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Effect of Subzero-Balanced Ultrafiltration on Lung Gas Exchange Capacity after Cardiopulmonary Bypass in Adult Patients with Heart Valve Disease

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ABSTRACT

Objectives: This study was conducted to evaluate the effect of a new ultrafiltration technique—the subzero-balanced ultrafiltration (SBUF)—on lung gas exchange capacity after cardiopulmonary bypass (CPB) in adult patients with heart valve disease.

Background: Attenuation of lung gas exchange capacity is one of the most common manifestations of an inflammatory response after CPB.

Methods: Ninety-four patients who required CPB for cardiac surgery were randomized into 2 groups according to whether they received SBUF. Gas exchange capacity expressed as the oxygen index (OI), the respiratory index (RI), and the alveolar-arterial oxygen pressure difference ($P_{(A-a)}O_2$) were measured after intubation (T_1), at the termination of CPB (T_2), on admission to the intensive care unit (ICU) (T_3), at postoperative hour 6 (T_4), and at postoperative hour 12 (T_5).

Results: There were no significant differences in gas exchange capacity between the 2 groups at T_1, T_4, and T_5. CPB produced significant changes in OI, RI, and $P_{(A-a)}O_2$ in the control group, whereas these changes were not significantly different in the study group. The OI in the study group was significantly higher at T_2, and RI and $P_{(A-a)}O_2$ were significantly lower at T_2 and T_3. In the study group, the intubation time was shorter, and the transfusion volume within 24 hours postoperatively was less. The 2 groups were comparable with respect to the incidence of respiratory complications, length of stay in the ICU, duration of hospital stay, need for infusions of inotropic agents, and drainage volumes within 24 hours postoperatively.

Conclusions: SBUF during CPB can produce an immediate improvement in lung gas exchange capacity, which may effectively minimize pulmonary dysfunction in adult patients undergoing cardiac surgery.

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INTRODUCTION

The nonphysiological procedure of cardiopulmonary bypass (CPB) during open heart surgery can cause systemic inflammatory response syndrome and thus contribute to postoperative pulmonary dysfunction [Kirklin 1983; Tönz 1995; Wan 1997]. The disturbance in pulmonary function after CPB may be manifested as conditions that range from clinical pulmonary dysfunction in most patients, to acute respiratory distress syndrome in <2% of cases [Messent 1992; Asimakopoulos 1999], thereby leading to increased postoperative morbidity and mortality [Marenzi 2001]. Observations have demonstrated that modified ultrafiltration (MUF) after CPB can effectively minimize pulmonary dysfunction and that zero-balanced ultrafiltration (ZBUF) performed during CPB can improve pulmonary oxygenation [Journois 1996; Huang 2003; Berdat 2004; Mahmoud 2005]. The purpose of this study was to observe the impact of a new ultrafiltration technique—subzero-balanced ultrafiltration (SBUF)—on the postoperative lung gas exchange capacity of adults undergoing cardiac operations.

MATERIALS AND METHODS

Patient Selection

After obtaining approval from the Hospital Ethics Committee, all consecutive patients who were ≥18 years old and with heart valve disease and who were referred to our institution for a cardiac surgical procedure requiring the use of CPB between July 1 and September 31, 2009, were eligible for the study. All patients provided written informed consent. Exclusion criteria were an age <18 years, diabetes, kidney disease, infection, bleeding diathesis, and failure to obtain consent. Ninety-four patients were subsequently enrolled and randomized to receive either SBUF (SBUF group, n = 49) or no ultrafiltration (control group, n = 45).

Operative and Anesthesia Management

Patients received oral midazolam (0.7 mg/kg) as premedication. Anesthesia was induced and maintained with a continuous infusion of 4 μg/kg midazolam per minute and 5 μg/kg fentanyl per minute. Vecuronium boluses (0.1 mg/kg) were administered as required. All patients were intubated orally

with cuffed endotracheal tubes. The operative procedure was performed in accordance with local hospital policies and protocols.

Perfusion Technique

The extracorporeal circuit included a hollow-fiber membrane oxygenator (Polystan Safe Maxi; Maquet, Hirrlingen, Germany) and a roller pump system (Stockert; Sorin Group, Munich, Germany). The circuit was primed with lactated Ringer solution, $NaHCO_3$, and hydroxyethyl starch 130/0.4. Anticoagulation management was achieved with the Hemochron microcoagulation system (Jr. Signature II; ITC Europe Strade Rivoltana, Rodano, Italy). Heparin was administered to maintain an activated coagulation time of >480 seconds. Cannulation was accomplished by using the ascending aorta for the inflow and the right atrium or 2-stage caval cannulae for the outflow. During CPB, nonpulsatile flow was maintained at 1.8 to 2.4 L/min per m^2 to achieve a venous saturation of 65% to 75%. Mean arterial blood pressures were targeted at 40 to 70 mm Hg by the addition of phenylephrine or isoflurane as required. Packed red cells were added to the priming solution whenever necessary to maintain a minimum calculated hematocrit of 25%. Arterial blood gases were measured every 20 to 30 minutes to maintain the arterial CO_2 partial pressure between 35 and 40 mm Hg (unadjusted for temperature [alpha-stat]) and the oxygen partial pressure between 150 and 250 mm Hg. Cooling was achieved with an in-line heat exchanger (3T Heater-Cooler System 3T; Sorin Group) to achieve a moderate hypothermic state (rectal temperature, 28°C) for all patients. Once surgery was completed, patients were rewarmed to 36°C to 37°C and weaned from CPB. One milligram of protamine sulfate was administered for every 100 IU of the total heparin dose to reverse the anticoagulant effect of heparin. Aprotinin was never used during the study period.

Myocardial protection was achieved with antegrade intermittent cold blood cardioplegia via a standard 4:1 integrated delivery set (MYOtherm XP 41-B; Medtronic, Minneapolis, MN, USA). The initial dose of cardioplegia was 20 mL/kg and was followed by half the initial dose every 20 minutes, or earlier if electrical activity returned. Before aortic declamping, 500 mL warm blood cardioplegia was administered at 37°C for 2 minutes at a pressure of 50 mm Hg.

SBUF Technique

SBUF was accomplished with a Terumo hemofilter that uses polysulfone fibers (CAPIOX Hemoconcentrator CX-HC11S; Terumo Corporation, Tokyo, Japan). The hemofilter was placed in the CPB circuit with blood access from the 1/4-in recirculation port of the microembolus filtrator and return to the venous reservoir of the membrane oxygenator. SBUF was initiated with the start of aortic clamping. Filtration rates were adjusted to 10 to 20 mL/kg during the aortic-clamping period. They were adjusted to 50 to 100 mL/kg during the rewarming period and for extreme target effluent removal of 1 to 3 equivalent blood volumes during the procedure. Lactated Ringer solution or packed red cells were administered to maintain sufficient venous reservoir volumes and a minimum calculated hematocrit >25%. For achieving a subzero-balanced state during the entire SBUF procedure, we applied a vacuum-assisted venous drainage (VAVD) system (VAVD Controller; Maquet) and controlled the negative pressure to –20 to –40 mm Hg to maintain sufficient venous reservoir volumes. The processed residual circuit volume was returned to the patient through an intravenous line. The volumes of fluid administered, including cardioplegia crystalloid, effluent removed, and resulting balance, were recorded in the perfusion record.

Gas Exchange Capacity Measurements

We measured the lung gas exchange capacity, which was expressed as the oxygen index (OI), the respiratory index (RI), and the alveolar-arterial oxygen pressure difference ($P_{(A-a)}O_2$), at 5 times: after intubation (T_1), at the termination of CPB (T_2), on admission to the intensive care unit (ICU) (T_3), at postoperative hour 6 (T_4), and at postoperative hour 12 (T_5). OI was calculated according to the following formula:

$$OI = MAP \times FiO_2/PaO_2,$$

where MAP is the mean airway pressure, FiO_2 is the fraction of inspired oxygen, and PaO_2 is the arterial partial pressure of oxygen. $P_{(A-a)}O_2$ was calculated according to the following formula:

$$P_{(A-a)}O_2 = [FiO_2 \times (760 - 47)] - PaCO_2/R - PaO_2,$$

where 760 is the barometric pressure at sea level in millimeters of mercury, 47 is the water vapor pressure in millimeters of mercury at 37°C, $PaCO_2$ is the arterial partial pressure

Table 1. Demographic and Operative Data*

	Control Group	SBUF Group	*P*
Patients, n	45	49	—
Male sex, n	29 (64%)	27 (55%)	.357
Age, y	63.8 ± 11.8	61.5 ± 12.6	.355
Weight, kg	66.2 ± 13.9	61.3 ± 14.3	.101
Previous cardiac operation, n	1 (2%)	2 (4%)	.940
Tricuspid valve disease, n	20 (44%)	24 (49%)	.659
Procedure(s), n			
AVR	10	13	.627
MVR/repair	2	5	.288
MVR/repair + TVP	17	21	.616
AVR + MVR + TVP	8	7	.644
AVR + CABG	2	3	.717
NYHA class, n			
II	9	10	.796
III	25	24	.524
IV	11	15	.504

*Data are presented as the number (percent) or as the mean ± SD. SBUF indicates subzero-balanced ultrafiltration; AVR, aortic valve replacement; MVR, mitral valve replacement; TVP, tricuspid valvuloplasty; CABG, coronary artery bypass graft surgery; NYHA, New York Heart Association.

of CO_2, and R is the respiratory exchange ratio. The RI was calculated according to the following formula:

$$RI = P_{(A-a)}O_2/PaO_2.$$

Statistical Methods

Statistical analysis was performed with SPSS software (version 11; SPSS, Chicago, IL, USA). Continuous variables were expressed as the mean ± SD, and values for the 2 groups were compared by a 2-tailed Student *t* test. Multiple mean values were compared by analysis of variance. Discrete variables were expressed as percentages, and values were evaluated with the Pearson χ^2 test. Statistical significance was inferred at *P* values <.05.

RESULTS

Ninety-four patients were enrolled in this study. Demographic characteristics, diagnoses, and operation procedures were similar for the 2 groups (Table 1).

There were no statistically significant differences between the 2 groups in priming volume, duration of CPB, duration of aortic cross-clamping, and intraoperative cell saver volume. The percentage of patients requiring tranexamic acid after perfusion and the mean amount of blood products transfused were similar for the 2 groups (Table 2). In contrast, the SBUF group had a more negative mean intraoperative fluid balance and a larger mean filtrate volume. On average, SBUF yielded 30 mL of filtrate per kilogram body weight. The mean fluid balance during CPB in the treatment group (–1147.92 ± –564.02 mL) was significantly different from that in the control group (878.91 ± 189.68 mL, *P* < .0001). This difference was greater in the patients with severe congestive heart failure (–2421.03 ± –926.45 mL in the SBUF group versus 811.36 ± 375.31 mL in the control group, *P* < .0001). In addition, the mean hematocrits were similar in the 2 groups before CPB but were much higher in the SBUF group after CPB (30.69% ± 3.42% versus 34.25% ± 4.15%, *P* < .0001) (Table 2).

After the operations, the incidence of respiratory complications was lower in the SBUF group, and the lengths of stay in the ICU and the hospital were shorter. These differences did not reach statistical significance, however. Similar results were observed with respect to the need for inotropic agent infusion and drainage volume within 24 hours postoperatively. On the other hand, the SBUF group had a much shorter mean intubation duration and a much lower mean transfusion volume within 24 hours postoperatively (14.50 ± 2.43 hours versus 18.02 ± 2.36 hours, *P* < .0001; 2.27 ± 2.27 units/patient versus 3.76 ± 3.07 units/patient, *P* = .009) (Table 3). Mean blood lactate, glucose, and urea nitrogen values were similar for the 2 groups at the different postoperative time points, both before and after CPB (Figure 1).

Before CPB, no significant difference existed between the 2 groups in lung gas exchange capacity. In the control group, CPB had a significant impact on lung gas exchange capacity, with a decrease in the mean OI from 4.45 ± 0.33 to 3.26 ± 1.64 (*P* = .005), an increase in the mean RI from 2.02 ± 0.16 to 2.52 ± 0.17 (*P* = .039), and an increase in the mean $P_{(A-a)}O_2$ from 373.69 ± 18.73 mm Hg to 494.59 ± 12.19 mm Hg (*P* < .0001). In contrast, the use of SBUF attenuated this impact of CPB on lung gas exchange capacity. In the SBUF group, the mean OI after CPB decreased from 4.55 ± 0.32 to 4.07 ± 0.27, the RI increased from 1.96 ± 0.15 to 2.06 ± 0.13, and the $P_{(A-a)}O_2$ increased from 359.00 ± 21.67 mm Hg to

Table 2. Intraoperative Data*

	Control Group	SBUF Group	*P*
Priming volume, mL	1461.48 ± 105.71	1423.05 ± 101.74	.076
CPB time, min	92.8 ± 34.6	101.0 ± 35.5	.257
Aortic cross-clamping time, min	62.3 ± 19.5	67.8 ± 17.3	.174
Tranexamic acid use, n	32 (71%)	41 (84%)	.144
Furosemide dose, mg	13.67 ± 4.32	15.10 ± 4.14	.104
Ultrafiltration volume, mL	—	3159.18 ± 940.28	—
Intraoperative fluid balance, mL	878.91 ± 189.68	–1147.92 ± –564.02	<.0001
Cell saver volume, mL	331.17 ± 111.89	362.24 ± 116.43	.191
Transfusion during CPB, units/patient	2.20 ± 1.34	1.84 ± 1.52	.224
Hematocrit, %			
Before CPB	38.55 ± 4.74	36.68 ± 5.77	.089
After CPB	30.69 ± 3.42	34.25 ± 4.15	<.0001

*Data are presented as the number (percent) or as the mean ± SD. SBUF indicates subzero-balanced ultrafiltration; CPB, cardiopulmonary bypass.

Table 3. Postoperative Outcomes*

	Control Group	SBUF Group	*P*
Respiratory complication, n	4 (9%)	2 (4%)	.596
Respiratory failure, n	0	1	1.000
Pneumonia, n	1	0	1.000
Pneumothorax, n	1	0	1.000
Hydrothorax, n	2	1	.940
Inotropic agent, n	35 (78%)	32 (65%)	.182
Intubation time, h	18.02 ± 2.36	14.50 ± 2.43	<.0001
ICU stay, h	75.52 ± 16.75	71.24 ± 12.28	.164
Hospital stay, d	12.04 ± 3.25	10.97 ± 3.87	.152
Transfusion within 24 h postoperatively, units/patient	3.76 ± 3.07	2.27 ± 2.27	.009
Drainage volume within 24 h postoperatively, mL	562.21 ± 310.39	463.91 ± 213.67	.080

*Data are presented as the number (percent) or as the mean ± SD. SBUF indicates subzero-balanced ultrafiltration; ICU, intensive care unit. Inotropic agent means either dopamine administration exceeding 5 μg/kg per minute and lasting >24 hours or the use of other inotropic agents (dobutamine, norepinephrine, or phosphodiesterase inhibitors).

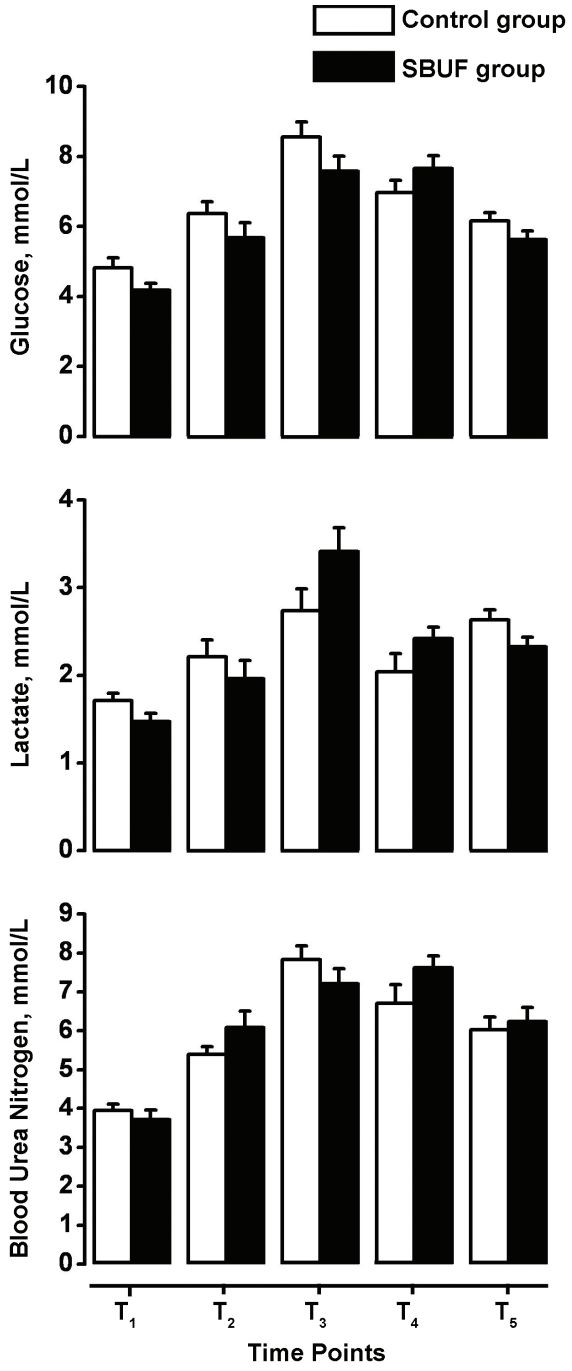

Figure 1. Time courses of blood lactate, glucose, and urea nitrogen values in the 2 groups before and after cardiopulmonary bypass (CPB). Values are expressed as the mean ± SD. SBUF indicates subzero-balanced ultrafiltration; T_1, after intubation; T_2, after the termination of CPB; T_3, on admission to the ICU; T_4, 6 hours postoperatively; T_5, 12 hours postoperatively.

380.89 ± 17.31 mm Hg; however, these differences were not statistically significant (P = .248, .617, and .432, respectively). Compared with the control group, the mean OI in the SBUF group was significantly higher at T_2 (4.07 ± 0.27 versus 3.26 ± 1.64, P = .031), and the mean RI and $P_{(A-a)}O_2$ values were significantly lower at T_2 (2.06 ± 0.13 versus 2.52 ± 0.17 [P = .039] and 380.89 ± 17.31 mm Hg versus 494.59 ± 12.19 mm Hg [P < .0001], respectively) and T_3 (2.11 ± 0.15 versus 2.55 ± 0.73 [P = .017] and 361.72 ± 19.64 mm Hg versus 424.99 ± 15.11 mm Hg [P = .012], respectively). At T_4 and T_5, however, the differences between the 2 groups in OI, RI, and $P_{(A-a)}O_2$ were not significantly different. These results indicated that the effect of SBUF on patients' gas exchange capacity was not sustained after 6 hours or 12 hours postoperatively. Figure 2 shows the effect of SBUF on gas exchange capacity.

No complication specifically related to SBUF, such as electrolyte imbalance, anticoagulation insufficiency, hypoglycemia, arrhythmia, hypothermia, or sustained systemic hypotension, could be identified. All patients were able to tolerate SBUF and were weaned off CPB successfully.

DISCUSSION

CPB in cardiac surgery contributes the most to the inflammatory response leading to the accumulation of body water and organ dysfunction [Wang 1998], and, clinically, pulmonary dysfunction is one of the most common inflammatory responses [Tönz 1995]. Severe acute pulmonary dysfunction, including lower pulmonary compliance, higher pulmonary resistance, and poorer alveolar gas exchange ability, may increase the mortality after CPB [Raijmakers 1993; Miller 1997; Griese 1999].

Various strategies have been used to minimize and reverse the pulmonary damage that occurs after CPB. Ultrafiltration is one effective strategy that has been used for many years in an effort to attenuate the effects of fluid accumulation, capillary leak syndrome, homologous blood use, and the systemic inflammatory response syndrome. Observations have demonstrated that applying MUF after CPB can remove total body water, improve oxygenation, and pulmonary compliance and can decrease the duration of ventilatory support [Kameyama 2000; Keenan 2000; Mahmoud 2005]. Similarly, studies have shown that ZBUF can remove mediators and products of inflammatory mediators from the blood and thus improve pulmonary oxygenation [Huang 2003; Berdat 2004].

Since 2008, we have applied the SBUF technique during CPB to reduce the accumulation of total body water and simultaneously remove inflammatory mediators without prolonging the duration of the operation. This study was designed to establish whether this new ultrafiltration technique could improve the lung gas exchange capacity of adult patients undergoing cardiac operations.

The studies of Schlünzen et al [1998] and Onoe et al [2001] showed that MUF can decrease $P_{(A-a)}O_2$ and increase the partial pressure of oxygen in patients who have undergone CPB by the time they are transferred to the ICU. Mahmoud et al [2005] reported that the use of MUF after CPB could produce an immediate improvement in lung compliance and gas exchange capacity, which may effectively minimize the postoperative pulmonary dysfunction of congenital heart disease [Mahmoud 2005]. Song et al [2007] found that ZBUF can efficaciously decrease a patient's procalcitonin concentration,

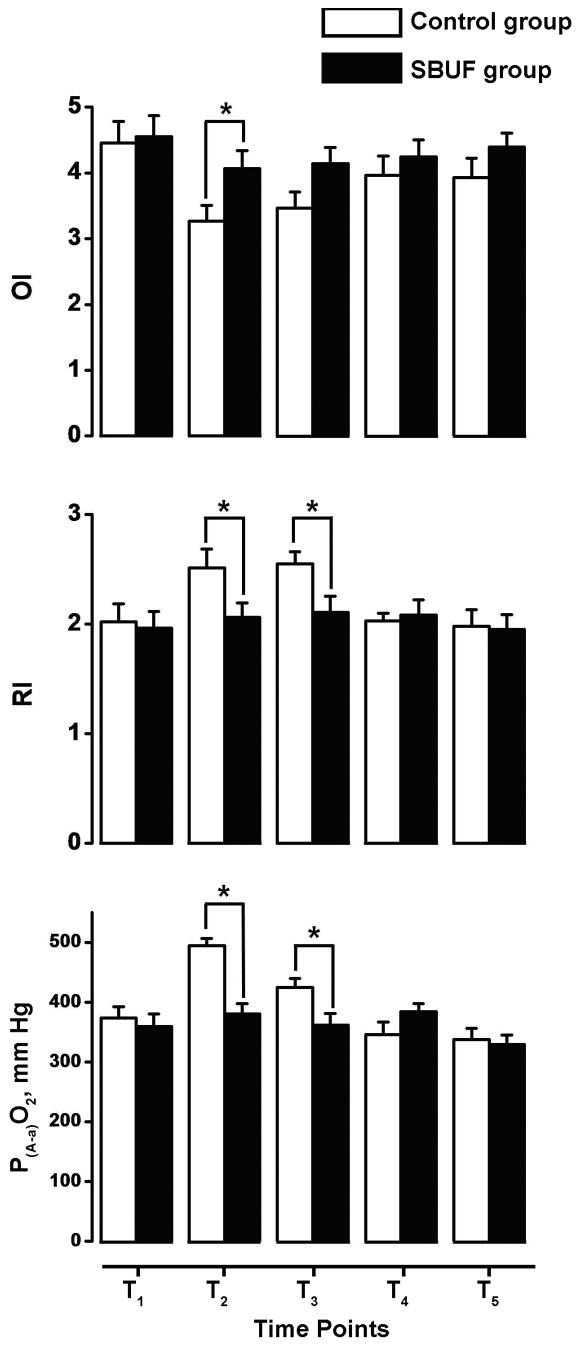

Figure 2. Time courses of the arterial oxygen index (OI), the respiratory index (RI), and the alveolar-arterial oxygen pressure difference ($P_{(A-a)}O_2$) in the 2 groups before and after cardiopulmonary bypass (CPB). Values are expressed as the mean ± SD. SBUF indicates subzero-balanced ultrafiltration; T_1, after intubation; T_2, after the termination of CPB; T_3, on admission to the ICU; T_4, 6 hours postoperatively; T_5, 12 hours postoperatively. *$P < .05$, versus the control group.

improve respiratory function, and shorten the intubation time [Song 2007]. The present study demonstrated that CPB had a significant impact on the lung gas exchange capacity in the control group, which decreased the OI and increased RI and $P_{(A-a)}O_2$. In contrast, the use of SBUF attenuated this impact of CPB on the lung gas exchange capacity. In the SBUF group, the decrease in OI and the increases in RI and $P_{(A-a)}O_2$ were statistically insignificant. On the other hand, compared with the control group, the SBUF group had significantly higher OI values at the termination of CPB, whereas RI and $P_{(A-a)}O_2$ values were significantly lower at the termination of CPB and on admission to the ICU. These results documented that SBUF during CPB can produce an immediate improvement in adult patients' lung gas exchange capacity. These findings are comparable with the results of previous studies.

The significant immediate improvement in gas exchange capacity could be important, especially in patients with pulmonary hypertension. The improvement in gas exchange capacity is likely mediated by the successful removal of water from the body. In our study, to achieve a subzero-balanced state during the entire SBUF procedure required that a VAVD system with the negative pressure controlled within –20 to –40 mm Hg be applied to maintain a sufficient venous reservoir volume. Reports have confirmed that the use of VAVD during minimally invasive cardiac surgery is a safe, simple, and effective technique for increasing the venous return [Murai 2005; Colangelo 2006]. Our study showed that subzero fluid balance can be achieved during CPB with this technique. Therefore, removal of a large volume of water during CPB may improve gas exchange capacity.

In our study, however, the differences between the 2 groups in OI, RI, and $P_{(A-a)}O_2$ at postoperative hour 6 or 12 did not achieve statistical significance. This finding demonstrated that the effect of SBUF on patients' gas exchange capacity was not sustained by 6 or 12 hours after the operation. Our results partly agreed with those of Mahmoud et al [2005], who reported on a series of 40 infants in whom MUF after CPB contributed to an immediate improvement in lung compliance and gas exchange capacity. Discordantly with their result, however, the present study has shown that the effect of SBUF on patients' gas exchange capacity was sustained after admission to the ICU and that intubation times were much shorter in patients who received SBUF. This result may be because pulmonary function is affected by both excess fluid from hemodilution and the systemic inflammatory response. We presume that SBUF can effectively decrease total body water as well as inflammatory cytokines.

The present study has shown that the hematocrits of patients in the SBUF group were higher than those in the control group after the termination of CPB, even though the hematocrits were comparable before CPB. Because of the higher hematocrits of the treated patients, transfusion volumes within 24 hours postoperatively were less than those in the control group. This SBUF effect of a lower requirement for blood transfusions is similar to the reported effect of MUF or conventional ultrafiltration.

Finally, this study found no significant differences between the 2 groups with respect to length of stay in the ICU, duration of hospital stay, the need for infusions of inotropic agents, and the drainage volume within 24 hours postoperatively. These results are comparable to those of a previous study [Grünenfelder 2000].

One limitation of our study was the absence of another control group (either a MUF or ZBUF group). This study carried out no measurements of inflammatory mediators; consequently, our judgment that SBUF can remove inflammatory mediators is just a deduction that remains to be proved.

CONCLUSIONS

In conclusion, use of the SBUF technique during CPB can effectively improve a patient's lung gas exchange capacity, decrease the volume of blood transfusion, and promote a patient's early postoperative recovery.

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