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# High-Exchange Ultrafiltration to Enhance Recovery After Pediatric Cardiac Surgery: The ULTRA Randomized Controlled Trial

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## ABSTRACT

**BACKGROUND** Pediatric cardiac surgery with cardiopulmonary bypass (CPB) is associated with systemic inflammation. This trial aimed to determine whether continuous high-exchange ultrafiltration during CPB has a clinical immunomodulatory effect.

**METHODS** This single-center, double-blind trial enrolled pediatric patients weighing <15 kg undergoing cardiac surgery who were randomly allocated to continuous high-exchange subzero-balance ultrafiltration (H-SBUF; 60 mL/kg per hour effluent extraction) or continuous low-exchange subzero-balance ultrafiltration (L-SBUF; 6 mL/kg per hour effluent extraction) administered during CPB. The primary outcome was peak postoperative vasoactive-ventilation-renal (VVR) score. Secondary outcomes included acute kidney injury, low cardiac output syndrome, health care utilization, and inflammatory mediator fold change throughout CPB (NCT04920643).

**RESULTS** A total of 104 patients were randomly allocated to H-SBUF (n = 52) or L-SBUF (n = 52). The primary outcome was similar between groups as the peak VVR score was 26.9 (2.1-77.9) in the H-SBUF group and 27.8 (0.8-76.7) in the L-SBUF group ($P = .67$). There were no operative deaths and no significant differences in acute kidney injury, low cardiac output syndrome, ventilation time, inotropic agent use time, intensive care unit stay, or hospital length of stay ($P > .05$). The H-SBUF group had a higher fold change for interleukin-1α, P-selectin, and vascular cell adhesion molecule 1 ($P < .05$), whereas 36 other mediators were not significantly different between groups ($P > .05$).

**CONCLUSIONS** In pediatric patients undergoing cardiac surgery with CPB, continuous high-exchange SBUF did not reduce peak VVR score compared with low-exchange SBUF. Furthermore, there were no differences in secondary clinical outcomes, and the immunologic profile was largely similar between groups.

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Cardiopulmonary bypass (CPB) during children's heart surgery is associated with systemic inflammation.[1-3] Exposure to the nonendothelialized bypass circuit triggers a sterile innate response of circulating proinflammatory mediators, including complement anaphylatoxins

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**Abbreviations and Acronyms**

CPB = cardiopulmonary bypass
CUF = conventional ultrafiltration
CXCL = C-X-C motif chemokine ligand
H-SBUF = high-exchange subzero-balance ultrafiltration
ICU = intensive care unit
IL = interleukin
LCOS = low cardiac output syndrome
L-SBUF = low-exchange subzero-balance ultrafiltration
SBUF = subzero-balance ultrafiltration
STAT = The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery
TNF = tumor necrosis factor
VVR = vasoactive-ventilation-renal score

(C3a and C5a), cytokines (tumor necrosis factor, interleukin [IL] 1α, IL-1β, and IL-6), and chemokines (C-X-C motif chemokine ligand 8 [CXCL-8]), which cause vasodilation and stimulate endothelial leak, neutrophil recruitment, translocation, and ultimately tissue injury.[1,2,4] Clinically, the systemic inflammatory response syndrome is manifested as cardiopulmonary and vasomotor dysfunction, yielding hours or days of intensive care management and, potentially, secondary organ dysfunction in the postoperative period.[2-4] CPB-associated inflammatory syndrome lacks effective treatment options as corticosteroids and nitric oxide during CPB have independently shown neutral results in multicenter randomized trials.[3,5,6]

Ultrafiltration has been used during pediatric cardiac surgery since the 1990s, primarily to remove excess volume and to prevent tissue edema.[3,7] In addition, 22 inflammatory mediators—including C3a, C5a, tumor necrosis factor (TNF), IL-1β, IL-6, and CXCL-8, among others—are known to be extracted by this modality throughout CPB.[3,8] Subzero-balance ultrafiltration (SBUF) was designed to maximize the extraction of proinflammatory mediators throughout the entire CPB exposure while simultaneously preventing tissue edema with sustained negative volume balance during CPB.[9] We hypothesized that a high-exchange rate of SBUF (H-SBUF) would extract more proinflammatory mediators from the patient's circulation and dampen the systemic inflammatory response relative to a low-exchange SBUF (L-SBUF), thereby ameliorating the clinical sequelae of CPB-associated inflammation.[10,11] The objective of this trial was to test whether, in pediatric patients undergoing heart surgery, H-SBUF results in superior clinical outcomes compared with L-SBUF as assessed by the validated peak postoperative vasoactive-ventilation-renal (VVR) score.[12]

## PATIENTS AND METHODS

**TRIAL DESIGN.** The ULTRA trial was an investigator-initiated, double-blind, parallel-group randomized controlled trial conducted at the academic IWK Health Centre, Nova Scotia, Canada. The detailed protocol was previously published and registered (NCT04920643).[13] The Research Ethics Board at the IWK Health Centre approved this study (#1024932). This report follows Consolidated Standards of Reporting Trials guidelines (Supplemental Table 1).[14]

**PATIENT POPULATION.** Neonatal, infant, and child patients weighing <15 kg undergoing cardiac surgery with CPB as well as any patient undergoing a Fontan operation were eligible for inclusion. Exclusion criteria included absence of informed written consent by a substitute decision maker, isolated secundum atrial septal defect repair, severe organ dysfunction, genetic syndrome with severe multiorgan abnormalities, and preoperative mechanical circulatory support.

**RANDOMIZATION AND TREATMENT.** Eligible consented patients were randomized 1:1 to either H-SBUF or L-SBUF throughout CPB by permuted block randomization, consisting of randomly permuted block sizes 2 and 4, and stratified by 2 risk groups defined by the updated 2020 Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) score (STAT = 1 and STAT = 2 to 5).[15] Randomization occurred after the preoperative surgical team briefing on the day of operation on Research Electronic Data Capture software (REDCap).[16]

The treatment arm consisted of H-SBUF administered throughout the entire CPB time, with effluent extraction of 60 mL/kg per hour and physiologic crystalloid volume replacement of 55 mL/kg per hour. The control arm was L-SBUF administered throughout the entire CPB time, with effluent extraction of 6 mL/kg per hour and physiologic crystalloid volume replacement of 1 mL/kg per hour. The technical details of SBUF during pediatric CPB have previously been published.[9] In addition to SBUF, conventional ultrafiltration (CUF) was used to immediately remove cardioplegia or surgical field irrigation and simple modified ultrafiltration (SMUF) after the cessation of CPB.[9]

Both groups received institutional standard of care perfusion techniques. Preparation of sanguineous and crystalloid CPB prime was standardized and followed the principles of buffered ultrafiltration of the prime to achieve a

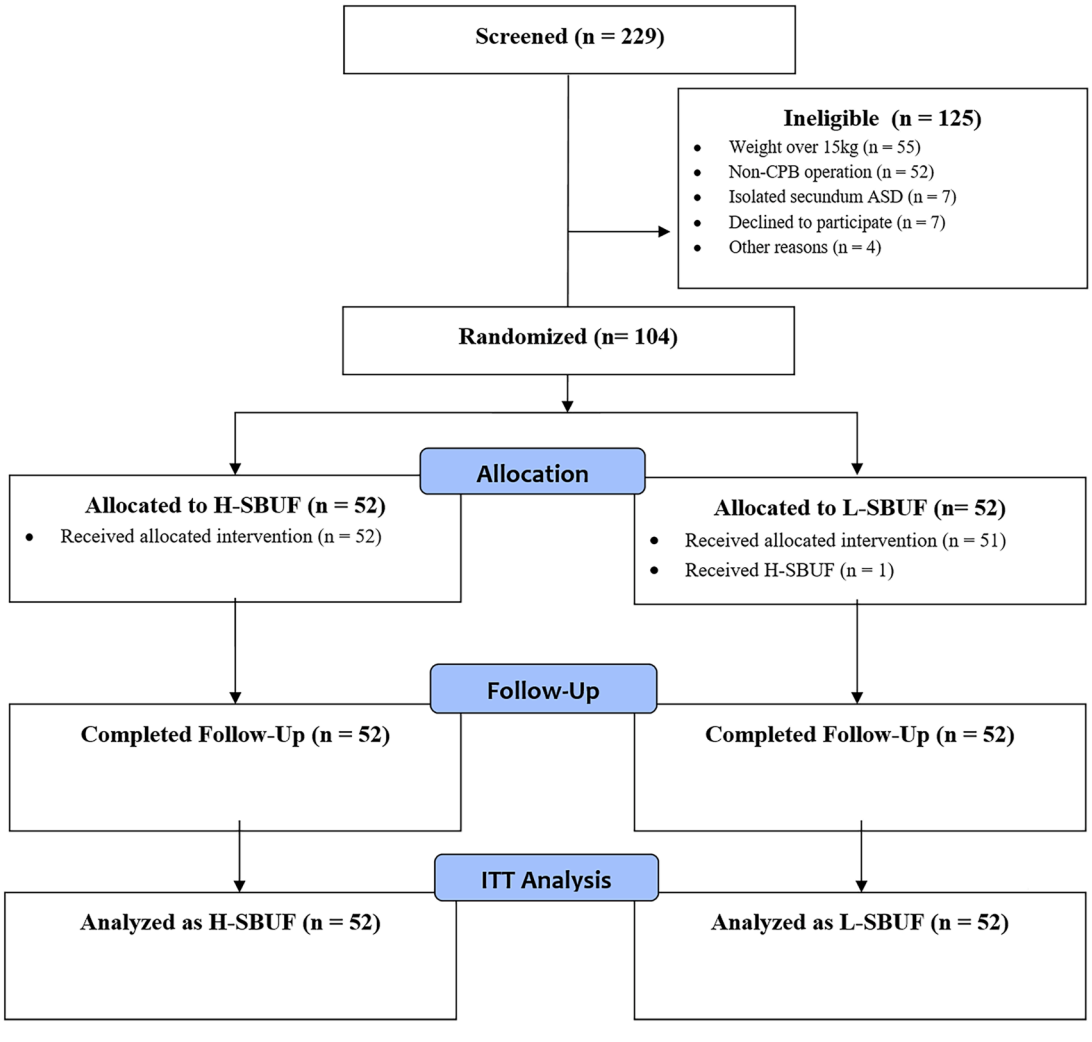


**FIGURE 1** Participant flow diagram. (ASD, atrial septal defect; CPB, cardiopulmonary bypass; H-SBUF, high-exchange subzero-balance ultrafiltration; L-SBUF, low-exchange subzero-balance ultrafiltration; ITT, intention to treat.)

physiologic solution for the patient.[17,18] Patients who weighed <10 kg received a sanguineous prime, whereas those who weighed >10 kg received a crystalloid prime. The hematocrit target during normothermic CPB was >30%, with adjustments made during hypothermia. Blood transfusion products were administered at the discretion of the intraoperative team. LivaNova S5 CPB system with phosphorylcholine coating (48-40-00) and Terumo FX05 or FX15 oxygenators (1CX*FX05RE/1CX*FX15E) were used. Because of commercial availability, the first 65 patients were treated with Terumo Capiox hemoconcentrator HCO5 (1CX*HC05S); the final 39 patients received Maquet hemoconcentrator BC 20 plus or BC 60 plus (P-0420/P-0410), depending on their weight.

All postoperative clinical care in the intensive care unit (ICU) and ward were per the standard practices of the blinded multidisciplinary team.

**BLINDING.** Patients and their families and the surgeon, anesthetist, critical care physician, cardiologist, nursing, outcome assessor, research coordinator, and statistician were blinded to the assigned treatment group. Only the perfusionist who executed the randomization and the perfusionist who administered the ultrafiltration treatments were aware of the treatment allocation. Physical barriers were used to mask the infusion pumps and ultrafiltration effluent reservoir. Perfusion and ultrafiltration data were recorded by perfusionists and stored in a locked data sheet.

**TABLE 1 Baseline Patient Demographics**

| Variable | H-SBUF (n = 52) | L-SBUF (n = 52) |
|---|---|---|
| Age, mo | 5.2 (0.3–56.8) | 4.1 (0.2–65.3) |
| Neonate | 5 (10) | 12 (23) |
| Infant | 34 (65) | 29 (56) |
| Child | 13 (25) | 11 (21) |
| Male sex | 35 (67) | 26 (50) |
| Weight, kg | 6.1 (3.1–16.3) | 5.7 (2.7–17.5) |
| Body surface area, $m^2$ | 0.32 (0.20–0.67) | 0.30 (0.19–0.72) |
| STAT score | 2 (1–4) | 3 (1–4) |
| STAT 1 | 13 (25) | 14 (27) |
| STAT 2 | 13 (25) | 10 (19) |
| STAT 3 | 15 (29) | 14 (27) |
| STAT 4 | 11 (21) | 14 (27) |
| Single ventricle pathway | 8 (16) | 9 (18) |
| Systemic–pulmonary shunt | 2 (4) | 2 (4) |
| Bidirectional Glenn | 3 (6) | 1 (2) |
| Fontan | 3 (6) | 6 (12) |
| Genetic syndrome | 15 (29) | 12 (23) |
| Trisomy 21 | 7 (14) | 6 (12) |
| VACTERL | 4 (8) | 1 (2) |
| DiGeorge 22q11 deletion | 0 | 2 (4) |
| Other | 4 (8) | 3 (6) |

Categorical variables are presented as number (percentage). Continuous variables are presented as median (interquartile range). H-SBUF, high-exchange subzero-balance ultrafiltration; L-SBUF, low-exchange subzero-balance ultrafiltration; STAT, The Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery; VACTERL, vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities syndrome.

**STUDY OUTCOMES.** The primary outcome was peak VVR score in the postoperative period.[12] The VVR score and other secondary outcome parameters, namely, vasoactive-inotropic score, ventilation index, and oxygenation index, are defined in Supplemental Table 2 and were collected in a prespecified time series throughout the perioperative period.[12,19-21] Specifically, clinical scores were calculated after sternotomy but before CPB initiation as a baseline, immediately after CPB weaning (−0 hours), and at regular intervals after CPB cessation in the ICU (−12, −24, −36, −48, −72, −96, −120 hours). The peak clinical score is the single highest measurement for each score collected after ICU admission; intraoperative measurements were not eligible for the primary outcome of peak VVR score or any other peak clinical score. Prespecified secondary clinical outcomes are outlined in Supplemental Table 3. Complement factors, cytokines, chemokines, and soluble adhesion molecules as well as troponin I were quantified in biologic samples, before CPB initiation (pre-CPB) and immediately after CPB cessation and SMUF (post-CPB), by multiplex immunoassay following the manufacturer's instruction.

**SAMPLE SIZE.** A 2-way analysis of variance considered a relative reduction in the primary outcome of 25%, $\alpha = .05$ and $\beta = .20$; 48 patients in each group were required. Because of faster than expected enrollment and without any interim analysis, the investigators elected to decrease the $\beta$ from .20 to .17 on January 6, 2025, yielding a final sample size of 52 patients in each group.

**STATISTICAL ANALYSES.** The analysis followed the intention-to-treat principle. Nonparametric continuous data were compared by the Wilcoxon rank sum test reported as median with 95th interpercentile range (2.5%-97.5%) or median difference [95% CI]; ordinal and dichotomous variables (numbers and percentages) were compared by either Pearson $\chi^2$ test or Fisher exact test. Time-to-event analyses were conducted by the Kaplan-Meier method and the log-rank test. Inflammatory mediators were compared in time series and fold change analysis, where fold change was calculated by $([\text{mediator}]_{\text{Post-CPB}} - [\text{mediator}]_{\text{Pre-CPB}}) / [\text{mediator}]_{\text{Pre-CPB}}$ and presented as median fold change with [95% CI] estimated by 1000 nonparametric bootstrap samples with adjusted percentile interval.[22] There were no interim analyses and no imputation of missing data. $P$ values $< .05$ were considered statistically significant.

## RESULTS

**PATIENTS.** Between September 2021 and May 2025, 104 patients consented to participate, were randomized, and completed the study protocol. Fifty-two patients in each group completed follow-up and were analyzed (Figure 1). Patient baseline characteristics were well balanced through the randomization process and are outlined in Table 1. Seven of 9 patients who underwent Fontan procedure had a weight in excess of 15 kg (range, 16.0-18.6 kg), as allowed in the prespecified protocol. There were no differences in any inflammatory mediator mass at baseline.

**INTERVENTIONS.** H-SBUF and L-SBUF treatments were administered as allocated, except for 1 patient allocated to the L-SBUF group who erroneously received the H-SBUF treatment because of a logistical error. The H-SBUF group had significantly more SBUF effluent volume (180 [81-346] mL/kg vs 19 [10-41] mL/kg; $P = 1.7 \times 10^{-17}$) and total ultrafiltration effluent volume (83 [62-126] mL/kg per hour vs 36 [13-79] mL/kg per hour; $P = 9.4 \times 10^{-17}$) compared

**TABLE 2 Intraoperative Data**

| Variable | H-SBUF (n = 52) | L-SBUF (n = 52) | *P* Value |
|---|---|---|---|
| Prophylactic corticosteroid (hydrocortisone-eq) | 34 (65); 5.6 (0-100.0) | 29 (57); 4.7 (0-111.2) | .65 |
| CPB time, min | 201 (95-353) | 182 (103-412) | .39 |
| Myocardial ischemia time, min | 48 (92); 98 (0-214) | 44 (85); 102 (0-192) | .83 |
| Deep hypothermic circulatory arrest, min | 5 (10); 0 (0-43) | 9 (18); 0 (0-43) | .27 |
| Sanguineous CPB prime | 45 (86) | 44 (85) | 1 |
| Ultrafiltration therapies | | | |
| SBUF, effluent mL/kg | 52 (100); 180 (81-346) | 52 (100); 19 (10-41) | $1.7 \times 10^{-17}$ |
| CUF, effluent mL/kg | 52 (100); 65 (25-226) | 52 (100); 67 (9-150) | .58 |
| SMUF, effluent mL/kg | 52 (100); 19 (6-57) | 49 (94); 26 (0-64) | .27 |
| Total ultrafiltration effluent, mL/kg | 287 (142-547) | 111 (38-303) | $4.5 \times 10^{-13}$ |
| Total ultrafiltration effluent, mL/kg/h | 83 (62-126) | 36 (13-79) | $9.4 \times 10^{-17}$ |
| Transfusion | | | |
| pRBC, mL/kg | 49 (94); 21 (0-79) | 46 (89); 22 (0-98) | .45 |
| FFP, mL/kg | 41 (79); 11 (0-51) | 39 (75); 13 (0-37) | .89 |
| Platelets, mL/kg | 38 (73); 15 (0-48) | 43 (83); 15 (0-59) | .65 |
| Perfusion case balance, mL/kg | −14 (−41 to 5) | −11 (−80 to 9) | .32 |
| Anesthesia volume balance, mL/kg | 16 (−113 to 75) | 12 (−68 to 76) | .53 |

Categorical variables are presented as number (percentage). Continuous variables are presented as median (interquartile range). Total ultrafiltration effluent volume includes SBUF, CUF, and SMUF. CPB, cardiopulmonary bypass; CUF, conventional ultrafiltration; eq, equivalent; FFP, fresh frozen plasma; H-SBUF, high-exchange subzero-balance ultrafiltration; L-SBUF, low-exchange subzero-balance ultrafiltration; pRBC, packed red blood cells; SBUF, subzero balance ultrafiltration; SMUF, simple modified ultrafiltration.

**TABLE 3 Clinical Results**

| Variable | H-SBUF (n = 52) | L-SBUF (n = 52) | Median Difference [95% CI] |
|---|---|---|---|
| Clinical Scores | | | |
| Peak VVR | 26.9 (2.1-77.9) | 27.8 (0.8-76.7) | 1.3 [−5.1 to 8.2] (*P* = .67) |
| Peak VIS | 9.8 (2.1-77.9) | 9.0 (0-45.0) | 1.0 [−1.5 to 4.0] (*P* = .40) |
| Peak VI | 16.5 (0-34.2) | 17.3 (0-38.1) | 0 [−3.7 to 4.4] (*P* = .95) |
| Peak OI | 4.8 (0-20.3) | 3.8 (0 -17.8) | 0.3 [−0.2 to 2.5] (*P* = .31) |
| Clinical Care Usage | | | |
| Ventilation-free days | 27.3 (16.1-30.0) | 27.9 (18.8-30.0) | 0 [−0.7 to 0.8] (*P* = .89) |
| Ventilation time, d | 0.8 (0.9-13.9) | 0.9 (0-9.2) | 0 [−0.5 to 0.3] (*P* = .80) |
| Inotropic agent-free days | 26.9 (16.6-29.8) | 27.0 (18.2-29.3) | 0 [−0.8 to 0.7] (*P* = .95) |
| Inotropic support time, d | 1.5 (0.1-11.6) | 1.6 (0-11.3) | 0 [−0.5 to 0.6] (*P* = .84) |
| ICU LOS, d | 2.2 (0.8-20.1) | 2.3 (0.5-16.7) | 0.2 [−0.5 to 0.8] (*P* = .59) |
| Hospital LOS, d | 9.0 (3.9-69.0) | 10.5 (3.9-59.3) | −0.1 [−2.9 to 1.9] (*P* = .83) |
| Clinical Outcomes | | | |
| Mortality | 0 | 0 | *P* = 1 |
| Mechanical circulatory support | 1 (2) | 1 (2) | *P* = 1 |
| Low cardiac output syndrome | 17 (33) | 13 (25) | *P* = .52 |
| Vasoplegic shock | 4 (8) | 4 (8) | *P* = 1 |
| Delayed sternal closure | 8 (16) | 6 (12) | *P* = .50 |
| Inotropic agent dependence | 10 (19) | 8 (16) | *P* = .80 |
| Prolonged intubation | 4 (8) | 3 (6) | *P* = 1 |
| Acute kidney injury | 16 (31) | 13 (25) | *P* = .66 |
| Grade 1 | 13 (25) | 8 (16) | |
| Grade 2 | 1 (2) | 4 (8) | *P* = .23 |
| Grade 3 | 2 (4) | 1 (2) | |
| Chylothorax | 11 (21) | 8 (15) | *P* = .51 |
| Haptoglobin, g/L | 0.33 (0.08-0.67) | 0.34 (0.08-0.83) | −0.01 [−0.09 to 0.07] (*P* = .83) |
| C-reactive protein, mg/L | 56.2 (15.7-161.8) | 55.3 (11.6-169.7) | 5.0 [−9.4 to 18.9] (*P* = .45) |

Categorical variables are presented as number (percentage). Continuous variables are presented as median (interquartile range). The normal reference for haptoglobin is 0.47 to 2.03 g/L; and for C-reactive protein, <5.0 mg/L. H-SBUF, high-exchange subzero-balance ultrafiltration; ICU, intensive care unit; LOS, length of stay; L-SBUF, low-exchange subzero-balance ultrafiltration; OI, oxygenation index; VI, ventilation index; VIS, vasoactive-inotropic score; VVR, vasoactive ventilation renal score.

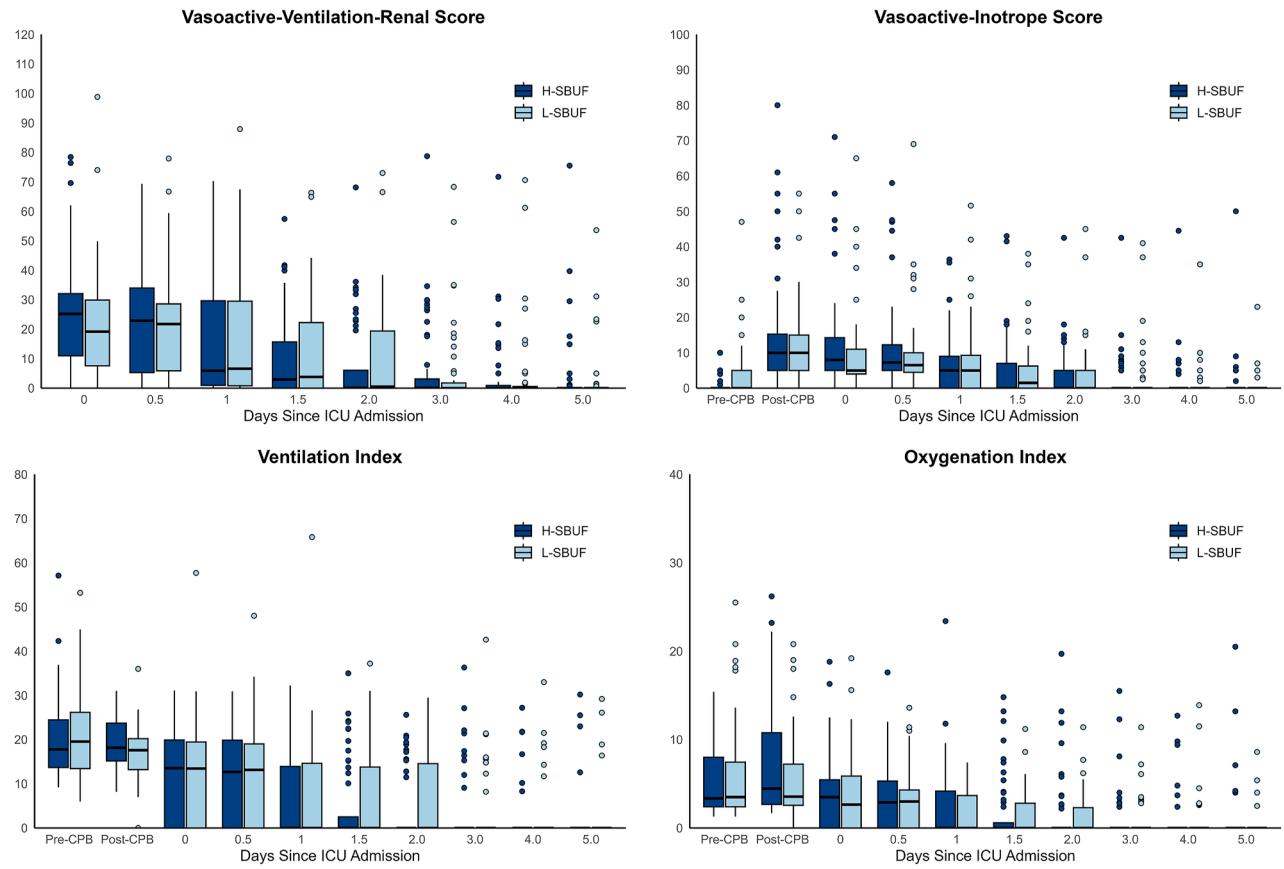


**FIGURE 2** Clinical score time series (n = 52 in each group). Day 0 indicates intensive care unit (ICU) admission. There were no statistically significant differences between groups. (CPB, cardiopulmonary bypass; H-SBUF, high-exchange subzero-balance ultrafiltration; L-SBUF, low-exchange subzero-balance ultrafiltration.)

with the L-SBUF group. The CPB time, myocardial ischemia time, CUF effluent volume, SMUF effluent volume, and perfusion volume balance were not statistically different between groups (Table 2). The only recorded perfusion complication was a single observation of subtherapeutic activated clotting time <480 seconds during CPB in the L-SBUF group, with no associated thrombotic complications.

**PRIMARY END POINT.** Peak VVR score was not significantly different between H-SBUF and L-SBUF treatments. The high-exchange group had a peak VVR score of 26.9 (2.1-77.9) and the low-exchange group had a peak VVR score of 27.8 (0.8-76.7), with a median difference [95% CI] of 1.2 [−5.1 to 8.2] ($P = .67$). Peak VVR score occurred commonly at ICU admission with a median time to peak VVR score of 0 (0-2.5) days in the H-SBUF group and 0 (0-4.4) days in the L-SBUF group (Supplemental Figure). There was no difference in peak VVR score through prespecified subgroup analyses of STAT 1 patients, STAT 2-4 patients, sanguineous CPB prime, male sex, or female sex ($P > .05$).

**SECONDARY END POINTS.** No operative deaths were recorded in the study, and 1 patient from each group required postoperative mechanical circulatory support. There were no differences in the peak vasoactive-inotropic score, ventilation index, or oxygenation index or any secondary clinical outcome (Table 3). There were no statistical differences in any clinical score in the postoperative time series (Figure 2). Only 8 patients (8%) suffered a grade 2 or grade 3 acute kidney injury, which was not different between groups. No patients required postoperative renal replacement therapy. The patients in each group had similar durations of ventilation, inotropic support, ICU requirements, and hospital admission length of stay (Figure 3).

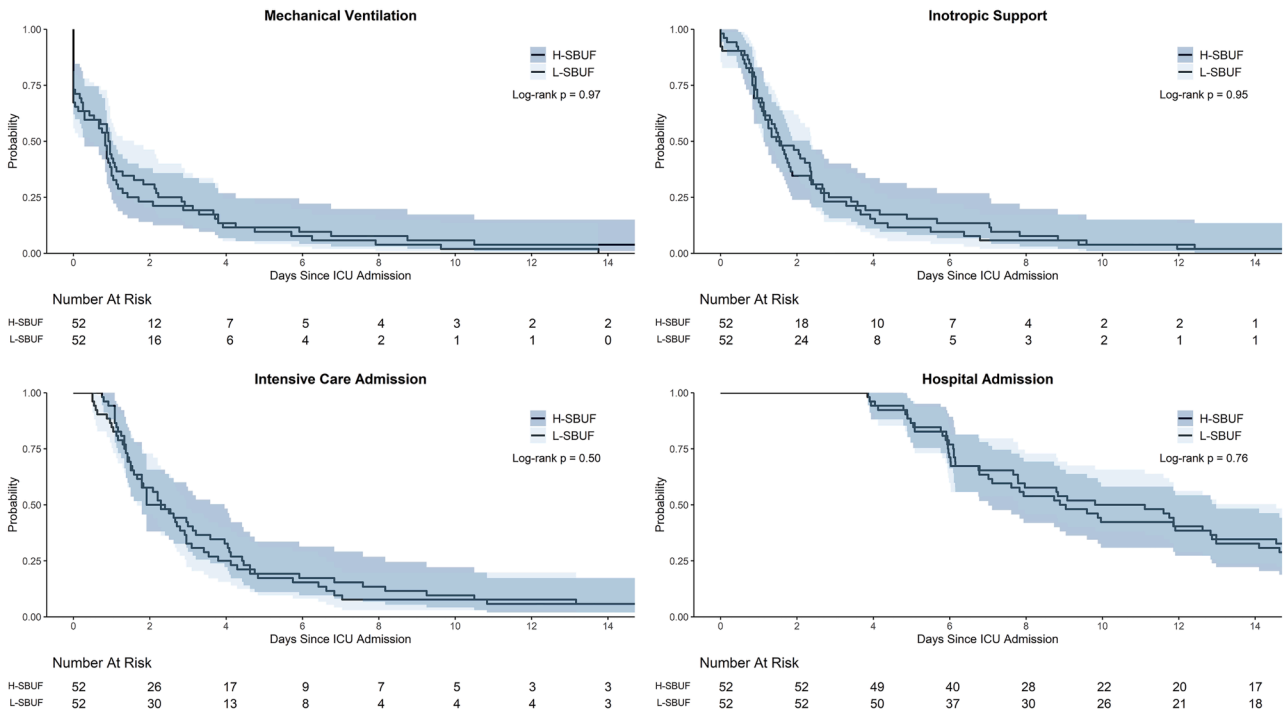


**FIGURE 3** Time-to-event analysis for health care utilization measures (n = 52 in each group). (H-SBUF, high-exchange subzero-balance ultrafiltration; ICU, intensive care unit; L-SBUF, low-exchange subzero-balance ultrafiltration.)

**IMMUNOLOGIC MEDIATORS.** Inflammatory mediator mass was not statistically different between H-SBUF and L-SBUF before or at the end of CPB ($P > .05$; Supplemental Table 4). Mediator concentrations measured in the effluent at the end of CPB were also not different between treatment groups ($P > .05$). The H-SBUF group had a higher fold increase for IL-1α (0.22 [0.14-0.25] vs 0.10 [0.05-0.17]; $P = .02$), P-selectin (0.29 [0.17-0.37] vs 0.04 [−0.04 to 0.16]; $P = 5.0 \times 10^{-4}$), and vascular cell adhesion molecule 1 (0.26 [0.14-0.38] vs 0.07 [−0.03 to 0.27]; $P = .03$) during CPB; all other mediators were not different ($P > .05$) between groups (Figure 4).

## COMMENT

In this double-blind randomized trial, H-SBUF did not reduce the primary outcome of peak postoperative VVR score compared with L-SBUF during pediatric CPB. There was also no difference in secondary clinical scores or clinical outcomes, and the immunologic profiles were similar between groups. Patients in both groups exhibited evidence of a significant complement reaction, characterized by dynamic increases in circulating C2, C3, C3a, C3b, C5a, and terminal complement complex C5b-9. In addition to the complement reaction, both groups experienced elevated levels of IL-6, CXCL-8, IL-1Ra, and IL-10, often observed during cardiac surgery with CPB.[2,4,11]

Prior research has suggested that the complement system and activated anaphylatoxins C3a and C5a are related to clinical inflammation and prolonged postoperative recovery.[11] C3a and C5a along with cytokines and chemokines have been measured in the ultrafiltration effluent with a wide range of sieving coefficients (1% to 1019%), specifically, C3a (1019%) and C5a (46%).[8] Subsequent and more detailed analyses have contextualized the sieving coefficient for each mediator relative to the effluent volume extracted and circulating patient volume.[10] This more useful assessment of extraction fraction indicates that 148% of C3a mediator mass, only 7% of C5a mediator mass, and <10% of cytokines and chemokines are extracted by a moderate-intensity ultrafiltration during CPB (52 mL/kg per hour).[10] This suggests a modest immunomodulatory effectiveness ultrafiltration during CPB and potential explanation to the neutral immunologic and clinical effect in ULTRA.

ULTRA was designed to examine the immunomodulatory effect of SBUF by continuous mediator

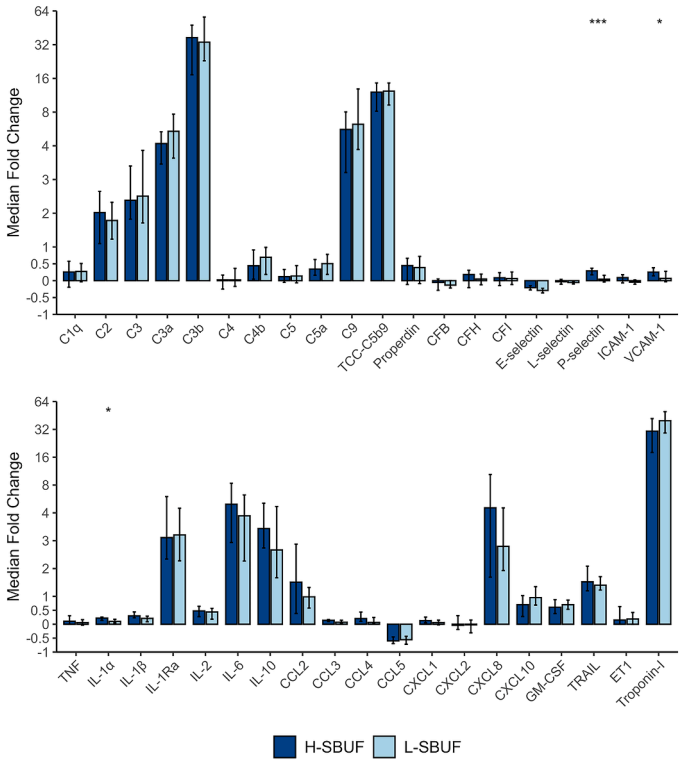


**FIGURE 4** Inflammatory mediator fold change over the cardiopulmonary bypass exposure and exchange subzero-balance ultrafiltration treatment (n = 52 in each group). *$P$ < .05. **$P$ < .01. ***$P$ < .001. (C, complement; CF, complement factor; CCL, C-C motif chemokine ligand; CXCL, C-X-C motif chemokine ligand; ET1, endothelin 1; GM-CSF, granulocyte-macrophage colony-stimulating factor; H-SBUF, high-exchange subzero-balance ultrafiltration; L-SBUF, low-exchange subzero-balance ultrafiltration; ICAM-1, intracellular adhesion molecule 1; IL, interleukin; TCC, terminal complement complex; TNF, tumor necrosis factor; TRAIL, tumor necrosis factor–related apoptosis-inducing ligand; VCAM-1, vascular cell adhesion molecule 1).

extraction, comparing a high-exchange and low-exchange regimen in addition to the standard of care CUF and SMUF. In the H-SBUF group, the median SBUF volume was 180 mL/kg, and the median CUF volume was 65 mL/kg; the L-SBUF group had a median SBUF volume of 19 mL/kg and median CUF volume of 67 mL/kg. Therefore, the total ultrafiltration effluent volumes were more similar than anticipated, with some overlap between groups, as H-SBUF was 83 (62-126) mL/kg per hour and L-SBUF was 36 (13-79) mL/kg per hour. It is possible that the total ultrafiltration treatments may not have been sufficiently different to produce a significant difference in clinical or immunologic outcomes.

Continuous ultrafiltration as immunomodulatory therapy during pediatric CPB has been sparsely investigated yet forms the basis for designing ULTRA. Journois and coworkers[23] published the original evaluation of continuous ultrafiltration in children's heart surgery under randomized conditions, assessing 20 patients. Relative to a control, the zero-balance ultrafiltration group had statistically less C3a and TNF at the end of CPB and also shorter postoperative ventilation time.[23] Liu and coworkers[24] randomized 30 patients to either continuous zero-balance ultrafiltration during aortic cross-clamp and rewarming or methylprednisolone and found no differences in TNF, IL-6, IL-8, or IL-10 at the end of CPB but did measure a statistically significant reduction in ventilation time with ultrafiltration. Huang and coworkers[25] randomized 30 patients to continuous ultrafiltration or no ultrafiltration and found that the ultrafiltration treatment improved measures of pulmonary function, reduced IL-6 at the end of CPB, and also reduced ICU length of stay. The ULTRA trial was unable to replicate any positive findings.

Hemodynamic and clinical instability after pediatric cardiac surgery is often attributed to systemic inflammation and low cardiac output syndrome (LCOS), which is well characterized by hemodynamic deterioration and the need for cardiopulmonary support during the initial 12 to 24 hours.[19,26] LCOS was observed in 17 (33%) patients in the H-SBUF group and 12 (25%) in the L-SBUF group, rates that are consistent with those reported.[6,26] Despite the need for inotropic support and mechanical ventilation to support patients through systemic inflammation and any LCOS, patients in this study had stable clinical scores from post-CPB to the 12-hour postoperative period, signs of improvement by 24 hours, and a trend toward resolution by 48 hours postoperatively.

Several other anti-inflammatory therapies have been trialed to enhance recovery after children's heart surgery. Nitric oxide during CPB showed initial promise in pilot studies; however, the multicenter NITRIC trial did not demonstrate a reduction in ventilator-free days attributable to nitric oxide.[6,27] Prophylactic corticosteroids have been well studied in this population of patients, with meta-analyses indicating a reduction in ventilation time that did not translate into reduced ICU length of stay.[28] Furthermore, the randomized STRESS trial found that methylprednisolone had a neutral result against placebo for its primary composite outcome.[5] Hemadsorption devices during CPB also showed initial promise but did not reduce proinflammatory burden or improve clinical outcomes after adult cardiac surgery.[29]

Ultrafiltration appears also to have limited immunomodulatory efficacy,[10] although it is known to have other proven benefits, including the prevention of volume overload, hemoconcentration of coagulation factors, and reduced bleeding and transfusion.[3] The ULTRA trial was not designed to test these parameters as volume balance was equal between groups. Ultimately, CPB-associated inflammation after children's heart surgery remains an unsolved challenge and should be an important focus to enhance recovery for these vulnerable patients.

**LIMITATIONS.** The trial results should be interpreted considering limitations. First, the study was conducted at a single center, which may limit generalizability. Second, the study is relatively small, and heterogeneity in the patient population could result in higher than expected variance in the results, thereby impeding the detection of statistically significant differences between groups. Finally, despite the H-SBUF and L-SBUF effluent extraction being 10-fold different, at 60 mL/kg per hour and 6 mL/kg per hour, the total ultrafiltration treatments were more similar between groups at 83 mL/kg per hour and 36 mL/kg per hour.

**CONCLUSION.** For pediatric patients undergoing cardiac surgery with CPB, high-exchange SBUF did not reduce peak VVR score, postoperative clinical outcomes, or inflammatory mediator burden compared with continuous low-exchange SBUF. Innovative technologies and therapies will be required to prevent CPB-associated inflammation and to enhance recovery after children's heart surgery.

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## DISCLOSURES

The authors have no conflicts of interest to disclose.

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