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## Platelet activation in the postoperative period after lung transplantation

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### Abstract

**Objective**—During lung transplantation, cells in the pulmonary parenchyma are subjected to ischemia, hypothermic storage, and reperfusion injury. Platelets, whose granular contents include adhesion receptors, chemokines, and coactivating substances that activate inflammatory and coagulant cascades, likely play a critical role in the lung allograft response to ischemia and reperfusion. The platelet response to the pulmonary allograft, however, has never been studied. Here we report significant platelet activation immediately after lung transplantation.

**Methods**—We performed a prospective cohort study comparing markers of platelet activation in patients undergoing lung transplantation and patients undergoing nontransplant thoracotomy. Plasma levels of soluble P-selectin, soluble CD40 ligand, and platelet–leukocyte conjugates were measured before surgery, after skin closure, and at 6 postoperative hours.

**Results**—Both soluble P-selectin and soluble CD40 ligand levels increased significantly after lung transplantation but not after thoracotomy. Additionally, platelet–monocyte conjugate fluorescence was significantly higher after lung transplantation than after thoracotomy alone.

**Conclusion**—These findings suggest that platelet activation is significantly increased after lung transplantation beyond that expected from the postoperative state. The increase in circulating platelet–monocyte conjugates suggests an important interaction between platelets and inflammatory cells. Further research should examine whether platelet activation affects early graft function after lung transplantation.

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Lung transplantation has emerged as a successful surgical therapy for end-stage pulmonary disease.<sup>1</sup> The lung is the most richly vascular transplanted organ, and each milliliter of blood coursing through the transplanted lungs often contains more than 300,000 platelets. Platelets contain potent thrombotic and vasoactive compounds and mediate key pathways in inflammation. To our knowledge, however, the platelet response to lung transplantation has not been previously studied in human beings.

Platelets adhere to activated endothelium, crosslinking leukocytes to injured endothelial surfaces.<sup>2</sup> Platelet-mediated leukocyte adherence, diapedesis, and infiltration of the lung allografts are integral to early graft failure after lung transplantation. Several biomarkers with potential physiologic significance reflect *in vivo* platelet activity. P-selectin (CD62P) is a 140-kDa transmembrane protein that is stored in the alpha and dense granules of platelets and in endothelial cells; this protein is expressed on the cell surface, and some is shed during degranulation (soluble P-selectin [sP-selectin]).<sup>3</sup> sP-selectin binds P-selectin glycoprotein ligand-1 on leukocytes, arresting them in transit and upregulating inflammation at the blood-tissue interface.<sup>4</sup> CD40 ligand (CD154) is a trimeric transmembrane protein that also mobilizes to the cell surface of the activated platelet before being shed (soluble CD40 ligand [sCD40L]).<sup>5,6</sup> As the cognate interaction between CD154 and CD40 (on endothelial and other cells) can contribute not only to immune cell coactivation but also platelet clumping, this interaction is likely important in the context of lung ischemia and reperfusion.<sup>5</sup> Platelets produce more than 95% of all sCD40L, which stimulates cyclooxygenase-2 and prostaglandin E<sub>2</sub> synthesis, leading to inflammation.<sup>7,8</sup> Further, circulating platelet-leukocyte conjugates, as assessed by flow cytometry, are considered to be a sensitive marker of the complex interactions that occur between platelet activation and inflammation pathways *in vivo*.<sup>9</sup>

Because platelets play a key role in the recruitment and binding of leukocytes to vascular sites of inflammation, platelet activation could be an integral component of early inflammatory and thrombotic processes in the reperfused lung allograft. The effects of lung transplantation on sP-selectin, sCD40L, and circulating platelet-leukocyte conjugates are, however, unknown. We therefore aimed to determine whether platelet activation is increased after lung transplantation. We hypothesized that sP-selectin, sCD40L, and circulating platelet-leukocyte conjugates would be increased in patients undergoing lung transplantation relative to patients undergoing other types of thoracic surgery.

## Materials and Methods

### Study Design and Subjects

We performed a prospective cohort study of patients undergoing lung transplantation and patients undergoing nontransplant thoracotomy. Patients with a known history of platelet disorders or recent antiplatelet medication use, including aspirin or ticlopidine, were excluded from study. Patients with planned cardiopulmonary bypass or a history of chemotherapy or radiation therapy to the chest were also excluded, because platelet reactivity is altered by cardiopulmonary bypass and advanced malignancy.<sup>10,11</sup> All patients in this study underwent preoperative induction of immunosuppression with tacrolimus (0.04 mg/kg), azathioprine (2 mg/kg), methylprednisolone (1 g), and basiliximab (20 mg).

### Blood Sampling

After informed consent was obtained, blood sampling was performed (1) before induction of anesthesia and immunosuppression, (2) immediately postoperatively, after skin closure, and (3) 6 hours later. Clinical data, including platelet counts, were recorded. Phlebotomy was performed through a fresh needle stick at each point with a 21-gauge butterfly into Vacutainer tubes (BD, Franklin Lakes, NJ) containing EDTA. Whole blood was spun at 7000g for 15 minutes, and plasma was frozen at -80°C until batch analysis. All blood samples were processed within 15 minutes of phlebotomy.

Plasma sP-selectin and sCD40L levels were measured in triplicate with commercially available assays (R&D Systems, Minneapolis, Minn) according to the manufacturer protocol.

## Platelet–Leukocyte Conjugates

Circulating platelet–leukocyte conjugates were quantified by flow cytometry, as previously described.<sup>2,12,13</sup> Briefly, 200  $\mu$ L whole blood was used from each sample for analysis. Three samples were run in parallel: a negative control, an unstimulated sample, and 10-mmol/L adenosine diphosphate–stimulated sample. The samples were labeled sequentially with phycoerythrin-labeled antihuman platelet CD42 antibody (BD) and then fluorescein isothiocyanate–labeled antihuman leukocyte CD14 antibody (BD). After labeling, all samples were fixed and then lysed with Optilyse solution (Beckman Coulter, Inc, Fullerton, Calif) according to manufacturer protocol. All tubes were then immediately analyzed on a FACSCalibur Flow Cytometer (BD) according to the method of Michelson with Cell Quest Pro software.<sup>14</sup> Isotype-matched fluorescein isothiocyanate–labeled IgG (BD) served as negative control preparations. Particles expressing both CD42 and CD14 were identified as platelet–leukocyte conjugates and then further subdivided into either platelet–monocyte or platelet–neutrophil conjugates. Differences in granularity and the intensity of CD14 expression allowed differentiation between monocyte and neutrophil populations.<sup>2,12,13</sup> Measures of conjugates were expressed as the mean intensity of phycoerythrin-labeled CD42 per particle, reflecting the number of platelets bound per monocyte–neutrophil conjugate, and as the percentage of the particles positive for phycoerythrin-labeled CD42 and fluorescein isothiocyanate–labeled CD14. Flow cytometric platelet–leukocyte conjugate data are presented as fractional change from baseline.

## Statistical Analysis

Continuous variables are summarized with mean  $\pm$  SE or median with interquartile range, as appropriate. Comparison of preoperative with postoperative plasma biomarkers and flow cytometric results was performed with signed rank tests. We compared patients undergoing lung transplantation with those undergoing thoracotomy alone at each postoperative time point with Mann–Whitney *U* tests. Multivariate linear regression was also performed for postoperative plasma biomarker levels with adjustment for baseline levels.

Before the study, we performed power analyses that indicated that a sample size of 7 patients undergoing transplantation and 10 control patients would provide 80% power ( $\alpha = .05$ ) to detect a difference between the groups of 1.5 SD, the effect size seen in previous studies of platelet activation.<sup>15–17</sup> Statistical analyses were performed using Analyze-it! (Analyze-it Software, Ltd, Leeds, UK) and STATA (Stata Corporation, College Station, Tex) software packages.

## Ethical Guidelines

This study was approved by the Western Institutional Review Board (Nov 16, 2004, WIRB Protocol No. 2198). All patients voluntarily participated after signing a consent form before the scheduling of their surgery. There were no patient exposures to any dangerous chemical or toxic substance. Funding agencies did not participate in data analysis or manuscript preparation.

## Results

### Study Population

Twenty-six patients were enrolled between March and August 2005. Ten patients were enrolled in the lung transplant study group; 3 were subsequently excluded because of unplanned cardiopulmonary bypass. Four patients underwent bilateral transplantation. The indications for transplantation were pulmonary fibrosis ( $n = 5$ ) and cystic fibrosis ( $n = 2$ ). Sixteen patients were recruited into the reference thoracotomy group; 6 were excluded intraoperatively after the procedure was aborted because of advanced malignancy. The indications for thoracotomy

in the final reference group were cancer (n = 9) and thymic cyst (n = 1). Lobectomy was performed in 7 cases, thymectomy in 1, and pleurodesis in 2, after formal resection was abandoned because of unexpected advanced malignancy. The final study population comprised 7 patients who underwent lung transplantation and 10 patients who underwent nontransplant thoracotomy (Table 1).

### sP-Selectin Levels

Baseline pre-operative sP-selectin levels in the lung transplant group were similar to those in the thoracotomy group (Figure 1). Significant increases in sP-selectin levels were seen in the lung transplant group at both the postoperative and 6-hour times relative to baseline ( $P < .05$ ), however, no change in sP-selectin was observed in the thoracotomy group. Mean sP-selectin levels were significantly higher in the lung transplant group than in the thoracotomy group during the immediate postoperative period (59 vs 33 pg/mL,  $P = .03$ ) and at 6 hours (104 vs 40 pg/mL,  $P = .001$ ).

Higher sP-selectin levels immediately after lung transplantation were associated with a greater decrease in platelet count on routine phlebotomy from baseline to postoperative day 1 ( $P = .006$ ) and day 2 ( $P = 0.002$ ). Similar associations between the 6-hour postoperative sP-selectin level and changes in platelet counts at days 1 and 2 were shown, although these were not statistically significant ( $P = .10$  and  $P = .06$ , respectively).

### sCD40L Levels

Mean sCD40L levels were similar between the lung transplant and thoracotomy groups at baseline (481 vs 524 ng/mL,  $P = .53$ ; Figure 2). The lung transplant group demonstrated a significant increase in sCD40L at the 6-hour point relative to the baseline value ( $P < .05$ ), whereas no difference was observed in the control group. sCD40L levels were higher in the transplant group than in the thoracotomy group after skin closure (577 vs 524 ng/mL,  $p = 0.08$ ), but this difference did not reach statistical significance. sCD40L levels at the 6-hour time point were significantly higher in the lung transplant recipients than in the control group (815 vs 547 ng/mL,  $P = .022$ ).

Immediately after lung transplantation, higher sCD40L levels were associated with a decrease in platelet count on postoperative day 1 or 2 ( $P = .058$  and  $P = .05$ , respectively). There were no associations between sCD40L levels at 6 hours and the change in platelet count on days 1 or 2 ( $P > .50$  for both).

### Circulating Platelet–Leukocyte Conjugates

Figure 3 shows platelet–monocyte conjugates, expressed as the median (with interquartile range) fluorescent intensity of platelets per conjugate. No differences in the fluorescent intensity of platelets per platelet–monocyte conjugate were observed at the preoperative point, nor in the immediate postoperative period ( $P = .55$ ). A significant increase in the fluorescent intensity of platelets per conjugate from baseline, however, was seen at 6 postoperative hours in transplant recipients relative to thoracotomy patients ( $P = .02$ ). No differences in the percentage of monocytes engaged in circulating platelet–monocyte conjugates were observed between lung transplant and thoracotomy groups (Figure 4). Also, no differences were seen between patient groups in the fluorescent intensity of platelets per platelet–neutrophil conjugate or in the percentage of neutrophils with bound platelets (data not shown).

## Discussion

To our knowledge, this is the first study to measure platelet activation before and after human lung transplantation. Although any surgical procedure might be expected to result in systemic

platelet activation, we have shown that sP-selectin, sCD40L, and platelet–monocyte conjugates increase after lung transplantation to a greater degree than after other types of thoracic surgery. This implies that platelet activation is particularly pronounced after lung transplantation, which could modulate graft function or failure after transplantation.

Previous studies have demonstrated pulmonary platelet deposition 24 hours after lung transplantation in dogs.<sup>18</sup> Platelet deposition has also been reported during reperfusion injury of rat and human lungs.<sup>19–21</sup> In a rat model of lung transplantation, platelet accumulation was shown to contribute to postischemic graft dysfunction.<sup>22</sup> Okada and coworkers<sup>23</sup> reported that treatment with a prostacyclin analog with antiplatelet activity attenuated reperfusion injury by abrogating platelet sequestration in rat lung grafts.<sup>23</sup> In addition, antiplatelet agents attenuate hyperacute xenograft failure.<sup>24</sup>

We presume that the site of platelet release of sP-selectin and sCD40L and monocyte interaction is the newly reperfused pulmonary vascular bed. Evidence suggests that leukocyte activation, adhesion, and infiltration are integral to the development of ischemia–reperfusion injury after lung transplantation.<sup>25,26</sup> P-selectin binding is an important element of this process, as evidenced by the reduction of lung injury with P-selectin blockade at the time of reperfusion.<sup>27</sup> Further, there is strong link between CD154/CD40 interaction and interleukin 8 upregulation, which also happens to be associated with poorer graft function.<sup>28,29</sup> The results of these studies, in combination with our findings, suggest an important role of platelets in mediating ischemia–reperfusion injury after lung transplantation. Future studies should focus on the relationships among platelet activation, the risk of ischemia–reperfusion injury, and clinical outcomes after lung transplantation. Platelets may offer a promising target in preventing or treating ischemia–reperfusion injury and primary graft dysfunction, which currently have no specific medical therapy, in lung transplant recipients.

Although the number of platelets bound per monocyte conjugate increased after lung transplantation, we were unable to detect an increased percentage of monocytes with bound platelets. A possible explanation for this finding is that there may be a rapid sequestration of activated platelets in the lung allograft, as previously described,<sup>20,21,23</sup> limiting the number of platelets that would interact with circulating monocytes. We suggest that this could occur to a greater extent in lung than in other solid organ transplantation because of the large surface area of dysfunctional endothelium. In addition, the low-pressure pulmonary circulation may facilitate platelet endothelial binding, as previous histologic studies of fresh lung allografts have shown the deposition of platelets in the lungs early after reperfusion.<sup>20</sup>

There are several possible limitations of this study. First, endothelial release of sP-selectin or sCD40L could account for the findings in our study. The vast majority of sCD40L is platelet-derived, however, and it is, therefore, a highly specific marker of platelet activation.<sup>7</sup> Second, biomarker analysis was performed at two time points after transplantation; we cannot exclude the possibility that assessment after reperfusion might show even more substantial differences. Third, the sample size was small; however, we detected differences consistent with our hypothesis, likely attributable to the prospective planning and sample size calculations based on previous work. It should be noted that this is the first direct study of platelet activation after human lung transplantation, as well as the first study to use the sensitive techniques afforded by flow cytometry to examine platelet–leukocyte conjugates directly. Fourth, we did not investigate the association between platelet biomarkers and indicators of graft function (eg, ratio of PaO<sub>2</sub> to inspired oxygen fraction). Larger, multicenter studies will be necessary to study whether indicators of platelet activation correspond to such clinical indices. Fifth, all lung transplant recipients received preoperative induction of immunosuppression before transplantation, and the possibility of interactions of these pharmacologic agents with platelets has not been studied.

In summary, this study shows that sP-selectin, sCD40L, and platelet–leukocyte interactions are significantly increased after human lung transplantation but not after thoracotomy alone. Future studies should attempt to replicate our findings and focus on the relationship to clinical markers of reperfusion injury with sP-selectin, sCD40L, and platelet–leukocyte conjugate formation. Abrogation of the platelet activation and adhesion cascades in lung transplantation may offer a future clinical avenue to decrease the impact of reperfusion injury.

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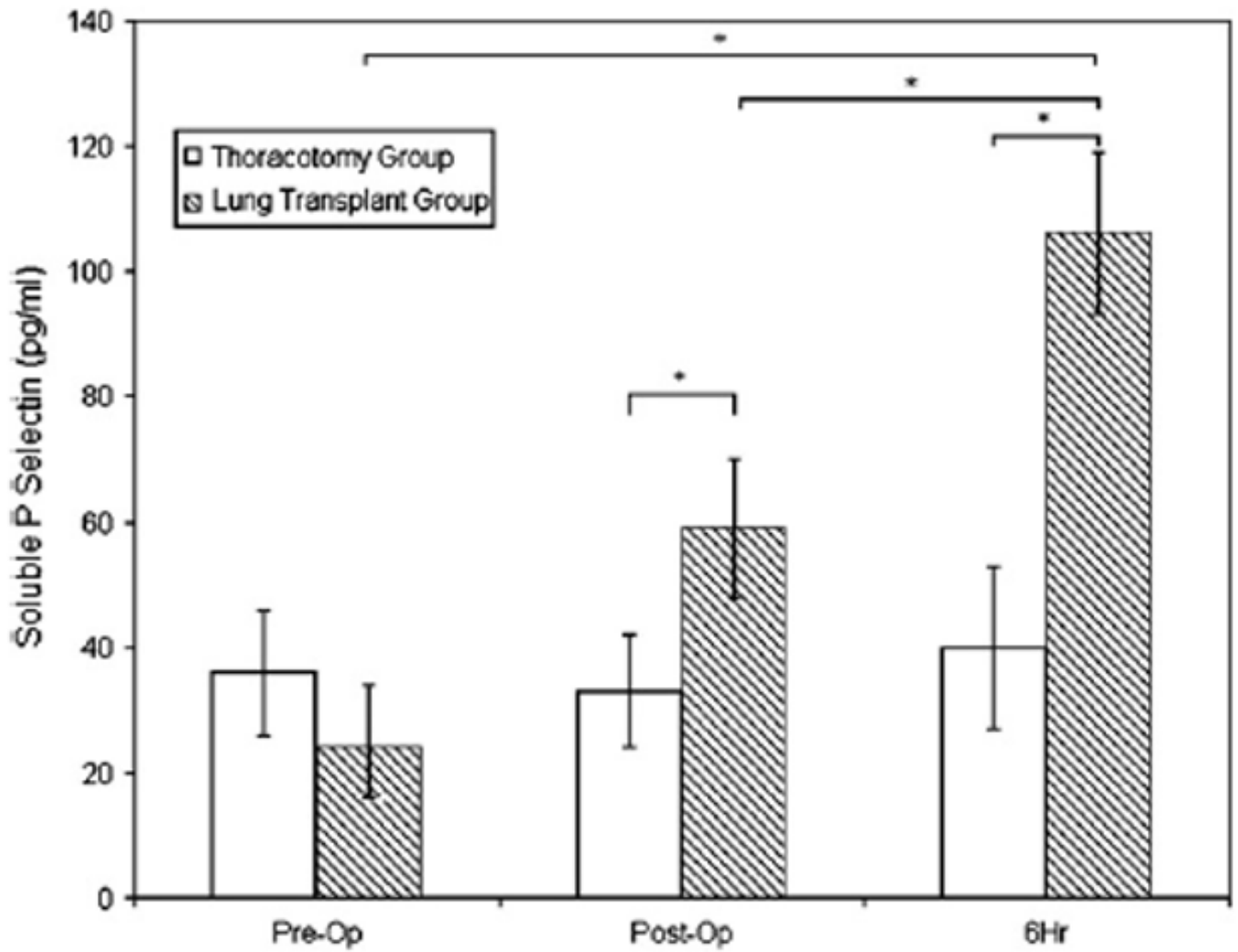
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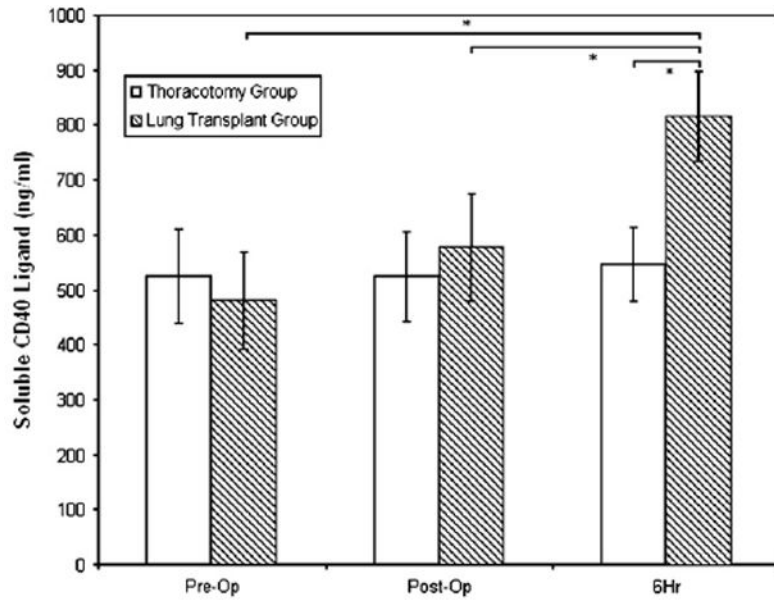
## Abbreviations and Acronyms

sCD40L	soluble CD40 ligand
sP-selectin	soluble P-selectin

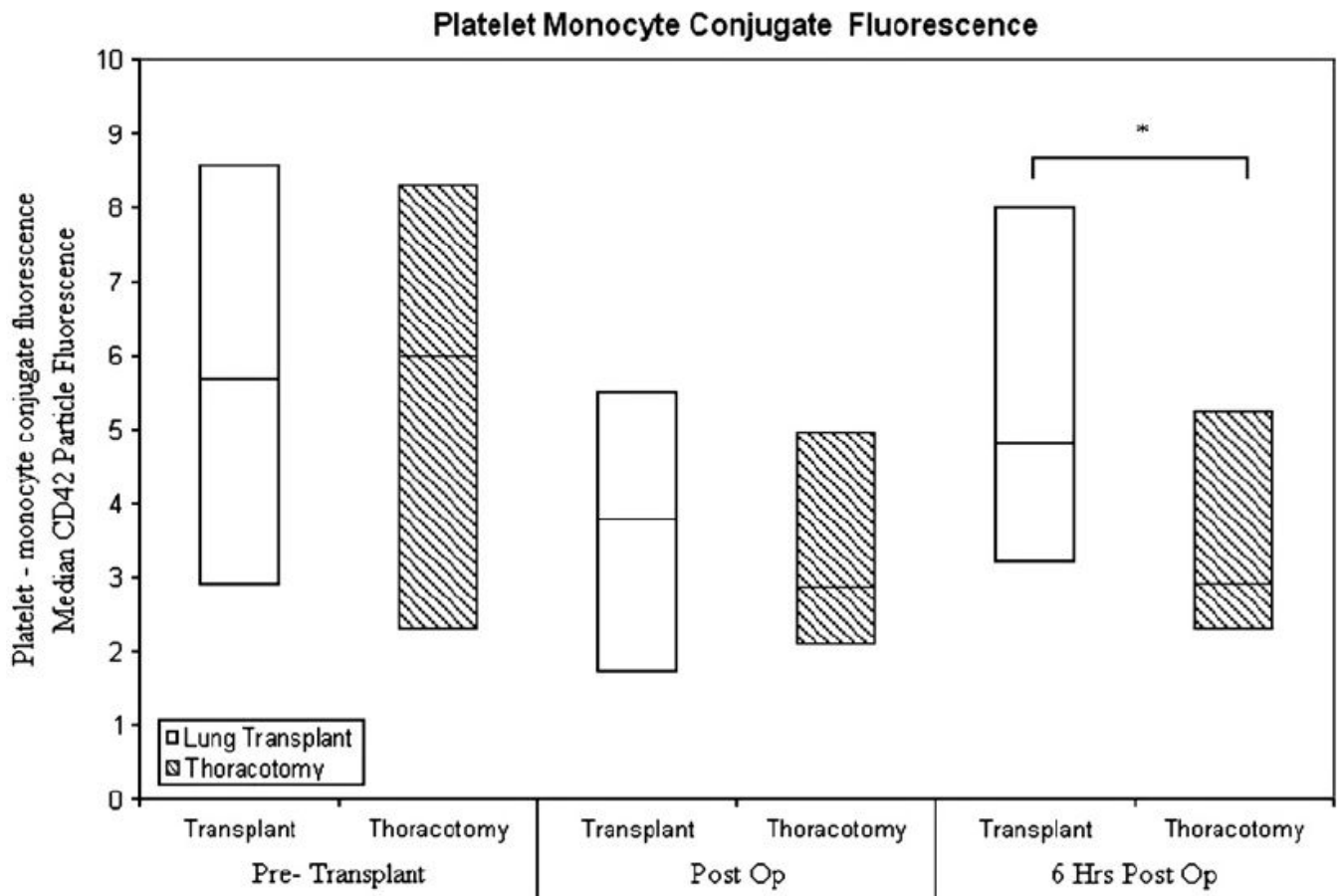


**Figure 1.** sP-selectin levels before surgery (*Pre-Op*), immediately after surgery (*Post-Op*), and 6 hours later (*6Hr*). Asterisk indicates  $P < .05$ .

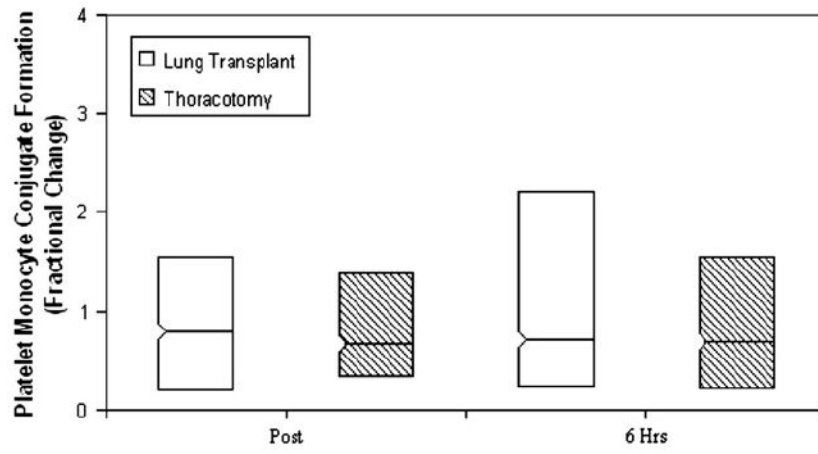




**Figure 2.** SCD40L levels before surgery (*Pre-Op*), immediately after surgery (*Post-Op*), and 6 hours later (*6Hr*). Asterisk indicates  $P < .05$ .



**Figure 3.** Platelet-monocyte conjugate fluorescence before surgery (*Pre-Transplant*), immediately after surgery (*Post Op*), and 6 hours later (*6 Hrs Post Op*). Asterisk indicates  $P < .05$ .



**Figure 4.** Fractional change from baseline in platelet–monocyte conjugate formation immediately after surgery (*Post*) and 6 hours later (*6 Hrs*). Asterisk indicates  $P < .05$ .

**TABLE 1**

Patient characteristics of the lung transplant and thoracotomy groups

	Transplant (n = 7)	Thoracotomy (n = 10)
Age (y, mean $\pm$ SD)	51 $\pm$ 16	59 $\pm$ 13
Sex (% male)	57%	70%
Transplant type (% bilateral)	57%	—
Ischemia time (min)		
First lung	180	—
Second lung (n = 4)	247	—
Lung resection	—	70%
Platelets ( $10^3$ cells/cm <sup>3</sup> , mean $\pm$ SE)		
Preoperative	365 $\pm$ 174	221 $\pm$ 48
Day 1	205 $\pm$ 114	194 $\pm$ 69
Day 2	159 $\pm$ 83	183 $\pm$ 61
Day 3	160 $\pm$ 83	184 $\pm$ 64