions: In patients scheduled for a cardiac surgery with prolonged CPB, the authors could not demonstrate the benefit on microcirculation and major cardiovascular events.

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Complex cardiac surgery procedures and the use of cardiopulmonary bypass (CPB) can lead to an excessive systemic inflammatory response with a release of free plasma hemoglobin, a high production of cytokines and endotoxins, increased free radical release, and activation of the complement system.[1–5] Altogether, these mechanisms can lead to a systemic inflammatory response that

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can compromise organ perfusion and increase postoperative adverse outcomes. Among the keys to improving organ outcomes in cardiac surgery, the modulation of cytokines stands out. Indeed, correlations between inflammation and microcirculation are well established, with microcirculatory flow disturbances, shedding of the glycocalyx and other endothelial biomarkers, and increased capillary leak.[6–9] The more inflammation there is, the more the microcirculation is impaired. The clinical impact of proinflammatory cytokines, notably interleukin-6, is well documented, with an association between high cytokine values and adverse outcomes.[10–12]

Beyond the proinflammatory state, patients with a dysregulated immune response are more likely to experience adverse postoperative outcomes after major surgeries.[13] In these patients, inflammation modulation response represents a perspective to improve postoperative course. Hemadsorption techniques could represent a means to improve outcomes and attenuate an excessive proinflammatory state.[14] Among hemadsorption devices, the Oxiris membrane (Baxter, USA) has the properties to chelate various molecules in the plasma, including cytokines and complement activation, as demonstrated *in vitro* studies.[15] The Oxiris membrane is an AN-69 membrane, surface-treated with polyethylenimine and grafted with heparin. These properties could allow for nonselective adsorption of all cytokines, meaning both proinflammatory and anti-inflammatory cytokines. The use of the Oxiris membrane in cardiac surgery remains undetermined so far, with no reports in cardiac surgery to our knowledge. Other hemadsorption membranes have been tested in cardiac surgery with randomized controlled trials, but without evidence of benefit to our knowledge.[16–18] These findings conflict with a recent meta-analysis reporting a reduction in 30-day mortality.[19]

Here, we hypothesized that the application of the Oxiris membrane during CPB could be beneficial for patients undergoing scheduled cardiac surgery at risk of dysregulated inflammation during CPB. We proposed that these patients could benefit from the Oxiris membrane by chelating cytokines and toxic products of CPB.

The primary objective was to improve microcirculation the day after cardiac surgery. The secondary objectives were to improve clinical outcomes, report findings, and demonstrate the *in vitro* protection of the endothelium.

Methods

Ethics and Study Design

We conducted a single-center, randomized, nonblind, 1:1 ratio, parallel, controlled trial at Amiens University Hospital (Amiens, France). The study protocol has been previously described.[20] The study protocol was approved by the institutional review board of Amiens University Hospital (registration identifier, 2019-A02437-50; accepted in February 2020). The study was conducted in accordance with French legislation on human clinical research.[21] Oral information was delivered and written consent was obtained before inclusion. The trial was registered on ClinicalTrials.gov on February 28, 2020 (registration identifier, NCT04201119).

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Population Study

The inclusion criteria were adult patients greater than 18 yr old, scheduled for cardiac surgery (aortic valve replacement, coronary artery bypass graft, mitral valve plasty or replacement, intracardiac mass removal, aortic root replacement), with an expected CPB duration greater than 90 min. The exclusion criteria were age under 18 yr old, planned hypothermia less than 32°C, emergency surgery, active endocarditis, immunosuppressive treatment or steroids (prednisone greater than 0.5 mg · kg^{-1} · d^{-1} or equivalent), human immunodeficiency virus infection with a CD4 count less than 200 mm^3, autoimmune disease, transplant recipient, advanced chronic kidney disease (stage 4 or 5), renal replacement therapy within 90 days before surgery, known allergy to the device, history of heparin-induced thrombocytopenia, and coexisting illness with a high probability of death.

Intervention

In the Oxiris group, the Oxiris membrane was fitted to a dedicated Prismaflex machine (Baxter, USA) at the maximum flow rate recommended by the pharmaceutical laboratory, with a blood flow rate of 450 ml/min. The inflow of the Prismaflex (and the Oxiris membrane) was positioned between the venous line of the 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 was performed without the use of the Oxiris membrane.

Standard Procedures in Both Groups

CPB was conducted in line with our institutional protocol. The CPB circuit was primed with a volume of 1,400 ml (1,000 ml crystalloid and 400 ml colloid solution). CPB was performed using nonpulsatile flow at 2.5 l · min^{-1} · m^{-2}, a non–heparin-coated circuit, and a membrane oxygenator (Quadrox [Maquet, Germany] or Capiox [Terumo, Germany]). The conduct of CPB was standardized for the study with normothermia (greater than 36°C), hematocrit more than 20%, pH at 7.35 to 7.45, and a mean arterial pressure between 50 and 80 mmHg according to the most recent guidelines on CPB management.[22,23] Coagulation and transfusion management were performed according to European guidelines.[24] All patients received 2 g tranexamic acid during the CPB management. Anticoagulation was performed using unfractionated heparin at 400 U/kg to achieve an activated clotting time greater than 450 seconds. Heparin was reversed after CPB weaning using protamine at 1 mg for every 100 U of the initial dose of heparin.

After surgery, all patients were admitted to a cardiac intensive care unit. Mechanical ventilation, nutrition, sedation, anticoagulation, and blood glucose control were performed according to local protocols. Hemodynamic management was standardized to achieve a cardiac index greater than 2.5 l/min, mean arterial pressure greater than 65 mmHg, and arterial lactate less than 2 mM using fluid therapy, vasopressors, and inotropic drugs.

Endpoints and Definitions

The primary endpoint was the variation in microcirculation on day 1 from baseline. Microcirculation was defined by measuring the microcirculatory flow index at the sublingual site using an incident dark field imaging device (CytoCam, Braedius Medical, The Netherlands). Microcirculatory flow index is a semiquantitative method assessing the erythrocyte velocity at the microcirculation level. As recommended by the European Society of Intensive Care Medicine (Brussels, Belgium) task force in their second consensus, five video sequences of 20 s each were recorded from four different sublingual areas for each patient.[25] According to the classification of Boerma *et al.*, microcirculatory flow index values were recorded as follows: 0, no flow; 1, intermittent flow; 2, sluggish flow; and 3, continuous flow. The microcirculatory flow index value is the average of the four quadrants.[26] In our study, an off-record assessment of microcirculatory flow index was performed by an assessor (Y.M.) blinded to the arm allocation and to other study endpoints (supplemental video, https://links.lww.com/ALN/D834).

The secondary endpoints were the assessment of other parameters of microcirculation using the incident dark field imaging device from baseline to the end of CPB, on day 1 and day 2 after surgery: proportion of perfused vessels, perfused vessel density, and total vessel density; the occurrence of a composite adverse outcome within 30 days after surgery, including stroke, and type 5 myocardial infarction based on the fourth universal definition,[27] acute kidney injury defined by an increase in serum creatinine greater than 26.5 μmol/l from baseline value,[28] mesenteric ischemia, and successful resuscitated cardiac arrest.

The other endpoints were the rate of delirium using the Confusion Assesment Method–Intensive Care Unit (CAM-ICU),[29] the postoperative cumulative dose of norepinephrine (milligrams), the comparison of day 1 Sequential Organ Failure Assessment score, the intensive care unit and hospital stays (days), and 28-d mortality.

Plasmatic Cytokines and Endothelial Biomarkers Measurement

Peripheral blood samples were collected on intensive care unit admission in EDTA-containing tubes and centrifuged within 30 min of sampling for 10 min at 1,000*g*. Plasma samples were collected and stored at –80°C until use. One anti-inflammatory cytokine (interleukin-10) and two proinflammatory cytokines (interleukin-6 second generation and tumor necrosis factor-α) were analyzed in the trial. Plasmatic levels of cytokines were analyzed in twofold diluted plasma samples using a custom Simple Plex assay panel for detection of IL-10, IL-6 second generation, and tumor necrosis factor-α second generation (kit ID, 258028,

ProteinSimple, USA) by microfluidic enzyme-linked immunosorbent assay technology on the Ella Automated Immunoassay System (Bio-Techne, USA), according to the manufacturer's instructions. The interassay and intraassay coefficients of variation for tumor necrosis factor-α and interleukin-6 were all less than 9%. We also assessed endothelial biomarkers of endothelial injury: angiopoietin-1, angiopoietin-2, and tyrosine kinase with immunoglobulin 2 (Tie2). In cardiac surgery, the dysregulation in angiopoietin is well reported with a decrease in angiopoietin-1 and an increase in both angiopoietin-2 and tyrosine kinase with immunoglobulin 2.[30] That dysregulation is associated with microcirculation disturbance with a decrease in microcirculatory flow index.[31] The same technology was used for quantitative measurement of plasmatic angiopoietin-1 (Simple Plex Human Angiopoietin-1 Cartridge, second generation, SPCKB-PS-003640), angiopoietin-2 (Simple Plex Human Angiopoietin-2 Cartridge, SPCKB-PS-000244), and tyrosine kinase with immunoglobulin 2 (Simple Plex Human Tie-2, SPCKB-PS-000532) in 10-fold diluted plasma.

Endothelial Cell Culture

Human umbilical vein endothelial cells were obtained from Promocell (Germany; pooled donors, C12203). As recommended by the manufacturer, human umbilical vein endothelial cells were grown in ECGM-2 medium containing 2.5% supplement mix (which corresponds to all media supplements; Promocell, C22011), named "complete ECGM-2 medium," under standard cell culture conditions (humidified atmosphere, 5% CO_2, 37°C). The "complete ECGM-2 medium" was changed every 2 days. Cells were passed when cell confluence reached 80 to 90%.

Cell Viability Assay

To measure the *in vitro* protective effects of Oxiris membrane on endothelium, we treated human umbilical vein endothelial cells with plasma from patients who had a CBP with or without Oxiris membrane. These plasmas were collected at baseline and at 6 h after the end of CPB. Human umbilical vein endothelial cell viability was then assessed by a colorimetric assay. In living cells, the water-soluble yellow dye is converted into an insoluble purple formazan by the action of mitochondrial reductase. Formazan is then solubilized and the concentration determined by optical density at 570 nm. Briefly, human umbilical vein endothelial cells were seeded in triplicate in a 96-well plate at 10,000 cells/well. Human umbilical vein endothelial cells were cultured in "complete ECGM-2 medium" where the 2.5% supplement mix provided by the manufacturer was replaced by 2.5% plasma from standard group patients (n = 15) or 2.5% plasma from Oxiris group patients (n = 15). The medium was removed every 2 days. After 6 days, the dye was added to each well and incubated for 2 h at 37°C. Then, cells were washed with phosphate-buffered saline and incubated with dimethyl sulfoxide at 37°C with gentle shaking for 1 h. Absorbance was measured by a microplate reader (Tecan, Switzerland) at 570 nm with a reference wavelength of 650 nm, according to the manufacturer's instructions.

Randomization

Patients were randomized in a 1:1 ratio into two parallel open-label groups, with no stratification. Randomization was conducted using Clinsight (Sweden) software, implemented by a data manager. To ensure balance between each group, random block sizes of 10 were generated.

Sample Size Calculation

Based on a previous study, the expected baseline value in cardiac surgery of microcirculatory flow index is 2.8 ± 0.5.[32] To achieve a power of 80% with an alpha risk of 5%, we estimated a sample size of 70 patients (35 per arm) to detect a difference of 0.4 in microcirculatory flow index value on day 1.

Statistical Analysis

Data were presented as median [interquartile range] or as numbers (percentage) according to the variable type. The primary analysis was performed using a predefined linear mixed model, including the arm of allocation (Oxiris or standard arm) and baseline microcirculatory flow index adjustment variable. Categorical secondary outcomes were compared between groups using a chi-square or a Fisher exact test. Repeated measures of cytokines and endothelial injury markers were compared between groups using a linear mixed model including arm, time, and an interaction between arm and time as fixed effects; the random effect concerned patient number with a random intercept. Continuous secondary outcomes were compared between groups using a Student's *t* test. An intention-to-treat analysis was performed. To account for multiple testing, *P* values for secondary endpoints were adjusted using the Hochberg method. A *P* value under 0.05 was considered significant. Statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria), version 2024.04.1 + 748.

Results

Participants and Flow Chart

From October 2019 to November 2022, 70 patients were randomized in the study (table 1 and fig. 1). After randomization, two patients in the Oxiris group were excluded: one procedure under deep hypothermia and one procedure cancellation. A total of 33 and 35 patients were analyzed, respectively, for the Oxiris and standard groups.

Briefly, patients were mainly men, with a median age of 78 yr in both groups. The main surgery type was combined surgery (respectively for the Oxiris and standard groups, 12

Table 1. Preoperative and Intraoperative Characteristics

Variables	Oxiris Group (n = 33)	Standard Group (n = 35)
Age, yr	68 [61; 71]	68 [60; 74]
Male sex, %	25 (76)	27 (77)
BMI, kg/m^2	28.0 [25.4; 30.1]	26.2 [23.3; 29.1]
Medical history, n (%)		
Smoking	4 (12)	3 (9)
Coronary disease	15 (45)	13 (37)
Hypertension	23 (70)	25 (71)
Atrial fibrillation	15 (45)	7 (20)
Diabetes	7 (21)	7 (20)
Chronic medication, n (%)		
ß Blocker	20 (61)	20 (57)
ARBs/ACEi	11 (33)	16 (46)
Aspirin	13 (39)	19 (54)
Statin	18 (55)	18 (51)
Surgery type, n (%)		
AVR	3 (9)	4 (11)
CABG	7 (21)	6 (17)
Mitral valve plasty or replacement	5 (15)	1 (3)
Aortic root	6 (18)	8 (23)
Combined	12 (36)	13 (41)
Biologic investigations		
Hemoglobin, g/dl	13.7 [12.6; 14.3]	13.3 [12.2; 14.4]
Creatinine, µmol/l	86 [72; 97]	82 [76; 89]
Albumin, g/l	37 [35; 42]	39 [35; 41]
C-reactive protein, mg/l	1 [0; 5]	1 [0; 2]
Euroscore II, %	1.19 [0.94; 1.58]	1.00 [0.76; 1.58]
Intraoperative time		
CPB time, min	127 [97; 154]	128 [97; 154]
Aortic clamp time, min	95 [71; 104]	97 [67; 124]
Fluid administration, ml	500 [500; 500]	500 [0; 1,000]
Norepinephrine use, n (%)	19 (58)	20 (61)
Dobutamine use, n (%)	7 (21)	3 (9)
Intraoperative transfusions		
RBCs, n (%)	6 (18)	9 (26)
RBC units	2 [1; 2]	4 [3; 5]
Platelets, n (%)	3 (9)	4 (11)
Platelet units	2 [2; 2]	3 [3; 4]
Fresh frozen plasma, n (%)	1 (3)	7 (20)
Fresh frozen plasma units	6 [6; 6]	2 [2; 5]
Fibrinogen, n (%)	10 (30)	14 (42)
Fibrinogen dose, g	3.2 [2.9; 4.6]	3.0 [2.8; 3.4]

Data are expressed as number (percentage) or median [interquartile range].

ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; AVR, aortic valve replacement; BMI, body mass index; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; RBC, erythrocyte.

[36%] and 13 [41%]). The median Euroscore II was 1.19% [0.94; 1.58] and 1.00% [0.76; 1.58], respectively, for the Oxiris and the standard groups. The median time of CPB was 127 min [97; 154] and 128 min [97; 154], respectively, for the Oxiris and the standard groups.

Main Endpoint

After adjustment for the baseline value of microcirculatory flow index, the increase in microcirculatory flow index induced by the Oxiris membrane was not significant between groups on day 1 after surgery: change in microcirculatory flow index at 0.17 [–0.10; 0.44]; $P = 0.20$. On day 1, microcirculatory flow index was 2.17 [1.83; 2.46] and 1.92 [1.58; 2.22], $P = 0.2$, respectively, for the Oxiris and the standard groups.

The between-group comparison in microcirculatory flow index from baseline to day 1 after surgery did not significantly differ ($P = 0.2163$). The evolution between groups is presented in figure 2.

Other parameters of sublingual microcirculation are presented in supplemental file 1 (https://links.lww.com/ALN/D835). The evolution of perfused vessel density, proportion of perfused vessels, and total vessel density did not differ between groups from baseline to day 2 after surgery.

Secondary Endpoints

Secondary endpoints are presented in table 2. Postoperative outcomes did not significantly differ between groups, notably for the rate of composite adverse outcome (42% *vs.* 35% for the Oxiris and standard groups, respectively; $P = 0.5$). We did not find a significant difference in the occurrence of delirium, the rate of postoperative atrial fibrillation, and the rate of postoperative pulmonary complications. No difference in 28-day mortality was found: one (3%) *vs.* zero (0%), respectively, for the Oxiris and standard groups ($P = 0.5$).

The cumulative dose of norepinephrine was similar between groups, with doses of 0.16 [0.11; 0.31] and 0.46 [0.23; 0.73], respectively, for the Oxiris and standard groups ($P = 0.068$).

Cytokines and Endothelial Injury

Plasma levels of tumor necrosis factor -α, IL-6, and IL-10 are presented in figure 2 and supplemental file 2 (https://links.lww.com/ALN/D836). The levels of tumor necrosis factor -α, interleukin-6, and interleukin-10 did not significantly differ from baseline to day 2 after surgery between groups.

Regarding endothelial injury, a dysregulation in angiopoietins was observed with an increase in the Ang2/Ang1 ratio; no between-group difference was found ($P = 0.3620$) as reported in figure 2 and supplemental file 3 (https://links.lww.com/ALN/D837). An endothelial injury was observed with an increase in angiopoietin-2 and a decrease in both tyrosine kinase with immunoglobulin 2 and angiopoietin-1 with no significant difference between groups as presented in figure 3 and supplemental file 3 (https://links.lww.com/ALN/D837).

Endothelial Viability

Human umbilical vein endothelial cell treatment with plasma from the Oxiris group did not show a significant protective effect on cell viability compared to treatment with plasma from the standard group as reported in figure 4.

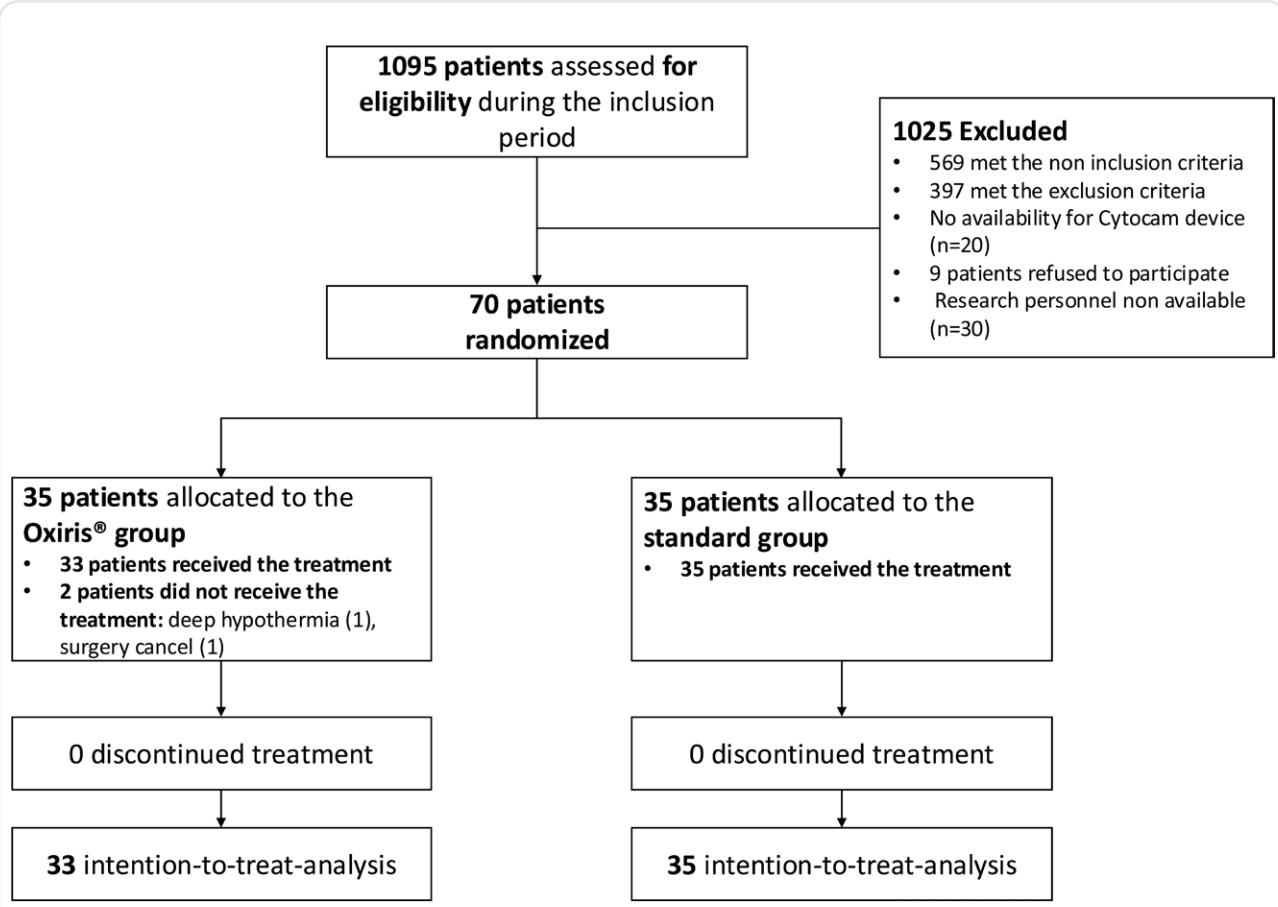

Fig. 1. Study flow chart. Cytocam device (Braedius Medical, The Netherlands); Oxiris (Baxter, USA).

Sensitivity Analysis

The effect of baseline interleukin-10, baseline tumor necrosis factor-α, erythrocyte transfusion, baseline microcirculatory flow index, and arm allocation was assessed in a mixed model effect on microcirculatory flow index variation at day 1. We did not find any statistical influence of theses variables on the variation in primary endpoint (supplemental file 4, https://links.lww.com/ALN/D838)

Discussion

In our trial assessing the use of the Oxiris membrane in scheduled cardiac surgery, we failed to demonstrate a benefit regarding the preservation of microcirculation and the prevention of adverse outcomes (table 2). The clearance of proinflammatory (interleukin-6 and tumor necrosis factor-α) or anti-inflammatory (interleukin-10) cytokines was also similar between groups. Endothelial injury could not be prevented, as reflected by the increase in angiopoietin-2 and the decrease in both tyrosine kinase with immunoglobulin 2 and angiopoietin-1. Last, the coincubation of human umbilical vein endothelial cells with plasma treated with the Oxiris membrane did not show protection in terms of human umbilical vein endothelial cell viability.

Although cardiac surgery is known to induce a proinflammatory state and a production of cytokines, evidence is lacking on the benefit of its treatment. As hypothesized, we expected to decrease the proinflammatory state related to cardiac surgery and CPB. Beyond inflammation control, we expected to improve microcirculation and postoperative outcomes. When looking at previous trials in cardiac surgery, most reported findings similar to ours, with the absence of cytokine clearance and the absence of clinical benefits.[18,33] Indeed, in two randomized trials, the authors failed to decrease cytokine levels with hemadsorption. These results could be explained by various factors: small sample size (around 30 patients) and low risk of inflammation. In our trial, we tried to compensate for these limitations with a larger sample size and by selecting patients at risk of inflammation with a long CPB time. To our knowledge, only one large randomized trial has reported efficiency in cytokine hemadsorption in cardiac surgery.[16] In the Revealing Mechanisms and Investigating Efficacy of Hemoadsorption for Prevention of Vasodilatory Shock in Cardiac Surgery Patients With Infective Endocarditis (REMOVE) trial, the authors randomized 288

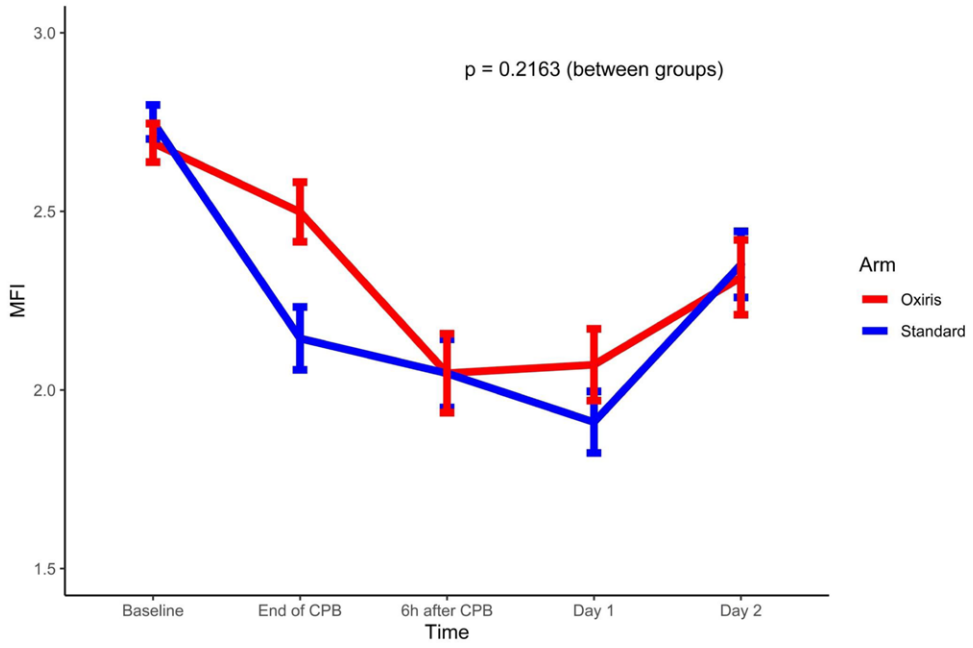

Fig. 2. Sublingual microcirculation evolution from baseline to day 2 after surgery. Oxiris (Baxter, USA). CPB, cardiopulmonary bypass; MFI, microcirculatory flow index.

Table 2. Endpoints for the Two Groups

Variables	Oxiris Group (n = 33)	Standard Group (n = 35)	Difference (95% CI)	*P* Value	Adjusted *P* Value
Primary endpoint					
MFI at day 1	2.17 [1.83; 2.46]	1.92 [1.58; 2.22]	0.16 (–0.10 to 0.43)	0.2	
Secondary endpoints					
Composite adverse outcome, n (%)	14 (42)	12 (35)	7.1 (–19 to 33)	0.5	0.9
AKI, n (%)	14 (42)	12 (35)	7.1 (–19 to 33)	0.7	0.9
Stroke, n (%)	0 (0)	2 (6)	–6 (17 to 5)	0.5	0.9
Myocardial infarction, n (%)	1 (3)	1 (3)	0 (–1 to 1)	0.9	0.9
Delirium, n (%)	1 (3)	4 (11)	–9 (–24 to 7)	0.12	0.9
POAF, n (%)	13 (39)	10 (29)	10 (–16 to 36)	0.5	0.9
PPC, n (%)	7 (21)	10 (29)	–8 (–32 to 16)	0.6	0.9
Norepinephrine, mg	0.16 [0.11; 0.31]	0.46 [0.23; 0.73]	—	0.068	0.816
Day 1 SOFA score	4 [2; 4]	3 [1; 3]	—	0.3	0.9
ICU stay, d	3 [2; 5]	3 [2; 5]	–1 (–4 to 1)	0.2	0.9
Hospital stays, d	11 [9; 15]	13 [10; 18]	–3 (–4 to 1)	0.2	0.9
28-Day mortality, n (%)	1 (3)	0 (0)	3 (–6 to 12)	0.5	0.9

Difference is the absolute difference (Oxiris minus standard group). Unless otherwise defined, data are median [interquartile range]. Oxiris (Baxter, USA).

AKI, acute kidney injury; ICU, intensive care unit; MFI, microvascular flow index; POAF, postoperative atrial fibrillation; PPC, postoperative pulmonary complication; SOFA, Sequential Organ Failure Assessment.

patients in a multicenter trial in Germany. Despite including patients at risk of inflammation (*i.e.*, endocarditis), no benefit was observed in postoperative severity or mortality, but the authors did observe decreased cytokine levels.

Nevertheless, to explain all these negative results, we believe that all these trials, including ours, share common limitations. First, the hemadsorption treatment duration might be insufficient. Indeed, treatment was limited to the CPB duration. So far, no study has assessed a prolonged time of hemadsorption during postoperative care. As shown in figure 3, the peak of cytokines is around 6 h after surgery, suggesting that the peak of inflammation is delayed from the surgical time. A study assessing the Oxiris membrane in patients with refractory cardiogenic shock is ongoing and

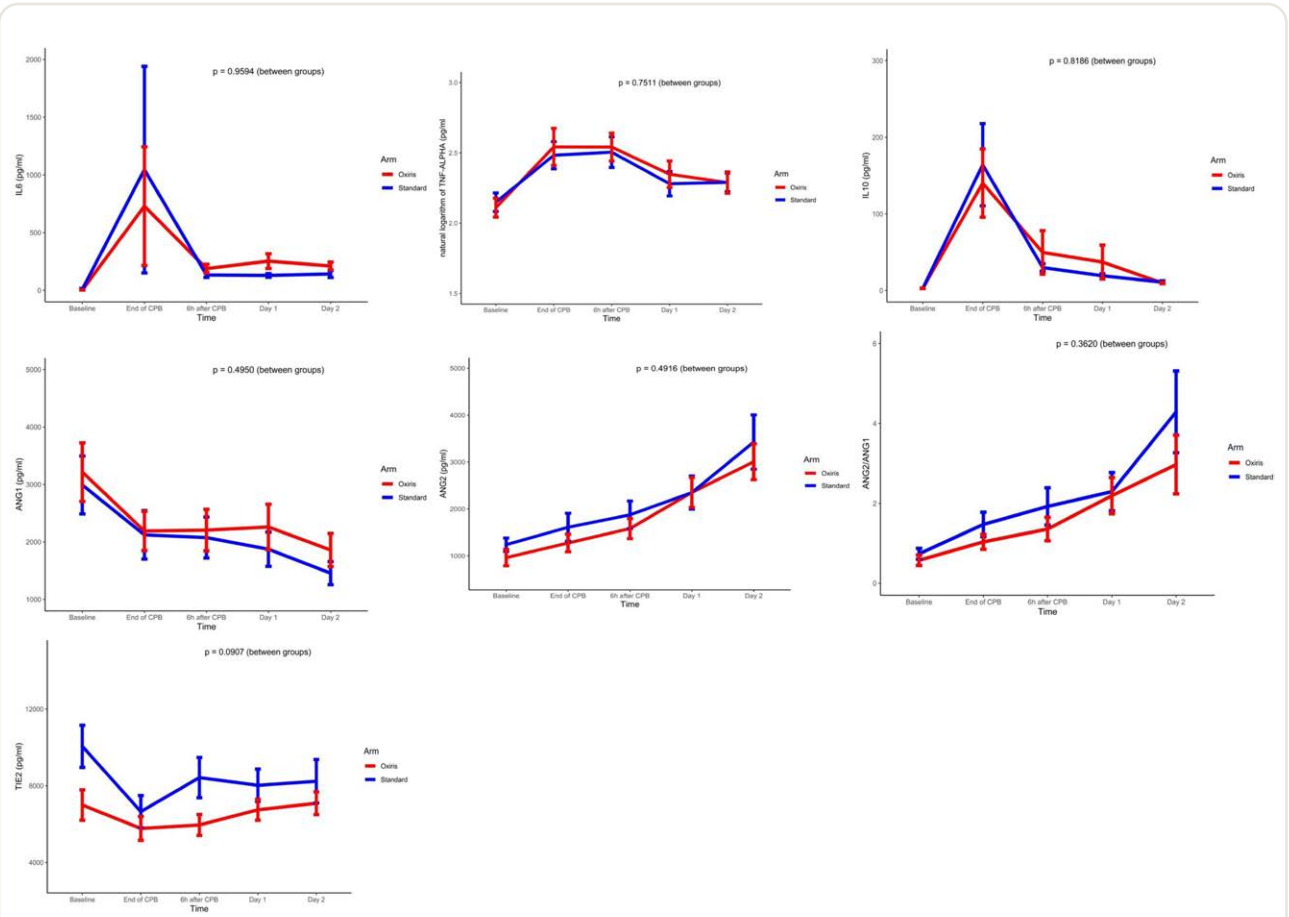

Fig. 3. Cytokines and angiopoietin levels from baseline to day 2 after surgery. Oxiris (Baxter, USA). ANG, angiopoietin; CPB, cardiopulmonary bypass; IL, interleukin; TIE, tyrosine kinase with immunoglobulin; TNF, tumor necrosis factor.

will provide answers on the hypothetical effect of prolonged treatment.[34] Second, we believe the whole blood might not have been adequately treated with the membrane. In our trial, the pump flow rate of the Oxiris membrane was set at 450 ml/min. Additionally, blood samples were collected from the patient and not from the Prismaflex device. To assess the clearance of cytokines, we should have collected blood from the arterial and venous lines of the Prismaflex device. However, we believe that clearing cytokines in the patient is more important than focusing on clearance within the Prismaflex circuit.

Regarding the cytokine levels in our trial, the real risk of inflammation is questionable. Indeed, the peak level of interleukin-6 is around 160 pg/ml, as shown in supplemental file 2 (https://links.lww.com/ALN/D836) and figure 3. When compared to the REMOVE trial, which had a peak of 400 pg/ml interleukin-6, it suggests that our population was not at as high a risk of inflammation.[16] Furthermore, when looking at other acute inflammatory states, such as acute respiratory distress syndrome, the level of interleukin-6 is greater than 1,000 pg/ml.[35] Beyond the issue of high-risk inflammation, the threshold for pathologic values of cytokines remains unknown to date. Despite various studies on the topic, no one defined threshold value. Last, apart from hemadsorption therapies, large randomized trials were conducted with others therapies to target inflammation without any benefit in comparison to standard care, leaving the issue unresolved.[36–38]

Apart from inflammation, we expected to protect the endothelium and preserve microcirculation. Most studies in cardiac surgery report an increase in angiopoietin-2 and a decrease in both angiopoietin-1 and tyrosine kinase with immunoglobulin 2.[39,40] In healthy subjects, angiopoietin-1 binds to tyrosine kinase with immunoglobulin 2 and allows the preservation of endothelial architecture.[41] During inflammation, there is an overexpression of angiopoietin-2, which binds excessively to tyrosine kinase with immunoglobulin 2, leading to the loss of endothelial architecture and an increase in capillary permeability.[42] Angiopoietin dysregulation is often associated with microcirculation disturbances.[8]

For these reasons, we assessed sublingual microcirculation. However, given the absence of cytokine clearance in our trial, we could not have expected an improvement in microcirculation.

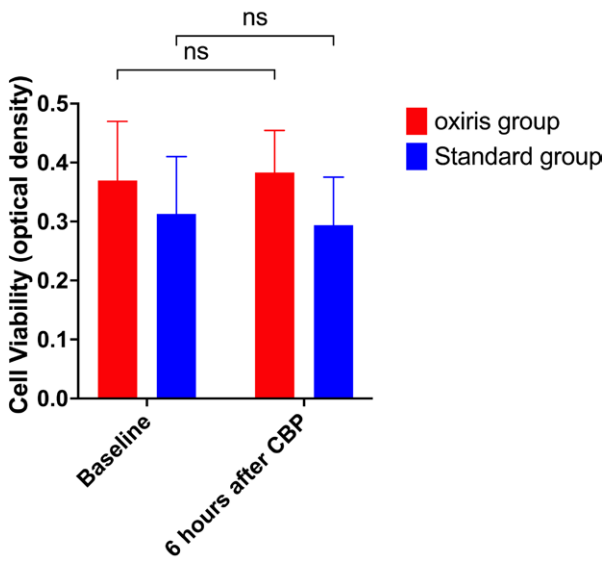

Fig. 4. Human umbilical vein endothelial cells viability at baseline and at 6 h after cardiopulmonary bypass (CPB). Coincubation with plasma from the standard group and the Oxiris (Baxter, USA) group. ns, nonsignificant.

Our trial has some limitations. As aforementioned, we believe that blood samples should have been collected from the Prismaflex arterial and venous lines just before and after the membrane. This approach would have provided a more accurate assessment of the membrane's function.

Another limitation is the absence of selection of patients at high risk of inflammation. While inflammation is expected in all patients after cardiac surgery, adverse outcomes are more likely to occur in severe proinflammatory states or when there is a dysregulation between pro- and anti-inflammatory states. This last statement is supported by a recent report that highlighted a phase of immunodepression that might occur after CPB.[43] Monitoring the expression of HLA-DR on monocytes offers the perspective to detect this immunodepression.[44]

The final limitation concerns the study power. The power is probably underpowered to adequately account for the multifactorial effects of CPB. Moreover, when considering the pooled SD of microcirculatory flow index, the value is higher than the expected value of 0.5 reported in the sample size section. Hence, caution is warranted in the interpretation of our data given that limited statistical power. We aimed to investigate endothelial function in greater depth, along with other descriptions as reported in the trial declaration on ClinicalTrials.gov. However, given the absence of study findings, we discontinued further investigations.

We believe that further trials should take into account these dysregulations in inflammation and should consider a prolonged period of hemadsorption treatment in these highly selected patients.

Conclusions

The use of the Oxiris membrane in prolonged cardiac surgery did not prevent microcirculation impairment or postoperative adverse outcomes. Further investigations should focus on patients at high risk of inflammation through cytokine monitoring.

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Competing Interests

Dr. Nguyen reports personal fees from Fresenius Kabi (Bad Homburg vor der Höhe, Germany) outside the submitted work. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: osama.abouarab@gmail.com. Raw data available at: osama.abouarab@gmail.com.

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Supplemental Digital Content

Supplemental video. Sublingual microcirculation, https://links.lww.com/ALN/D834
Supplemental file 1. Microcirculation patterns evolution from baseline to day 2 from the surgery, https://links.lww.com/ALN/D835
Supplemental file 2. Plasmatic level of interleukin-10, tumor necrosis factor-α, and interleukin-6 from baseline to day 2 after surgery, https://links.lww.com/ALN/D836
Supplemental file 3. Plasmatic levels of angiopoietin (Ang)1 and 2, the ratio Ang2/Ang1, and
tyrosine kinase with immunoglobulin (Tie) 2 from baseline to day 2 after surgery, https://links.lww.com/ALN/D837

Supplemental file 4. Determinants of microvascular flow index at day 1 using a mixed effect model, https://links.lww.com/ALN/D838

References

1. Laffey JG, Boylan JF, Cheng DCH: The systemic inflammatory response to cardiac surgery: Implications for the anesthesiologist. Anesthesiology 2002; 97:215–52
2. Wan IYP, Arifi AA, Wan S, et al.: Beating heart revascularization with or without cardiopulmonary bypass: Evaluation of inflammatory response in a prospective randomized study. J Thorac Cardiovasc Surg 2004; 127:1624–31
3. Wetz AJ, Richardt EM, Schotola H, Bauer M, Bräuer A: Haptoglobin and free haemoglobin during cardiac surgery – Is there a link to acute kidney injury? Anaesth Intensive Care 2017; 45:58–66
4. Klein DJ, Briet F, Nisenbaum R, Romaschin AD, Mazer CD: Endotoxemia related to cardiopulmonary bypass is associated with increased risk of infection after cardiac surgery: A prospective observational study. Crit Care 2011; 15:R69
5. McGuinness J, Bouchier-Hayes D, Redmond JM: Understanding the inflammatory response to cardiac surgery. Surgeon 2008; 6:162–71
6. Koning NJ, Overmars MH, van den Brom CE, et al.: Endothelial hyperpermeability after cardiac surgery with cardiopulmonary bypass as assessed using an in vitro bioassay for endothelial barrier function. Br J Anaesth 2016; 116:223–32
7. Abou-Arab O, Kamel S, Beyls C, et al.: Vasoplegia after cardiac surgery is associated with endothelial glycocalyx alterations. J Cardiothorac Vasc Anesth 2019; 34:900–5
8. Den Os MM, Van Den Brom CE, Van Leeuwen ALI, Dekker NAM: Microcirculatory perfusion disturbances following cardiopulmonary bypass: A systematic review. Crit Care 2020; 24:218
9. 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
10. Zhang WR, Garg AX, Coca SG, et al.; TRIBE-AKI Consortium: Plasma IL-6 and IL-10 concentrations predict AKI and long-term mortality in adults after cardiac surgery. J Am Soc Nephrol 2015; 26: 3123–32
11. Halter J, Steinberg J, Fink G, et al.: Evidence of systemic cytokine release in patients undergoing cardiopulmonary bypass. J Extra Corpor Technol 2005; 37:272–7
12. Puchinger J, Ryz S, Nixdorf L, et al.: Characteristics of interleukin-6 signaling in elective cardiac surgery—A prospective cohort study. J Clin Med 2022; 11:590
13. Bain CR, Myles PS, Corcoran T, Dieleman JM: Postoperative systemic inflammatory dysregulation and corticosteroids: A narrative review. Anaesthesia 2023; 78:356–70
14. Supady A, Brodie D, Wengenmayer T: Extracorporeal haemoadsorption: Does the evidence support its routine use in critical care? Lancet Respir Med 2022; 10:307–12
15. 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
16. Diab M, Lehmann T, Bothe W, et al.; REMOVE Trial Investigators: Cytokine hemoadsorption during cardiac surgery versus standard surgical care for infective endocarditis (REMOVE): Results from a multicenter randomized controlled trial. Circulation 2022; 145:959–68
17. Alarie M, Savelberg M, Vautour D, Ribeiro IB: Use of CytoSorb® hemoadsorption column during prolonged cardiopulmonary bypass in complex cardiac surgery patient. J Cardiothorac Surg 2022; 17:172
18. Poli EC, Alberio L, Bauer-Doerries A, et al.: Cytokine clearance with CytoSorb® during cardiac surgery: A pilot randomized controlled trial. Crit Care 2019; 23:108
19. Naruka V, Salmasi MY, Arjomandi Rad A, et al.: Use of cytokine filters during cardiopulmonary bypass: Systematic review and meta-analysis. Heart Lung Circ 2022; 31:1493–503
20. Abou-Arab O, Huette P, Haye G, et al.: Effect of the oXiris membrane on microcirculation after cardiac surgery under cardiopulmonary bypass: Study protocol for a randomised controlled trial (OXICARD Study). BMJ Open 2021; 11:e044424
21. Toulouse E, Lafont B, Granier S, Mcgurk G, Bazin J-E: French legal approach to patient consent in clinical research. Anaesth Crit Care Pain Med 2020; 39:883–5
22. Kunst G, Milojevic M, Boer C, et al.; Authors/Task Force Members: 2019 EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery. Br J Anaesth 2019; 123:713–57
23. Mertes P-M, Kindo M, Amour J, et al.: Guidelines on enhanced recovery after cardiac surgery under cardiopulmonary bypass or off-pump. Anaesth Crit Care Pain Med 2022; 41:101059
24. Boer C, Meesters MI, Milojevic M, et al.; Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA): 2017 EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. J Cardiothorac Vasc Anesth 2018; 32:88–120
25. Ince C, Boerma EC, Cecconi M, et al.; Cardiovascular Dynamics Section of the ESICM: Second consensus on the assessment of sublingual microcirculation

in critically ill patients: Results from a task force of the European Society of Intensive Care Medicine. Intensive Care Med 2018; 44:281–99
26. Boerma EC, Mathura KR, van der Voort PHJ, Spronk PE, Ince C: Quantifying bedside-derived imaging of microcirculatory abnormalities in septic patients: A prospective validation study. Crit Care 2005; 9:R601–606
27. Thygesen K, Alpert JS, Jaffe AS, et al.; ESC Scientific Document Group: Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019; 40:237–69
28. Kellum JA, Lameire N; KDIGO AKI Guideline Work Group: Diagnosis, evaluation, and management of acute kidney injury: A KDIGO summary (part 1). Crit Care 2013; 17:204
29. Ely EW, Margolin R, Francis J, et al.: Evaluation of delirium in critically ill patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001; 29:1370–9
30. Clajus C, Lukasz A, David S, et al.: Angiopoietin-2 is a potential mediator of endothelial barrier dysfunction following cardiopulmonary bypass. Cytokine 2012; 60:352–9
31. Dekker NAM, van Leeuwen ALI, van Strien WWJ, et al.: Microcirculatory perfusion disturbances following cardiac surgery with cardiopulmonary bypass are associated with in vitro endothelial hyperpermeability and increased angiopoietin-2 levels. Crit Care 2019; 23:117
32. Koning NJ, Vonk ABA, Meesters MI, et al.: Microcirculatory perfusion is preserved during off-pump but not on-pump cardiac surgery. J Cardiothorac Vasc Anesth 2014; 28:336–41
33. 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
34. Andrei S, Nguyen M, Berthoud V, Morgant M-C, Bouhemad B, Guinot P-G; ECMORIX Study Group: Evaluation of the Oxiris membrane in cardiogenic shock requiring extracorporeal membrane oxygenation support: Study protocol for a single center, single-blind, randomized controlled trial. Front Cardiovasc Med 2021; 8:738496
35. Sinha P, Matthay MA, Calfee CS: Is a "cytokine storm" relevant to COVID-19? JAMA Internal Med 2020; 180:1152
36. Dieleman JM, Nierich AP, Rosseel PM, et al.; Dexamethasone for Cardiac Surgery (DECS) Study Group: Intraoperative high-dose dexamethasone for cardiac surgery: A randomized controlled trial. JAMA 2012; 308:1761–7
37. Whitlock RP, Devereaux PJ, Teoh KH, et al.; SIRS Investigators: Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): A randomised, double-blind, placebo-controlled trial. Lancet 2015; 386:1243–53
38. Abbasciano RG, Roman MA, Rizzello A, et al.: Effects of interventions targeting the systemic inflammatory response to cardiac surgery on clinical outcomes in adults. Cochrane Database Syst Rev 2020
39. Abou-Arab O, Kamel S, Bar S, et al.: Changes in plasma angiopoietin levels after transcatheter aortic valve replacement and surgical aortic valve replacement: A prospective cohort study. J Cardiothorac Vasc Anesth 2021; 35:3215–22
40. Jongman RM, van Klarenbosch J, Molema G, Zijlstra JG, de Vries AJ, van Meurs M: Angiopoietin/Tie2 dysbalance is associated with acute kidney injury after cardiac surgery assisted by cardiopulmonary bypass. PLoS One 2015; 10:e0136205
41. Saharinen P, Eklund L, Alitalo K: Therapeutic targeting of the angiopoietin-TIE pathway. Nat Rev Drug Discov 2017; 16:635–61
42. Dekker NM, 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
43. Justus G, Walker C, Rosenthal L-M, Berger F, Miera O, Schmitt KRL: Immunodepression after CPB: Cytokine dynamics and clinics after pediatric cardiac surgery – A prospective trial. Cytokine 2019; 122:154018
44. Asmussen A, Busch H-J, Helbing T, et al.: Monocyte subset distribution and surface expression of HLA-DR and CD14 in patients after cardiopulmonary resuscitation. Sci Rep 2021; 11:12403