Artificial Organs

Zero-Balance Ultrafiltration of Priming Blood Attenuates Procalcitonin and Improves the Respiratory Function in Infants After Cardiopulmonary Bypass: A Randomized Controlled Trial

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Abstract: Blood priming is needed for cardiopulmonary bypass (CPB) in neonates and infants to avoid exceeding hemodilution; however, transfusion-related inflammation affects post-CPB outcomes in infant open-heart surgery. Procalcitonin, a newly detected inflammatory moderator and a sensitive parameter for predicting pulmonary dysfunction secondary to CPB, rises after CPB. We hypothesized that the hemofiltration of priming blood before CPB might decrease inflammatory mediators in the blood and post-CPB inflammatory replications, thereby improving the respiratory function after CPB in infants. Sixty infants with a weight below 10 kg were divided randomly into two equal groups of CPB with the zero-balance ultrafiltration (Z-BUF) of priming blood and CPB without it. The procalcitonin level was measured before anesthesia, after admission to the intensive care unit (ICU), and 24 h afterward. The respiratory index and pulmonary compliance were measured after anesthesia, at the end of CPB, and 2 h after admission to the ICU. Additionally, time to extubation was recorded. The Z-BUF of priming blood maintained electrolytes within a physiologic level, and procalcitonin had a slighter rise in the Z-BUF Group at 24 h after admission to the ICU ($P = 0.05$). The respiratory index was decreased in the Z-BUF Group, but the difference with the control group did not reach statistical significance ($P > 0.05$). The change in pulmonary compliance was significantly increased in the cyanotic patients in the intervention group, but there was no significant difference between the two groups. The time to extubation and the ICU stay were shorter in the Z-BUF Group ($P < 0.05$). A positive correlation was found between the peak procalcitonin concentration and the time to extubation directly and pulmonary compliance reversely. These results suggest that the Z-BUF of priming blood may have some beneficial clinical effects such as improved respiratory function and attenuated procalcitonin. **Key Words:** Cardiopulmonary bypass–Infant–Respiratory function test–Ultrafiltration–Procalcitonin.

To preserve the hematocrit level of infant patients and to prevent hemodilution during cardiopulmonary bypass (CPB), most cardiac surgery centers prime the CPB circuit with homologous packed red blood cells (PRBCs). Because PRBCs have excessive inflammatory cytokines, potassium, lactic acid, and other metabolic products—which may harm infants—it is useful to eliminate these products before CPB (1). The plasma from stored PRBCs has been shown to activate neutrophils and to promote an inflammatory reaction (2). The ultrafiltration of priming blood can diminish the initial rush of inflammatory mediators after the beginning of CPB and prevent the increment of cytokines thereafter (3). Procalcitonin is a protein of 116 amino acids with a molecular weight of 13 kDa (4). During CPB, the release of tumor necrosis factor, interleukin-1 IL-1), IL-2, and IL-6 leads to

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a rise in the procalcitonin level. Procalcitonin seems to be a sensitive diagnostic parameter for pulmonary dysfunction secondary to CPB (5).

It has been suggested that zero-balance ultrafiltration (Z-BUF) simplifies the elimination of inflammatory mediators and corrects the postoperative pulmonary function (6). Hypothesizing that the Z-BUF of priming blood might decrease the procalcitonin level and lessen pulmonary injury, we conducted the present randomized controlled trial to assess the effects of this priming method on the procalcitonin concentration and the postoperative pulmonary function among infants following CPB.

PATIENTS AND METHODS

Study design and patients

The current randomized controlled trial was approved by the Ethics Committee of Rajaie Cardiovascular, Medical, and Research Center, Iran University of Medical Sciences, Tehran, Iran (approval code: RHC.AC.IR.REC. 1396.45), and informed consent was obtained from the parents of all the infants recruited. The criteria for the inclusion of infants were comprised of being younger than 18 months old, weighing less than 10 kg, having a congenital heart disease, being scheduled for corrective surgery on CPB in the department of cardiovascular surgery of the abovementioned hospital, having no other major congenital anomalies, and having no history of previous surgery. Patients were excluded if they were older than 18 months at the time of surgery and had preoperative mechanical ventilation. Thirty infants who underwent CPB with the Z-BUF of priming blood (Z-BUF Group) were compared with 30 infants who underwent CPB without that process (non—Z-BUF Group). During surgery, conventional ultrafiltration was used for the patients in both groups. The anesthetic and surgical techniques as well as the strategy for CPB were similar in the two study groups.

Anesthesia and cardiopulmonary bypass

Anesthesia was induced with 10 μg/kg of fentanyl and 0.1 mg/kg of midazolam. Standard monitoring—including pulse oximetry, ECG leads II and V, and continuous measurements of arterial and central venous pressures as well as nasopharyngeal temperature—was conducted. Efforts were made to sustain a balanced anesthetic technique via the use of fentanyl and intermittent boluses of pancuronium bromide at 0.1 mg/kg every 45 minutes. Anesthesia was maintained using 0.5 mg/kg/hr of fentanyl and 1.0 μg/kg/min of midazolam. Ventilation was adjusted to reach a partial arterial oxygen pressure (PaO_2) above 150 mm Hg and a partial arterial carbon dioxide pressure ($PaCO_2$) between 30 and 35 mm Hg. A median sternotomy was performed in all the patients, and CPB was established in standardized manner through the use of the roller pump and the nonpulsatile flow via the cannulation of the superior and inferior vena cavae and the ascending aorta. A heparinization protocol of 300 U/kg was followed to maintain the activated clotting time at more than 480 seconds. Systemic hypothermia (28°C) was established upon the cross-clamping of the aorta and the temperature was increased to 37°C after aortic declamping. Alpha-stat blood gas management was applied in all the procedures. Filters (Kewei Medical Instrument Company, Dongguan, China), roller pumps (SV Roller Pump, Stockert, Munich, Germany), and oxygenators (D901 or D902 Lilliput, Sorin Group Italia, Modena, Italy) were utilized. The recirculation line from the arterial filter was connected to the inlet of a polysulfone hemofilter (Capiox HC 11S, Terumo Corporation, Tokyo, Japan). The outlet of the hemofilter was drained into the venous reservoir. The initial perfusion flow rate was 150 mL/kg/min, which was subsequently adjusted based on the temperature and the venous blood oxygen saturation. The Z-BUF of priming blood was initiated at a rate of 300 mL/min and 150–180 mm Hg of positive pressure after the use of priming Ringer's, albumin 2%, and 10 mL of $NaHCO_3$ 7.5%. There was an addition of PRBCs, to reach a hematocrit level of 25–28%, and 20 mg of heparin. The volume of the replacement fluid (Ringer's and NaCl 0.45%) used was 40 mL per 10 mL of PRBCs. An additional 1000 U of heparin was given after the Z-BUF of priming blood, and a $NaHCO_3$ 7.5% solution was injected as needed according to the blood gas analysis of the priming solution.

Ventilator management

After the operations, all the patients were placed on a respirator in the synchronized intermittent mandatory ventilation mode upon arrival at the intensive care unit (ICU). The initial ventilator settings were as follows: intermittent mandatory ventilation rate of 25–30 breaths/min, airway peak pressure of 18 cm H_2O, positive end-expiratory pressure (PEEP) of 3–5 cm H_2O, and inspired oxygen fraction (FiO_2) of 70%. The patients were extubated once the following criteria had been met: FiO_2 of 60%, PEEP of 5 cm H_2O, intermittent mandatory ventilation rate of 5 breaths/min, spontaneous breath tidal volume of 5 mL/kg, PaO_2 of 80 mm Hg, and $PaCO_2$ of 50 mm Hg.

Blood sampling

The levels of electrolytes and lactate were measured before the Z-BUF of priming blood and after filtration (before the administration of the other priming solutions). Blood samples required

for detecting procalcitonin were obtained from the patients' arterial line at the following time points: before the operation (T1), after admission to the ICU (T2), and at 24 h after the operation (T3). Procalcitonin detection was carried out using a Cobas E601 electrochemiluminescence immunoassay analyzer (Roche, Basel, Switzerland). The results are expressed as ng/mL.

Pulmonary function test

The pulmonary function parameters, comprising the respiratory index (RI) and pulmonary compliance (PC), were computed preoperatively after the induction of anesthesia, at the end of the operation, and 2 h postoperatively using the following formula: PC = TV/(P peak—PEEP), RI = P(A_a)O_2/PaO_2, P(A_a)O_2 = (P atmosphere_P steam) × FiO_2_$PaCO_2$_PaO_2, where P atmosphere equals to 664 mm Hg, P steam is 47 mm Hg, and FiO_2 is the fraction of the inspired oxygen (1). The patients' times to extubation were also recorded.

Statistical analysis

The collected data were analyzed with IBM SPSS Statistics 20 for Windows (IBM Inc, Armonk, NY, USA). The normal distribution for the interval data was confirmed using the one-sample Kolmogorov–Smirnov test. The normally distributed data were expressed as means ± standard deviations, and medians (interquartile ranges) were applied for the non-normally distributed variables. The categorical data were described as counts (%). Comparisons between the study groups were performed via the Student's *t*-test (for the interval data with normal distributions), the Mann–Whitney *U*-test (for the interval data without normal distributions), and the Pearson's χ^2 or Fisher exact test (for the nominal data). Changes in the interval variables over time were investigated using the repeated measure analysis of variance models. The relationships between the peak procalcitonin concentration and the time to extubation and PC were investigated using the Pearson correlation coefficient (*r*). Multivariate analysis was performed with a multiple linear regression model. A *P* value equal to or less than 0.05 was considered statistically significant.

RESULTS

The patients' characteristics and their CPB data are presented in Table 1. As is depicted in Table 1, there were no significant differences in terms of age, body weight, and congenital heart disease type between the Z-BUF Group and the non—Z-BUF Group. Furthermore, no differences were found between the two groups with respect to the CPB time and aortic cross-clamp time. The difference in the mean volume of the ultrafiltrate collected during conventional ultrafiltration failed to reach statistical significance between the groups (190 ± 56 mL in the case group vs 181 ± 64 mL in the control group). The volume of the ultrafiltrate obtained in the Z-BUF of priming blood was 381 ± 146 mL.

Procalcitonin

Compared with the baseline, the procalcitonin level began to increase postoperatively. The peak procalcitonin concentration rose at 24 h after the operation. The peak procalcitonin concentration of the Z-BUF Group exhibited a smaller rise than that in the non—Z-BUF Group, with the difference constituting statistical significance (*P* = 0.05) Table 2. A

TABLE 1. *Comparisons of the patients' characteristics between the 2 groups*

Variable	Z-BUF Group (*n* = 30)	Non–Z-BUF Group (*n* = 30)	P
Age (mo)*	9 ± 5.7	5.1 ± 6	0.19
Sex			
(female %)†	15(50%)	10(33.3%)	0.44
(male %)	15(50%)	20(66.6%)	—
Weight (kg)*	6.5 ± 2.2	6.4 ± 2.4	0.83
Cross-clamp time (min)‡	92.5(70–120)	90(56–125)	0.68
CPB time (min)*	140 ± 37	142 ± 48	0.85
Volume of CU (mL)*	192 ± 58	189 ± 66	0.81
Volume of the blood primed with Z-BUF (mL)*	—	381 ± 148	—
CHD type†	—	—	—
(cyanotic %)	20(66.7%)	17(56.7%)	0.42
(acyanotic %)	10(33.3%)	13(43.3%)	—
Time to extubation (h)‡	17(15–36)	20(17–60)	0.03

Data are presented as *mean ± SD, †count(%), or ‡medians (IQR 25-75).
Z-BUF, zero-balance ultrafiltration; CPB, cardiopulmonary bypass; CU, conventional ultrafiltration; CHD, congenital heart disease

TABLE 2. *Comparisons of the mean serum procalcitonin level (ng/mL) between the 2 study groups*

	Baseline	At ICU Admission	24 h Postoperatively
Z-BUF Group	0.2 ± 0.26	1.2 ± 1.4	2.1 ± 1.6
Non–Z-BUF Group	0.3 ± 0.37	1.9 ± 1.3	3.3 ± 2.7
P	0.2	0.8	0.05*

Data are reported as means ± SDs.
Z-BUF, zero-balance ultrafiltration; ICU, intensive care unit
*$P < 0.05$ compared with the Non—Z-BUF Group; *P* for the main effect of time = 0.001; *P* for interaction = 0.12.

positive correlation was observed between the peak procalcitonin concentration and the time to extubation directly ($P = 0.001$) and PC reversely ($P = 0.003$) Table 3.

Respiratory function

The postoperative mechanical ventilation time was significantly lower in the Z-BUF Group than in the non—Z-BUF Group (17 [15–36] vs. 20 [17–60]; $P = 0.03$).

In the cyanotic patients, the two groups had a decreasing trend (*P* for the main effect of time = 0.001) in the RI; this decrease was similar in both groups and did not differ significantly at the different time points (*P* for interaction = 0.4) Fig. 1. According to Fig. 1, in the acyanotic patients, there was an increasing trend in the RI and this trend was similar in both groups and did not differ significantly at the different points of time (*P* for the main effect of time = 0.01 and *P* for interaction = 0.24).

In the cyanotic patients, PC was significantly decreased in the Non—Z-BUF Group over time, whereas a recovery and increasing trend was observed at T2 in the Z-BUF Group—with the course of change being statistically significant (*P* for the main effect of time = 0.003 and *P* for interaction = 0.02) Fig. 2.

There was no change in the amount of PC in the subgroup of acyanotic patients over time, and the type of intervention did not change this index (*P* for the main effect of time = 0.58 and *P* for interaction = 0.67) Fig. 2.

After adjustments were made for the other covariates via multivariate analysis, it was observed that the Z-BUF of priming blood significantly reduced procalcitonin ($\beta = -1.15 \pm 0.48$; $P = 0.02$) and increased PC ($\beta = 0.99 \pm 0.31$; $P = 0.002$). In addition, the body surface area affected the RI more than any of the other variables ($\beta = 11.3 \pm 4.3$; $P = 0.010$).

TABLE 3. *Correlations between the peak procalcitonin level and PC and the time to extubation*

	Peak Procalcitonin Level	
	Correlation coefficient	*P*
Time to extubation	0.44	0.001
PC (mL/cmH_2O) at ICU	– 0.38	0.003

$P < 0.05$ illustrates a positive correlation between the peak procalcitonin concentration and the time to extubation directly and PC reversely.
PC, pulmonary compliance; ICU, intensive care unit

DISCUSSION

Current infant CPB circuits require priming with PRBCs. Nonetheless, PRBCs—especially when stored for long periods of time—tend to generate an inflammatory response and may contribute to myocardial and pulmonary dysfunction following CPB (7). The release of inflammatory media such as tumor necrosis factor, IL-1, IL-2, and IL-6 leads to an increment of procalcitonin (5). The Z-BUF of priming blood is capable of washing out the inflammatory media from the blood stored for the priming of the CPB circuit (8). Level et al. (9) suggested that in septic patients, the effect of procalcitonin removal with a conventional continuous venovenous hemofiltration substitution fluid rate (<2.5 L/h) on the plasma concentration of procalcitonin was limited. In our study, the procalcitonin level was significantly lower in the Z-BUF Group within 24 h after surgery, which may have been a result of the clearance of inflammatory media through the Z-BUF of the priming blood. In a study by Song et al. (5), the procalcitonin concentration of the intervention group was lower than that of the control group at 12 h and 48 h postoperatively, but the difference was not statistically significant—probably due to their small sample volume and the significant impact of their use of the filter on the priming blood. We found that the RI in the Z-BUF Group was better in the cyanotic patients than that in the cyanotic patients of the non—Z-BUF Group, but there was no significant difference between the groups in all the cyanotic and acyanotic patients. In contrast to our finding, Zhou et al. (1) in their study achieved statistical significance differences. The disparity between our results may have stemmed from differences in methods insofar as in their investigation, ultrafiltration was accomplished for the circuit's prime solution, Z-BUF was accomplished

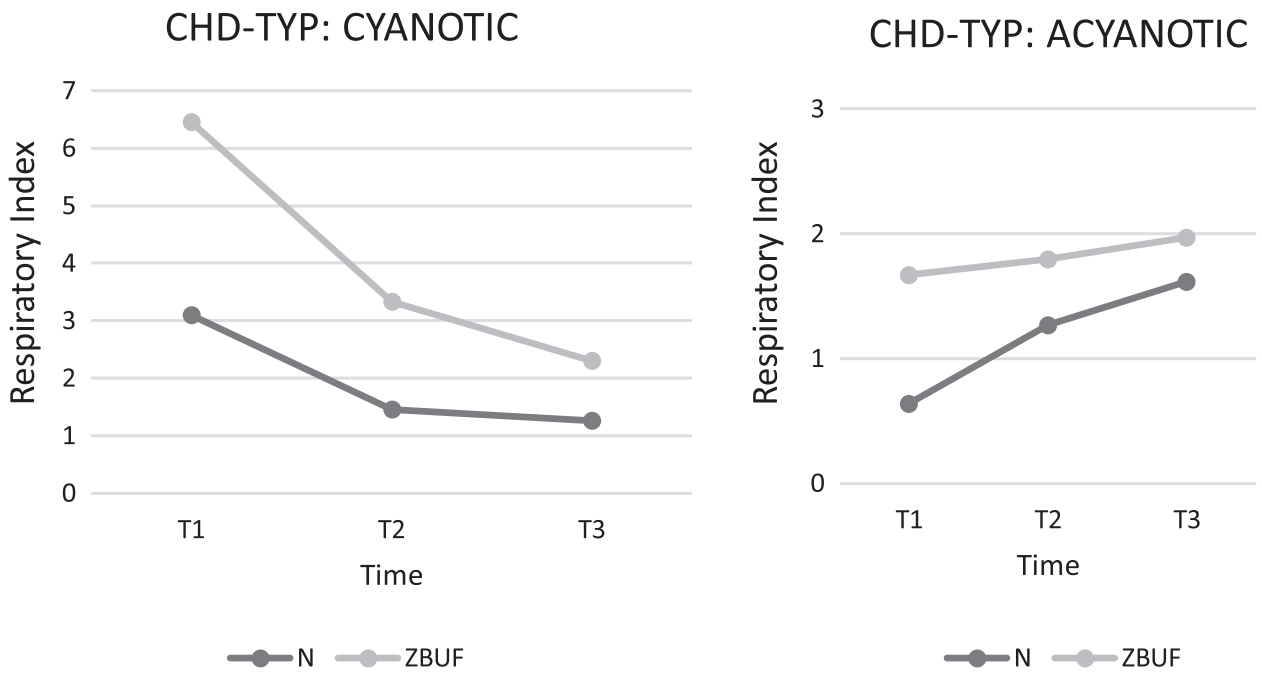

FIG. 1. Comparisons of the respiratory index between the intervention and control groups in the subgroups of cyanotic and acyanotic patients. PZBUF, zero-balance ultrafiltration of priming blood; CHD, congenital heart disease.

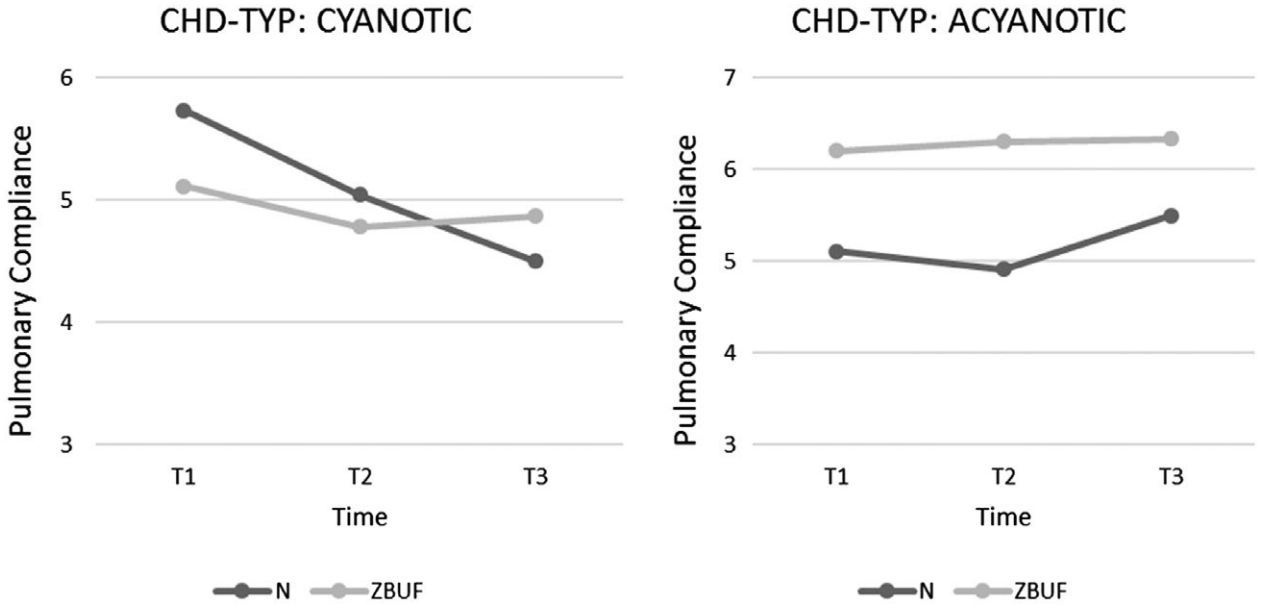

FIG. 2. Comparisons of pulmonary compliance between the control and intervention groups in the subgroups of cyanotic and acyanotic patients. PZBUF, zero-balance ultrafiltration of priming blood; CHD, congenital heart disease.

after the removal of the aortic clamp, and modified ultrafiltration was performed after the completion of CPB; in addition, this combination must have exerted a more significant impact on the RI (1). PC in the present study was not significantly different between the two groups at post-anesthesia stages, the end of the pump, and 2 h after admission to the ICU. However, the trend in time changes in the cyanotic patients in the Z-BUF Group was significantly increased. We also found a direct correlation between the peak procalcitonin concentration and the time to extubation. Song et al. (5) investigated the effects

of Z-BUF on the procalcitonin level and the respiratory function among infants with the tetralogy of Fallot after CPB. They reported that PC in the intervention group was increased compared with that in the control group at 12 h postoperatively and there was a positive correlation between the peak procalcitonin concentration and the time to extubation. In our study, we observed a significant correlation between the peak procalcitonin concentration and the PC level. This clinical improvement in the respiratory function, according to the existing literature, can be attributed to the reduction in the concentration of procalcitonin (5).

CONCLUSIONS

The zero-balance ultrafiltration of priming blood could reduce the risk of injury induced by inflammatory mediators after cardiopulmonary bypass initiation. In addition, this method may prevent an increase in inflammatory mediators during and after CPB, thereby diminishing the ensuing respiratory complications. We recommend that future studies be conducted with larger sample sizes to determine whether the application of the Z-BUF of priming blood can improve other postoperative outcomes. Furthermore, inflammatory factors in the priming solution before CPB and in patients' blood during CPB should be measured so as to assess the patterns between the Z-BUF and non—Z-BUF of priming blood vis-à-vis clearance through ultrafiltration or an inhibitory process for proinflammatory factors.

Conflict of Interest: The authors have declared no conflicts of interest for this article.

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