

Cardiopulmonary bypass reduction of bronchial blood flow: A potential mechanism for lung injury in a neonatal pig model

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Background: During total cardiopulmonary bypass, blood flow to the lungs is limited to flow through the bronchial arteries. We tested the hypothesis that bronchial blood flow during cardiopulmonary bypass is insufficient to prevent ischemia of the lung and that perfusion of the pulmonary arteries with oxygenated blood during bypass would reduce lung injury.

Methods: Eighteen piglets (5.0 ± 0.5 kg) were subjected to 120 minutes of normothermic total cardiopulmonary bypass, followed by 60 minutes of postbypass perfusion. Nine of them received continuous pulmonary perfusion with oxygenated blood during bypass. Six additional piglets served as a control group and were mechanically ventilated after sternotomy for 180 minutes only. We quantitated bronchial arterial blood flow, tissue lactate content, and alveolar septal thickness and surface area. We also obtained bronchoalveolar lavage fluid samples.

Results: With the beginning of cardiopulmonary bypass, bronchial arterial blood flow decreased to 13% of baseline (42.1 ± 10.4 to 5.6 ± 1.0 mL/min). It remained decreased until the end of bypass and returned to starting levels 60 minutes after bypass. The decrease in bronchial blood flow was associated with a 3-fold increase in tissue lactate content. At the end of reperfusion there was a 2-fold increase in alveolar septal thickness and significant accumulations relative to control in the bronchoalveolar lavage fluid of albumin, lactate dehydrogenase, neutrophils, and elastase. Controlled pulmonary perfusion significantly ameliorated all the observed changes.

Conclusion: Cardiopulmonary bypass caused a reduction in bronchial arterial blood flow, which was associated with injury of the lung. Controlled pulmonary perfusion reduced injury to the lung during bypass. The inflammatory response, as evidenced by bronchoalveolar lavage fluid, may be caused by ischemia.

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C.S. was supported by the Zentrum für Klinische Forschung of the University of Freiburg. T.D. was supported by the Emmy Noether-Program of the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG, Do602/2-1).

Received for publication Aug 16, 2001; revisions requested Oct 24, 2001; revisions received Nov 14, 2001; accepted for publication Nov 20, 2001.

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J Thorac Cardiovasc Surg 2002;123:1199-205

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0022-5223/2002 \$35.00+0 12/1/121977

doi:10.1067/mtc.2002.121977

Pulmonary dysfunction is a frequent complication during the postoperative course after cardiac surgery with cardiopulmonary bypass (CPB). Young age, preoperative pulmonary disease, and extended duration of CPB are all risk factors for such dysfunction.¹ CPB is also associated with a complex whole-body inflammatory reaction that may contribute to the development of multiple organ dysfunction, including postoperative lung injury.²⁻⁴ Recent investigations imply that pulmonary dysfunction may be related to an ischemic injury of the lung during CPB.⁵ Because blood flow to the lungs is limited to flow through the bronchial arteries during total CPB, ischemic injury of the lung will occur if bronchial blood flow is insufficient

to meet metabolic demands. When pulmonary blood flow ceases, bronchial arterial blood flow might be expected to increase as a compensatory measure. This expectation was observed experimentally when in 1847 Virchow⁶ described an increased bronchial flow after ligation of the pulmonary artery (PA) in dogs. Thus far there are no reliable techniques available for the quantitation of bronchial arterial blood flow during CPB. It is unknown whether the bronchial arterial blood flow during total CPB is increased and whether it is sufficient to prevent ischemic lung injury. It is also unknown whether the reason for pulmonary dysfunction is related to ischemia of the lung, an inflammatory reaction, or both. The aim of this study was to quantitate bronchial arterial blood flow during CPB and to assess the effects of controlled perfusion of the PA during total CPB. Contrary to expectations, bronchial arterial blood flow was substantially decreased during CPB, rendering the lung ischemic, and controlled pulmonary perfusion was able to reverse these changes.

Methods

Animals and Protocols

Male piglets ($n = 24$, Deutsche Landrasse; Rein, Sulzfeld, Germany) with a mean weight of 5.0 ± 0.5 kg (equivalent to 4 weeks of age) were used for the study. Use of the animals was approved by the animal welfare committee of the University of Freiburg. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council, and published by the National Academy Press, revised 1996.

The animals were divided into three experimental groups. Group 1 (conventional CPB, $n = 9$) was subjected to 120 minutes of normothermic total CPB without aortic crossclamping, followed by normal unsupported circulation for 60 minutes (reperfusion). Group 2 (CPB with PA perfusion, $n = 9$) was treated as group 1 but also received controlled perfusion of the PA. Controlled perfusion was performed with oxygenated, normothermic, autologous blood through a 6-mm polytetrafluoroethylene* tube, which was anastomosed to the main PA and connected to the CPB circuit beyond the membrane oxygenator. Lung perfusion was adjusted to a maximal pressure of 20 mm Hg, which was equivalent to a blood flow of 100 to 150 mL/min. During CPB, mechanical ventilation was interrupted. A positive end-expiratory pressure of 4 to 5 mm Hg was maintained for the duration of CPB. No protamine was given at the end of CPB. Group 3 (control, $n = 6$) served as control and was ventilated after sternotomy for 180 minutes without establishment of CPB. CPB was established as described previously elsewhere.⁷

Bronchial Arterial Blood Flow

Bronchial blood flow was determined with fluorescent microspheres with four different color codes before CPB, at the beginning and at the end of CPB, and after 60 minutes of reperfusion.⁷ Microspheres (15.1 ± 0.2 μm diameter) were injected in a bolus (2×10^6 over 5 seconds) into the proximal aortic arch, distal to the arterial cannula.

*Gore-Tex; registered trademark of W. L. Gore & Associates, Inc, Flagstaff, Ariz.

The reference samples were withdrawn from the descending aorta at the level of the diaphragm. The reliability of this approach was verified by ensuring identical results obtained by injecting microspheres into the left atrium or the aorta and collecting the reference sample in the descending aorta.⁷ At the end of the experiments, the lungs were resected, the microspheres were filtered out of the digested lung tissue, and the light emission of the fluorescent dye was quantitated as described previously elsewhere.^{7,8}

Lung Tissue lactate

We determined lactate content of lung tissue as a marker for anaerobic metabolism before CPB and at the end of CPB. To assess the effects of the same period of total global ischemia on lactate production, parts of 6 samples (all before CPB) were subjected to 120 minutes of *in vitro* ischemia by being placed in a vacuum-sealed plastic bag at 37°C in a water bath.

Bronchioalveolar Lavage

A bronchioalveolar lavage (BAL) was performed at the end of reperfusion, as described by Riedler and colleagues.⁹ Cell counts and solute components in the BAL fluid were analyzed.

Histologic Examination

At selected time points, samples were taken for histologic examination. At the end of the experiments, the lungs were explanted quickly and divided into 14 segments according to a standardized pattern. Tissue samples (25×25 mm) were taken out of each segment and stored in a 4% formalin solution before the remaining lung tissue was digested to filter out the microspheres. At the time of specimen collection, the lungs were regularly ventilated. All histologic specimens were embedded in paraffin and serially sectioned. The sections were stained with hematoxylin and eosin, and alveolar septal thickness and alveolar surface area were quantified in each specimen by morphometric analysis (50 alveolar septa and 50 alveolar surface areas per biopsy specimen after randomization; Soft Imaging System GmbH, Münster, Germany). Comparisons between the two time points were made between samples from the same side.

Hemodynamic Data

Standard hemodynamic monitoring was performed in all animals. Arterial blood pressure was monitored continuously in the abdominal aorta. Cardiac output was measured with a thermistor catheter (Pulsion-Cold-System; Pulsion & Co Medical System KG, München, Germany) that was placed into the descending aorta.

Statistical Analysis

Statistical analysis was performed by repeated measures analysis of variance with post hoc analysis by Newman-Keuls test. Values are given as mean \pm SD.

Results

Hemodynamic Data

Table 1 shows cardiac outputs and aortic pressures before and after CPB and pump flows and mean aortic pressures during CPB. Pump flow was adjusted to match cardiac output before CPB. Maintenance of this flow rate did not result in significant changes in mean aortic pressure. During

reperfusion, both cardiac output and mean aortic pressure were slightly lower than before CPB, although these changes were not statistically significant.

Bronchial Blood Flow

Figure 1 shows bronchial blood flows before CPB, at the beginning and end of CPB, and after 60 minutes of postbypass perfusion, either with or without controlled PA perfusion. There was a significant decrease in bronchial blood flow with the beginning of total CPB (5.6 ± 1.0 mL/min vs 42.1 ± 10.4 mL/min, or 0.7% vs 5.0% of cardiac output, $P < .01$), which remained decreased until the end of CPB (5.1 ± 1.8 mL/min). Bronchial blood flow returned to nearly normal values during 60 minutes of postbypass perfusion (25.6 ± 10.8 mL/min). To examine the effects of pulmonary perfusion on bronchial blood flow during CPB, microsphere injections into the aorta were performed while controlled perfusion to the PA was applied. The decrease in bronchial blood flow during CPB was unaffected by pulmonary perfusion (5.4 ± 1.6 mL/min, $P < .01$ vs before CPB) and also normalized during the reperfusion period (34.7 ± 13.5 mL/min).

Lung Tissue Lactate

Table 2 shows lactate contents of lung tissue before CPB and at the end of CPB with or without controlled PA perfusion. It also shows lactate content of lung tissue subjected to 120 minutes of total global ischemia in the water bath. During CPB, there was a 3-fold increase in tissue lactate content. The same period of in vitro ischemia caused a 10-fold increase in tissue lactate content. Controlled PA perfusion attenuated the CPB-associated increase.

Histologic Examination

Figure 2 shows representative histologic specimens before CPB and after CPB with or without controlled PA perfusion. Figure 3, A, shows the average alveolar septal thickness from tissue samples of lungs before CPB and at the end of reperfusion after 120 minutes of CPB with or without controlled PA perfusion. Figure 3, B, shows the average alveolar surface area of the same samples. At the end of reperfusion after CPB without PA perfusion, there was a 2-fold increase in alveolar septal thickness and a 50% decrease in alveolar surface area relative to prebypass values. Both the increase in alveolar septal thickness and the decrease in alveolar surface area were significantly reduced by controlled PA perfusion relative to values after CPB without PA perfusion. Alveolar septal thickness and alveolar surface area were identical in all corresponding lung areas.

Bronchioalveolar Lavage

Table 3 shows solute components and cell counts in BAL fluids obtained before CPB and at the end of reperfusion

TABLE 1. Cardiac output or pump flow during CPB and mean arterial perfusion pressure before CPB, at the beginning and end of CPB, and at the end of 60 minutes of reperfusion

	CO/pump flow (mL · kg ⁻¹ · min ⁻¹)	MAP (mm Hg)
Before CPB	162 ± 40	58 ± 5
Beginning of CPB	178 ± 42	65 ± 6
End of CPB	184 ± 34	65 ± 9
After 60 min of reperfusion	134 ± 34	55 ± 10

Values are given mean ± SD, n = 18 in each group. CO, Cardiac output; MAP, mean arterial pressure.

after 120 minutes of CPB with or without controlled PA perfusion. At the end of reperfusion after CPB without PA perfusion, there was a significant elevation of neutrophil counts, albumin content and lactate dehydrogenase activity in BAL fluid, which was not present in the group with controlled PA perfusion.

Discussion

During CPB in piglets, bronchial arterial blood flow was significantly reduced. This reduction in flow was independent of pulmonary perfusion and was present despite unaltered systemic arterial perfusion pressure. It was associated with metabolic and ultrastructural changes of lung tissue suggesting the presence of ischemia of the lungs during CPB, which could be ameliorated by controlled perfusion of the PA. Furthermore, we demonstrated that indicators for an inflammatory response of the lungs obtained from BAL fluids could also be reversed by controlled perfusion of the lung. Because blood flow to the lung is limited to flow through the bronchial arteries during total CPB, bronchial arterial blood flow might be expected to increase as a compensatory measure to prevent ischemia of the lung.¹⁰ Bronchial arterial blood flow has been measured previously in animals with a variety of techniques.¹¹⁻¹⁵ However, the results of these studies are inconclusive. Bronchial arterial blood flow was found to be increased¹⁰ or decreased¹⁶ after acute obstruction of the PA. During CPB, an estimate of bronchial blood flow is possible by collecting the blood returning to the vent catheter.^{11,12} Measurements of blood flow with this technique are likely to be inaccurate, however, because bronchial blood flow can accumulate in the lungs, and inadequate venting may occur during surgical intervention.¹¹ Also, no information on bronchial blood can be obtained before or after CPB.

We assessed bronchial arterial blood flow with fluorescent microspheres before, during, and after CPB. In a previous study, we determined the accuracy of bronchial arterial blood flow measurement with this method.⁷ We found that the onset of CPB was associated with a persistent

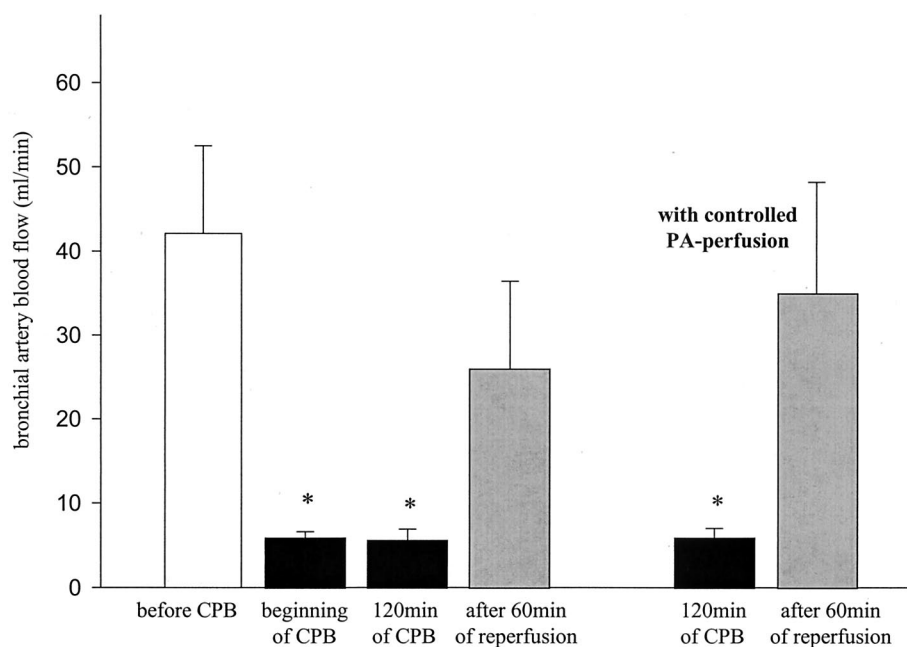


Figure 1. Bronchial arterial blood flows before CPB, at beginning and end of CPB with and without controlled PA perfusion, and after 60 minutes of reperfusion. Bar heights represent mean; error bars represent SD; n = 9 in each group. Asterisk indicates $P < .01$ versus before CPB.

TABLE 2. Lactate content of lung tissue before CPB and after 120 minutes of CPB without and with controlled PA perfusion; additionally, separate tissue samples were exposed to 120 minutes of total, global ischemia (in vitro ischemia)

	Tissue lactate ($\mu\text{mol/g}$ dry weight)
Before CPB (n = 6)	13.6 \pm 6.2
120 min of CPB without PA perfusion (n = 9)	36.5 \pm 10.9*
120 min of CPB with PA perfusion (n = 9)	25.4 \pm 12.3
120 min of in vitro ischemia (n = 6)	133 \pm 33.9*†

Values are given as mean \pm SD. PA, Pulmonary artery.

* $P < .05$ versus before CPB.

† $P < .05$ versus after 120 minutes of CPB.

decrease in bronchial arterial blood flow. Bronchial blood flow normalized once physiologic perfusion conditions were reestablished by terminating CPB. The reason for this decrease in bronchial blood flow is currently not clear. Bronchial blood flow is thought to be regulated by the inflation state of the lung as well as by the pulmonary perfusion pressure. The inflation state of the lung in our study was maintained by keeping a positive end-expiratory pressure of 5 mm Hg. Because there was no ventilation, it is conceivable that carbon dioxide accumulated during CPB,

causing bronchial arterial constriction. However, the sudden decrease in bronchial blood flow with the beginning of CPB and the constancy of this value until the end of CPB argue against this explanation. The absent pulmonary perfusion pressure during total CPB has to be considered as another potential explanation for our findings. For this reason, we assessed bronchial blood flow during CPB while controlled pulmonary perfusion was applied to maintain a physiologically usual pulmonary perfusion pressure. The decrease in bronchial blood flow was unaffected by pulmonary perfusion, eliminating this potential explanation. We therefore conclude that the decrease in bronchial blood flow appears to be a specific feature associated with CPB.

Because the perfusion pressure was unchanged with CPB in our experiments, it seems reasonable to speculate that the lack of pulsatile flow was responsible for the decreased bronchial flow. Decreased organ perfusion during nonpulsatile flow has been described for other organ systems (eg, kidneys, splanchnic region).^{17,18} If this speculation is accurate, the decrease in bronchial flow could be expected to be worse in actual patients, because the mean perfusion pressure is usually decreased with the beginning of CPB. One way to approach this problem would be the use of pulsatile CPB. Because of technical difficulties, the controversy of quantifying pulsatility, and the lack of superior clinical results, however, pulsatile perfusion has received only limited acceptance in clinical practice. Controlled pulmonary perfusion may provide an alternative approach.

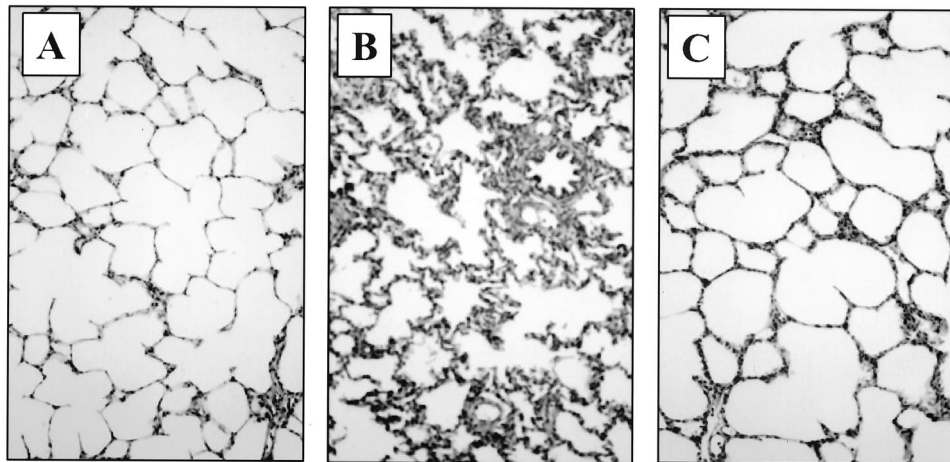


Figure 2. Representative light microscopic images of lung tissue (hematoxylin and eosin, original magnification 40 \times) before CPB (A), after 120 minutes of CPB without PA perfusion (B), and after 120 minutes of CPB with controlled PA perfusion (C).

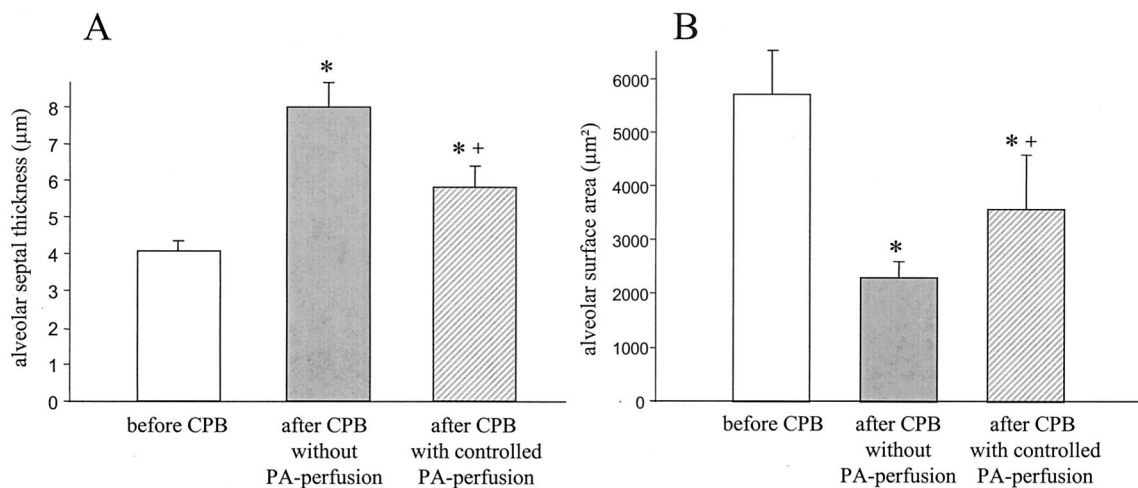


Figure 3. Alveolar septal thickness (A) and alveolar surface area (B) before CPB and at the end of reperfusion after CPB with or without controlled PA perfusion. Bar heights represent mean; error bars represent SD; $n = 9$ in each group. Asterisk indicates $P < .01$ versus before CPB; plus sign indicates $P < .01$ versus CPB without controlled PA perfusion.

We have demonstrated that perfusion of the lung with normothermic, oxygenated blood during CPB can significantly reduce metabolic and ultrastructural changes of lung tissue. Similar parenchymal alterations have been reported in children with pulmonary hypertension at the end of CPB after surgical repair of congenital heart anomalies.¹⁹ In infants younger than 6 months, the ultrastructural changes (eg, increase in alveolar septal thickness) were correlated with early death and prolonged mechanical ventilation.¹⁹ There is already clinical evidence that pulmonary perfusion has beneficial effects on the maintenance of lung function in infants.^{20,21} Continuous perfusion of the lung during CPB

resulted in a higher arterial oxygen tension in infants after CPB than was seen with conventional CPB techniques.²⁰ Suzuki and coworkers²⁰ speculated that the impaired arterial oxygen tension is related to ischemic injury of the lung during conventional CPB. We provide experimental evidence that this speculation is accurate. An unexpected observation was the prevention of changes caused by CPB in the BAL fluids when the pulmonary arteries were perfused. Accumulation of neutrophils and increases in lactate dehydrogenase and elastase activities in BAL fluids are considered indicators of an inflammatory response of the lungs,^{22,23} which in turn is thought to be caused by the CPB

TABLE 3. Solute components and cell counts detected in BAL fluids obtained before CPB and at the end of reperfusion after CPB with or without controlled perfusion of the PA

Parameter	Control (n = 6)	CPB without PA perfusion (n = 9)	CPB with PA perfusion (n = 9)
Albumin (mg/L)	7.5 ± 4.5	24.2 ± 8.9*	11.1 ± 6.9
Lactate dehydrogenase (IU/L)	5.4 ± 4.4	11.6 ± 5.7	4.3 ± 2.8
Elastase (μg/L)	4.1 ± 3.2	9.5 ± 6.2	5.5 ± 5.7
Macrophages (%)	97.9 ± 1.4	92.2 ± 5.3*	94.3 ± 2.0
Neutrophils (%)	0.7 ± 0.5	6.1 ± 4.8*	3.1 ± 1.0*
Lymphocytes (%)	1.4 ± 1.4	1.7 ± 0.6	2.6 ± 1.5

Values are mean ± SD.

*P < .02 versus control.

circuit. If this were the case, pulmonary perfusion during CPB should not have been able to affect these parameters. Yet controlled perfusion of the PA prevented the accumulation of neutrophils and the leakage of lactate dehydrogenase and elastase into the BAL fluids. This observation may suggest a different pathologic mechanism for CPB-associated inflammatory changes, at least in lungs.

Clinical Relevance

A specific problem that may provide an example of the clinical relevance of our conclusions is the treatment of infants with single-ventricle physiology and shunt-dependent pulmonary circulation. These patients may have to be given postoperative mechanical support by extracorporeal membrane oxygenation (ECMO).²⁴⁻²⁶ During ECMO, the mode of perfusion is comparable to the mode during CPB. The difference is the duration of support (days on ECMO vs hours on CPB). This patient population has a poor outcome after ECMO support, which among other things is due to severe pulmonary dysfunction. Thus far, complete occlusion of the systemic-pulmonary shunt has been recommended to avoid an overcirculation to the lung and has been performed by most surgeons.²⁵ Recently, Jaggars and coworkers²⁴ left the shunt open while the patients were receiving ECMO support. In this small series of infants, survival after ECMO support was improved relative to a group of patients in whom the shunts were closed. Our experimental finding that the bronchial arterial blood flow is minimized during CPB may also hold true during ECMO, although there may be still some antegrade flow to the right ventricle. We demonstrated, however, that flow to the PA did not affect the decrease in bronchial flow with the beginning of CPB. Because perfusion of the lung with oxygenated blood during CPB was able to ameliorate the ischemic changes of the lung, the improved outcome of the infants in whom the shunt was left open by Jaggars and coworkers²⁴

may possibly be explained by the prevention of ischemia of the lungs. These observations warrant further investigation.

We conclude that CPB causes a reduction in bronchial arterial blood flow, which is associated with an injury of the lung. Controlled pulmonary perfusion reduces injury to the lung during CPB. The inflammatory response, as evidenced by BAL fluid, may be caused by ischemia.

We thank Dr W.G. Williams (Hospital for Sick Children, Toronto, Canada) for helpful discussions and valuable suggestions and Dr K. Sarai for surgical mentoring.

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