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CLINICAL TRIAL REPORT

Differential Effects of Sevoflurane and Propofol on Perioperative Glomerular Permselectivity During Cardiopulmonary Bypass: A Randomized Trial

Linya Feng[1,*], Yuyan Lin[1,*], Wei Xi[2], Qiaolin Wu[1], Feixiang Wu[1], Jianan Mao[3], Wei Gao[1], Weijian Wang[1]

[1]Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China; [2]Department of Anesthesiology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, People's Republic of China; [3]Operating Room, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wei Gao; Weijian Wang, Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China, Tel +86-577-55579098, Email 13736360269@163.com; wangweijian@wmu.edu.cn

Background: Creatinine-defined acute kidney injury does not capture early, compartment-specific renal responses to cardiopulmonary bypass (CPB). Whether anesthetic choice modulates the charge and size selectivity of the glomerular filtration barrier (GFB) remains unknown.

Methods: In this single-center randomized trial, 106 adults undergoing elective cardiac surgery with CPB were assigned 1:1 to sevoflurane-based anesthesia or propofol-based total intravenous anesthesia. The primary outcome was longitudinal urinary albumin-to-creatinine ratio (UACR). Secondary outcomes included plasma heparan sulfate (HS), syndecan-1, clearance-derived charge and size selectivity indices, and postoperative acute kidney injury.

Results: The UACR group-by-time interaction was significant (P = 0.001). Sevoflurane-to-propofol ratios were 0.785 (95% CI 0.714–0.863) 10 min after aortic unclamping, 0.826 (0.751–0.908) 1 h after surgery, and 0.779 (0.708–0.856) 24 h after surgery (all Holm-adjusted P < 0.001). Coordinated separation was also observed for HS (interaction P = 0.001), charge selectivity (P = 0.013), and size selectivity (P = 0.011). HS was associated with UACR and both selectivity indices. Postoperative acute kidney injury occurred in 13/53 (24.5%) participants receiving sevoflurane and 17/53 (32.1%) receiving propofol.

Conclusion: Sevoflurane attenuated a coordinated perioperative GFB phenotype characterized by albumin leakage, HS release, and deterioration of charge and size selectivity. Functionally resolved glomerular permselectivity may provide exploratory pharmacodynamic measures for studying renal effects of anesthetic regimens during CPB, but their measurement properties and clinical utility require further validation. Outcomes-powered trials are required to determine whether modulation of this early phenotype improves renal recovery.

Plain Language Summary: During cardiac surgery, a heart-lung machine temporarily takes over circulation. This process can disturb the kidney surface that normally prevents blood proteins from leaking into urine. Standard blood tests such as creatinine may detect kidney injury only after it has become established. We asked whether two common anesthesia approaches, sevoflurane inhalation and propofol infusion, affect this filter differently. We randomly assigned 106 adults undergoing cardiac surgery with cardiopulmonary bypass to one of the two anesthesia approaches. We measured albumin leakage into urine, a blood marker related to the vessel lining, and how well the kidney filter separated proteins according to electrical charge and molecular size. After circulation through the heart-lung machine, participants receiving sevoflurane had approximately 17–22% lower albumin leakage and smaller changes in the other barrier measurements than those receiving propofol. The study was not designed to establish a reduction in postoperative acute kidney injury. These findings show that anesthetic choice can influence an early, coordinated pattern of kidney-filter dysfunction. The measurements may help researchers evaluate perioperative renal drug effects before conventional blood tests reveal a difference, but larger trials are needed to determine whether this biological difference improves recovery.

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Keywords: albuminuria, cardiopulmonary bypass, endothelial glycocalyx, glomerular filtration barrier, propofol, sevoflurane

Introduction

Acute kidney injury (AKI) remains a frequent complication of cardiac surgery with cardiopulmonary bypass (CPB) and is associated with persistent renal dysfunction and adverse outcomes.[1–6] Creatinine-based criteria identify established AKI but provide limited resolution of the renal compartments and biological events affected during CPB.[7] An early functional phenotype that captures glomerular injury could therefore complement conventional postoperative renal outcomes.

The glomerular filtration barrier (GFB) maintains protein restriction through coordinated endothelial, basement-membrane, and podocyte properties.[8,9] CPB exposes this barrier to ischemia-reperfusion, oxidative stress, inflammation, and enzymatic degradation of the endothelial glycocalyx.[10–15] Urinary albumin-to-creatinine ratio (UACR) and circulating glycocalyx fragments can detect perioperative biological changes, but neither determines whether albumin leakage reflects impaired charge discrimination, impaired molecular-size restriction, or a coordinated loss of both functions.[10–12,16–19] This unresolved functional dimension limits mechanistic interpretation of perioperative albuminuria.

CPB also provokes a systemic inflammatory response that includes perioperative changes in IL-6 and TNF-α. These cytokines may amplify endothelial activation, oxidative stress, glycocalyx shedding, and altered glomerular permeability; their perioperative profiles were therefore evaluated as exploratory mechanistic context rather than as prespecified mediators. Experimental studies indicate that volatile anesthetics can modify glycocalyx degradation and preconditioning-related signaling during ischemia-reperfusion.[20–22] Propofol also has documented antioxidant and anti-inflammatory activity during cardiac surgery, so it should not be regarded as a biologically inert comparator.[23] In an earlier, nonoverlapping 51-patient randomized trial, our group observed less glycocalyx shedding and lower UACR with sevoflurane than with propofol during cardiac surgery.[24] That study established an anesthetic-dependent biomarker signal but did not determine whether the signal extended to the selective permeability functions of the GFB. Clearance ratios of proteins with contrasting charge and molecular size provide a means to resolve these functional axes.[9,25]

We therefore conducted a randomized trial integrating albumin permeability, glycocalyx shedding, and clearance-derived charge and size selectivity in a distinct 2023 cohort. We hypothesized that sevoflurane-based anesthesia would attenuate a coordinated perioperative GFB phenotype compared with propofol-based total intravenous anesthesia. The primary outcome was longitudinal UACR; secondary outcomes included heparan sulfate (HS), syndecan-1, charge selectivity index, size selectivity index, and postoperative AKI. By resolving glomerular permeability across complementary functional dimensions, the study tested whether anesthetic-dependent renal biological divergence emerges before conventional creatinine-based outcomes separate.

Materials and Methods

Study Design, Ethics, and Registration

This prospective, single-center, parallel-group randomized controlled trial was conducted at a tertiary university hospital in China and is reported in accordance with CONSORT. The original protocol received approval from the institutional ethics committee (approval no. 2019–081), and the revised protocol applicable to this trial was approved on April 1, 2022 (approval no. 2019–081-01) before participant recruitment. Written informed consent was obtained from all participants. The study was registered prospectively in the Chinese Clinical Trial Registry (ChiCTR2300067723) on January 19, 2023, before enrollment commenced on January 20, 2023. Recruitment continued until December 31, 2023. Patients and members of the public were not involved in the design, conduct, reporting, or dissemination planning of the trial. No changes were made to the prespecified eligibility criteria, interventions, outcomes, or analysis methods after trial commencement.

Participants

Adults between 18 and 85 years of age who were scheduled for elective cardiac surgery requiring CPB were considered eligible for inclusion. Exclusion criteria were previous cardiac surgery or planned surgery for aortic dissection; preoperative hemodynamic instability requiring continuous intravenous vasoactive support; severe hepatobiliary dysfunction (alanine aminotransferase or aspartate aminotransferase >150 U L^{-1}); preoperative renal insufficiency (serum creatinine >133 μmol L^{-1}); chronic obstructive pulmonary disease (forced expiratory volume in 1 s <0.8 L); neurologic disease or confirmed carotid artery stenosis; severe infection, defined as both a procalcitonin concentration >0.5 μg L^{-1} and a C-reactive protein concentration >8.5 mg L^{-1}; pregnancy or lactation; known allergy to sevoflurane or propofol; or inability to comply with study procedures. Sex was obtained from the medical record and summarized descriptively; the trial was not designed to test sex-specific treatment effects. The single participating site was the study hospital; interventions were delivered by credentialed anesthesiologists. No additional site or intervention-provider eligibility criteria were prespecified.

Randomization and Blinding

Participants were randomized 1:1 to sevoflurane-based inhalational anesthesia or propofol-based total intravenous anesthesia using a computer-generated permuted block sequence with a fixed block size of 4, generated by an independent statistician. Allocation was concealed using sequentially numbered, opaque, sealed envelopes. A trained investigator enrolled participants, and a second investigator opened the next envelope and assigned the intervention. Anesthesiologists could not be blinded because administration differed. Participants, postoperative intensive care physicians, laboratory personnel, and data analysts remained blinded to allocation.

Anesthetic Intervention and Perioperative Management

Anesthesia induction was performed using midazolam (0.05–0.1 mg kg^{-1}), etomidate (0.3 mg kg^{-1}), sufentanil (1.0–2.0 μg kg^{-1}), and cisatracurium besilate (0.2 mg kg^{-1}). During maintenance, patients in the sevoflurane group received 0.5–2.0 MAC of sevoflurane, whereas those in the propofol group received continuous propofol infusion at 3–8 mg kg^{-1} h^{-1}. Anesthetic depth was adjusted to maintain a bispectral index between 40 and 60.

Mean arterial pressure was maintained, whenever possible, within ±20% of baseline and at ≥65 mm Hg. Vasoactive and inotropic agents were titrated when clinically required to achieve these prespecified targets. During CPB, sevoflurane was delivered through a vaporizer and air-mixing system connected to the oxygenator, with concentration monitored at the outlet; no volatile anesthetic was given in the propofol group. Other management was standardized, including nonpulsatile CPB flow of 2.2–2.4 L min^{-1} m^{-2}, mean arterial pressure of 50–70 mm Hg during CPB, and mild-to-moderate systemic hypothermia. Both groups received propofol 0.3–3 mg kg^{-1} h^{-1} for early ICU sedation, titrated clinically and stopped when ready for ventilator weaning and extubation. Available vasoactive and inotropic exposure data comprised the highest recorded infusion rate for dobutamine, epinephrine, norepinephrine, and milrinone for each participant from anesthesia induction to completion of anesthesia; contemporaneous timestamps and cumulative doses were not available. We therefore reported each agent's use and maximum recorded rate and calculated a component-based VIS summary as dobutamine + 100 × epinephrine + 100 × norepinephrine + 10 × milrinone, with rates in μg kg^{-1} min^{-1}. Because the component maxima need not have occurred simultaneously, this summary was not interpreted as an instantaneous same-time VIS or cumulative exposure. Allogeneic transfusion variables included platelets (U), fresh frozen plasma (mL), and suspended red blood cells (U). In the final analytic dataset, participants recorded as not receiving a product were coded as zero; no missing values remained in these three fields. Routine intraoperative cell salvage and autologous red-cell reinfusion were used in all participants and were not included in the allogeneic transfusion analyses. Vasoactive-inotropic therapy and allogeneic transfusion were administered according to intra-anesthetic clinical requirements.

Sampling and Laboratory Measurements

Venous blood and urine were collected before induction (T1), before aortic cross-clamping (T2), 10 min after removal of the ascending aortic cross-clamp (T3), 1 h after surgery (T4), and 24 h after surgery (T5). Urine was aspirated from the urinary catheter sampling port after brief drainage of retained urine and short reclamping. Samples were immediately processed, divided into aliquots, and stored at −80 °C until analysis. Plasma syndecan-1 (Sdc-1) and heparan sulfate (HS) were measured using human ELISA kits (Sdc-1/CD138: catalog no. ab46506, Abcam, Cambridge, UK; HS: catalog no. CSB-E09585h, CUSABIO, Wuhan Huamei Biotech Co., Ltd., Wuhan, China). Plasma and urinary IgG, IgA, and transferrin were measured using the corresponding human ELISA kits (IgG: catalog no. CSB-E07979h, CUSABIO; IgA: catalog no. ab196263, Abcam; transferrin: catalog no. CSB-E13093h, CUSABIO). ELISA assays were performed following the manufacturers' protocols by laboratory personnel who were unaware of treatment assignment. Urinary albumin was measured by immunoturbidimetry on an AU5800 automated clinical chemistry analyzer using the Urine/CSF Albumin Reagent (catalog no. B38858) and Urine/CSF Albumin Calibrator (catalog no. B38859; Beckman Coulter, Brea, CA, USA). Manufacturer-reported AU5800 performance for urine included an analytical range of 7–450 mg/L, a limit of detection of 0.7 mg/L, a limit of quantification of 7 mg/L, repeatability CVs of 0.6%–1.4%, and within-laboratory CVs of 2.1%–4.3%; these values are not presented as local validation estimates. Urinary creatinine was measured on the same analyzer by an enzymatic sarcosine oxidase method using Creatinine (Enzymatic) reagent OSR61204 and Urine Calibrator B64606 (Beckman Coulter, Brea, CA, USA). The manufacturer-stated urine analytical range was 88–44,200 μmol/L (1–500 mg/dL). The instructions for use reported a urine detection limit of 13.9 μmol/L on the AU640 and within-run CVs of 1.1–1.6% and total CVs of 2.2% in AU2700 precision studies; these cross-platform manufacturer data are not presented as local AU5800 validation. A separate urinary creatinine limit of quantification was not stated. UACR was calculated from matched urinary albumin and urinary creatinine concentrations. Separately, blood samples for IL-6 and TNF-α measurement were collected after anesthesia induction, 10 min after initiation of CPB, and 1 h after surgery. IL-6 and TNF-α were quantified using the Human Th1/Th2 Subset Detection Kit (lot no. 20200701; flow-cytometric fluorescence assay; Jiangxi Saiji Biotechnology Co., Ltd., Nanchang, China; medical-device registration certificate no. 赣械注准 20222400225) on a BD FACSCanto II flow cytometer (BD Biosciences, San Jose, CA, USA). The assay used cytokine-specific antibody-coated fluorescent capture microspheres and PE-labeled detection antibodies in a double-antibody sandwich format. For both cytokines, the kit documentation reported a detection limit no greater than 2.5 pg/mL, a linear range of 2.5–2500 pg/mL ($r \geq 0.99$), and repeatability and between-lot CVs no greater than 15%; it did not state a catalog number or an independent limit of quantification. These are manufacturer-reported characteristics, not local validation estimates. Results were retrieved from the hospital electronic medical record and laboratory information system.

GFB Indices and Outcomes

Relative protein clearance was calculated as: Rprotein = Uprotein/Pprotein. The charge selectivity index (CSI) was calculated as: RIgA/RIgG = (UIgA/PIgA)/(UIgG/PIgG), and the size selectivity index (SSI) was calculated as: RIgG/RTf = (UIgG/PIgG)/(UTf/PTf).

An increase in CSI reflects impaired charge selectivity, whereas an increase in SSI reflects impaired size selectivity. These clearance-based parameters provide functional assessments of glomerular barrier properties but do not directly represent structural alterations of the filtration barrier.

The primary outcome was the longitudinal perioperative change in urinary albumin-to-creatinine ratio (UACR). Secondary outcomes included longitudinal changes in HS, Sdc-1, CSI, SSI, and postoperative AKI.

Postoperative AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine criteria. The most recent stable preoperative creatinine value was used as baseline, and the highest creatinine values recorded within 48 h and 7 days after surgery were used for diagnosis and staging.

Exploratory outcomes included creatinine-based estimated glomerular filtration rate (eGFR), plasma interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and longitudinal associations among glycocalyx biomarkers, GFB indices, and UACR. Major perioperative adverse events were assessed as safety outcomes.

Statistical Analysis

Sample size estimation was based on the primary endpoint, longitudinal UACR measured at five perioperative time points.

Pilot data informed a gamma generalized linear mixed-effects model with log link, fixed effects for group, time, and their interaction, and a participant random intercept. Estimated coefficients, random-intercept variance, and dispersion were used in parametric Monte Carlo simulations. For each sample size, 1,000 datasets were generated and analyzed using the same model; power was the proportion with a significant interaction at two-sided $\alpha = 0.05$.

Simulations indicated 48 participants per group for approximately 80% power. Allowing 10% attrition or unavailable serial samples, 106 participants (53 per group) were planned. Analyses followed the intention-to-treat principle. Because all participants received their assigned intervention, completed follow-up, and had no missing outcomes or major protocol deviations, intention-to-treat, per-protocol, and safety populations were identical. No interim analysis or formal stopping guideline was planned.

Longitudinal outcomes, including UACR, HS, Sdc-1, CSI, and SSI, were analyzed using generalized linear mixed-effects models. Treatment group, time, and group-by-time interaction were treated as fixed effects, and participant was included as a random intercept.

Results were expressed as estimated marginal means, geometric mean ratios, and 95% confidence intervals (CIs). Prespecified comparisons at individual time points were adjusted for multiple testing using the Holm procedure.

To assess the robustness of the longitudinal findings to clinically relevant baseline imbalances, we performed post hoc sensitivity analyses. First, the primary Gamma mixed-effects models across T1–T5 were additionally adjusted for hypertension, diabetes mellitus, and preoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use. Second, to account for the corresponding baseline outcome value without including T1 simultaneously as both an outcome and a covariate, complementary models were restricted to T2–T5 and additionally adjusted for the corresponding natural-log-transformed T1 value (baseline UACR for the UACR model and the respective baseline measure for HS, Sdc-1, CSI, and SSI), together with hypertension, diabetes mellitus, and preoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use. Both sensitivity-model sets included group, time, and group-by-time interaction as fixed effects and a participant-specific random intercept. Adjusted time-specific contrasts were summarized as sevoflurane-to-propofol geometric mean ratios with 95% confidence intervals; P values for time-specific comparisons were adjusted using the Holm method.

Because plasma glycocalyx marker concentrations may be influenced by renal function and CPB exposure,[26–28] sensitivity analyses incorporated baseline serum creatinine as an additional covariate in HS and Sdc-1 models and repeated analyses after excluding participants who developed postoperative AKI.

Exploratory creatinine-based eGFR was calculated using the 2021 CKD-EPI equation[29] and analyzed longitudinally on the natural-log scale. IL-6 and TNF-α were natural-log-transformed and analyzed using linear mixed-effects models with group, time, and their interaction as fixed effects and participant as a random intercept. All recorded cytokine concentrations were above 2.5 pg/mL, and no zero or low-value substitution was required before transformation. Longitudinal associations of HS and Sdc-1 with CSI, SSI, and natural-log-transformed UACR were evaluated using analogous models with biomarker concentration and time as fixed effects. These exploratory analyses were not adjusted for multiplicity.

Because the sampling schedules for cytokines and barrier-related measures differed at other perioperative stages, exploratory cytokine-barrier association analyses were restricted to the nominally matched 1-h postoperative time point. Participant-level collection timestamps were not present in the analytic dataset, so exact temporal pairing was not assumed. Natural-log-transformed IL-6 and TNF-α were each evaluated in separate linear regression models with natural-log-transformed HS, Sdc-1, UACR, CSI, or SSI as the dependent variable. Each model was adjusted for treatment group. Unadjusted Spearman correlation coefficients were additionally reported descriptively. The 10 association tests were considered one exploratory family, and P values from the group-adjusted regression models were adjusted using the Benjamini–Hochberg false-discovery-rate procedure.

Model assumptions were assessed using DHARMa. Statistical analyses were performed using R version 4.2.2 with the glmmTMB, emmeans, lme4, lmerTest, and DHARMa packages. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Participant Flow, Baseline Characteristics, and Intra-Anesthetic Management

Among 114 patients screened for eligibility, 8 were excluded (2 because of ineligibility and 6 because of refusal to participate). The remaining 106 participants underwent randomization, with 53 assigned to the sevoflurane group and 53 assigned to the propofol group. All participants received the allocated intervention and completed follow-up with prespecified sample collection. No missing outcome data or major protocol deviations occurred (Figure 1). Baseline and perioperative characteristics are summarized in Table 1. Recruitment ended after the planned sample size had been enrolled. Available vasoactive-inotropic records showed support in 7 of 53 participants (13.2%) in the propofol group and 13 of 53 (24.5%) in the sevoflurane group. The component-based VIS summary was 0 (IQR 0–0) in both full groups because most participants received no support; among exposed participants, the median (range) was 5.0 (3.0–11.0) and 5.0 (2.0–14.0), respectively. Drug-specific use and maximum recorded rates are reported in Table 1. These values describe the available maximum-rate data and do not represent cumulative doses or necessarily simultaneous infusion rates. Any allogeneic blood product transfusion was recorded in 4 of 53 participants (7.5%) in the propofol group and 5 of 53 (9.4%) in the sevoflurane group. Component-specific allogeneic transfusion volumes were low.

Anesthetic-Dependent Perioperative Albumin Permeability

The UACR trajectory differed between anesthetic groups (group-by-time interaction, $P = 0.001$). Before aortic cross-clamping, the sevoflurane-to-propofol ratio was 0.908 (95% CI 0.826–0.999; Holm-adjusted $P = 0.095$). Between-group separation emerged after aortic unclamping and persisted through 24 h: the ratios were 0.785 (95% CI 0.714–0.863; $P < 0.001$) at T3, 0.826 (0.751–0.908; $P < 0.001$) at T4, and 0.779 (0.708–0.856; $P < 0.001$) at T5 (Figure 2).

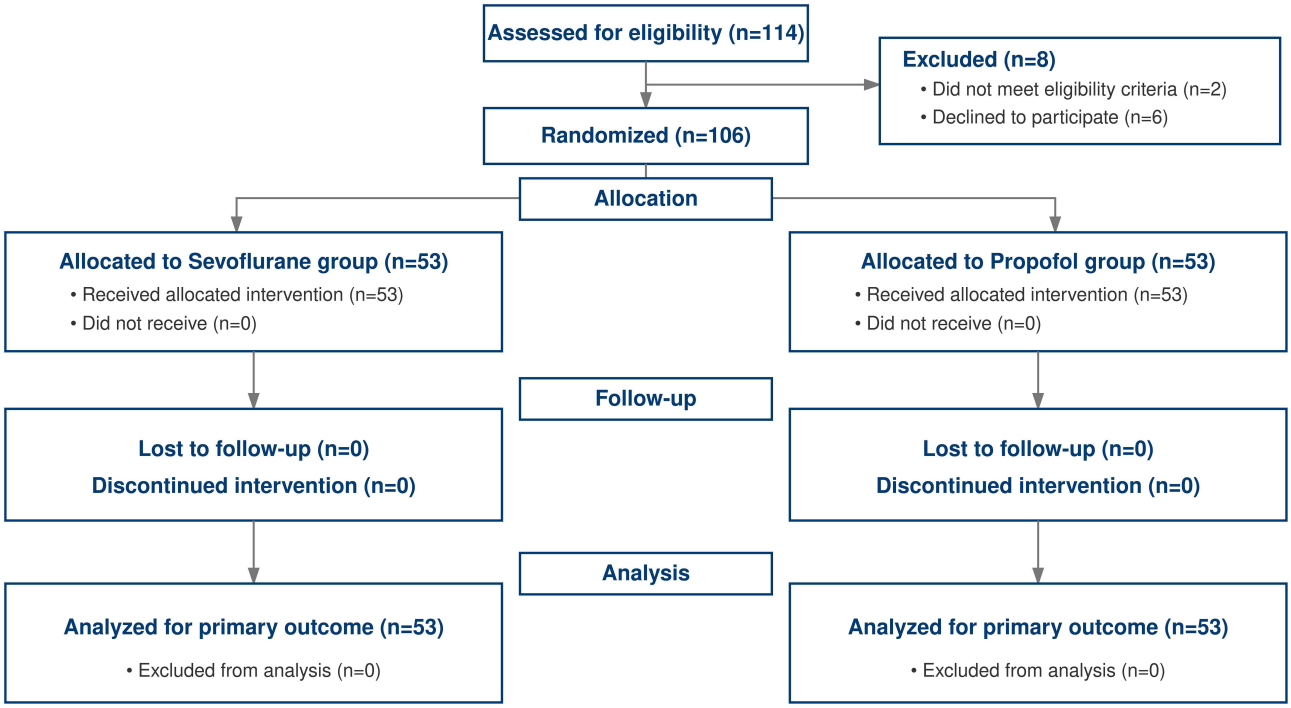


Figure 1 CONSORT participant flow diagram. Of 114 patients assessed, 106 were randomized equally to sevoflurane or propofol; all received the assigned intervention and were included in the primary analysis.

Table 1 Baseline Characteristics and Perioperative Variables

Characteristic	Propofol Group (n = 53)	Sevoflurane Group (n = 53)
Age, years	65 (56–70)	66 (61–70)
Female sex, n (%)	24 (45.3)	32 (60.4)
ASA physical status, n (%)		
II	21 (39.6)	15 (28.3)
III	28 (52.8)	32 (60.4)
IV	4 (7.5)	6 (11.3)
Type of surgery, n (%)		
Coronary artery bypass grafting	8 (15.1)	11 (20.8)
Valve surgery	45 (84.9)	42 (79.2)
Body mass index, kg m^{-2}	24.0 (22.0–26.2)	23.0 (20.6–25.2)
Hypertension, n (%)	20 (37.7)	29 (54.7)
Diabetes, n (%)	7 (13.2)	11 (20.8)
Diuretic use, n (%)	8 (15.1)	5 (9.4)
Calcium channel blocker use, n (%)	5 (9.4)	12 (22.6)
β-blocker use, n (%)	9 (17.0)	10 (18.9)
ACE inhibitor or ARB use, n (%)	13 (24.5)	8 (15.1)
Operation time, min	330 (270–378)	320 (276–360)
Anesthesia time, min	426 (360–480)	408 (372–480)
Aortic cross-clamp time, min	114 (98–142)	106 (90–130)
Cardiopulmonary bypass time, min	143 (122–173)	135 (112–165)
Area under |ΔMAP|-time curve, mm Hg·min	2977.7 (654.0)	3112.2 (582.2)
Baseline serum creatinine, μmol L^{-1}	70 (57–81)	70 (59–91)
Intraoperative fluid volume, mL	1697 (1390–1795)	1582 (1220–1814)
Baseline UACR, mg g^{-1}	20.2 (17.3–25.0)	19.3 (16.4–23.0)
Any vasoactive/inotropic support, n (%)	7 (13.2)	13 (24.5)
Dobutamine use, n (%); maximum recorded rate among exposed, median (range), μg kg^{-1} min^{-1}	2 (3.8); 4.0 (3.0–5.0)	7 (13.2); 3.0 (2.0–5.0)
Epinephrine use, n (%); maximum recorded rate among exposed, median (range), μg kg^{-1} min^{-1}	3 (5.7); 0.060 (0.060–0.060)	4 (7.5); 0.100 (0.050–0.140)
Norepinephrine use, n (%); maximum recorded rate among exposed, median (range), μg kg^{-1} min^{-1}	1 (1.9); 0.020 (0.020–0.020)	2 (3.8); 0.050 (0.040–0.060)
Milrinone use, n (%); maximum recorded rate among exposed, median (range), μg kg^{-1} min^{-1}	4 (7.5); 0.500 (0.500–0.500)	2 (3.8); 0.275 (0.050–0.500)
Component-based VIS summary, all participants	0 (0–0)	0 (0–0)
Component-based VIS summary among exposed, median (range)	5.0 (3.0–11.0)	5.0 (2.0–14.0)
Platelet transfusion, n (%)	2 (3.8)	1 (1.9)
Platelet transfusion, U	0 (0–0)	0 (0–0)
Fresh frozen plasma transfusion, n (%)	4 (7.5)	4 (7.5)

(*Continued*)

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Table 1 (Continued).

Characteristic	Propofol Group (n = 53)	Sevoflurane Group (n = 53)
Fresh frozen plasma transfusion, mL	0 (0–0)	0 (0–0)
Suspended red blood cell transfusion, n (%)	3 (5.7)	4 (7.5)
Suspended red blood cell transfusion, U	0 (0–0)	0 (0–0)
Any allogeneic blood product transfusion, n (%)	4 (7.5)	5 (9.4)

Notes: Data are presented as median (interquartile range), mean (SD), or n (%), except that drug-specific maximum recorded rates and the component-based VIS summary among exposed participants are median (range). Baseline variables are descriptive and were not subjected to hypothesis testing. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, American Society of Anesthesiologists; MAP, mean arterial pressure; UACR, urinary albumin-to-creatinine ratio; VIS, vasoactive-inotropic score. The area under the absolute ΔMAP-time curve was calculated by the trapezoidal rule from absolute deviations of MAP from the mean MAP recorded at 10-s intervals. Baseline serum creatinine and UACR were measured before anesthesia induction. Available vasoactive-inotropic records contained one maximum infusion rate per agent during anesthesia. The component-based VIS summary was calculated as dobutamine + 100 × epinephrine + 100 × norepinephrine + 10 × milrinone, with rates in μg/kg/min. Component maxima were not assumed to be contemporaneous, and cumulative doses were unavailable. Platelet transfusion is reported in units, fresh frozen plasma in mL, and suspended red blood cell transfusion in units. All participants received routine intraoperative cell salvage and autologous red-cell reinfusion; autologous blood was not included in the allogeneic transfusion variables.

Glycocalyx Shedding and the Barrier Phenotype

HS showed an anesthetic-dependent longitudinal pattern that paralleled UACR (interaction P = 0.001). Sevoflurane-to-propofol ratios were 1.032 (95% CI 0.914–1.164; Holm-adjusted P = 0.612) at T2, 0.852 (0.755–0.961; P = 0.009) at T3, 0.807 (0.715–0.910; P < 0.001) at T4, and 0.808 (0.716–0.911; P < 0.001) at T5. The Sdc-1 interaction was not significant (P = 0.078); time-specific comparisons were lower with sevoflurane at T4 (ratio 0.831, 95% CI 0.742–0.930; P = 0.001) and T5 (0.847, 0.756–0.949; P = 0.004) and were interpreted in the context of the nonsignificant global interaction (Figure 3).

Charge and Size Selectivity of the GFB

Both functional axes of glomerular permselectivity separated during reperfusion. Group-by-time interactions were significant for charge selectivity index (CSI; P = 0.013) and size selectivity index (SSI; P = 0.011). CSI was lower

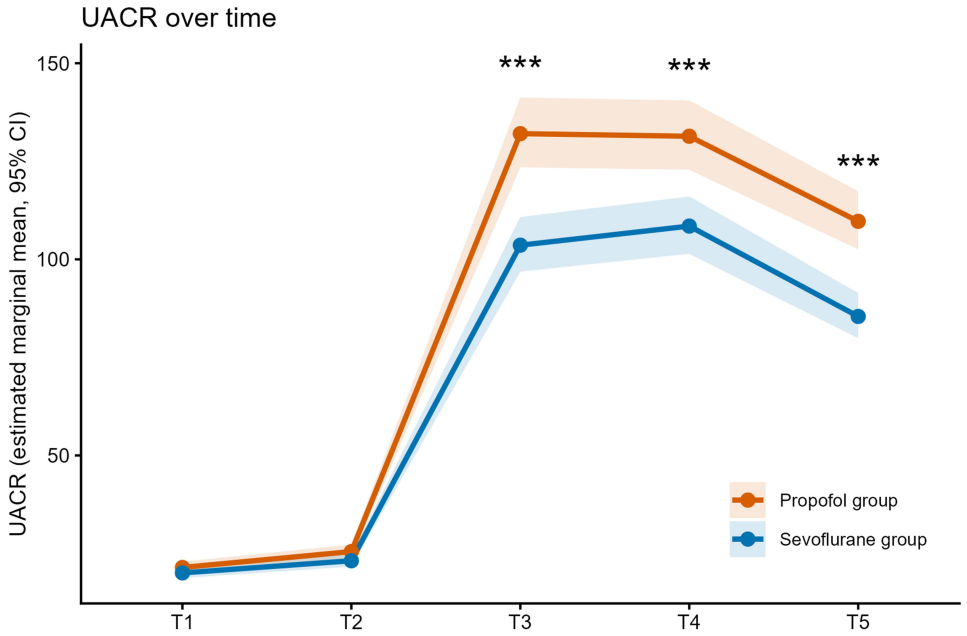


Figure 2 Longitudinal perioperative urinary albumin-to-creatinine ratio (UACR). Points and shaded bands are estimated marginal means and 95% confidence intervals from a generalized linear mixed-effects model with gamma distribution and log link. The model included group, time, and group-by-time interaction as fixed effects and participant as a random intercept. Asterisks denote Holm-adjusted between-group comparisons at each time point (***P < 0.001). T1, before induction; T2, before aortic cross-clamping; T3, 10 min after removal of the ascending aortic cross-clamp; T4, 1 h after surgery; T5, 24 h after surgery.

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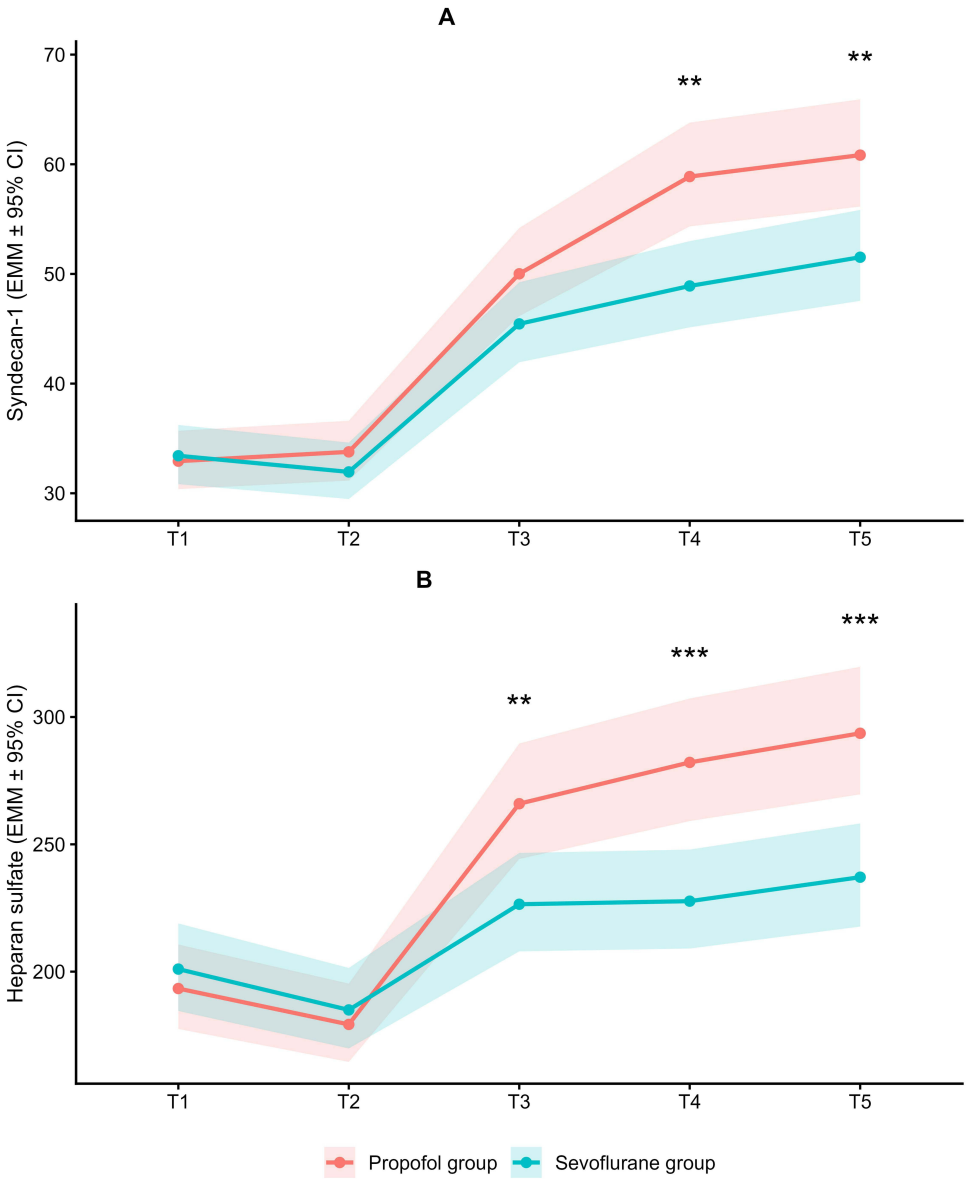


Figure 3 Longitudinal plasma glycocalyx markers: (**A**) syndecan-1 and (**B**) heparan sulfate. Points and shaded bands are estimated marginal means and 95% confidence intervals from generalized linear mixed-effects models. Asterisks denote Holm-adjusted between-group comparisons (**P < 0.01; ***P < 0.001). The syndecan-1 global group-by-time interaction was not significant (P = 0.078), whereas the heparan sulfate interaction was significant (P = 0.001). T1, before induction; T2, before aortic cross-clamping; T3, 10 min after removal of the ascending aortic cross-clamp; T4, 1 h after surgery; T5, 24 h after surgery.

with sevoflurane at T3 (ratio 0.730, 95% CI 0.612–0.870; Holm-adjusted P = 0.002), T4 (0.800, 0.671–0.954; P = 0.038), and T5 (0.774, 0.649–0.922; P = 0.017). SSI was likewise lower at T3 (0.711, 0.573–0.883; P = 0.010), T4 (0.724, 0.583–0.899; P = 0.011), and T5 (0.718, 0.578–0.892; P = 0.011) (Figure 4).

Integrated Barrier Phenotype and Robustness Analyses

The HS interaction remained significant after adjustment for baseline serum creatinine (P = 0.001) and after exclusion of participants with postoperative AKI (P = 0.012). Corresponding Sdc-1 interactions remained nonsignificant (P = 0.080 and P = 0.157, respectively) (Supplementary Table S1). The biomarker and functional components of the barrier phenotype were directionally coherent. In exploratory mixed-effects models, HS was positively associated with CSI, SSI, and log-transformed UACR, whereas Sdc-1 was associated with SSI but not CSI or log-transformed UACR (Supplementary Table S2). These association analyses were not adjusted for multiplicity. Creatinine-based eGFR

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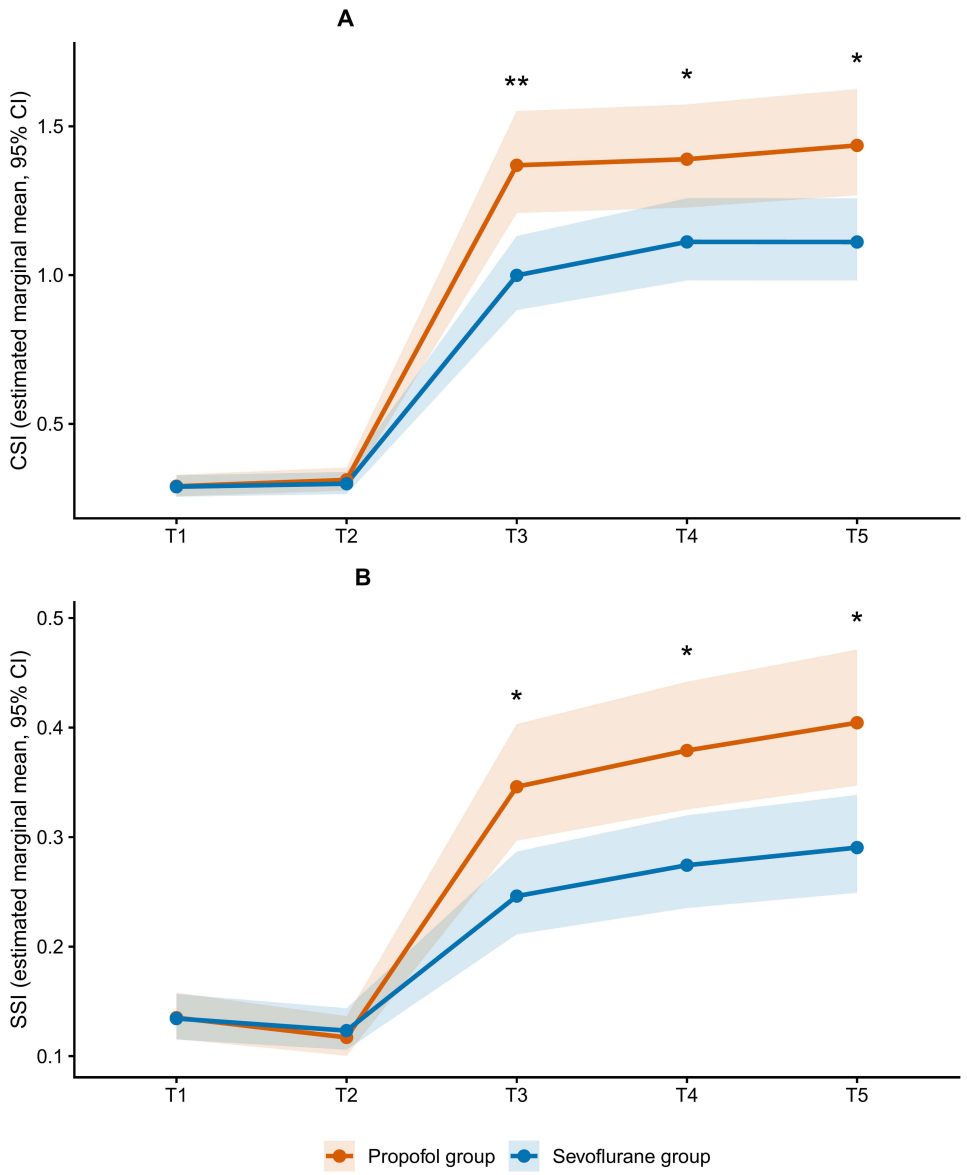


Figure 4 Functional glomerular filtration barrier indices: (**A**) charge selectivity index (CSI) and (**B**) size selectivity index (SSI). Higher values indicate greater impairment. Points and shaded bands are estimated marginal means and 95% confidence intervals from generalized linear mixed-effects models. Asterisks denote Holm-adjusted between-group comparisons (*P < 0.05; **P < 0.01). T1, before induction; T2, before aortic cross-clamping; T3, 10 min after removal of the ascending aortic cross-clamp; T4, 1 h after surgery; T5, 24 h after surgery.

decreased postoperatively in both groups without differential longitudinal trajectories (interaction P = 0.291) (Supplementary Table S3). IL-6 and TNF-α changed over time but did not differ longitudinally between groups (interaction P = 0.546 and P = 0.342, respectively) (Supplementary Table S4).

To assess the robustness of the longitudinal findings to clinically relevant baseline imbalances, we performed post hoc sensitivity analyses. In models across T1–T5 adjusted for hypertension, diabetes mellitus, and preoperative angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, the group-by-time interactions remained significant for UACR (P = 0.00139), HS (P = 0.000982), CSI (P = 0.0119), and SSI (P = 0.0113), but not for Sdc-1 (P = 0.0813). In complementary models restricted to T2–T5 and additionally adjusted for the corresponding log-transformed T1 value, the interactions likewise remained significant for UACR (P = 0.0115), HS (P = 0.00127), CSI (P = 0.0472), and SSI (P = 0.00307), whereas the overall Sdc-1 interaction was not significant (P = 0.195). At T3, the adjusted sevoflurane-to-propofol geometric mean ratios were 0.796 (95% CI 0.731–0.867) for UACR, 0.838 (95% CI 0.750–0.936) for HS, 0.708

Table 2 Postoperative Clinical and Safety Outcomes

Outcome	Propofol Group (n = 53)	Sevoflurane Group (n = 53)	P value
Acute kidney injury, n (%)	17 (32.1)	13 (24.5)	0.518
Mechanical ventilation >24 h, n (%)	7 (13.2)	8 (15.1)	1.000
Mechanical ventilation duration, h	19.0 (18.0–23.0)	20.0 (18.0–23.0)	0.939
Adverse respiratory events, n (%)	10 (18.9)	7 (13.2)	0.597
Adverse cardiovascular events, n (%)	19 (35.8)	20 (37.7)	1.000
Intensive care stay, h	78.0 (63.0–91.0)	67.0 (44.0–92.0)	0.569
Hospital stay, days	24.0 (17.0–27.0)	22.0 (19.0–29.0)	0.867

Notes: Data are median (interquartile range) or n (%). Continuous outcomes were compared with the Wilcoxon rank-sum test; categorical outcomes used Pearson χ^2 or Fisher exact tests as appropriate. The AKI absolute risk difference was −7.5% (95% CI −24.6% to 9.5%) and risk ratio was 0.76 (95% CI 0.41–1.41). Adverse respiratory events included pulmonary infection, imaging-confirmed atelectasis, apnea ≥20 s, respiratory rate <8 min^{-1} for ≥1 min, or SpO_2 <90% for ≥10 s requiring intervention. Adverse cardiovascular events included treated arrhythmia, bradycardia, tachycardia, hypotension, or hypertension during intensive care; only the first event in each category was counted per participant.

(95% CI 0.602–0.834) for CSI, and 0.707 (95% CI 0.580–0.862) for SSI. All models included 106 participants and converged successfully, with positive-definite Hessian matrices and optimizer convergence codes of 0. Complete adjusted estimates are provided in Supplementary Table S5.

To address the nonidentical sampling schedules across perioperative stages, exploratory association analyses were restricted to the nominally matched 1-h postoperative time point. After adjustment for treatment group, neither log-transformed IL-6 nor log-transformed TNF-α was associated with HS, Sdc-1, UACR, CSI, or SSI (all group-adjusted regression $P \geq 0.083$; all Benjamini–Hochberg false-discovery-rate-adjusted $q \geq 0.813$; Supplementary Table S6).

Clinical Outcomes and Safety

Postoperative AKI developed in 13 of 53 participants (24.5%) in the sevoflurane group and 17 of 53 participants (32.1%) in the propofol group (absolute risk difference −7.5%, 95% CI −24.6% to 9.5%; risk ratio 0.76, 95% CI 0.41–1.41; P = 0.518). Duration of mechanical ventilation, adverse respiratory or cardiovascular events, intensive care stay, and hospital stay were similar between groups (Table 2). No serious anesthesia-related adverse events occurred.

Discussion

The central finding of this randomized trial was a coordinated, anesthetic-dependent GFB phenotype during CPB. Sevoflurane was associated with smaller perioperative increases in albumin permeability and HS and with less deterioration of charge and size selectivity than propofol. The concordance across these complementary dimensions moves the interpretation beyond an isolated biomarker difference and identifies glomerular permselectivity as a pharmacologically responsive perioperative phenotype.

The longitudinal differences in UACR, HS, CSI, and SSI remained after post hoc adjustment for hypertension, diabetes mellitus, preoperative renin-angiotensin system blockade, and the corresponding baseline outcome values, supporting the robustness of these biomarker and functional findings to the measured baseline imbalances. However, these post hoc analyses cannot exclude residual confounding or establish direct renal protection or improved clinical renal outcomes.

Functional resolution of the barrier response is the principal advance of this study. UACR quantifies albumin leakage but does not identify the filtration property responsible for that leakage. CSI and SSI separately interrogate charge discrimination and molecular-size restriction, and both indices separated between anesthetic groups during early reperfusion. Their temporal agreement with UACR, together with the associations of HS with all three functional measures, supports a linked barrier response involving glycocalyx-related biology and altered glomerular protein

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handling. Because these are clearance-derived measures, they define a functional phenotype rather than a structural lesion.

The present trial extends a previous 51-patient randomized study from our group without reusing participants or data.[24] The earlier study established that sevoflurane was associated with less glycocalyx shedding and albuminuria during cardiac surgery. The current study addresses the unresolved mechanistic question by showing in a larger, distinct cohort that the anesthetic-dependent signal spans both charge and size selectivity. The contribution is therefore not another general comparison of sevoflurane with propofol, but functional decomposition of the renal barrier response to CPB.

Several processes may contribute to this phenotype. CPB exposes the endothelial surface layer to ischemia-reperfusion, oxidative stress, inflammation, and protease or heparanase activation.[10–15] Experimental studies suggest that volatile anesthetics can modify glycocalyx degradation and preconditioning-related signaling during ischemia-reperfusion.[20–22,30] Conversely, clinical studies indicate that propofol can attenuate lipid peroxidation and inflammatory signaling during cardiac surgery.[23] The present comparison therefore cannot be reduced to an active anesthetic versus an inert control. The parallel attenuation of HS release, CSI, SSI, and UACR with sevoflurane is consistent with reduced disruption of the endothelial-barrier interface, but the study did not directly measure local oxidative, inflammatory, or preconditioning pathways. Circulating HS is not specific to the glomerulus; the data support a coherent functional mechanism without establishing its molecular or anatomical origin.

No statistically significant between-group differences in the longitudinal trajectories of the measured circulating cytokines were detected. In exploratory analyses restricted to the nominally matched 1-h postoperative time point, neither IL-6 nor TNF-α was associated with the measured glycocalyx-, functional-, or permeability-related indices after treatment-group adjustment and false-discovery-rate correction. These findings do not establish equivalence or exclude an inflammatory contribution to perioperative barrier disturbance. Circulating cytokine concentrations may not reflect local endothelial or renal inflammatory activity, and the temporal relationship between cytokine release and barrier injury may not be captured by a single nominally matched postoperative measurement. Accordingly, these exploratory analyses do not establish or refute a causal inflammatory pathway.

The functional phenotype complements rather than replaces clinical renal outcomes. A multicenter randomized trial involving 3123 cardiac surgical patients found similar major complications and mortality with volatile and propofol-based anesthesia.[31] In the present trial, creatinine-based eGFR trajectories and AKI incidence were also similar, but the study was powered for longitudinal UACR rather than clinical events. These observations suggest that glomerular permselectivity may serve as an exploratory early pharmacodynamic measure of renal biological divergence within a time window not resolved by creatinine; its sensitivity and clinical utility require further validation. Whether modifying this phenotype improves renal recovery requires an outcomes-powered trial.

Strengths include randomized allocation, complete follow-up, serial sampling centered on reperfusion, and integration of albumin leakage with glycocalyx and functional selectivity measures. The single-center setting limits generalizability, and clearance-derived indices and circulating biomarkers cannot provide direct structural localization. Barrier-related sampling ended 24 h after surgery, whereas AKI surveillance continued through postoperative day 7; therefore, the persistence or normalization of the observed differences beyond 24 h cannot be determined. Future studies should extend barrier-related measurements to 48 h and postoperative day 7. Exposure to propofol during early intensive care sedation in both groups may also have attenuated later separation. These boundaries affect anatomical and clinical extrapolation but do not alter the randomized longitudinal differences observed during the perioperative window.

Taken together, the data define CPB-related glomerular barrier dysfunction as a multidimensional and anesthetic-responsive phenotype. Resolving albumin permeability into glycocalyx-related, charge-selective, and size-selective components provides a mechanistic framework for evaluating perioperative renal effects before conventional clinical measures diverge.

Conclusions

During cardiopulmonary bypass, sevoflurane- and propofol-based anesthesia produced distinct early glomerular filtration barrier phenotypes. Sevoflurane attenuated coordinated increases in UACR, HS, CSI, and SSI, indicating less disruption

of albumin permeability, glycocalyx-related biology, and charge and size selectivity. This functionally resolved framework offers an exploratory pharmacodynamic approach for evaluating perioperative renal effects, but its measurement properties and clinical relevance require external validation. Multicenter, outcomes-powered trials should determine whether modulation of this phenotype improves renal recovery.

AI Declaration

During preparation of this manuscript, the authors used OpenAI ChatGPT (GPT-5; OpenAI, San Francisco, CA, USA; accessed October 2026) for language refinement, formatting, and consistency checks. The authors confirmed the originality and accuracy of the content, independently verified the scientific statements, numerical results, and references, reviewed the tool's terms of use and suitability for publication, and take full responsibility for the integrity and accuracy of the submitted work, including its references. The tool was not used to generate research data, perform statistical analyses, or determine the study conclusions.

Trial Registration

Chinese Clinical Trial Registry, ChiCTR2300067723 (registered January 19, 2023; enrollment began January 20, 2023). Registry record: https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2300067723.

Abbreviations

AKI, acute kidney injury; CI, confidence interval; CPB, cardiopulmonary bypass; CSI, charge selectivity index; eGFR, estimated glomerular filtration rate; GFB, glomerular filtration barrier; HS, heparan sulfate; ICU, intensive care unit; IL-6, interleukin-6; KDIGO, Kidney Disease: Improving Global Outcomes; MAC, minimum alveolar concentration; Sdc-1, syndecan-1; SSI, size selectivity index; TNF-α, tumor necrosis factor-α; UACR, urinary albumin-to-creatinine ratio.

Data Sharing Statement

Deidentified individual participant data underlying the results reported in this article, together with a data dictionary, study protocol, statistical analysis plan, and statistical code, will be available from the corresponding author beginning 3 months and ending 5 years after publication. Access will be considered for investigators whose proposed use has been approved by the corresponding authors and the institutional ethics committee and will require a data-use agreement. Requests should be directed to wangweijian@wmu.edu.cn. The dataset will not be posted publicly because it contains potentially sensitive clinical information.

Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki. The original protocol was approved by the Ethics Committee in Clinical Research of The First Affiliated Hospital of Wenzhou Medical University (approval no. 2019-081). The revised protocol applicable to this trial was approved on April 1, 2022 (approval no. 2019-081-01), before participant enrollment. All participants provided written informed consent.

Consent for Publication

Not applicable. The manuscript contains no identifiable participant information.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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