Evaluation of Leukocyte-Reducing Arterial Line Filter (LG6) for Postoperative Lung Function, Using Cardiopulmonary Bypass

Objective: **To prevent postoperative pulmonary dysfunction, we have investigated the effect of the Leuko-Guard 6 leukocyte-reducing arterial line filter (LG6) on postoperative lung function.** *Methods:* **Twenty-six cases of adult valvular heart disease were included in this study. Thirteen cases were operated upon using the LG6 (Group LG), and 13 cases were operated upon using a conventional arterial line filter (Group C). Neutrophil, polymorphonuclear leukocyte elastase and lipoperoxide were measured for this study, and the lung function was evaluated using the Oxygenation Index (PaO_2/FiO_2).** *Results:* **Statistically significant differences were observed in neutrophil counts between Group LG and Group C (LG = 2225 ± 572/mm^3, C = 3157 ± 1413/mm^3, p = 0.04) at 5 minutes after the onset of cardiopulmonary bypass. In simultaneous blood sampling from the pulmonary artery and the pulmonary vein, the sequestration of neutrophil in the lung decreased in Group LG after the discontinuation of cardiopulmonary bypass. Release of polymorphonuclear leukocyte elastase from the lungs was significantly decreased (p = 0.04) in the Group LG at 1 hour post-bypass. Significant differences were observed in the Oxygenation Index between Group LG and Group C (LG = 398 ± 72, C = 326 ± 71, p = 0.019) at 3 hours post-bypass.** *Conclusion:* **We concluded that LG6 improved the postoperative lung function, and its mechanism might be derived from the prevention of leukosequestration in the lungs that occurs during the rewarming phase due to selective absorption of activated leukocyte by the LG6. (JJTCVS 2000; 48: 295–300)**

Key words: cardiopulmonary bypass, postoperative pulmonary dysfunction, neutrophil depleting filter, leukosequestration

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Various organ disorders such as post-perfusion lung syndrome[1-3] may develop after surgery using cardiopulmonary bypass (CPB). Studies in recent years have shown that free radicals and proteolytic enzymes released from activated leukocytes, particularly neutrophils, contributed to the development of post-perfusion lung syndrome,[4-6] suggesting this injury occurred in response to the accumulation of leukocytes within the lung (leukosequestration).[7,8] We have evaluated the efficacy of a leukocyte depleting arterial line filter, the LG6, for its ability to decrease or prevent postoperative pulmonary disorders following bypass surgery.

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Subjects and Methods

Twenty-six adults operated for valvular heart disease were included in this study. Blood samples were taken from the arterial sampling port of the CPB system or radial arterial line, and simultaneously from the pulmonary artery and the pulmonary vein, in order to determine the neutrophil count, the polymorphonuclear leukocyte elastase (PMNE), and the lipoperoxide (LPO) concentrations. The neutrophil count in the systemic circulation was determined before CPB, and at 5, 15, 30, 45, 60, 90, and at 120 minutes after the onset of CPB, and at 10 minutes

Table I. *Characteristics of patients*

	Group C	*Group LG*
Age	56 ± 14 y	55 ± 11 y
Sex	M:7 F:6	M:5 F:8
CPB time	176 ± 45 m	199 ± 43 m
Arrest time	110 ± 24 m	121 ± 25 m
Blood transfusion	5 cases	8 cases

There was no significant difference between the two groups with respect to age, sex, CPB time, duration of cardiac arrest, or use of transfused blood.
CPB, Cardiopulmonary bypass; *M*, male; *F*, female.

after aortic unclamping, as well as at 10 minutes and at 1 hour after discontinuation of CPB. PMNE and LPO were determined before and at 5 minutes after the initiation of CPB, at 10 minutes after aortic unclamping and at 10 minutes and at 1 hour after discontinuation of CPB. Neutrophil counts, PMNE and LPO from the pulmonary artery and pulmonary vein were determined at 5 minutes after the onset of CPB, at 10 minutes after aortic unclamping, and at 10 minutes and at 1 hour after discontinuation of CPB. All values were corrected based on hematocrit values to exclude effects of dilution as follows (A: preoperative hematocrit value, B: hematocrit value of sampled specimen).

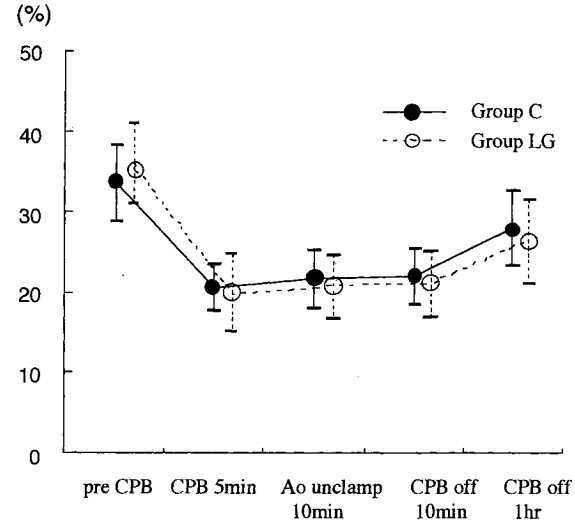

Fig. 1. Changes in the hematocrit values.
No significant difference was noted between the two groups in hematocrit values.
CPB, Cardiopulmonary bypass; *Ao unclamp 10 min*, at 10 minutes after aortic unclamping.

$$\text{leukocyte count} \times \frac{A}{B}$$

$$\text{PMNE or LPO value} \times \frac{(100\text{-}B) \times A}{(100\text{-}A) \times B}$$

In order to evaluate leukosequestration within the lungs, neutrophil counts were corrected as follows:

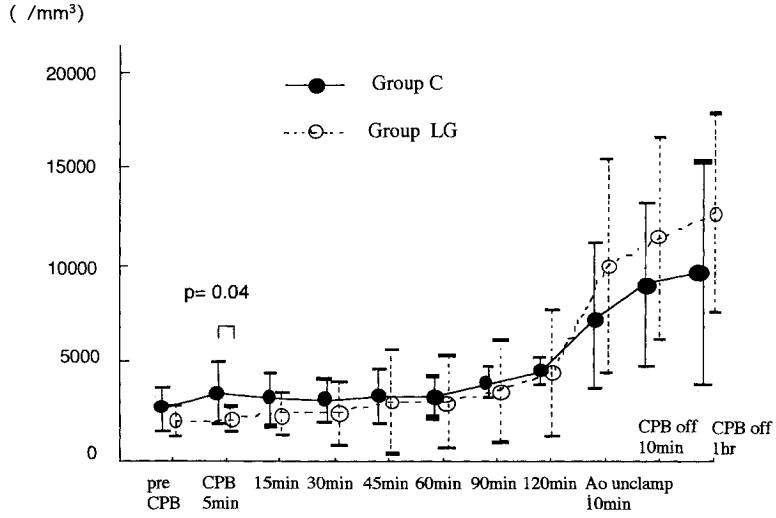

Fig. 2. Changes in neutrophils of the systemic bloodstream.
Neutrophil counts were significantly lower in Group LG than in Group C at 5 minutes on bypass. After aortic unclamping, they increased in both groups, and showed a tendency to be greater in Group LG than in Group C.
CPB, Cardiopulmonary bypass; *Ao unclamp 10 min*, at 10 minutes after aortic unclamping.

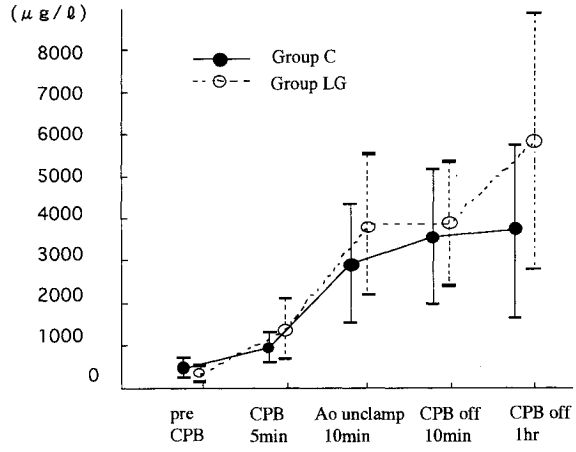

Fig. 3. Changes in PMNE values.
There were no significant differences in the PMNE values. However, there was a tendency at 1 hour after discontinuation of CPB to be greater in Group LG ($p = 0.062$).
CPB, Cardiopulmonary bypass; *Ao unclamp 10 min*, at 10 minutes after aortic unclamping, *PMNE*, polymorphonuclear leukocyte elastase.

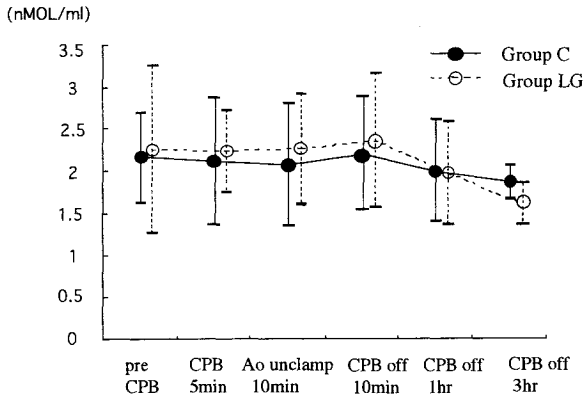

Fig. 4. Changes in LPO values.
There was no significant difference in the LPO values at any time point.
CPB, Cardiopulmonary bypass; *Ao unclamp 10 min*, at 10 minutes after aortic unclamping, *LPO*, lipoperoxide.

(neutrophil count in pulmonary artery) — (neutrophil count in pulmonary vein), while releases of PMNE and LPO from the lungs were determined as follows: (PMNE or LPO value in pulmonary vein) — (PMNE or LPO value in pulmonary artery). The pulmonary function was evaluated using the Oxygenation Index (PaO_2/FiO_2) before CPB and at 10 min., at 3 and 6 hours post-bypass.

Of the 26 cases, 13 cases used a conventional arterial line filter (Auto Vent-SV; Pall Biomedical Products Co.; Group C), while the remaining 13 cases used an arterial line filter with an ability to deplete

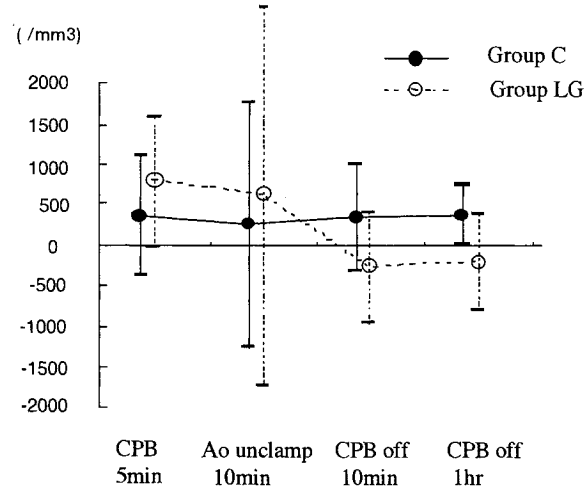

Fig. 5. Accumulation in neutrophils in the lungs (neutrophil count in pulmonary artery) — (neutrophil count in pulmonary vein).
Leukosequestration within the lungs showed a tendency to be lower in Group LG than in Group C at 10 minutes ($p = 0.092$) and 1 hour ($p = 0.057$) after CPB was discontinued.
CPB, Cardiopulmonary bypass; *Ao unclamp 10 min*, at 10 minutes after aortic unclamping.

leukocytes (LG6; Pall Biomedical Products Co. East Hills, NY, USA; Group LG). The lowest rectal temperature was aimed at 28°C, while the CPB flow rate was aimed at 2.4 l/min/m^2. The above-mentioned parameters were compared between two groups using student's t-test. Any difference was regarded as statistically significant at $p < 0.05$.

Results

As shown in Table I, there were no significant differences between two groups with respect to age, sex, CPB time, duration of cardiac arrest, and transfused blood products. Changes in hematocrit values during surgery are illustrated in Fig. 1. No significant differences were noted between the two groups.

Changes in neutrophils, PMNE and LPO value within the systemic circulation are shown in Figs. 2, 3 and 4 respectively. The neutrophil counts were significantly lower in Group LG ($2,225 \pm 572/mm^3$) than in Group C ($3,157 \pm 1,413/mm^3$) at 5 minutes after the onset of CPB ($p = 0.04$). After aortic unclamping they increased in both groups, and showed a tendency to be greater in Group LG than in Group C at 10 minutes ($p = 0.095$) and at 1 hour ($p = 0.078$) after discontinuation of CPB (Fig. 2). There was no significant difference in the PMNE values. However, there was a tendency only at 1 hour after discontinua-

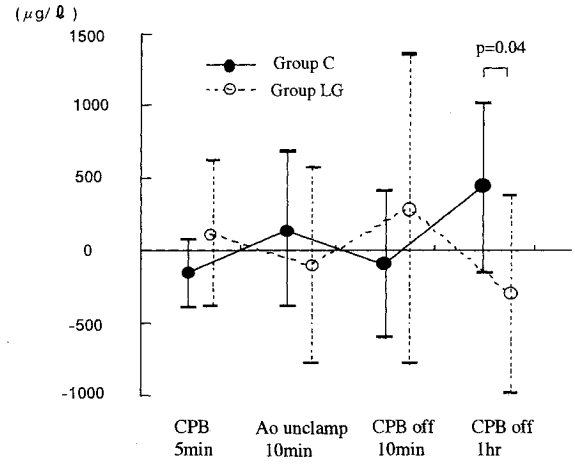

Fig. 6. PMNE released from the lungs (PMNE value in pulmonary vein) — (PMNE value in pulmonary artery).
The amount of PMNE released from the lungs was significantly lower in Group LG than in Group C ($p = 0.04$) at 1 hour after discontinuation of CPB.
CPB, Cardiopulmonary bypass; *Ao unclamp 10 min*, at 10 minutes after aortic unclamping, *PMNE*, polymorphonuclear leukocyte elastase.

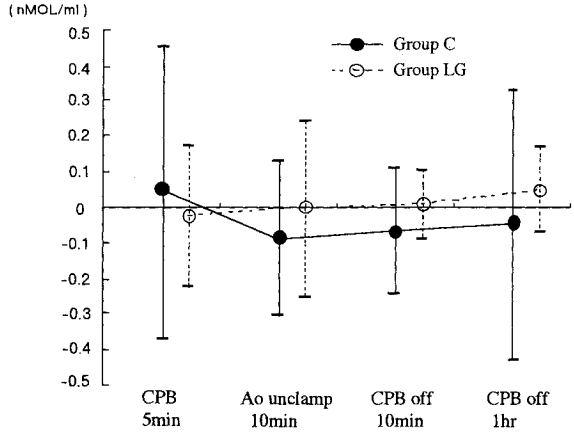

Fig. 7. LPO released from the lungs (LPO value in pulmonary vein) — (LPO value in pulmonary artery).
The amounts of LPO released from the lungs were comparable in the two groups at all time points.
CPB, Cardiopulmonary bypass; *Ao unclamp 10 min*, at 10 minutes after aortic unclamping, *LPO*, lipoperoxide.

tion of CPB to be greater in Group LG ($p = 0.062$) (Fig. 3). There was no significant difference in the LPO values at any time point (Fig. 4).

Findings obtained with blood samples simultaneously collected from the pulmonary artery and the pulmonary vein are shown in Fig. 5, 6 and 7. The extent of leukosequestration within the lungs showed a tendency to be lower in Group LG than in Group C at 10 minutes ($p = 0.092$) and 1 hour ($p = 0.057$) after

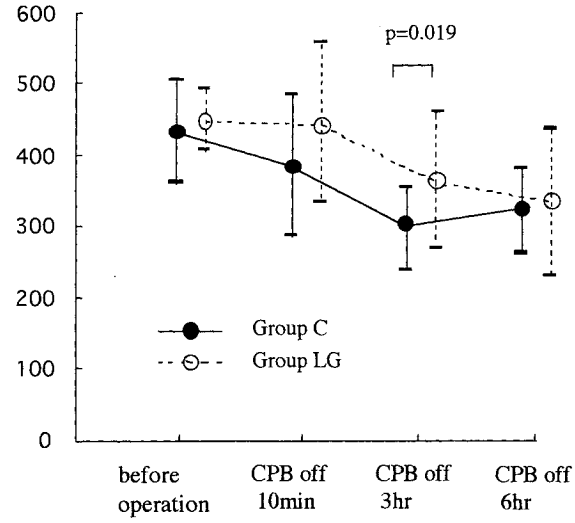

Fig. 8. Oxygenation Index (PaO_2/FiO_2).
The Oxygenation Index showed a tendency to be higher in Group LG than in Group C since immediately after discontinuation of CPB and was significantly greater in Group LG than Group C ($p = 0.019$) at 3 hours after discontinuation of CPB.
CPB, Cardiopulmonary bypass.

off bypass (Fig. 5). The amount of PMNE released from the lungs was significantly lower ($p = 0.040$) in Group LG (-285 ± 673 μg/l) than in Group C (426 ± 584 μg/l) 1 hour after off bypass (Fig. 6). The amounts of LPO released from the lungs were comparable in the two groups at all time points (Fig. 7).

The Oxygenation Index (PaO_2/FiO_2) showed a tendency to be higher in Group LG than in Group C since immediately after CPB was discontinued, and was significantly greater ($p = 0.019$) in Group LG (398 ± 72) than in Group C (326 ± 71) at 3 hours after off bypass (Fig. 8).

Discussion

Many investigators agree that activated leukocytes during CPB is one of the triggers of post-perfusion lung syndrome.[4–6] In recent years, leukocyte-reducing filters have been reported to be effective in improving pulmonary function after surgery.[9–11] The LG6 used in this study reduces leukocytes selectively by adsorbing them to non-woven polyester fibers and is reported to eliminate 50 to 70% of leukocytes when tested in vitro.[12–13]

In Group LG, the neutrophil counts within the systemic circulation decreased significantly at 5 minutes after the onset of CPB, indicating that the LG6 filter was effective at reducing leukocytes (Fig. 2). More-

over, leukosequestration within the lung showed a tendency to be less marked in Group LG than in Group C at 10 minutes and at 1 hour after off bypass (Fig. 5). In addition PMNE release from the lungs was significantly lower in Group LG at 1 hour after off bypass. According to Menashe and Deist et al., accumulation in neutrophils in the lungs is caused due to rewarming.[14,15] In the present study, it was inhibited after completion of CPB, i.e., after completion of rewarming in Group LG, and inhibition in the release of PMNE was observed for 1 hour after completion of CPB. This finding suggested that LG6 reduced the accumulation in neutrophils in the lungs due to warming, as well as the subsequent PMNE release, thereby contributing to improvement in the postoperative Oxygenation Index. Thurlow et al.[16] showed that LG6 adsorbed almost 100% of neutrophils activated by phorbol myristate acetate (PMA) at 30 minutes after the onset of closed circulation in an in vitro experiment, indicating that LG6 selectively adsorbs activated neutrophils. In our study, accumulation in neutrophils in the lungs showed a tendency to be inhibited in Group LG (Fig. 5), although the neutrophil counts in systemic blood were slightly higher in Group LG than in Group C at 1 hour after discontinuation of CPB (Fig. 2). This finding suggested that LG6 could have been operating to reduce pulmonary disorders by selectively adsorbing the activated neutrophils that were prone to accumulate in the lungs at the rewarming phase, rather than by decreasing the total number of neutrophils.

However, the following findings obtained in this study raised some questions about the efficacy of LG6: only small differences between the two groups in neutrophil counts in the systemic blood at all time points except at 5 minutes after onset of CPB (Fig. 2); no differences between the two groups in LPO values; and improvement in Oxygenation Index observed at only 3 hours after off bypass. While LG6 have been reported to deplete 50 to 70% of leukocytes in vitro closed circuits,[12,13] much lower elimination rates were reported in vivo clinical studies.[10,17] Larger adsorption capacity is expected to be required in CPB mediated by the human body, because filters must also deal with neutrophils migrating from the reticuloendothelial system. The fact that there was no significant difference between the two groups in neutrophil counts in the systemic circulation at any time point except at 5 min after the onset of CPB suggested that the filter's neutrophil absorbing capacity was so small that it was exhausted within a short period of time after the onset of CPB. LPO, which was determined as an index of tissue injury due to free radicals, showed only slight changes during surgery and no significant difference between the two groups, suggesting that operative stress was not so large as to cause major tissue injury in either group, and that pulmonary function escaped major damages in both groups.

Another unexpected finding was that neutrophil counts and PMNE in systemic blood showed a tendency to be greater in Group LG than Group C after discontinuation of CPB (Figs. 2, 3). This finding may be interpreted as evidence that LG6 induced, rather than prevented, post-perfusion lung syndrome. LG6 did not remove neutrophils from the blood, but merely adsorbed them. Therefore, it may increase PMNE values if adsorbed neutrophils released PMNE on the filter, and if released PMNE operated as a leukocytotactic agent,[18,19] LG6 may increase, rather than decrease, neutrophils. This is a serious problem if increased neutrophils and PMNE cause new organ disorders. But it seems that this possibility can be ruled out because for organ disorders due to activated leukocytes, accumulation of such leukocytes in particular organs and PMNE release in the proximity of organ cells are considered to be necessary. Furthermore, PMNE released into the blood is rapidly inactivated by an inhibitor (α-1-protease inhibitor) in the blood.[20] Therefore accumulation in artificial materials such as filters is not expected to cause organ disorders. Palanzo et al.[11] reported that proteolytic enzymes become more likely to be inactivated and less likely to cause organ disorders as the distance increases between the sites where proteolytic enzymes are released and the target organs. This report supports our interpretation of the results from this study.

In conclusion, our findings showed that LG6 was effective to some extent at improving the pulmonary function after open-heart surgery. And LG6 was concluded to show its effects by selectively adsorbing activated neutrophils at a distance from organs and thereby inhibiting any accumulation in activated neutrophils that might occur during the rewarming phase in the lungs.

Conclusion

1. The effects of a leukocyte-reducing arterial line filter (LG6) on leukosequestration in the lungs, the concentrations of leukocyte activation products and postoperative pulmonary functions were evaluated in

26 patients who underwent open-heart surgery under CPB.

2. The postoperative pulmonary function was significantly improved in Group LG, but the improvement was limited to the short period after the operation, and changes in neutrophil counts in the systemic circulation observed suggested that the LG6's ability to adsorb neutrophils was unsatisfactory.

3. The mechanism of this beneficial effect was thought to be derived from selectively adsorbing activated neutrophils at a distance from organs and thereby inhibiting leukosequestration that might occur during rewarming phase in the lungs.

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