

High-Volume, Zero Balanced Ultrafiltration Improves Pulmonary Function in a Model of Post-Pump Syndrome

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Abstract: The systemic inflammatory response syndrome (SIRS), which may develop following cardiopulmonary bypass (CPB), can cause postoperative complications that contribute to the morbidity and mortality associated with open-heart surgery. Inflammatory mediators such as cytokines, are thought to play an important role in SIRS. Zero Balance Ultrafiltration (Z-BUF) is thought to reduce the quantity of inflammatory mediators associated with CPB and may attenuate the adverse effects of bypass. Following ethics committee approval, both an unfiltered experimental group and Z-BUF treatment group consisting of Yorkshire pigs (41 ± 19 kg) were anesthetized, ventilated, instrumented, cannulated and placed on CPB for 60 minutes. Following CPB, an infusion of low-dose endotoxin ($1\mu\text{g}/\text{kg}$) was administered I.V. and the animals were monitored for 3.5 hours. The Z-BUF treatment group ($n = 5$) received high-volume Z-BUF ($122\text{ml}/\text{kg} \pm 41$) and the unfiltered experimental group ($n = 5$) did not. Hemodynamics, blood gases, and pulmonary functions were measured before, during, and after CPB. Following euthanasia, the middle lobe of the lung was prepared for histological analysis. Necropsy of the lung sample was weighed before and after dehydration to evaluate lung water content. During the

experimental time course, plasma samples were evaluated for Interleukin-8 (IL-8) concentrations. Arterial PO_2 's (mmHg) in the unfiltered experimental group showed a significant reduction at 3.5 hours post CPB when compared to baseline while the Z-BUF treatment group PaO_2 did not significantly change. There was a significant difference in the PaO_2 between the unfiltered experimental and Z-BUF group at the final 3.5 hour time point (78 ± 32 vs. 188 ± 92 mmHg respectively). Pulmonary compliance ($\text{ml}/\text{cmH}_2\text{O}$) was significantly reduced in both the unfiltered experimental and Z-BUF treatment groups with the unfiltered experimental group being the most significant. Lung wet/dry ratios were established and results found the unfiltered experimental group ratio significantly greater than that of the Z-BUF treatment group. Morphometric analysis of histologic lung sections confirmed pulmonary injury in the unfiltered experimental group and protection in the Z-BUF treatment group. This study suggests that Z-BUF provides higher arterial PO_2 's and lung compliances while reducing pulmonary edema and lung injury in a porcine model of PPS. **Keywords:** Z-BUF, cardiopulmonary bypass, inflammatory response, cytokines, ultrafiltration, pediatric. JECT. 2002;34:254-259

INTRODUCTION

The systemic inflammatory response syndrome (SIRS), which may develop following cardiopulmonary bypass (CPB) can cause postoperative complications that contribute to the morbidity and mortality associated with open-heart surgery (1-4). A particularly severe manifestation of this response has been termed "post pump syndrome"

(PPS), which is identical in pathophysiology to the acute respiratory distress syndrome (ARDS). It has been estimated that approximately 1.3% of all patients exposed to CPB will develop PPS (5,6).

Various strategies to reduce or attenuate SIRS during CPB are currently being studied. These include pharmacologic intervention, extracorporeal surface modifications, and ultrafiltration (1,7). Testing these strategies clinically can be challenging due to the patient and procedural variability and the low incidence of PPS. We previously reported a sequential injury CPB porcine model that is ideal for testing therapies as it consistently produces PPS (5,8).

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In that study, we demonstrated that acute lung injury following CPB could develop following sequential “hits” or insults, with CPB acting as the initial inflammatory event, or “first-hit”. A short period of CPB alone is rather innocuous. However, when combined with a normally benign sequential insult (“second-hit” such as low dose endotoxin) a systemic inflammatory response may develop leading to PPS.

SIRS is associated with leukocyte and complement activation along with the release of pro and anti-inflammatory cytokines. Pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- α) and various interleukins may play an important role in the development of PPS. TNF- α can cause myocardial dysfunction and hemodynamic instability while potent chemokine interleukin-8 (IL-8) can induce leukocyte sequestration within the pulmonary microvasculature (9–11).

It has been suggested that ultrafiltration during and after CPB facilitates clearance of inflammatory mediators, which may improve the post-operative course (12–14). As Journois et al. reported, one ultrafiltration strategy used during CPB is zero-balance ultrafiltration (Z-BUF) (15). Z-BUF involves simultaneous removal of ultrafiltrate and the equivalent replacement of a balanced electrolyte solution. However, it is not known whether Z-BUF is effective in reducing the morbidity and mortality associated with PPS.

We hypothesize that Z-BUF will attenuate the “first hit” caused by CPB thus minimizing the effects of the “second hit” and prevent the development of PPS. Using our “2-hit” PPS model with and without Z-BUF, we compare measurements of hemodynamics, lung function, serum cytokine concentrations, and lung histology.

MATERIALS AND METHOD

Protocol

Animals were randomized into two groups as follows.

Unfiltered experimental Group (n = 5) Subjected to 60 minutes of CPB followed by infusion low dose endotoxin, *E. coli* lipopoly saccharide (LPS) (Sigma, St. Louis, MO) and monitored for 270 minutes.

Z-BUF Treatment Group (n = 5) Subjected to 60 minutes CPB with zero-balance ultrafiltration followed by infusion of low dose LPS and monitored for 270 minutes.

Surgical preparation

Healthy Yorkshire pigs (31–62 Kg) were pre-anesthetized with ketamine (30 mg/kg, IM) and xylazine (2 mg/kg, IM) and then pretreated with atropine (0.05 mg/kg, IM) 10–15 minutes prior to intubation. Anesthesia was induced with intravenous (IV) sodium pentobarbital (50 mg/kg) and intubation was performed. Animals were ventilated using a Galileo ventilator (Hamilton Medical,

Reno, NV). Continuous anesthesia with sodium pentobarbital (6 mg/kg/min) was delivered using a Harvard pump (Model 907, Harvard Apparatus, Mills, MA), while bolus infusions of pancuronium bromide was given to maintain paralysis.

Electrocardiogram (ECG) monitoring was performed using a pacemaker/defibrillator system (Zoll Medical, Burlington, MA). A right carotid artery cutdown was performed and 2 mm catheter placed to measure systemic artery pressure and for acquisition of arterial blood gas samples. A 7.5 French dual lumen catheter was placed into the adjacent internal jugular vein for maintenance of IV fluids, and infusion of *Escherichia coli* lipopolysaccharide (LPS). A 7 French Swan-Ganz thermodilution catheter (Baxter Explorer, Edwards Critical Care, Irvine, CA) was passed through the left femoral vein and directed into the pulmonary artery for tracing analysis to assess pulmonary artery pressure (PAP) and pulmonary artery wedge pressure (PAWP) and used to obtain mixed venous blood samples. The thermodilution function of the Swan-Ganz catheter was used to obtain cardiac output (CO) derived through a Baxter Explorer system (Edwards Critical Care, Irvine CA). Cardiac output measurements were made in duplicate at end-expiration.

Pressure was measured using Argon transducers (Model 049-992-00A, CB Sciences Inc., Dover, NH) leveled at the right atrium and recorded using a sixteen channel PowerLab/16s (AD Instruments Pty Ltd., Milford, MA) interfaced with a Dell Dimensions XPS R400 computer (Dell Inc., Dallas, TX).

Urine output was collected with a Foley catheter inserted directly into the bladder via cystotomy.

Hematological analysis before, during, and after CPB included arterial and venous blood gas measurements using a Model ABL5 blood gas analyzer, (Radiometer Medical A/S, Copenhagen, Denmark), hemoglobin levels using a Model OSM3 device (Radiometer Medical A/S) and sodium, potassium and ionized calcium electrolytes using a blood gas analyzer (AUTO-trol PLUS, AVL Scientific Corp., Roswell, GA).

Throughout the experiment (excluding the CPB portion), both groups received Lactated Ringers solution (25 ml/kg/hr) in addition to bolus infusions of Dextran 70 to maintain CO within 10% of baseline.

Ventilator management

The FiO₂ was fixed at 0.50 throughout the duration of the experiment. Initial tidal volume was set at 12 ml/kg with a rate of 15 breaths/min (BPM) and a positive end expiratory pressure (PEEP) of 3 cmH₂O. Adjustments were made in ventilatory rate to achieve a PaCO₂ = 40–50 mmHg. An Alveolar recruitment maneuver was performed each hour by sequentially increasing the PEEP to 5, 8, 10, and 15 cm H₂O over the course of 1 minute (limit peak pressure to < 40) and then back to 3 cm H₂O. *Car-*

diopulmonary bypass. A rollerpump (Sarns 7000 MDX Ann Arbor, MI) was used. The circuit consisted of a hard-shell venous reservoir (Sorin VRF 40 3500ml, COBE Cardiovascular Inc., Arvada, CO), a hollow fiber membrane oxygenator (Affinity NT 511T, Medtronic, Minneapolis, MN) and an arterial line filter (Dideco D 734, Sorin Biomedica, Irvine, CA). The arterial-venous loop and pump raceway consisted of 3/8 inch I.D. PVC tubing. The circuit was primed with 1200 ml Lactated Ringers, 25 mEq Sodium Bicarbonate, 3000 units heparin, 0.5 g/kg mannitol.

A surgical cutdown was performed to identify and isolate the right femoral artery and vein for cannulation. Following full dose heparinization (300 units/kg), a 16 French venous cannula (Biomedicus, Eden Prairie, MN) was advanced through the femoral vein and a 14 French arterial cannula (BARD, Murray Hill, NJ) was inserted into the femoral artery and connected to the CPB circuit.

Initiation of bypass was achieved initially with gravity drainage and once established, vacuum assisted venous drainage (VAVD) was implemented (suction regulator model 7720, Baxter, Deerfield, IL). Arterial pump flow rates were maintained at 50–100 ml/kg/min. Alpha-stat blood gas management was used to maintain arterial line blood gas parameters as follows: pH = 7.35–7.45, pCO₂ = 30–45 mmHg, pO₂ = 200–400 mmHg, and venous saturations of >60%. Mild hypothermia (rectal temperature –34°C) was induced during the first 15 minutes of bypass. Temperature was returned to normal over the subsequent course bypass.

Following weaning from CPB, circuit volume was transfused into the pig for volume replacement as needed.

Zero-balance Ultrafiltration

In addition to the above, the Z-BUF treatment group received zero-balance ultrafiltration during CPB according to Journois (15). The Z-BUF was circuit incorporated into the CPB circuit by accessing blood from the venous line with a 1/4 inch I.D. tubing. This tubing was passed through a rollerpump and into a hemoconcentrator (HPH 400, Minntech, Minneapolis, MN) returning the concentrated blood back to the venous reservoir. A 1/4 inch I.D. ultrafiltrate line was attached to the hemoconcentrator and passed through a rollerpump to evacuate ultrafiltrate volume to a collecting reservoir. To replace fluid at an equal rate, a 1/4 inch I.D. reinfusion line was spiked to crystalloid replacement fluid and passed through the same rollerpump returning to the venous reservoir. The replacement fluid consisted of Plasmalyte A (Baxter, Deerfield, IL) supplemented with 200 mg CaCl₂/liter.

Ten minutes after initiation of CPB, blood was pumped through the hemoconcentrator (250 ml/min) and the ultrafiltrate/reinfusion pump was set to a rate of approximately 100 ml/min. Five liters of ultrafiltrate was removed with five liters of replacement fluid added during CPB.

Endotoxin Infusion

Following CPB, pigs in both groups received endotoxin (1µg/kg) of *E. coli* lipopolysacchride (Sigma 111:B4) mixed in 500 ml of saline delivered intravenous over 1 hour.

Lung Water

Lungs were rapidly dissected and a lung tissue sample was removed and weighed following euthanasia. The sample was completely dried in an oven at 65°C and then re-weighed to establish a wet/dry ratio.

Histological Assessment

Following euthanasia, the right cardiac lung lobe was removed and excised and the hilar airway cannulated. Gluteraldehyde fixation (2.5% phosphate-buffered) was slowly instilled through the cannula until air was no longer displaced from the airway; then, the lung was submerged in gluteraldehyde and additional fixative was infused with a syringe while pressure was monitored with a mercury manometer. When the pressure of the fixative stabilized at 25 mmHg, the cannula was clamped and the tissue was stored at a 25 mmHg airway pressure in gluteraldehyde, at room temperature for at least 24 hours.

Each lung specimen was studied according to a stratified and random sampling method that assured the unbiased coverage of parenchymal structures lacking a homogeneous distribution. The fixated lung was dissected into a block approximately 15mm × 20mm as previously described (5). From this ten serial 7µ sections were made and individually mounted on numbered slides.

Morphometric quantification of lung tissue density and white blood cell infiltration was determined using a scoring system previously described (5).

Cytokine Assay

Blood samples were drawn before, during and after CPB. Plasma was extracted via centrifugation. The cytokine IL-8 (Biosource International, Camarillo, CA) was measured using a commercially available ELISA assay kit.

Statistics

The mean values reported represent the average for the group ± standard deviation. Statistical analysis was performed using Statview 4.01 (Abacus Concepts Inc., Berkely, CA). Data within groups were compared using a repeating ANOVA with Scheffe post hoc analysis. Data was compared between groups using an unpaired *t* test. A *p* value less than 0.05 were considered significant.

Animals

Animals were euthanized with an overdose of pentobarbital (90 mg/kg, IV). All animals received care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of

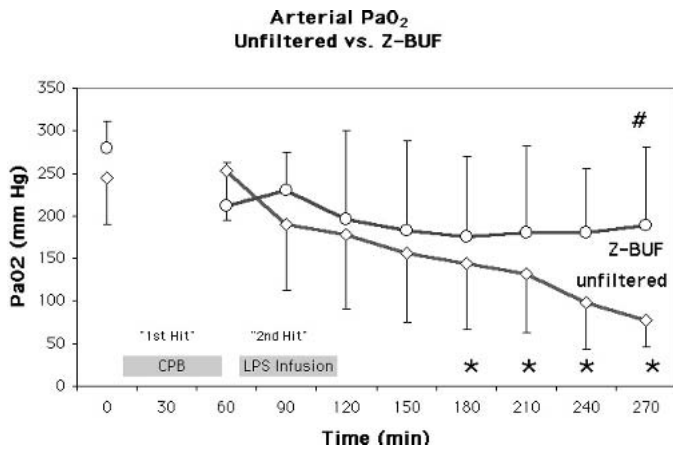


Figure 1. PaO₂ Comparison of Unfiltered Experimental Group, O, vs. Z-BUF Treatment Group, ◆. * denotes *p* < 0.05 compared to baseline (time 0). # denotes *p* < 0.05 between groups.

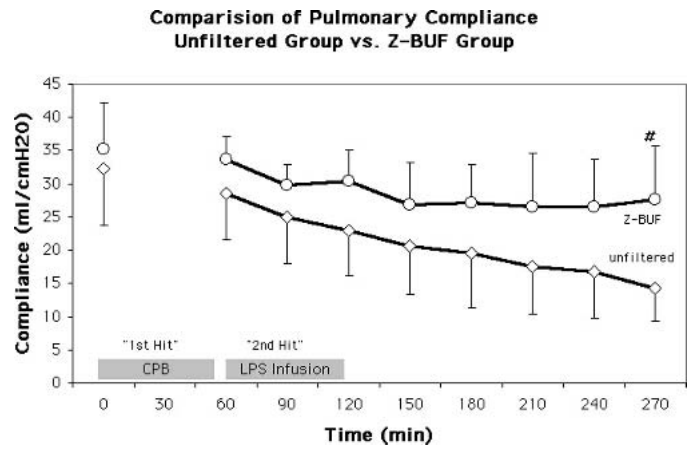


Figure 2. Pulmonary Compliance. Comparison of Unfiltered Experimental Group, O, vs. Z-BUF Treatment Group, ◆. * denotes *p* < 0.05 when compared to baseline (time 0). # denotes *p* < 0.05 between groups.

Health (NIH Publication 85-23, revised 1985). The protocol was approved by the Committee for the Humane Use of Animals at the SUNY Upstate Medical University, Syracuse, NY.

RESULTS

Physiologic Changes

Hemodynamics Average mean arterial pressure (MAP), pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP), and cardiac output (CO) in the unfiltered experimental group and Z-BUF treatment group during the experimental time course are illustrated in Table 1. There were no differences within groups regarding MAP, CO, and PAWP. Within each group there was a significant increase from baseline in PAP at the 90

minutes time point (30 minutes into LPS infusion). Following this timepoint, PAP (although lower than the 90-minute timepoint) remained above baseline in the unfiltered experimental group and significantly higher in the Z-BUF group. There were no differences between groups at the corresponding timepoints among these parameters.

Lung Function There was a significant fall in PaO₂ at the 180, 210, 240, and 270-minute timepoint in the unfiltered experimental group (CPB + LPS) when compared to baseline. The PaO₂ trended down in the Z-BUF treatment group [(CPB+ZBUF) + LPS], but was not significantly different from baseline at any time points (Figure 1). There was a significant difference (*p* = 0.036) in PaO₂ at the 270-minute timepoints in the unfiltered experimental and Z-BUF group, (78 ± 32.0 vs. 188.6 ± 92.5 mmHg, respectively).

Table 1. Hemodynamic response.

	Time	C.O.	MAP	PAWP	PAP
Unfiltered (n = 5)	0 (Begin CPB)	1.7 ± 0.6	100.2 ± 15.7	10.6 ± 2.7	30.6 ± 10.0
	60 (End CPB)	1.7 ± 0.6	104.0 ± 13.8	10.9 ± 2.3	27.6 ± 11.3
	90	1.5 ± 0.7	80.4 ± 15.1	12.9 ± 3.8	48.8 ± 7.6†
	120	1.5 ± 0.6	84.0 ± 39.1	12.0 ± 1.0	38.5 ± 6.0
	150	1.8 ± 0.6	89.2 ± 12.4	11.6 ± 1.8	34.8 ± 9.7
	180	1.5 ± 0.3	78.2 ± 16.7	12.2 ± 1.9	37.2 ± 5.5
	210	1.5 ± 0.3	77.6 ± 25.9	12.6 ± 1.8	38.0 ± 6.8
	240	1.3 ± 0.2	78.6 ± 31.6	13.3 ± 2.5	40.2 ± 7.3
Z-BUF Treatment (n = 5)	0 (Begin CPB)	2.0 ± 0.7	109.6 ± 9.1	10.0 ± 3.2	20.6 ± 4.9
	60 (End CPB)	1.7 ± 0.7	87.4 ± 21.9	10.4 ± 2.1	26.4 ± 5.6
	90	1.8 ± 0.7	105.0 ± 21.1	13.0 ± 2.4	46.6 ± 7.1†
	120	1.7 ± 0.6	89.2 ± 13.4	12.0 ± 2.2	34.6 ± 7.9
	150	1.7 ± 0.4	90.8 ± 12.3	11.5 ± 1.7	30.4 ± 6.8
	180	1.6 ± 0.5	86.6 ± 20.5	11.3 ± 1.2	30.8 ± 7.3
	210	1.7 ± 0.3	88.2 ± 22.7	13.8 ± 1.7	38.4 ± 8.2
	240	1.8 ± 0.6	92.8 ± 26.6	14.3 ± 3.4	34.2 ± 14.5
	270	1.6 ± 0.6	94.4 ± 27.4	14.5 ± 5.8	34.0 ± 14.3

†Denotes significantly different than baseline (0 time). Data mean ± SD.

Table 2. Electrolyte profile comparison.

Time Points	Sodium		Potassium		Calcium	
	Unfiltered	Z-BUF	Unfiltered	Z-BUF	Unfiltered	Z-BUF
Baseline	136.7 ± 2.2	135.6 ± 0.9	3.9 ± 0.5	3.9 ± 0.5	1.2 ± 0.02	1.24 ± 0.04
CPB-1	135.9 ± 0.8	137 ± 1.6	3.9 ± 0.5	3.7 ± 0.4	1.17 ± 0.08	1.14 ± 0.05
CPB-2	135.7 ± 1.8	135.2 ± 1.3	3.9 ± 0.2	3.7 ± 0.2	1.25 ± 0.09	1.19 ± 0.06
CPB-3	136.0 ± 1.8	135.8 ± 2.6	3.6 ± 0.2	3.8 ± 0.2	1.27 ± 0.07	1.14 ± 0.09*
Post CPB	137.4 ± 1.2	136.4 ± 2.0	3.6 ± 0.6	3.4 ± 0.5	1.22 ± 0.07	1.10 ± 0.12

* $p < 0.5$ vs. paired unfiltered group.
Data mean ± SD.

Static pulmonary compliance was significantly lower from baseline in the unfiltered experimental group at the 120-minute timepoint and remained significantly lower throughout the experiment. The Z-BUF group compliance was significantly lower than baseline at time points 150, 210, and 240 minutes, however, the final 270-minute timepoint was not significantly different than baseline in the Z-BUF group. There was a significant difference ($p = 0.013$) in the 270-minute timepoints between the unfiltered experimental group and Z-BUF group, (14.2 ± 4.7 vs. 27.6 ± 8.1 ml/cmH₂O, $p = 0.0134$, respectively) (Figure 2).

Electrolytes Average concentrations of sodium, potassium and ionized calcium at baseline, during CPB, and post CPB are shown in Table 2. When compared to baseline, there were no differences in average sodium and potassium concentrations during or after CPB. Ionized calcium was significantly lower at the CPB-3 time point in the Z-BUF group when compared to the unfiltered experimental group, (1.14 ± 0.09 vs. 1.27 ± 0.07) mmol/L respectively.

Lung water Lung water, as determined by the W/D ratio, was highest in the unfiltered experimental group, 8.44 ± 0.81 , and significantly greater than the Z-BUF group, 6.05 ± 0.65 ($p = 0.002$).

Histologic Analysis Under microscopy, lung sections showed visible differences in lung structure between groups (Figure 3). Morphometric quantification of sections (Table) indicated significant increases in alveolar tissue density and polymorphonuclear leukocyte (PMN) and monocyte sequestration in the unfiltered experimental group as compared to the Z-BUF treatment group. There were no significant differences in alveolar macrophage counts between groups.

Interleukin-8 Analysis Serum concentrations of IL-8 showed a high degree of variability in comparative serum samples within groups. There were no significant differences between groups at any time points during or after CPB. IL-8 levels trended higher at the 180 minute time point in both groups.

DISCUSSION

Lung injury following cardiopulmonary bypass contin-

ues to be a clinically relevant problem. A recent study suggests that the while incidence of PPS following CPB is only 1%, the associated mortality remains unacceptably high (40–60%) (16).

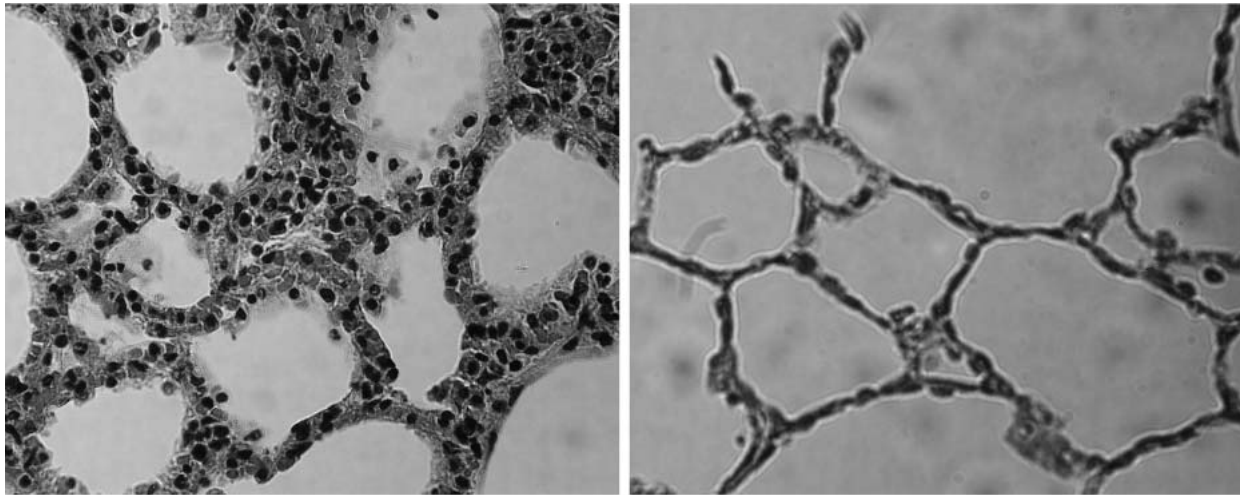
This study confirms earlier work demonstrating that PPS following CPB can be caused by sequential, seemingly innocuous insults. (2,3,5,6). The important findings of this study are that high volume, Z-BUF appears to significantly attenuate the normal progression of PPS in this model. Our two-hit (CPB then LPS) PPS model consistently produces profound pulmonary dysfunction resulting in cardiovascular collapse. Using this model, Z-BUF reduced pulmonary edema reflected in lung wet/dry ratios and improved pulmonary compliance. Histologically, lung sections from the Z-BUF group appeared to have more normal morphology than the unfiltered experimental group with less leukocyte infiltration into alveolar tissue. In addition, the abrupt decline in arterial PO₂'s normally seen in this model were attenuated and showed no significant changes in the experimental time course. The pulmonary compliance and arterial PO₂'s did appear to be trending downward, but it is unknown whether pulmonary collapse would have ultimately occurred with a longer period of time. The exact mechanism for the effectiveness of Z-BUF remains unclear.

It is compelling to conclude ultrafiltration removes one or more detrimental mediators (e.g., cytokines, complement) from the blood stream through bulk convection across the hemoconcentrator membrane. In pediatric CPB, modified ultrafiltration MUF (performed post-CPB) has been shown to reduce total body water, increase arterial blood pressure, and decrease pulmonary vascular resistance. There have been reports that this technique

Table 3. Morphologic quantification of cell number and tissue density per 6,400 μm².

Morphological Quantification	Unfiltered	Z-BUF	P-value
Tissue density	29.7 ± 16.6	20.7 ± 7.7	.0011
PMNs	3.6 ± 2.0	1.5 ± 1.4	<.0001
Monocytes	4.9 ± 3.1	2.6 ± 2.1	<.0001
Macrophages	3.0 ± 1.9	2.6 ± 1.8	0.2343

Data mean ± SD.



A. Unfiltered Group

B. Z-BUF Group

Figure 3. Histologic comparison of Unfiltered Experimental Group (A) and Z-BUF group (B). Note the increased alveolar density and thickness was reduced with Z-BUF.

can reduce inflammatory mediators (12–14). Other studies have shown that MUF can actually increase levels of some inflammatory mediators such as TNF (16).

The effectiveness of Z-BUF may be related to the continuous replacement of ultrafiltrate of “fresh” crystalloid solution and thereby diluting out offending mediators. A study comparing Z-BUF, MUF, and a combination approach, found that Z-BUF was effective at reducing concentrations of inflammatory mediators while MUF was not (17). In this study, no differences were seen in the concentration of IL-8 before during and after bypass between groups. This study limitation does not rule out the possibility that the profile of other cytokines were affected by Z-BUF.

This study shows that Z-BUF is effective in reducing pulmonary dysfunction in a PPS model. The clinical application of this technique may be warranted in patient populations at risk or vulnerable to CPB-induced pulmonary dysfunction.

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