LEUKOCYTE AND PLATELET DEPLETION WITH A BLOOD CELL SEPARATOR: EFFECTS ON LUNG INJURY AFTER CARDIAC SURGERY WITH CARDIOPULMONARY BYPASS

This study was undertaken to assess the effects of leukocyte and platelet depletion on postoperative lung injury in 42 patients who underwent heart operations. Blood was serially sampled before, during, and after cardiopulmonary bypass, and leukocyte count, platelet count, and thromboxane B_2 6-keto-$PGF_{1\alpha}$, leukocyte elastase, thrombin–antithrombin III complex, and D-dimer levels were determined. Postoperative respiratory function was assessed based on analyses of oxygenation and carbon dioxide elimination. Leukocyte and platelet depletion was performed in 21 patients (experimental group) but not in another (control group). In the experimental group, leukocytes and platelets were removed continuously by means of the blood cell separator CS-3000, beginning immediately after the start of the operation and ending 1 hour after the release of aortic occlusion. Leukocyte elastase, thromboxane B_2, ratio of thromboxane B_2 to 6-keto-$PGF_{1\alpha}$, thrombin–antithrombin III complex, and D-dimer were significantly lower in the experimental group than in the control group. Of the various indexes of oxygenation, arterial oxygen tension was significantly higher in the experimental group and the alveolar-arterial oxygen pressure difference and respiratory index were significantly lower in the experimental group. The positive end-expiratory pressure needed to achieve an appropriate arterial oxygen tension was significantly lower in the experimental group. The elimination of carbon dioxide was lower in the experimental group. Depletion of leukocytes and platelets reduced respiratory dysfunction after heart operations with cardiopulmonary bypass. It was particularly effective in patients with a low preoperative oxygenation capacity and in those for whom an extended period of cardiopulmonary bypass was required.
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Leukocytes have been reported to play a major role in "postperfusion lung syndrome," respiratory dysfunction after heart operations with cardiopulmonary bypass.[1] Recent animal studies[2] have demonstrated that the removal of leukocytes is effective in preventing reperfusion injury to the ischemic heart. However, few clinical studies have been performed regarding the effects of leukocyte removal on respiratory function after heart operations with cardiopulmonary bypass. Although other studies have reported the effects of preoperative collection of the patient's own platelets on reduction of bleeding after heart operations and on the coagulation system,[3, 4] no studies have examined how respiratory function is affected by the leukocytes and the platelets and their interaction. We recently have attempted continuous leukocyte and platelets depletion (LPD) by means of a blood cell separator during heart operations, beginning immediately after the start of operation. After the end of cardiopulmonary bypass, we serially evaluated the respiratory function of these patients to assess the effects of LPD.

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Patients and methods

The subjects were 42 adults who underwent heart operations. They were divided into two groups at random:

Table I. *Patient characteristics and operative parameters*

	LPD group (n = 21)	*Control group (n = 21)*	*p*
Age (yr)	62.6 ± 13.6	60.5 ± 13.8	NS
Sex (M/F)	11/10	12/9	NS
Height (cm)	157 ± 8.6	158 ± 8	NS
Weight (kg)	58.7 ± 11.8	60.9 ± 13.7	NS
CABG	12	14	NS
AVR or MVR	9	7	NS
CPB time (min)	171 ± 60	152 ± 34	NS
Aortic crossclamp time (min)	112 ± 40	99 ± 28	NS
Minimal rectal temperature (° C)	22.1 ± 2.1	22.3 ± 1.8	NS

Data are mean ± standard deviation. *NS,* Not significant; *CABG,* coronary artery bypass grafting; *AVR,* aortic valve replacement; *MVR,* mitral valve replacement.

the LPD group (21 patients in whom LPD was performed) and the control group (21 patients in whom LPD was not performed). In the LPD group, 12 patients underwent palliative coronary artery bypass grafting and nine underwent valve replacement. In the control group, 14 patients underwent coronary artery bypass grafting and seven underwent valve replacement. There were no significant differences between the two groups in terms of male-to-female ratio, age, duration of operation, duration of aortic occlusion, duration of cardiopulmonary bypass, or minimal rectal temperature (Table I). After the operation was started, a 10F venovenous shunt catheter was inserted percutaneously into the femoral vein to start continuous LPD by means of a blood cell separator (CS-3000; Baxter Healthcare Corp., Fenwal Autophor, Irvine, Calif.). The blood flow rate during LPD (50 ml/min) did not affect any patient's hemodynamic condition. The contents of the centrifuge were rotated at 1000 rpm. LPD was continued until 1 hour after the release of aortic occlusion. At 3 to 6 hours after the release of aortic occlusion, a fluid containing a high concentration of the removed leukocytes and platelets was returned through a peripheral vein. Operations were performed with the patient placed under anesthesia with high doses of fentanyl citrate (Fentanest), administered by means of a Narkomed 2A device (Drägerwerk AG, Lübeck, Germany). A membranous oxygenator (Bentley UNIVOX; Baxter, Fenwal Autophor) was used for cardiopulmonary bypass. The extracorporeal circuit was filled with a leukocyte-free erythrocyte preparation. In all cases, operations were performed with the patient in cardiac arrest with cold blood cardioplegia. During cardiopulmonary bypass, the flow rate was maintained at 2.4 $L \cdot min^{-1} \cdot m^{-2}$ body surface area and the arterial was maintained pressure at 55 to 65 mm Hg. After operation, the patients were cared for in the intensive care unit, where a Servo ventilator 900C (Siemens-Elema AB, Solna, Sweden) was used for assisted ventilation at a tidal volume of 10 ml/kg and a respiratory rate of 10 to 12 breaths/min.

Blood was sampled 5 minutes before and 5 minutes after the start of cardiopulmonary bypass, 2 minutes before the release of aortic occlusion, and 2 minutes, 15 minutes, 30 minutes, 1 hour, 3 hours, 6 hours, 12 hours, 24 hours, and 48 hours after the release of aortic occlusion. Blood gas analysis was performed within 30 minutes after the start of operation and 1 hour, 3 hours, 4 hours, 6 hours, 12 hours, and 18 hours after the release of aortic occlusion.

The levels of thromboxane B_2 (TxB_2), 6-keto-$PGF_{1\alpha}$, leukocyte elastase, complements (C3a, C4a, and C5a), thrombin–antithrombin III complexes (TAT), and D-dimer were measured in every blood sample. The leukocyte and platelet counts were determined in blood samples collected in a tube treated with sodium ethylenediamine tetraacetic acid (EDTA-Na_2). The TxB_2 and 6-keto-$PGF_{1\alpha}$ levels were measured by an antigen-antibody reaction with the radioimmunoassay–polyethylene glycol method.[5] For the measurement of these two parameters, blood was collected into a special test tube containing EDTA-Na_2 and indomethacin and was then immediately centrifuged at 4° C for 20 minutes. The separated plasma was stored frozen at −70° C until assay. For the measurement of leukocyte elastase, blood was collected into a sampling tube containing EDTA-Na_2 and the plasma was separated from it within 1 hour of collection. The separated plasma was stored frozen at −70° C until it was used for the measurement of the elastase concentration by enzyme immunoassay, a method that uses the binding of antibody to elastase and elastase a_1–proteinase inhibitor complex. Complement (C3a, C4a, and C5a) concentrations were measured with a radioimmunoassay (two-antibody method) that involves antigen-antibody reactions.[6] The TxB_2, 6-keto-$PGF_{1\alpha}$, leukocyte elastase, C3a, C4a, and C5a concentrations were measured at a laboratory center (SRL, Tokyo, Japan). As indexes of respiratory function, the arterial oxygen tension (Pao_2), alveolar-arterial oxygen difference ($A\text{-}aDo_2$), respiratory index (RI) and positive end-expiratory pressure (PEEP) were compared between the two groups. The elimination of carbon dioxide ($EIco_2$) was calculated by means of the following equation[7]:

$$EIco_2 = \frac{Paco_2 - Petco_2}{Paco_2}$$

where $Petco_2$ is the concentration of end-tidal carbon dioxide.

Blood collected through a catheter inserted into the radial artery was subjected to gas analysis with an ABL330 (Radiometer A/S, Copenhagen, Denmark). Each group was subdivided into two subgroups depending on the duration of cardiopulmonary bypass: one group had a duration of less than 160 minutes and one group had a duration of more than 160 minutes. The respiratory

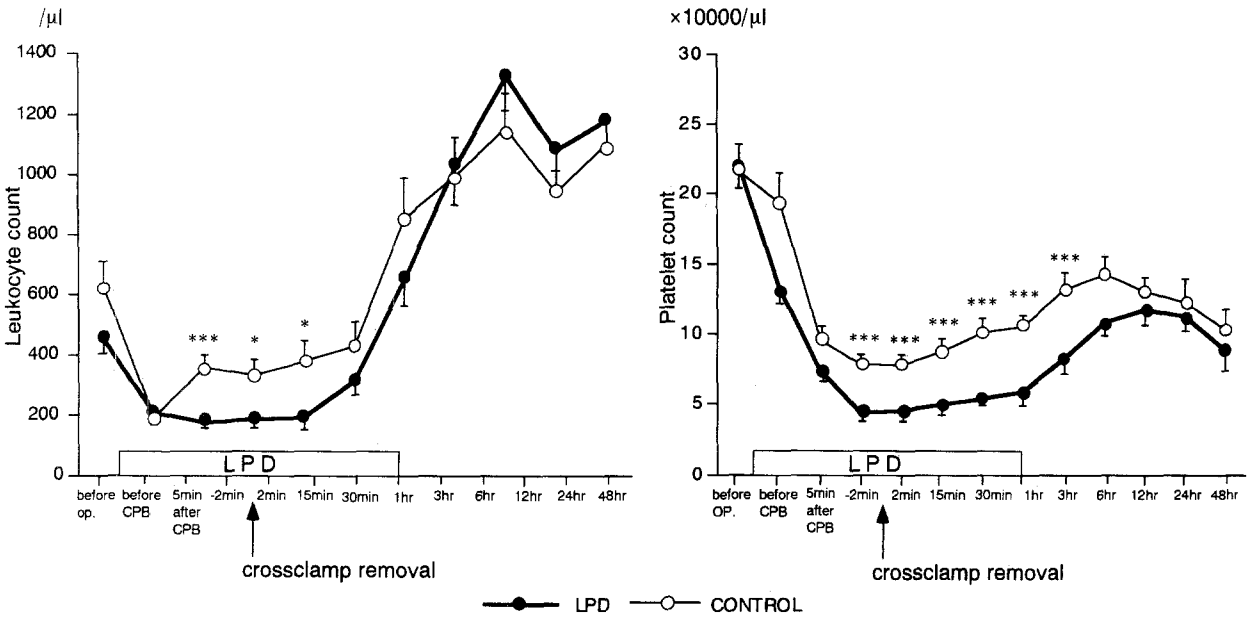

Fig. 1. Leukocyte count and platelet count in the control and leukocyte and platelet depleted groups before operation, 2 minutes before crossclamp removal and at various other times. *Asterisk* signifies $p < 0.05$; *Triple asterisk* signifies $p < 0.005$ compared with the LPD group. Data are mean ± SEM. *CPB,* Cardiopulmonary bypass.

functions of the patients in these two groups after the end of cardiopulmonary bypass were compared. The patients also were subdivided into two groups depending on preoperative oxygen tension (measured after the induction of general anesthesia at an inspired oxygen fraction of 1.0): one subgroup had Pao_2 greater than 520 mm Hg and one subgroup had Pao_2 less than 520 mm Hg. All parameters were expressed as the mean ± standard error of the mean (SEM). Repeated-measures analysis of variance and unpaired Student's t test was used to test the significance of differences. A p value less than 0.05 was regarded as statistically significant.

Results

The mean duration of LPD in the LPD group was 296 ± 81 minutes. The mean total number of leukocytes removed was $3.4 \pm 2.1 \times 10^{10}$, which is equivalent to 119% ± 46% of the estimated number of leukocytes in the circulating blood. The mean number of platelets removed was $2.8 \pm 1.2 \times 10^{11}$, which is equivalent to 27% ± 10% of the estimated number of platelets in the circulating blood. The leukocyte count in the peripheral blood was significantly lower in the LPD group than in the control group 2 minutes before ($1.8 \pm 0.2 \times 10^2$ vs $3.6 \pm 0.4 \times 10^2$ cells/μl) and 2 minutes ($1.9 \pm 0.3 \times 10^2$ vs $3.3 \pm 0.5 \times 10^2$ cells/μl) and 15 minutes after ($1.9 \pm 0.4 \times 10^2$ vs $3.8 \pm 0.7 \times 10^2$ cells/μl) the release of aortic occlusion (Fig. 1). The platelet count in the peripheral blood was significantly lower in the LPD group 2 minutes before ($4.4 \pm 2.0 \times 10^4$ vs $8.1 \pm 3.3 \times 10^4$ cells/μl) and 2 minutes ($4.5 \pm 2.0 \times 10^4$ vs $7.8 \pm 3.5 \times 10^4$ cells/μl), 15 minutes ($4.9 \pm 2.3 \times 10^4$ vs $8.8 \pm 4.0 \times 10^4$ cells/μl) and 30 minutes ($5.4 \pm 2.1 \times 10^4$ vs $10.1 \pm 4.8 \times 10^4$ cells/μl), 1 hour ($5.8 \pm 2.8 \times 10^4$ vs $10.5 \pm 4.2 \times 10^4$ cells/μl) and 3 hours ($8.2 \pm 3.6 \times 10^4$ vs $13.2 \pm 5.1 \times 10^4$ cells/μl) after the release of aortic occlusion (Fig. 1). The leukocyte elastase level was significantly lower in the LPD group than in the control group 2 minutes before ($0.88 \pm 0.16 \times 10^3$ vs $1.47 \pm 0.64 \times 10^3$ ng/ml), and 1 hour ($1.63 \pm 0.21 \times 10^3$ vs $2.64 \pm 0.24 \times 10^3$ ng/ml) and 3 hours ($1.49 \pm 0.29 \times 10^3$ vs $1.84 \pm 0.27 \times 10^3$ ng/ml) after the release of aortic occlusion (Fig. 2). No significant intergroup difference was noted in 6-keto-$PGF_{1\alpha}$ levels. The TxB_2 level was significantly lower in the LPD group than in the control group at 1 hour (152 ± 26 vs 276 ± 54 pg/ml), 6 hours (71 ± 18 vs 96 ± 18 pg/ml), and 12 hours (34 ± 4.4 vs 50 ± 6.3 pg/ml) after the release of aortic occlusion (Fig. 3). The ratio of TxB_2 to 6-keto-$PGF_{1\alpha}$ was significantly lower in the LPD group 2 minutes before (1.49 ± 0.12 vs 2.23 ± 0.48) and 1 hour (1.45 ± 0.16 vs 1.98 ± 0.35), 6 hours

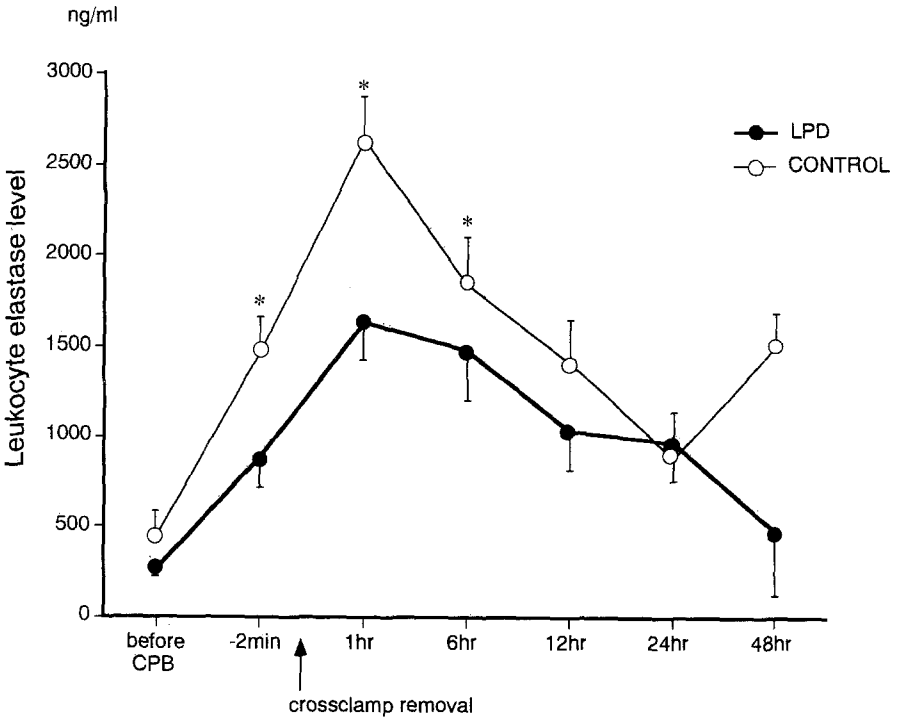

Fig. 2. Leukocyte elastase levels in the control and LPD groups; *Asterisk* signifies $p < 0.05$ compared with the LPD group. Intervals are as in Fig. 1. Data are mean ± SEM. *CPB,* Cardiopulmonary bypass.

(1.57 ± 0.22 vs 2.88 ± 0.52), and 12 hours (1.28 ± 0.14 vs 2.3 ± 0.45) after the release of aortic occlusion (Fig. 3). The D-dimer concentration was significantly lower in the LPD group from 5 minutes after the start of pumping to 24 hours after the release of aortic occlusion (Table II). TAT was significantly lower in the LPD group at 5 minutes after the start of pumping and 1 hour after the release of aortic occlusion (Table II). No significant intergroup differences were observed in the complement (C3a, C4a, and C5a) levels.

In the LPD group, there was no significant difference between preoperative and postoperative Pao_2; however, the Pao_2 was significantly better in the LPD group than in the control group at 1, 3, and 4 hours after the release of aortic occlusion (Table III). Starting from the sixth hour after the release of aortic occlusion, the Pao_2 levels were approximately equal to the preoperative levels in both groups and did not differ between the groups. In the LPD group, the RI measured at 1, 3, and 4 hours after the release of aortic occlusion was significantly lower than the preoperative level (Table III). PEEP, which was measured after operation, was significantly lower in the LPD group than in the control group at 4, 6, 12, and 18 hours after the release of aortic occlusion (Table III). In the same group, the $EIco_2$ differed significantly from the preoperative level at 1 hour (166% ± 38.3% vs 593% ± 121%), 6 hours (67% ± 25% vs 406% ± 135%), and 18 hours (72% ± 27% vs 257% ± 80%) after the release of aortic occlusion (Fig. 4). In patients in whom the preoperative Pao_2 was greater than 520 mm Hg at an inspired oxygen fraction of 1.0, the Pao_2 after the release of aortic occlusion did not differ significantly between the LPD group and the control group. In patients in whom the preoperative Pao_2 was less than 520 mm Hg, however, this parameter at 1 hour (115% ± 7.1% vs 83% ± 5.3%) and 3 hours (103% ± 3.1% vs 79% ± 8%) after the release of aortic occlusion was significantly better in the LPD group than in the control group (Fig. 5). In patients in whom the duration of cardiopulmonary bypass was less than 160 minutes, the postoperative Pao_2 did not differ significantly between the LPD and control groups. In patients in whom the duration was greater than 160 minutes, however, this parameter was significantly better in the LPD group than in the control group

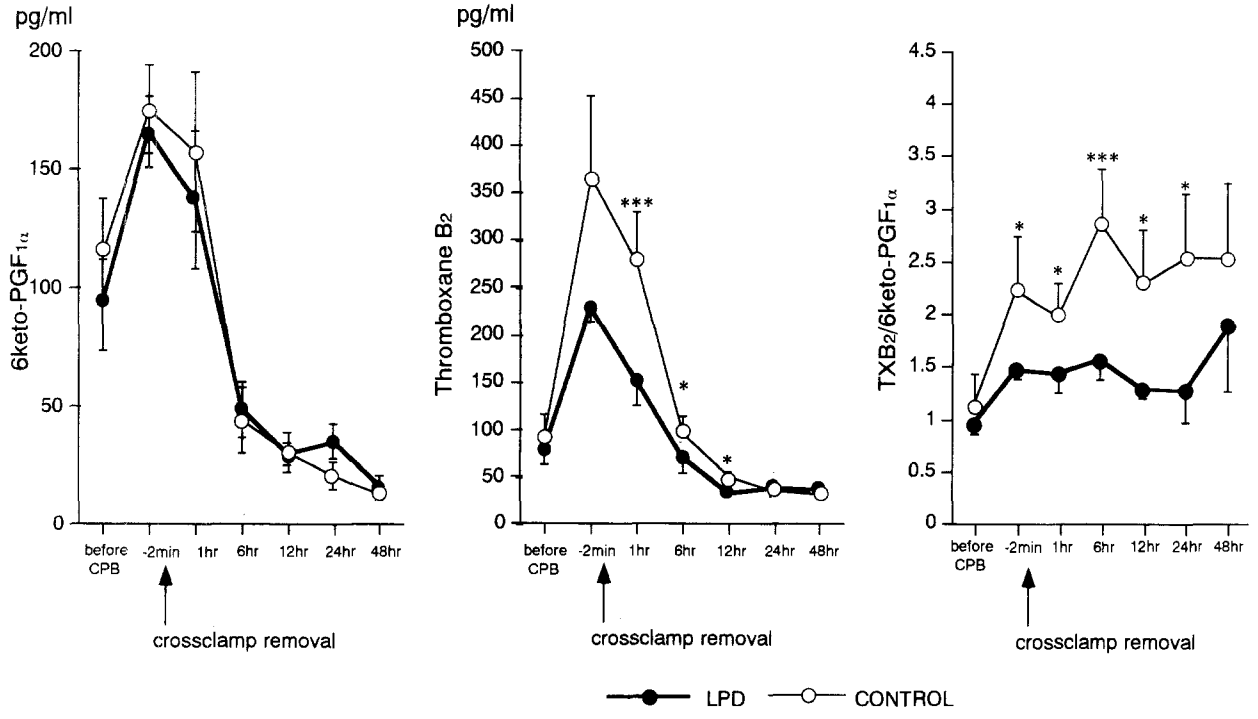

Fig. 3. Levels of 6-keto-$PGF_{1\alpha}$ and TxB_2 and the ratio of TxB_2 to 6-ketoPGF$_{1\alpha}$ in control and LPD groups. *Asterisk* signifies $p < 0.05$; *triple asterisk* signifies $p < 0.005$ compared with the LPD group. Intervals are in Fig. 1. Data are mean ± SEM. *CPB*, Cardiopulmonary bypass.

Table II. *Perioperative change in D-dimer and TAT*

	D-dimer		*TAT*	
	LPD	*Control*	*LPD*	*Control*
Before CPB	1.6 ± 0.7	1.7 ± 0.4	7.3 ± 1.9	9.0 ± 1.8
5 min after CPB	5.7 ± 1.3*	11.7 ± 2.8	66.8 ± 6.9*	94.0 ± 11.2
2 min before crossclamp removal	7.8 ± 1.3*	13.0 ± 2.1	86.6 ± 7.9	105.0 ± 8.7
2 min after crossclamp removal	8.1 ± 1.4*	13.5 ± 2.3	92.5 ± 7.5	107.7 ± 8.7
15 min after crossclamp removal	8.7 ± 1.5*	16.2 ± 2.9	92.6 ± 7.1	106.5 ± 7.7
30 min after crossclamp removal	9.2 ± 1.5*	17.4 ± 3.4	93.5 ± 6.8	107.9 ± 8.0
1 hr after crossclamp removal	9.2 ± 1.7†	19.5 ± 3.8	86.0 ± 27.4*	111.2 ± 9.1
3 hr after crossclamp removal	5.3 ± 1.1*	10.9 ± 2.2	58.2 ± 7.1*	73.2 ± 7.6
6 hr after crossclamp removal	3.8 ± 0.7*	7.4 ± 1.6	47.9 ± 8.2	36.5 ± 7.7
12 hr after crossclamp removal	2.4 ± 0.4*	4.7 ± 0.8	18.5 ± 6.9	19.2 ± 5.6
24 hr after crossclamp removal	1.7 ± 0.3*	3.4 ± 0.8	21.0 ± 3.2	23.3 ± 9.1
48 hr after crossclamp removal	1.2 ± 0.4	3.6 ± 1.3	10.6 ± 7.8	5.1 ± 1.8

Data are mean ± SEM. *CPB*, Cardiopulmonary bypass.
*$p < 0.05$ vs control.
†$p < 0.005$ vs control.

at 1 hour (108% ± 6.9% vs 79% ± 7.1%) and 3 hours (95% ± 6.5% vs 77% ± 7.1%) after the release of aortic occlusion (Fig. 6).

Discussion

Lung injury after heart operations has been reported to involve various factors, such as complement, platelets, endothelial cells, and inflammatory substances released from cells.[8, 9] Leukocytes are activated by complement and other factors during cardiopulmonary bypass, and leukocyte sequestration occurs primarily in the lungs.[10] At reperfusion, these activated leukocytes release proteases and oxygen free radicals, which destroy the tissue. The

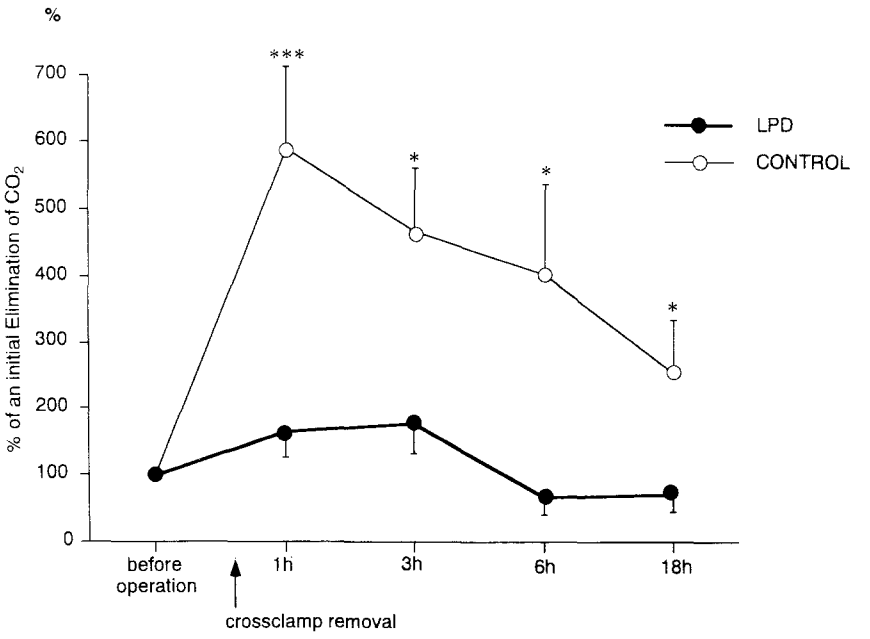

Fig. 4. Perioperative changes in $EIco_2$ in the control and LPD groups. *100%,* Preoperative level of $EIco_2$. *Asterisk* indicates $p < 0.05$; *triple asterisk* indicates $p < 0.005$ compared with the LPD group. Data are mean ± SEM.

Table III. *Perioperative change in Pao_2 and in RI and PEEP necessary to ensure adequate Pao_2*

	Pao_2*		RI		PEEP (cm H_2O)	
	LPD	*Control*	*LPD*	*Control*	*LPD*	*Control*
Fio_2	100%	100%				
Before operation	515 ± 20 mm Hg	532 ± 15 mm Hg	0.4 ± 0.04	0.3 ± 0.05		
After operation						
1 hr	106% ± 4.8%†	85.1% ± 4.4%	0.2 ± 0.05‡	0.6 ± 0.09		
3 hr	99.4% ± 3.7%‡	82.4% ± 5.5%	0.3 ± 0.05‡	0.6 ± 0.13		
4 hr	102% ± 1.4%‡	88.4% ± 6.8%	0.4 ± 0.05‡	0.8 ± 0.18	2.1 ± 0.3§	3.3 ± 0.3
6 hr	99.1% ± 4.7%	95.6% ± 4.0%	0.4 ± 0.07‡	0.5 ± 0.07	2.2 ± 0.3§	3.3 ± 0.3
12 hr	99.7% ± 3.0%	87.2% ± 7.6%	0.4 ± 0.05	0.7 ± 0.09	2.2 ± 0.3§	3.3 ± 0.2
18 hr	105% ± 5.7%	98.5% ± 4.7%	0.6 ± 0.12	0.7 ± 0.10	1.9 ± 0.3§	3.3 ± 0.3

Data are mean ± SEM. Fio_2, Inspired oxygen fraction.
*Value before operation is baseline; values after operation are percentages of baseline.
†$p < 0.005$ vs control.
‡$p < 0.05$ vs control.
§$p < 0.01$ vs control.

level of leukocyte elastase, a protease, was significantly lower in the LPD group in this study. Elastase-mediated injury to the endothelial cells of pulmonary vessels and to pulmonary epithelial cells has been previously reported.[11] In this study, the removal of leukocytes and platelets seemed to reduce the elastase-mediated adverse effects as well as postoperative lung injury.

During cardiopulmonary bypass, the platelet count decreases because platelets are trapped in the cardiopulmonary bypass circuit or in the pulmonary and systemic vascular bed. A decrease in the platelet count leads to an increase in postoperative bleeding. It also is known that platelets are activated during cardiopulmonary bypass, resulting in systemic inflammatory reactions involving neutrophils and many inflammatory substances, and that these platelets also affect the clotting and fibrinolytic systems.

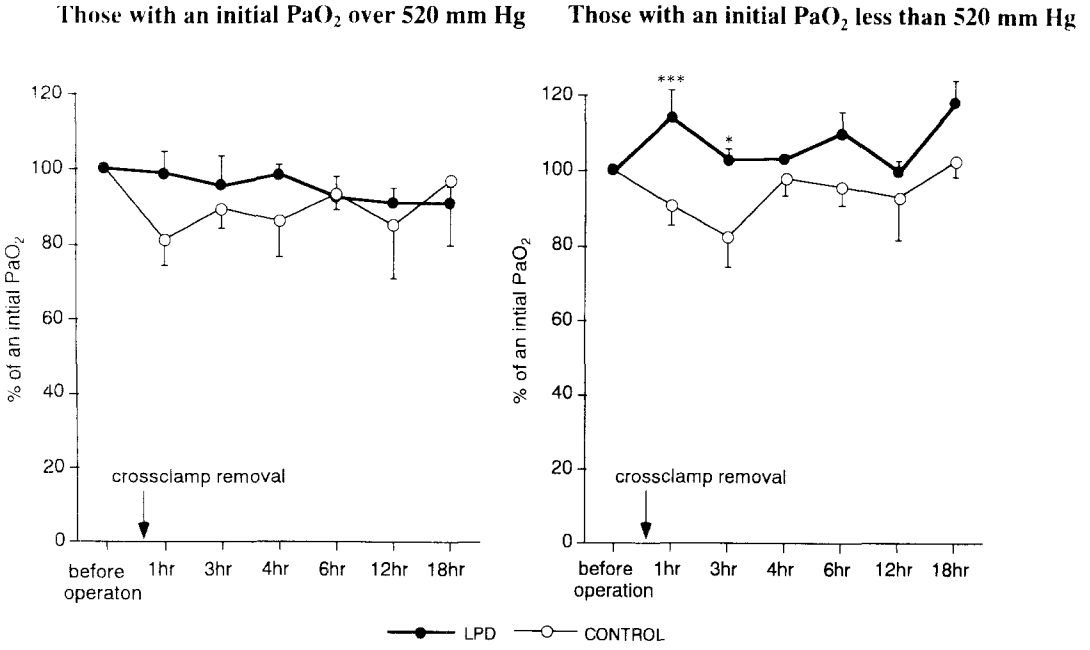

Fig. 5. Subgrouping of the control and LPD groups according to preoperative Pao_2, more than 520 mm Hg versus less than 520 mm Hg inspired oxygen fraction of 1.0, 100% represents preoperative Pao_2. *Asterisk* represents $p < 0.05$, *Triple asterisk* represents $p < 0.005$ compared with the control group. Data are mean ± SEM.

Thromboxane A_2 (TxA_2), which is produced primarily by activated platelets, is a metabolite of arachidonates. This substance has a potent vasoconstrictive action and is a potent agonist for platelet aggregation. Its stable metabolite, TxB_2, is reported to increase during cardiopulmonary bypass.[12, 13] In this study, the TxB_2 level was significantly lower in the LPD group than in the control group (Fig. 3).

Prostacyclin, which is produced primarily by endothelial cells, antagonizes TxA_2. The level of 6-keto-$PGF_{1\alpha}$, a stable metabolite of this substance, did not differ significantly between the two groups. The ratio of TxB_2 to 6-keto-$PGF_{1\alpha}$ is often used as an indicator of physiologic effects because the balance between these two substances is important in determining the effects of thromboxane.[14] In this study, this ratio was significantly lower in the LPD group than in the control group for a relatively long period, beginning immediately before the release of aortic occlusion and ending 12 hours after release. Fletcher and colleagues[15] found in animal experiments that TxA_2 was not produced by activated platelets alone but was produced by the interaction between leukocytes and platelets. The low ratio of TxB_2 to 6-keto-$PGF_{1\alpha}$ in the LPD group observed in this study seems to be attributable not only to the removal of platelets but also to the removal of leukocytes. When the TxA_2 concentration is higher than that of prostacyclin vascular contraction and platelet aggregation are accelerated, primarily in the lungs, resulting in injury to pulmonary microcirculation and the onset of respiratory dysfunction. The removal of leukocytes and platelets seems to reduce respiratory dysfunction after cardiopulmonary bypass by suppressing vascular contraction and platelet aggregation.

In this study there was no difference between the two groups in various complement levels. Complement activation during cardiopulmonary bypass is known to be caused by the contact of blood with foreign matter, such as an artificial lung and extracorporeal circulation circuit. The similar complement levels in the LPD and control groups may be attributable to the use of the same artificial lung in both groups.[10, 16]

In this study the leukocytes and platelets were temporarily removed by plasmapheresis instead being removed permanently with a filter.[17] The method we used permits the return of sequestered leukocytes and platelets into the body after operation and seems to be useful in preventing postoperative infection and reducing postoperative blood

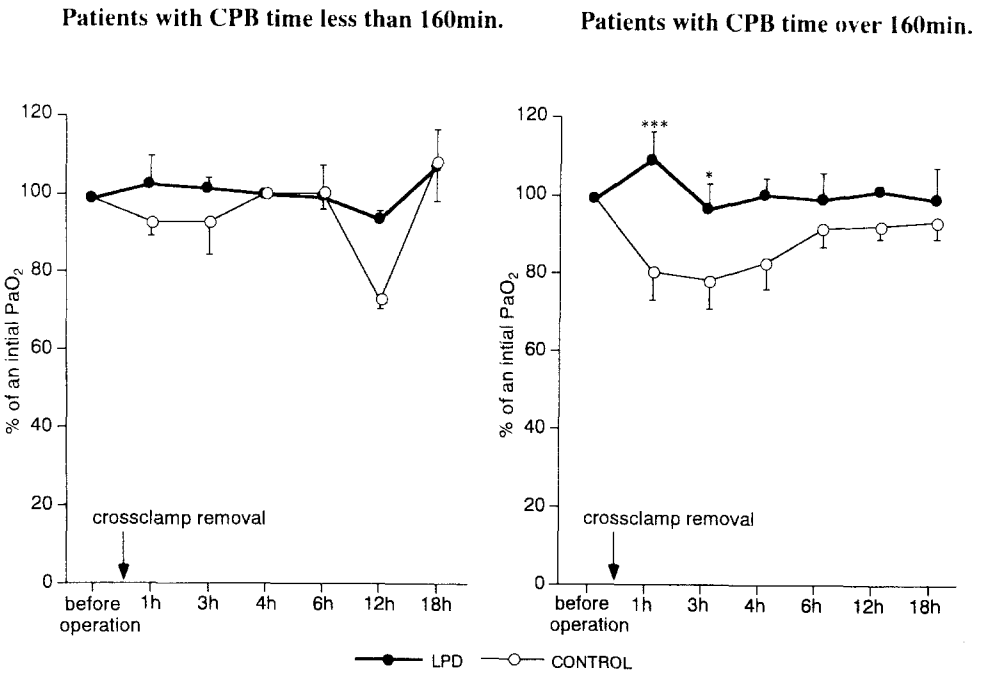

Fig. 6. Subgrouping of the control and LPD groups according to cardiopulmonary bypass *(CPB)* time, less than 160 minutes versus more than than 160 minutes. 100% represents preoperative Pao_2; *Asterisk* represents $p < 0.05$, *Triple asterisk* represents $p < 0.005$ compared with the control group. Data are mean ± SEM.

loss. The number of leukocytes that could be removed by plasmapheresis in this study averaged $3.4 \pm 2.1 \times 10^{10}$ cells (119% ± 46% of the estimated number of leukocytes in the circulating blood), which is about 10 times the number reported by Davies and coworkers[4] $3.4 \pm 1.9 \times 10^9$ cells/ml (equivalent to about 11% of the estimated number of leukocytes in the circulating blood). One reason for the greater number of leukocytes removed in this study is that the duration of removal was much longer than in previous studies. Another possible explanation is that the machine used in previous studies was designed primarily for the removal of platelets and was therefore less effective in removing the leukocytes than the machine used for this study. The number of platelets removed in this study averaged $2.8 \pm 1.2 \times 10^{11}$ cells (27% of the estimated number of platelets in the circulating blood), which is greater than the numbers reported by Mohr and associates[18] (1×10^{11} cells) and is comparable to the numbers reported by Giordano and coworkers[19] (2.0×10^{11}) and Davis and coworkers[4] ($3.5 \pm 1.4 \times 10^{11}$ cells). These investigators have reported that postoperative blood loss and the volume of homologous blood transfusion needed could be reduced by collecting platelets before the start of cardiopulmonary bypass and returning them after cardiopulmonary bypass. Postoperative blood loss also was significantly reduced by this technique in this study.

Levels of TAT and D-dimer, which are indicators of abnormal clotting and accelerated fibrinolysis, were lower in the LPD group than in the control group (Table III). The decreases in these parameters seem to be related to the decrease in blood loss in this group. In addition, the suppression of pulmonary microthrombus formation is thought to be related to the suppression of respiratory dysfunction. In this study we investigated lung injury after heart operations with cardiopulmonary bypass by means of analyses of oxygenation and carbon dioxide elimination. Of the conditions showing a ventilation-perfusion imbalance, the condition where ventilation is small relative to perfusion reflects oxygenation, whereas the condition where perfusion is small relative to ventilation reflects carbon dioxide elimination. The Pao_2, A-aDo_2, and RI, which were examined as indexes of oxygenation, differed significantly between the LPD group and the control group until the fourth hour after the release of

aortic occlusion but did not differ significantly between the two groups from the sixth hour after the release of aortic occlusion. The level of PEEP needed to obtain an appropriate Pao_2 during postoperative intensive care, however, was significantly higher in the control group than in the LPD group. The reason for this is that the PEEP had to be increased to offset the postoperative decrease in Pao_2 in these patients.

In this present study, the $EIco_2$, an indicator of carbon dioxide elimination, was significantly higher in the control group. Bohr's equation of dead spaces includes anatomic dead spaces (the volume of the airway that is not involved in gas exchange). The alveolar dead space ventilation rate indicates the relationship between the alveolar ventilation (excluding anatomic dead spaces) and the alveolar dead space ventilation (alveoli without capillary blood flow). If the imbalance between ventilation and perfusion becomes serious and if alveoli with low perfusion relative to ventilation increase, carbon dioxide elimination decreases, resulting in a difference in the carbon dioxide tension between the arterial blood and alveolar gas. $EIco_2$ therefore indicates the percentage of wasted ventilation (ventilation in nonperfused areas) relative to the total alveolar ventilation. An increase in $EIco_2$ causes an exponential increase in respiratory work and results in a large load on the cardiovascular system, which has little reserve after heart a heart operation.[7] It is likely that this value increased in the control group in pulmonary areas where perfusion was small relative to ventilation because of an increase in pulmonary microthrombi and other factors.

The results of this study can be summarized as follows: The removal of leukocytes and platelets suppressed the activation of leukocytes and platelets and the release of reactive substances from these cells, leading to the suppression of alveolar and interstitial edema, microatelectasis, and other pulmonary abnormalities. The effect of leukocyte and platelet removal on the oxygenation capacity was more marked in patients in whom the preoperative oxygenation capacity was lower and in patients in whom the duration of cardiopulmonary bypass was prolonged for more than 160 minutes.

The removal of leukocytes and platelets during heart operations with cardiopulmonary bypass is expected to prevent postoperative deterioration of respiratory function through the mechanisms described here. This technique is particularly recommended for severely ill patients or patients in whom the duration of cardiopulmonary bypass is expected to be long.

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