Role of anti-L-selectin antibody in burn and smoke inhalation injury in sheep

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Katahira, Jiro, Kazunori Murakami, Frank C. Schmalstieg, Robert Cox, Hal Hawkins, Lillian D. Traber, and Daniel L. Traber. Role of anti-L-selectin antibody in burn and smoke inhalation injury in sheep. Am J Physiol Lung Cell Mol Physiol 283: L1043–L1050, 2002. First published July 12, 2002; 10.1152/ajplung.00305.2001.—We hypothesized that the antibody neutralization of L-selectin would decrease the pulmonary abnormalities characteristic of burn and smoke inhalation injury. Three groups of sheep (n = 18) were prepared and randomized: the LAM-(1–3) group (n = 6) was injected intravenously with 1 mg/kg of leukocyte adhesion molecule (LAM)-(1-3) (mouse monoclonal antibody against L-selectin) 1 h after the injury, the control group (n = 6) was not injured or treated, and the nontreatment group (n = 6) was injured but not treated. All animals were mechanically ventilated during the 48-h experimental period. The ratio of arterial P02 to inspired O2 fraction decreased in the LAM-(1–3) and nontreatment groups. Lung lymph flow and pulmonary microvascular permeability were elevated after injury. This elevation was significantly reduced when LAM-(1–3) was administered 1 h after injury. Nitrate/nitrite (NO2−) amounts in plasma and lung lymph increased significantly after the combined injury. These changes were attenuated by posttreatment with LAM-(1–3). These results suggest that the changes in pulmonary transvascular fluid flux result from injury of lung endothelium by polymorphonuclear leukocytes. In conclusion, posttreatment LAM-(1–3) in burn and smoke inhalation injury.

MATERIALS AND METHODS

The experimental procedures were approved by the Animal Care and Use Committee of The University of Texas Medical Branch. During the course of the experiment, the guidelines for care and use of experimental animals, as established by the National Institutes of Health and the American Physiological Society, were strictly observed.

Antibody modification and flow cytometry. Purified LAM-(1–3) (14), a murine monoclonal anti-human L-selectin antibody that interferes with PMN attachment to human umbilical vein endothelial cells, was obtained from Abgenix (Foster City, CA). The whole antibody caused release of L-selectin from the surface of ovine PMNs. Therefore, F(ab′)2 fragments were prepared from the whole antibody by pepsin digestion, as previously described (13). This antibody blocks L-selectin function in ovine neutrophils (13). Each lot of antibody was tested by the Limulus assay and was free of endotoxin. Interaction of this antibody with ovine blood PMNs was measured using flow cytometry. Leukocytes were washed and resuspended in PBS supplemented with 1% newborn bovine serum (Flow Laboratories, McLean, VA) before incubation with antibody at a concentration of 40 μg/ml of cell suspension (0.4–1.0 × 106 cells) for 20 min at 4°C. The cells were then washed in PBS and fixed in 1% paraformaldehyde. Single-color flow cytometry was performed using FACScan (Becton-Dickinson, Mountain View, CA). An electronic gate was set on the neutrophil populations on the basis of forward-

POLYMORPHONUCLEAR LEUKOCYTES (PMNs) play an important role in the inflammatory processes of thermal burn and smoke inhalation injury. Endothelial damage by these activated cells is believed to increase microvascular permeability and edema. The selectin family of adhesion-promoting molecules, including L-selectin, appears to be involved in the early events of the acute inflammatory process (11). These molecules mediate initial contact between PMNs and endothelial cells, resulting in a “rolling” phenomenon, in which the leukocytes adhere intermittently to the endothelial cells. We previously investigated the effect of anti-L-selectin antibody [leukocyte adhesion molecule (LAM)-(1–3)] 1 h before burn and smoke inhalation injury (13). The results showed that pretreatment with LAM-(1–3) inhibited the increase in lung lymph flow and permeability index. Although L-selectin contributed to the pathogenesis of acute lung injury after burn and smoke, our previous study was not designed to answer whether anti-L-selectin could be used therapeutically. Therefore, in the present study, we tested the effect of posttreatment LAM-(1–3) in burn and smoke inhalation in sheep.

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angle vs. right-angle light scatter. All analyses were simultaneously run with a mouse isotype control. Analyses were conducted with the LYSIS II program. Becton-Dickinson CaliBRITE bands were run before each analysis to monitor instrument performance and to set detector levels for fluorescein isothiocyanate.

To test the nonspecific effects of the antibody, we injected LAM-(1–3) into healthy normal sheep and monitored the hemodynamic and blood gas changes. No obvious changes were observed in hemodynamic parameters or blood gases.

**Surgical preparation.** Eighteen female sheep [35.9 ± 1.2 (SE) kg] were surgically prepared for chronic study under halothane anesthesia. The right femoral artery and vein were cannulated with Silastic catheters (16 gauge, 24 in.; Intracath, Becton-Dickinson Vascular Access, Sandy, UT). A thermodilution catheter (Swan Ganz model 131F7, Baxter, Edwards Critical-Care Division, Irvine, CA) was introduced through the right external jugular vein into the pulmonary artery. Another catheter (0.062 in. ID, 0.125 in. OD; Durastic silicone tubing DT08, Allied Biomedical, Paso Robles, CA) was positioned in the left atrium to monitor the pressure. The lung lymphatic was cannulated according to the method of Staub et al. (15) using the modification of Demling and Gunther (6) to prevent systemic contamination of the lung lymph. A fifth-interspace right thoracotomy was performed, and an efferent lymphatic from the caudal mediastinal lymph node was ligated, and the systemic diaphragmatic lymph vessels were cauterized through a ninth-interspace thoracotomy incision. The incision sites were infiltrated with 2% lidocaine to minimize postoperative pain, and the wounds were closed. During the postoperative period, buprenex (0.3 mg iv) was administered as needed for pain. The animals were given 5–7 days to recover from the surgical procedure, during which time they had free access to food and water.

**Burn and smoke inhalation injury.** Before the injury, a tracheostomy was performed under ketamine anesthesia (Ketaset, Fort Dodge Animal Health, Fort Dodge, IA), and a cuffed tracheostomy tube (10 mm diameter; Shiley, Irvine, CA) was inserted. The anesthesia was continued with halothane. Twelve animals then received a combined injury with a 40% total body surface area (TBSA) third-degree burn and 48 breaths of cotton smoke inhalation. The technique has been described in more detail elsewhere (13). Briefly, after the wool was shaved from the animals, a Bunsen burner was used to make a 20% TBSA third-degree flame burn on the left side of the flank. Third-degree burn is not associated with pain, because nerves in the burned tissue are destroyed. Thereafter, inhalation injury was induced with a modified bee smoker, as previously described (9). The bee smoker was filled with 40 g of burning cotton toweling attached to the tracheostomy tube via a modified endotracheal tube containing an indwelling thermistor from a Swan Ganz catheter. Four sets of 12 breaths of smoke (total 48) were delivered, and the carboxyhemoglobin level was determined immedi-
ately after smoke inhalation. The bee smoker does not require recharging between sets, inasmuch as the amount of toweling (40 g) is adequate for the total 48 breaths. The temperature of the smoke was not allowed to exceed 40°C during the procedure. After smoke insufflations, another 20% TBSA third-degree burn was made on the right flank.

Hemodynamic and oxygenation variables. Vascular pressures were measured using transducers (model PX-1800, Baxter, Edwards Critical-Care Division) that were adapted with a continuous flushing device. The transducers were connected to a hemodynamic monitor (model 78304A, Hewlett-Packard, Santa Clara, CA). All hemodynamic measurements were made with the animals awake and in the standing position. Zero calibrations were taken at the level of the olecranon joints on the front leg of the animals. Cardiac output was measured by the thermodilution technique using a cardiac output computer (model COM-1, Baxter, Edward Critical-Care Division). A 5% dextrose solution was used as the indicator. Cardiac index was calculated using standard equations. Blood gases and acid-base balance were measured using a blood gas analyzer (model IL 1600, Instrumentation Laboratory, Lexington, MA). Arterial and mixed venous blood gas results were corrected for the body temperature of the sheep. Oxyhemoglobin saturation and carboxyhemoglobin concentration were analyzed with a CO-oximeter (model IL 482, Instrumentation Laboratory).

Lymph and plasma measurements. The protein composition of lung lymph collected from the major lung efferent lymphatic is considered to be representative of the free interstitial edema fluid (17). Lung lymph flow (QL,lymph) was measured with a graduated test tube and stopwatch. Lymph and blood samples were collected in EDTA tubes, and then the colloid osmotic pressure in plasma (πp) and lung lymph (πL,lymph) were determined through a semipermeable membrane in a colloid osmometer (model 4100, Wescor, Logan, UT). Lung permeability index (PIL) was calculated according to the following equation

\[ PIL = \frac{Q_{L,lymph}}{(\pi_{L,lymph}/\pi_p)} \]

Levels of NO2/NO3 (NOx), intermediate and end products of NO oxidation, in plasma and lymph were measured by a chemiluminescence assay using an NO analyzer (model 745, Antek, Houston, TX).

Study groups. Animals were randomized into three groups. The control group received no injury and no treatment (n = 6). The nontreatment group sustained thermal burn and inhalation smoke injury but was not treated with LAM-(1–3) (n = 6). The LAM-(1–3) group received LAM-(1–3) (1 mg/kg) 1 h after injury (n = 6). Saturating concentrations of LAM-(1–3) throughout the experiments were ensured by flow cytometric measurements of neutrophil surface L-selectin in the absence and presence of excess exogenous LAM-(1–3). In every instance, no increase in staining was noted by the addition of exogenous LAM-(1–3), indicating that saturating concentrations of LAM-(1–3) were present.

Experimental protocol. Twenty-four hours before the experiment, vascular catheters were connected to the monitoring devices and maintenance fluid administration (Ringer lactate, 2 ml/kg) via the femoral vein was started. After baseline measurements (0 h) and sample collections were completed, the nontreatment and LAM-(1–3) groups received burn and smoke inhalation injury (see above). The control group underwent the same procedure, including the tracheostomy and anesthesia, but did not receive any injury. A silicone Foley catheter (Dover, 14-Fr, 5 ml; Sherwood Medical, St. Louis, MO) was placed in the urinary bladder for...
determination of urine output. Immediately after injury, anesthesia was discontinued and the animals were allowed to awaken but were maintained on mechanical ventilation (Servo Ventilator 900C, Siemens-Elema) throughout the 48-h experimental period. Ventilation was performed with a positive end-expiratory pressure of 5 cmH₂O and a tidal volume of 15 mg/kg. During the first 3 h after injury, the inspiratory O₂ concentration was maintained at 100% and respiratory rate was kept at 30/min to induce rapid clearance of carboxyhemoglobin after the smoke inhalation. The control animals were obtained at 3, 6, 12, 18, 24, 30, 36, 42, and 48 h after injury in all three groups. Hemodynamic variables and blood gases were collected at 3, 6, 12, 18, 24, 36, and 48 h after injury in all groups.

**Death and necropsy.** Forty-eight hours after injury, all animals were anesthetized with 500 mg of ketamine and killed with a 60-ml bolus of a saturated KCl solution injected into the left atrial catheter. Once death was confirmed by absence of pulse and blood pressure, necropsy was performed. Lung tissue was obtained for histopathological examination following a standardized sampling protocol. A 1-cm slice through the lower lobe of the right lung was injected with 10% buffered formalin and then immersed in 10% buffered formalin and then immersed in 10% buffered formalin and then immersed in 10% buffered formalin and then immersed in 10% buffered formalin and then immersed in 10% buffered formalin and then immersed in 10% buffered formalin and then immersed in a single container with 10% buffered formalin for 10 min. From these data, mean degrees of bronchial, bronchiolar, and terminal/respiratory bronchiolar obstruction were then calculated and represented as milliliters per kilogram for the next 24 h. One-half of the volume for the 1st day was infused in the initial 8 h, and the remainder was infused in the next 16 h (5). Fluid balance was determined by urine output every 3 h subtracted from total fluid volume infused. Net fluid balance accumulation was calculated and represented as milliliters per kilogram per hour. During this experiment, the animals were allowed free access to food, but not water, to accurately measure fluid intake.

The lymph and blood samples for determination of total protein concentration, colloid osmotic pressure, and NO were collected at 3, 6, 12, 18, 24, 36, and 48 h after injury in all three groups. Hemodynamic variables and blood gases were obtained at 3, 6, 12, 18, 24, 30, 36, 42, and 48 h after injury in all groups.

**Statistical methods.** Summary statistics of data are expressed as means ± SE. Data were analyzed using analysis of variance for a two-factor experiment with repeated mea-

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### Table 1. Hemodynamic changes

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Nontreatment</th>
<th>LAM-(1–3)</th>
<th>MAP, mmHg</th>
<th>PAP, mmHg</th>
<th>CVP, mmHg</th>
<th>LAP, mmHg</th>
<th>Pc, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CL, l·min⁻¹·m⁻²</strong></td>
<td>5.0 ± 0.3</td>
<td>5.5 ± 0.4</td>
<td>5.3 ± 0.3</td>
<td>5.4 ± 0.2</td>
<td>5.2 ± 0.2</td>
<td>5.0 ± 0.2</td>
<td>5.1 ± 0.2</td>
<td>5.1 ± 0.3</td>
</tr>
<tr>
<td><strong>MAP, mmHg</strong></td>
<td>98 ± 3</td>
<td>110 ± 4</td>
<td>105 ± 4</td>
<td>102 ± 4</td>
<td>100 ± 1</td>
<td>102 ± 2</td>
<td>106 ± 4</td>
<td>100 ± 4</td>
</tr>
<tr>
<td><strong>PAP, mmHg</strong></td>
<td>108 ± 6</td>
<td>112 ± 4</td>
<td>112 ± 6</td>
<td>108 ± 5</td>
<td>102 ± 5</td>
<td>109 ± 4</td>
<td>103 ± 5</td>
<td>107 ± 5</td>
</tr>
<tr>
<td><strong>LAP, mmHg</strong></td>
<td>97 ± 4</td>
<td>105 ± 4</td>
<td>107 ± 6</td>
<td>106 ± 6</td>
<td>108 ± 9</td>
<td>107 ± 7</td>
<td>110 ± 9</td>
<td>105 ± 7</td>
</tr>
<tr>
<td><strong>CVP, mmHg</strong></td>
<td>19 ± 1</td>
<td>23 ± 1</td>
<td>24 ± 1</td>
<td>26 ± 1</td>
<td>25 ± 1</td>
<td>25 ± 2</td>
<td>25 ± 1</td>
<td>25 ± 1</td>
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<tr>
<td><strong>LAM-(1–3)</strong></td>
<td>7 ± 1</td>
<td>11 ± 1</td>
<td>10 ± 2</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
<td>8 ± 0</td>
<td>9 ± 1</td>
<td>9 ± 1</td>
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<tr>
<td><strong>Pc, mmHg</strong></td>
<td>13.6 ± 1.3</td>
<td>18.1 ± 0.9</td>
<td>18.0 ± 0.9</td>
<td>19.9 ± 0.5</td>
<td>18.6 ± 1.2</td>
<td>18.1 ± 1.2</td>
<td>18.3 ± 0.6</td>
<td>18.7 ± 1.2</td>
</tr>
</tbody>
</table>

Values are means ± SE. CI, cardiac index; MAP, mean arterial pressure; PAP, pulmonary arterial pressure; CVP, central venous pressure; LAP, left atrial pressure; Pc, pulmonary capillary wedge pressure; LAM, leukocyte adhesion molecule.
sures over time. Fisher’s least significant difference procedure was used for multiple comparisons (or post hoc analysis). For the histological study, a nonparametric Kruskal-Wallis test was performed, and Mann-Whitney’s U-test was used to compare data within the groups. Measurements at various times were tested at the 0.05 level of significance.

RESULTS

The arterial carboxyhemoglobin levels immediately after smoke exposure were 75.4 ± 9.1% in the nontreatment group and 55.9 ± 5.0% in the LAM-(1–3) group. There was no statistical difference between these values. All animals survived the 48-h experimental period.

Pulmonary transvascular fluid flux. The nontreatment group showed a significant increase in the lung lymph flow (Fig. 1A), whereas in the LAM-(1–3) group, antibody treatment significantly attenuated the increased lung lymph flow. Lung permeability index after the combined injury was significantly attenuated by LAM-(1–3) (Fig. 1B).

Gas exchange and pulmonary hemodynamics. The nontreatment group showed a progressive fall in the ratio of arterial Po2 to inspired O2 fraction (Pao2/FiO2 ratio). It fell significantly from the baseline value 12 h after injury. In the LAM-(1–3) group, it remained above that of the nontreatment group for a significant portion of the experimental period (12 h). There was no significant difference in the Pao2/FiO2 ratio between the nontreatment group and the LAM-(1–3) group during the remainder of the period of observation (Fig. 2A). Changes in the intrapulmonary shunt fraction paralleled those in the Pao2/FiO2 ratio (Fig. 2B).

Plasma and lung lymph NOx and conjugated dienes. In the control group, NOx amounts in plasma and lung lymph increased after anesthesia and then gradually returned toward baseline. In contrast, NOx levels increased significantly in the nontreatment and LAM-(1–3) groups throughout the experiment. The NOx amounts for the LAM-(1–3) group were lower during the latter part of the period of observation (Fig. 3A). NOx levels were virtually the same in the lung lymph of the injured groups (Fig. 3B). Plasma and lymph conjugated dienes did not increase in the control group. Conjugated dienes rose to the same extent in the injured animals with or without treatment (Fig. 4). However, given the fact that the lung lymph flow was much higher in the nontreatment group, nontreated sheep produced a much larger amount of NOx and lipid peroxidation than the LAM-(1–3)-treated animals.

Cardiopulmonary hemodynamics. A summary of the cardiopulmonary hemodynamic data is shown in Table 1. The control group did not show any significant changes in cardiopulmonary hemodynamic data during the experimental period. At 3 h after the combined injury in the LAM-(1–3) and nontreatment groups, cardiac index (cardiac output/body surface area) decreased significantly compared with baseline and gradually returned toward baseline values (Fig. 5A). Despite the initial decrease in cardiac index, mean arterial pressure was maintained during the study in the nontreatment and LAM-(1–3) groups (Table 1). The pulmonary arterial pressure rose in the injured animals. However, the increase was less in the group treated with the antibody to L-selectin before 36 h (Fig. 5B). Pulmonary capillary wedge pressure increased in all groups. No statistical differences were found between the groups (Table 1).

Lung wet-to-dry weight ratio. Lung wet-to-dry weight (W/D) ratio was assessed to evaluate the water content of the lung. The W/D ratio significantly increased after the smoke inhalation and burn in the nontreatment group. On the other hand, there was no
statistical difference between noninjured control and LAM-(1–3)-treated animals (Fig. 6).

**Histopathological examination.** Lung histological changes were evaluated by pathologists who were unaware of the animal grouping. Although blood gas exchange was decreased significantly in the injured animals (Fig. 4), we could not detect histological differences in the scores of edema, congestion, inflammation (leukocyte infiltration), and hemorrhage after injury with or without treatment (Fig. 7). In contrast, airway obstruction was significantly elevated in the injured groups, especially at the level of the bronchioles (Fig. 8). Administration of LAM-(1–3) tended to reduce the airway obstruction, but no statistical difference was found.

**Changes in leukocyte numbers.** Complete blood count was performed by Hemavet (automatic veterinary CBC analyzer; CDC Technologies, Oxford, CT) at the setting of sheep. Total white cell count was increased in the LAM-(1–3) and control groups but was less in the LAM-(1–3) group. The neutrophil count also increased in the control group but was significantly less in the LAM-(1–3) group than in the control group (Fig. 9).

### DISCUSSION

We previously reported that administration of LAM-(1–3) antibody could reduce the pulmonary transvascular fluid flux that occurs after the combination burn injury to skin and smoke (13). In this study, LAM-(1–3) was again administered as an F(ab')₂ fragment. In contrast to our previous work (pretreatment study), the antibody was administered 1 h after injury. Although our previous study indicated a role for L-selectin in the response, the therapeutic value of anti-L-
selectin antibody could not be ascertained, because the antibody was given before the injury. However, it is feasible that an injured patient might practically receive therapy 1 h after injury. Our demonstration that treatment with LAM-(1–3) 1 h after injury can minimize the changes in pulmonary transvascular fluid flux, urinary retention, and pulmonary arterial pressure may be of therapeutic advantage. The finding that gas exchange was not improved by treatment with the antibody is similar to the finding in our previous study (13). These data support the concept that the elevation in shunt blood flow seen with the injury is the result of a mechanism independent of L-selectin. A possible mechanism responsible for the increased pulmonary shunt blood flow is the increase in NO in the lung. Consistent with this speculation, LAM-(1–3) did not inhibit the increase in lung lymph NOx levels.

It is of interest that blockade of L-selectin can virtually prevent the early changes in pulmonary transvascular fluid flux, even though the antibody was not given until 1 h after insult. This finding is consistent with our former hypothesis that the airway was the site of the initial injury. We previously reported that bronchial blood flow (blood flow to the airway) increases almost immediately (2). Within 20 min of smoke inhalation, the bronchial blood flow increases 10- to 15-fold. Magno and Fishman (10) showed that the tracheal bronchial artery is one of the major sources of blood to the lung. We have also reported that occlusion of the bronchial artery prevented the increase in pulmonary transvascular fluid flux seen with inhalation injury (3, 12). These findings were recently confirmed by others (7). We originally suggested that the injury to the airway resulted in an increase in bronchial microvasculature flow and permeability. The injured airway possibly releases materials into the bronchial venous drainage that flow to the pulmonary microvasculature and cause neutrophils to adhere and become activated in the lung. We would now add to the hypothesis that the substance(s) released into the bronchial venous drainage leads to interaction of L-selectin with its counterstructure. We are now planning to investigate the effect of LAM-(1–3) on bronchial blood flow. Further study is warranted.

It is of considerable interest that LAM-(1–3) reduced cast formation at the alveolar level. Casting is a result of a plasma exudate, along with mucus secretion and inflammatory cell infiltration (8). We have reported that the airway epithelium is shed, leaving a naked basement membrane, immediately after smoke inhalation (1). As a result of the loss of the epithelium, an exudate is formed (4, 8). Exudate formation is not seen with bronchial artery occlusion, and there is no cast formation in these animals (12). Nor does the PaO2/FiO2 ratio fall after burn and smoke inhalation in these animals. Administration of LAM-(1–3) showed a trend for inhibiting the cast formation, possibly because casting at this level contains many neutrophils, and L-selectin is important for neutrophil infiltration into the airway. However, the trend was not statistically different. According to the power analysis, we need 7–20 more animals in each group to find differences in an airway obstruction study. Taken together, these findings suggest that obstruction at the bronchiolar level may not be strongly correlated with decreased gas exchange. They also suggest that neutrophil emigration into the airway is not necessary for compromise of gas exchange.

During the latter part of the period of observation, the lung lymph flow rose in the group given the antibody to L-selectin. We obtained plasma samples from several animals and ensured that neutralizing antibody remained throughout the experimental period. However, given the large number of occluded airways, it is possible that volutrauma/barotrauma is occurring in these animals because of the 15 ml/kg tidal volume. Stretch can cause the release of cytokines, which can lead to further damage to the alveoli (16).

Because we were blocking the interaction of neutrophils with endothelial cells, we tested the complete blood count during the study. As we showed in Fig. 9, the neutrophil number in the peripheral blood was significantly less in the LAM-(1–3) group. We expected that if the cell adhesion were inhibited by blocking L-selectin, peripheral neutrophil number would be higher, although the result was opposite. We cannot tell the exact reason for this finding. Probably the inhibition of interaction between neutrophils and endothelial cells might inhibit the cell activation, and, consequently, leukocyte induction from the bone marrow would be less.

In conclusion, the posttreatment with the antibody for L-selectin decreased the lung lymph flow and pulmonary permeability (W/D ratio). L-selectin appears to be principally involved in the increased pulmonary transvascular fluid flux observed with burn/smoke insult. L-selectin may be a useful target in the treatment of acute lung injury after burn and smoke inhalation.

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