Continuous perfusion of pulmonary arteries during total cardiopulmonary bypass favorably affects levels of circulating adhesion molecules and lung function

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Objectives: Lung injury is a serious complication of cardiopulmonary bypass in infants with congenital heart disease and pulmonary hypertension. Cessation of blood flow in the pulmonary arteries during cardiopulmonary bypass is known to provoke lung dysfunction. We assessed the effect of continuous pulmonary perfusion on circulating adhesion molecules and on lung function.

Methods: Fourteen infants with congenital heart disease and pulmonary hypertension were enrolled in the study. During total cardiopulmonary bypass, 8 patients underwent continuous perfusion of the pulmonary arteries (perfusion group), and the remaining 6 patients did not (control group). Plasma levels of circulating intercellular adhesion molecule 1, soluble granule membrane protein 140, and sialyl Lewis^x and PaO₂/fraction of inspired oxygen ratios were measured before commencement and serially for 24 hours after termination of bypass.

Results: Plasma levels of circulating intercellular adhesion molecule 1 decreased significantly at the termination of bypass in both groups but returned to prebypass levels immediately in the control group, whereas in the perfusion group the values remained significantly less than those before bypass. Plasma levels of soluble granule membrane protein 140 in the control group were significantly higher at 6 and 12 hours after bypass than levels before bypass, whereas in the perfusion group the values remained at the prebypass level throughout the postbypass period. Trends of plasma levels of sialyl Lewis^x were alike in both groups. PaO₂/fraction of inspired oxygen ratios in the control group decreased significantly from 6 hours after bypass, whereas values in the perfusion group remained at the prebypass value throughout the postbypass period.

Conclusions: This study suggests that in infants having congenital heart disease and pulmonary hypertension, continuous pulmonary perfusion during total cardiopulmonary bypass minimizes ischemic insult and neutrophil-endothelial interaction mediated by adhesion molecules in the pulmonary microvessels.

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Postoperative dysfunction of the lung remains a life-threatening complication of cardiopulmonary bypass (CPB), particularly in infants with congenital heart disease and pulmonary hypertension.¹ An earlier study demonstrated that exposure of blood to the synthetic surface of the CPB circuit activated complements, thereby provoking a systemic inflammatory response.² Activated complements in turn played a crucial role in the activation and sequestration of neutrophils in the lung, causing subsequent damage, particularly to the endothelium.

In the physiologic process of the inflammatory reaction, expression and release of cytokines are also known to play a crucial role in regulating the cell-to-cell interaction mediated by adhesion molecules.³ In addition, the systemic inflammatory response provoked by CPB has a particularly deleterious effect on the lung, with an additional insult occurring as a result of ischemia of the lung. During total CPB, the lung is perfused solely by the bronchial arterial system, and therefore the lung is at risk for the development of ischemic insult. Furthermore, accumulation or extensive sequestration of neutrophils is known to occur in the lung, commonly when the pulmonary circulation is reestablished.⁴ Earlier reports demonstrated further that reperfusion after an ischemic insult to the lung aggravated structural and functional abnormalities of the pulmonary endothelial cells, with an ensuing result of progressive injury to the lung. In such an injurious process, neutrophil-endothelial interaction mediated by adhesion molecules is known to play a crucial role.⁵ This evidence was partly exemplified by experimental studies in which the lung injury was much less severe with lesser deprivation of blood flow in the pulmonary arteries during CPB or partial CPB than during total CPB.^{6,7}

Cumulated knowledge referring to the mechanism of lung injury during CPB led us to an assumption that restored flow of blood in the pulmonary arteries during total CPB would prevent ischemic insult, as well as reperfusion injury, to the lung. We therefore performed continuous perfusion of the pulmonary arteries during total CPB in infants having congenital heart disease and pulmonary hypertension, with a favorable outcome represented by the well-preserved ratio of arterial oxygen tension to inspired oxygen fraction (P_{aO_2}/F_{iO_2} ratio), less duration of postoperative mechanical ventilation, and less neutrophil sequestration in the lung.⁸ In view of neutrophil-endothelial interaction, we conducted this study to identify whether continuous perfusion of the pulmonary arteries had any effect on plasma levels of circulating adhesion molecules.

Methods

Patients

Fourteen consecutive infants with either ventricular septal defect or atrioventricular septal defect and pulmonary hypertension underwent definitive surgical repair between January 1997 and June 1998 and were enrolled in the study. Pulmonary hypertension was defined as a pulmonary/systemic arterial systolic pressure ratio of greater than 0.5. Thirteen patients had a ventricular septal defect and 1 patient had the complete form of atrioventricular septal defect. Ages of the patients at the definitive surgical repair ranged from 2 to 11 months, with a mean of 6.2 ± 2.7 months. Patients were allocated randomly to the perfusion ($n = 8$) and control ($n = 6$) groups. During total CPB, the perfusion group underwent continuous perfusion of the pulmonary arteries, whereas the control group did not. This study was approved by the Ethics

Committee of Tokyo Metropolitan Children's Hospital, and informed consent was obtained from all parents of the patients.

Operative Techniques

CPB. The circuit of the CPB comprised a roller pump (Stöckert Instrument GmbH, Munich, Germany) and membrane oxygenator (Lilliput 1-D901, Lilliput 2-D902; DIDEKO S.p.A, Mirandola, Italy). The circuit was primed with lactated Ringer's solution, albumin, mannitol, and leukocyte-depleted packed red blood cells. Depletion of the leukocyte was achieved with a leukocyte removal filter (Sepacell; Asahi Medical Co, Ltd, Tokyo, Japan). Anticoagulation was accomplished by means of intravenous administration of heparin sulfate (300 IU/kg), which was neutralized with protamine sulfate at the end of CPB. A nonpulsatile flow of $150 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ was maintained throughout CPB. All patients were cooled to moderate hypothermia ranging from 30°C to 32°C . Cardiac arrest was accomplished by means of aortic crossclamping coupled with infusion of high-potassium (20 mEq/L) blood cardioplegic solution (20 mL/kg) through the aortic root. The same solution was repeatedly infused in 60-minute intervals (10 mL/kg) during aortic crossclamping and immediately before unclamping. Blood gas management during CPB was directed toward maintenance of pH at 7.35 to 7.40 and P_{aCO_2} at 35 to 40 mm Hg. P_{aO_2} was maintained higher than 200 mm Hg. Blood gas management was conducted according to the principle of alpha-stat management, in which temperature correction of the measured pH and P_{aCO_2} was not performed. Hemofiltration of the perfusate with the hemoconcentrator (PANFLO APF-01D; Asahi Medical Co, Ltd) with or without supplemental transfusion of leukocyte-depleted packed red blood cells was performed to keep the hematocrit level greater than 25%. As was described in the previous report,⁸ the perfusion group underwent continuous perfusion of the oxygenated blood to the pulmonary arteries at a flow rate of $30 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during total CPB. The perfusate was infused into the pulmonary trunk through an 18-gauge pediatric cardioplegia cannula (DLP, Inc, Grand Rapids, Mich) and was drained out from the left atrium through a vent circuit to secure a bloodless field. By contrast, the control group did not undergo the corresponding perfusion to the pulmonary arteries, with flow of blood to the pulmonary arteries being arrested during total CPB.

Anesthesia and postoperative management. Anesthetic management comprised weight-related doses of morphine sulfate ($50\text{--}100 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) and incremental doses of pancuronium bromide (0.2 mg/kg) as required for neuromuscular blockade. During total CPB, mechanical ventilation was arrested in both groups at the positive end-expiratory pressure of 5 cm H_2O . Postoperatively, all patients were kept sedated with continuous intravenous infusion of morphine sulfate ($30\text{--}80 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). Continuous infusion of midazolam ($0.05\text{--}0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) and repeated doses of pancuronium bromide (0.2 mg/kg) were added as needed. All patients' lungs were ventilated mechanically for at least 24 hours after termination of CPB with the pressure-limited and time-cycled ventilator. The tidal volume was maintained at 8 to 10 mL/kg, and positive end-expiratory pressure was maintained at 5 cm H_2O . F_{iO_2} and ventilation rates were adjusted to keep P_{aO_2} between 100 and 150 mm Hg and P_{aCO_2} between 30 and 35 mm Hg. The airway was kept clean by means of routine tracheal suctioning.

Figure 1. Perioperative trends of plasma levels of cICAM-1 in the perfusion (n = 8) and control (n = 6) groups. *P* values represent results compared with prebypass values within each group.

Figure 2. Perioperative trends of plasma levels of sGMP140 in the perfusion (n = 8) and control (n = 6) groups. *P* values represent results compared with prebypass values within each group.

Data Acquisition

Blood samples were taken from the peripheral systemic artery after induction of anesthesia (prebypass value), at the termination of CPB, and at 6, 12, and 24 hours after termination of CPB. Blood samples were transferred to tubes containing ethylenediaminetetraacetic acid, which were immediately cooled on ice, centrifuged at 4°C (3000 rpm for 10 minutes), and stored at -20°C for later measurements. Circulating intercellular adhesion molecule 1 (cICAM-1) was measured by means of a commercial standardized enzyme-linked immunosorbent assay (Bender Medsystems, Vienna, Austria). Soluble granule membrane protein 140 (sGMP140) was measured by means of a commercial standardized enzyme-linked immunosorbent assay (Takara Shuzo, Tokyo, Japan). Levels of sialyl Lewis^x (sLe^x) was measured by a commercial standardized immunoradiometric assay (Otsuka Pharmaceuticals, Tokyo, Japan). Plasma levels were not standardized by the hematocrit value.

Lung Function

Arterial blood gas analysis was performed concurrent with the above measurements and also at 3 hours after termination of CPB (Blood Gas System 288; Ciba Corning, Medfield, Mass). The P_{aO_2}/F_{iO_2} ratio was used as a parameter of lung function.

Statistical Analysis

Data were expressed as means ± SD. An unpaired *t* test was used to determine differences between the groups. One-way repeated-measures analysis of variance followed by the multiple comparison method was used to detect differences among the sampling points within each group. Two-way repeated-measures analysis of variance was used to determine differences between the groups over time of the study.

Results

There were no significant differences between groups in age, body weight, duration of CPB, duration of aortic cross-clamping, preoperative pulmonary/systemic arterial systolic pressure ratio, pulmonary/systemic flow ratio, and pulmonary/systemic vascular resistance ratio (Table 1). No postoperative deaths occurred in either of the groups. There was no significant difference in the volume of blood loss (perfusion group vs control group: 41.4 ± 26.6 vs 67.8 ± 77.9 mL, *P* = .4048) or the volume of transfused homologous blood (perfusion group vs control group: 39.7 ± 20.3 vs 45 ± 22.4 mL, *P* = .6634) during the period of this study. Renal function, represented by serum levels of creatinine and blood urea nitrogen, and the total volume of inotropic agents were not significantly different between groups. In addition, the ratio of pulmonary/systemic arterial systolic pressure at the termination of CPB revealed no significant difference between groups (perfusion group vs control group: 0.35 ± 0.10 vs 0.26 ± 0.08, *P* = .1136).

Plasma Levels of Measured Variables

cICAM-1. Plasma levels of cICAM-1 in both groups were similar before CPB (perfusion group: 332 ± 90.9 ng/mL; control group: 353.7 ± 97.1 ng/mL; *P* = .673), and those in both groups decreased significantly at the moment of its termination (perfusion group: 204.6 ± 37.9 ng/mL, *P* < .0001; control group: 156.2 ± 95.5 ng/mL, *P* = .0075) compared with prebypass levels (Figure 1). Plasma levels in the control group returned to prebypass levels by 6 hours

Figure 3. Perioperative trends of plasma levels of sLe^X in the perfusion (n = 8) and control (n = 6) groups. P values represent results compared with prebypass values within each group.

after termination of CPB, whereas those of the perfusion group remained significantly lower than the prebypass levels throughout the postbypass period (6 hours: 267 ± 49.5 ng/mL, $P = .0024$; 12 hours: 243.8 ± 39.8 ng/mL, $P < .0001$; 24 hours: 260.1 ± 47.3 ng/mL, $P = .0010$). Although the postbypass values at each time point were not significantly different between groups, the values later than 6 hours after termination of CPB tended to be lower in the perfusion group than in the control group, and the trend revealed significant differences between groups by means of 2-way repeated-measures analysis of variance ($P = .0386$).

sGMP140. Prebypass values of sGMP140 were similar in both groups (perfusion group: 177.2 ± 98.2 ng/mL; control group: 177.9 ± 98.3 ng/mL; $P = .6519$). Plasma levels in the control group increased stepwise during the first 12 hours after the termination of CPB and remained at a high level by 24 hours after CPB (Figure 2). By contrast, in the perfusion group the value increased slightly at the termination of and 6 hours after the termination of CPB and then remained at a low level at the ensuing time points. When compared with the prebypass value within each group, the postbypass values of the control group were significantly higher at 6 hours (306.1 ± 215.8 ng/mL; $P = .0425$) and 12 hours (303.6 ± 223.3 ng/mL; $P = .0462$) after termination of CPB, whereas those of the perfusion group did not show significant difference throughout the postbypass period. Although postbypass values at each time point were not significantly different between groups, they tended to be lower

Figure 4. Postoperative trends of Pao₂/FiO₂ ratios in the perfusion (n = 8) and control (n = 6) groups. P values represent results compared with prebypass values within each group.

in the perfusion group compared with those in the control group, with a trend toward significant difference between groups, as determined by using 2-way repeated-measures analysis of variance ($P = .0458$).

sLe^X. Prebypass values of sLe^X were almost similar in both groups (perfusion group: 35.6 ± 9.2 U/mL; control group: 36.5 ± 5.1 U/mL; $P = .627$). The values of the control group decreased significantly at the termination of and 6 hours after the termination of CPB (termination of CPB: 30.2 ± 7.4 U/mL, $P = .0291$; 6 hours: 29.3 ± 4.9 U/mL, $P = .0155$) and then returned to the prebypass level by 24 hours after termination of CPB (Figure 3). By contrast, values of the perfusion group remained significantly lower than the prebypass value up to 12 hours after termination of the CPB (termination of CPB: 27.1 ± 7.1 U/mL, $P = .009$; 6 hours: 24.9 ± 7.3 U/mL, $P = .0009$; 12 hours: 28.6 ± 6.4 U/mL, $P = .0357$) and then returned to the prebypass value. Although the postbypass values at each time point were not significantly different between groups, they tended to be lower in the perfusion group than in the control group.

Lung Function

Prebypass values of lung function were similar in both groups (perfusion group: 388.7 ± 98.1 ; control group: 390.5 ± 96.2). In the control group Pao₂/FiO₂ ratio decreased significantly at 6 hours (269.6 ± 144.5 ; $P = .0109$), 12 hours (259.5 ± 119.8 ; $P = .0065$), and 24 hours (290.5 ± 127.1 ; $P = .0310$) after termination of CPB (Figure 4). By contrast,

TABLE 1. Characteristics of patients in perfused and control groups

Characteristic	Perfusion group (n = 8)	Control group (n = 6)	P value
Age (mo)	5.9 ± 2.8	6.6 ± 2.7	.637
Body weight (kg)	4.2 ± 0.8	5.1 ± 1.0	.087
Pp/Ps	0.81 ± 0.21	0.76 ± 0.07	.646
Qp/Qs	3.18 ± 0.94	4.41 ± 1.9	.139
Rp/Rs	0.17 ± 0.05	0.16 ± 0.03	.901
Duration of CPB (min)	134.9 ± 35.5	134.2 ± 19.1	.966
Duration of AoX (min)	52.1 ± 22.9	51.2 ± 12.8	.929

AoX, Aortic crossclamp; CPB, cardiopulmonary bypass; Pp/Ps, pulmonary/systemic arterial systolic pressure ratio; Qp/Qs, pulmonary/systemic flow ratio; Rp/Rs, pulmonary/systemic vascular resistance ratio.

in the perfusion group the values remained at the prebypass level during the first 6 hours after termination of CPB and then decreased at 12 and 24 hours after termination of CPB, although not significantly. Duration of the mechanical support of ventilation tended to be less in the perfusion group compared with that in the control group (perfusion group vs control group: 34.5 ± 15.6 vs 65.8 ± 42.3 hours; $P = .1896$), although the differences could be due to chance. Two patients in the control group required nitric oxide inhalation therapy for the management of episodic elevation of the pulmonary arterial pressure. The treatment was commenced on postoperative days 2 and 3, respectively, and was terminated within 3 days.

Discussion

In addition to the widely accepted concept that exposure of blood to CPB is in itself the cause of lung injury, an increasing number of studies have endorsed the view that cessation of flow of blood in the pulmonary arteries during total CPB aggravated the lung injury. Indeed, experimental studies clarified the fact that lung injury was much less severe with lesser deprivation of blood flow in the pulmonary arteries during CPB or partial CPB than during total CPB.^{6,7} This could be ascribed to the hemodynamic features during the conventional total CPB when the lung was perfused solely by the bronchial arterial system, with the lung being exposed at the risk of ischemic insult. On the basis of this evidence, we reasoned that restored flow of blood in the pulmonary arteries during total CPB would offset the ischemic insult, as well as the reperfusion injury, to the lung. Our previous study demonstrated that the pulmonary perfusion technique favorably affected the postoperative lung function, as was exemplified by well-preserved P_{aO_2}/F_{iO_2} ratios during the postbypass period coupled with less duration of postoperative support for ventilation.⁸ This view was consistent with that of a recent experimental work, in which the authors demonstrated that additional low-flow perfusion of the lung during total CPB demonstrated better preservation of tissue adenosine triphosphate stores and P_{aO_2} in the neonatal piglet model.⁹

Meanwhile, recent advances of molecular biology have expanded our view of the intricate mechanism of lung injury and demonstrated that adhesion molecules, which regulated interactions of the activated cell, were one of the initiating factors of the pathophysiologic response of the inflammatory reaction.^{10,11} Horgan and associates¹² endorsed this concept by claiming that in the setting of postischemic reperfusion of the lung, upregulation of adhesion molecules on the endothelial cell surface enhanced neutrophil-endothelial cell adhesion and neutrophil sequestration, thereby producing endothelial dysfunction and neutrophil-led tissue damage. The adhesion molecule family of selectins, such as GMP-140, mediated the initial rolling phase of neutrophil attachment to endothelium binding to sLe^x, which was found on the neutrophil surface as a ligand. Subsequently, interaction between the adhesion molecule families of integrins and immunoglobulins, such as leukocyte function-associated antigen, membrane attack complex-1, and ICAM-1, facilitated firm binding of neutrophils to the activated endothelium.¹⁰ Additionally, soluble isoforms of adhesion molecules were found to modulate the inflammatory process in many different ways: by acting as a chemotoxin, by blocking neutrophil activation, or by competing with a membrane-bound form of cell-to-cell adhesion.¹³

In view of the intrinsic role of the adhesion molecules, the present study provided us with evidence that the continuous perfusion of the pulmonary arteries suppressed elevation of plasma levels of cICAM-1 and sGMP140 during the postbypass period. Recent investigators demonstrated elevated plasma levels of cICAM-1 in patients with systemic inflammatory response and organ dysfunction. Another report supported this concept with pertinent evidence that plasma levels of cICAM-1 were of prognostic value in patients with organ failure.¹⁴ Recently, Rothlein and colleagues¹⁵ reported elevated plasma levels of cICAM-1 in the setting of activated adhesion between membrane-bound ICAM-1 and neutrophils and then presented a deductive theory that cICAM-1 competed with membrane-bound ICAM-1 for leukocyte adhesion to endothelium, thereby

preventing neutrophil-induced tissue damage. In fact, inasmuch as the plasma level of cICAM-1 shows positive correlation with the risk of organ dysfunction mediated by neutrophils, it is conceivable that the high plasma level is in itself an important predictor of immune activation. Regarding the effect of CPB on the plasma levels of cICAM-1, the results of our study coincided with those of another study arguing that in conventional CPB without perfusion of the pulmonary arteries, plasma levels of cICAM-1 decreased significantly during CPB and returned to baseline value within a day after termination of CPB.¹⁶ Initial descent of cICAM-1 could be attributed to its binding with neutrophils activated by the systemic inflammatory response to CPB. By contrast, ensuing low levels of cICAM-1 throughout the postbypass period in the perfusion group could be explained by the reasoning that the continuous perfusion of the pulmonary arteries suppressed neutrophil-endothelial interaction in the pulmonary microvessels and release of cICAM-1, with a subsequent result of well-preserved $\text{PaO}_2/\text{Fio}_2$ levels throughout the postbypass period.

Sakamaki and associates¹⁷ demonstrated elevated plasma levels of sGMP140 in patients with neutrophil-mediated lung injury. The soluble form of GMP140 has been shown to prevent CD18-dependent neutrophil adhesion to endothelial cells in vitro, with elevated sGMP140 levels reflecting a physiologic response in which excessive adhesion of neutrophils to endothelial cells has been downregulated. Therefore, high plasma levels of sGMP140 are considered to be another isolated predictor of lung injury mediated by neutrophils. Regarding the effect of CPB without perfusion of the pulmonary arteries on plasma levels of sGMP140, our result was in agreement with that of another study.¹⁹ Initial increase of sGMP140 in both groups reflected systemic inflammatory response derived from CPB. High plasma levels throughout the postbypass period in the control group were consistent with low values of $\text{PaO}_2/\text{Fio}_2$. In the perfusion group low levels of sGMP140 throughout the postbypass period reflected less activation of neutrophil-endothelial interaction in the pulmonary microvessels, with concurrent results of well-preserved $\text{PaO}_2/\text{Fio}_2$ ratios.

sLe^X is the oligosaccharide ligand for selectins like GMP140 and is expressed on the neutrophil surface, which is rapidly shed after initial binding between neutrophils and endothelium. Therefore, plasma levels of sLe^X may increase during the initial adhesion process between neutrophils and endothelium. A recent study has demonstrated further that infusion of a synthetic sLe^X analog attenuated neutrophil-dependent lung injury by binding to selectins.²⁰ Although there was no report describing the effect of CPB on the plasma levels of sLe^X, early descent of sLe^X during the postbypass period implied that binding on the activated endothelium selectins occurred. By contrast, subsequent lower levels

of sLe^X in the perfusion group implied that the continuous perfusion of the pulmonary arteries during total CPB favorably affected the inflammatory process, suppressing neutrophil-endothelial interaction and release of sLe^X in the pulmonary microvessels.

In the various models of ischemia-reperfusion injury, neutrophil recruitment was an indispensable event for the full development of injury to organs. In our previous study, we found that neutrophil sequestration in the lung was less severe in the perfusion group.⁸ Moreover, our present results suggested that continuous perfusion of the pulmonary arteries during total CPB minimized ischemic insult and inhibited neutrophil sequestration by minimizing the neutrophil-endothelial interaction mediated by adhesion molecules in the pulmonary microvessels, with the evidence of suppressed elevation of plasma levels of circulating adhesion molecules and well-preserved values of $\text{PaO}_2/\text{Fio}_2$. A new promising area of specific inhibition of inflammatory mediators involves the use of a blocking monoclonal antibody.²¹ Although such an antibody is specifically effective in mitigating the inflammatory response, there remains some concern as to whether exposure of patients to foreign proteins is harmless. Moreover, the cause of lung injury derived from CPB can be multifactorial. In this context, the continuous pulmonary perfusion technique is a promising adjunctive method that preserves lung function with a physiologic mean during CPB. However, the clinical significance of soluble adhesion molecules in plasma is still not fully understood. Because no experimental work has been done related to the endothelial expression of adhesion molecules during total CPB coupled with or without pulmonary perfusion technique, further investigative work may be required to determine the precise effect of the continuous pulmonary perfusion technique on the lung.

In conclusion, results of this study demonstrated that ischemia and reperfusion of the lung during CPB were the major factors contributing to lung injury in infants with congenital heart disease and pulmonary hypertension. Our results suggest that continuous perfusion of the pulmonary arteries during total CPB is a promising adjunctive method to minimize the ischemic insult to the lung, as well as neutrophil-endothelial interaction mediated by adhesion molecules in the pulmonary microvessels.

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