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Effect of Lidocaine Pretreatment on Endotoxin-induced Lung Injury in Rabbits

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Background: It is well known that endotoxin causes acute lung injury resulting in adult respiratory distress syndrome. Numerous cellular and humoral factors such as macrophages, neutrophils, platelets, and inflammatory mediators (e.g., activated complements, cytokines, and arachidonic acid metabolites) are thought to play a pivotal role in the pathogenesis of endotoxin-induced lung injury. Furthermore, pulmonary edema in acute lung injury is associated with an increase in vascular permeability that may arise from a perturbation of the endothelial cell surface membrane. Lidocaine has been shown to inhibit function of these cells and stabilize cell membranes. The aim of the current study was to determine whether pretreatment with intravenous lidocaine could attenuate acute lung injury induced by endotoxin in rabbits.

Methods: Twenty-seven anesthetized male rabbits were randomly assigned to receive one of three treatments (n = 9 for each group); infusion of saline (as a control), infusion of *Escherichia coli* endotoxin (30 µg kg⁻¹ over a 60-min period) without treatment with lidocaine, and infusion of endotoxin with treatment with lidocaine. A single dose of intravenous lidocaine 2 mg · kg⁻¹ was administered 10 min before infusion of endotoxin and thereafter infused at a rate of 2 mg · kg⁻¹ · h⁻¹ until 6 h after the start of endotoxin administration, when the animals were killed. The lungs of the rabbits were ventilated with 40% oxygen. Hemodynamics, peripheral leukocytes counts, and arterial oxygen tension were recorded during the ventilation period. After the observation, lung mechanics, cell fraction of bronchoalveolar lavage fluid (BALF), activated complements, cytokines, and arachidonic acid metabolites concentrations in BALF were measured and analyzed. The lung wet- to dry-weight ratio and albumin concentrations in BALF were analyzed as an indices of pulmonary edema. The *cypridina* luciferin analog-dependent chemiluminescence (representing superoxide production) by neutrophils isolated from the pulmonary artery and light microscopic findings were compared among the three groups.

Results: Endotoxin caused decreases in peripheral leukocyte counts, lung compliance, and arterial oxygen tension, and increases in the lung wet- to dry-weight ratio, polymorphonuclear cell counts in BALF, and albumin, C3a, C5a, tumor necrosis factor α, interleukin-1β, and thromboxane B₂ concentrations in BALF. Lidocaine pretreatment attenuated these changes. The *cypridina* luciferin analog--dependent chemiluminescence was greater in rabbits receiving endotoxin than in the control. Lidocaine pretreatment attenuated the increase in chemiluminescence. Endotoxin caused extensive morphologic lung damage, which was lessened by lidocaine.

Conclusions: These results suggest that intravenous lidocaine pretreatment has a prophylactic effect on endotoxin-induced lung injury in rabbits. However, further studies are required to investigate the therapeutic (as an early posttreatment) effect of the drug given after lung injury because rabbits in the current study received lidocaine before endotoxemia. (Key words: Anesthetics, local: lidocaine. Immune response: neutrophils; superoxide anions. Lung(s): adult respiratory distress syndrome; edema; lavage.)

IT is well known that gram-negative bacterial sepsis is the most common clinical setting in which diffuse lung injury resulting in adult respiratory distress syndrome (ARDS) develops.¹ Intravenous infusion of *Escherichia coli* endotoxin causes acute lung injury and alterations in lung physiologic processes similar to those in humans.^{2,3} The precise mechanism through which endotoxin induces respiratory failure is not as yet fully understood. However, numerous factors have been shown to be involved in the initiation and perpetuation of endotoxin-induced acute lung injury. They are grouped into three major categories: complement--neutrophil mediators, products of coagulation--fibrinolysis, and macrophages (pulmonary or intravascular). In complement--neutrophil mediators, neutrophils are thought to play an important role in the pathogenesis of the lung injury by releasing lipid and enzyme mediators and oxygen radicals.⁴⁻⁸ Several studies have shown that depletion of neutrophils markedly reduces the intensity of lung injury in several experimental preparations.^{9,10} Pentoxifylline and

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dibutyryl cyclic adenosine monophosphate, both of which have inhibitory effects on the function of neutrophils, have been reported to successfully attenuate acute lung injury in endotoxemia or bacteremia.¹¹⁻¹⁴ Lidocaine has been shown to have various inhibitory effects on neutrophil and macrophage function.¹⁵⁻¹⁷ These include chemotaxis¹⁵ and superoxide anion (O_2^-) release.¹⁵⁻¹⁷ However, a study from the National Institutes of Health on ARDS in neutropenic patients suggests that although neutrophils are important in the injury process, they may not be an essential component.¹⁸ On the other hand, in coagulation-fibrinolysis, platelets have the potential for causing injury by the release of various compounds found in their granules, including serotonin, lysosomal enzymes, and thromboxane B_2 (TxB_2).¹⁹ Furthermore, degradation products of fibrinolysis and humoral substances derived from blood coagulation could mediate ARDS.¹⁹

Lidocaine possibly reduces platelet aggregability and decreases the serum level of TxB_2 .²⁰⁻²² The role of macrophages appears important in the early phase as well as the later phase of the lung injury.¹⁹ The activated macrophages release virtually all of the toxic mediators released by neutrophils. Lidocaine has been reported to inhibit O_2^- release from macrophages.²³ Thus, inhibition of function of neutrophils, platelets, and macrophages by lidocaine could be expected to attenuate endotoxin-induced lung injury.

Pulmonary edema observed as a main pathologic change in the endotoxin-induced lung injury is associated with an increase in vascular permeability that may arise from a perturbation of the endothelial cell surface membrane partly as a direct response to the injury.²⁴ Lidocaine, which has been shown to stabilize cell membranes^{25,26} and interfere with binding of endotoxin to membranes,²⁷ may provide an effective means of attenuating increases in endothelial permeability in endotoxin-induced lung injury. Recently, successful use of lidocaine to reduce lung extravascular protein accumulation as an index of endothelial permeability after thiourea-induced lung injury has been reported.¹⁶ Thus, we conducted the current study to determine whether intravenous pretreatment with lidocaine (bolus injection followed by continuous infusion) can attenuate endotoxin-induced lung injury in rabbits.

Materials and Methods

Animal Preparation and Protocol

The current study was conducted according to the guidelines worked out by the animal care review board

of Kobe University School of Medicine. Twenty-seven male Japanese white rabbits weighing 2.1–2.4 kg were used in this study and randomly divided into three groups ($n = 9$ for each group). Rabbits in group S received saline alone as a control for 6 h, group E received endotoxin from *E. coli* (O55:B5 from the same lot, Difco, Detroit, MI) $30 \mu\text{g} \cdot \text{kg}^{-1}$, without lidocaine treatment, and group E-L received $30 \mu\text{g} \cdot \text{kg}^{-1}$ of endotoxin in the presence of pretreatment with lidocaine.

After the rabbits were sedated with $2 \text{ mg} \cdot \text{kg}^{-1}$ ketamine, tracheostomy was performed aseptically and a 3.5-mm uncuffed tracheal tube was inserted and tied in place. Anesthesia was maintained with continuous infusion of ketamine at a rate of $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. The lungs of the rabbits were ventilated using an infant ventilator (IV100B, Sechrist, Anaheim, CA) at an inspired oxygen concentration of 40%. Tidal volume was set to $10 \text{ ml} \cdot \text{kg}^{-1}$ measured by pneumotachograph. Respiratory rate was adjusted to produce initial arterial carbon dioxide tension of 35–40 mmHg.

Via femoral cutdown, a catheter was placed in the distal aorta to monitor arterial pressure and to take samples for blood gas analysis. Pulmonary arterial pressure (PAP) was continuously monitored with a Swan-Ganz catheter (3-French, Baxter, IL) inserted through the right internal jugular vein. Central venous pressure also was monitored *via* a catheter inserted through the femoral vein. The animals were placed on a heating pad under a radiant heat lamp so that the body temperature could be kept at 37.8–40.2°C. Lactated Ringer's solution was intravenously administered at $8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$.

Immediately after the baseline measurement of lung mechanics, hemodynamics, peripheral leukocyte count, and arterial blood gas analysis, group S received continuous infusion of saline. In contrast, rabbits in group E received endotoxin $30 \mu\text{g} \cdot \text{kg}^{-1}$ over a 60-min period without treatment with lidocaine. In many previous studies, endotoxin was injected as a bolus or infused for a short period (*e.g.*, 20–60 min) to assess lung injury 5–6 h after endotoxin.²⁸⁻³⁰ group E-L received a bolus of lidocaine $2 \text{ mg} \cdot \text{kg}^{-1}$ (Fujisawa, Osaka, Japan), 10 min before administration of endotoxin, followed by continuous infusion of lidocaine at a rate of $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ until sacrifice of the rabbits. The rationale for the dose of intravenous lidocaine treatment was based on the following reports.^{17,31-37} Intravenous infusion of lidocaine at a rate of $1-2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ has been shown to improve survival in baboon endotoxin shock.^{32,33} A single bolus dose of

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lidocaine, $2.5 \text{ mg} \cdot \text{kg}^{-1}$ intravenously, inhibits granulocyte adherence in rabbits.³¹ Release of O_2^- by neutrophils obtained from lidocaine-treated patients with coronary arterial disease, in whom serum lidocaine concentrations ranged between 1.0 and $5.6 \text{ } \mu\text{g} \cdot \text{ml}^{-1}$, was reported to be lower than in normal subjects and in coronary patients not receiving lidocaine.¹⁷ Continuous infusion of lidocaine at $2\text{--}3 \text{ mg} \cdot \text{min}^{-1}$, corresponding to $1.68\text{--}2.58 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in a 70-kg patient, resulted in plasma concentrations of $2\text{--}5 \text{ } \mu\text{g} \cdot \text{ml}^{-1}$.³⁴ Lidocaine, $1.5 \text{ } \mu\text{g} \cdot \text{ml}^{-1}$, reportedly reduced free radical production by neutrophils *in vitro*.³⁵ In a study using rats, lidocaine infusion at a rate of $0.6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ has been shown to reduce albumin extravasation in burn injuries.³⁶ The infusion rate of lidocaine employed in the current study is in the low therapeutic dose range recommended for the treatment of clinical cardiac arrhythmias.³⁷

All rabbits were killed 6 h after the start of endotoxin treatment by injection of thiamylal. In group E-L, arterial blood samples were obtained at 0, 0.5, 1, 2, 3, 4, 5, and 6 h after the start of administration of lidocaine to determine plasma concentrations of the drug using fluorescence polarization immunoassay (TDX system, Abbott, IL).

Estimation of Acute Lung Injury

Measurement of Lung Mechanics. During each experimental period, we obtained arterial blood specimens for analysis of oxygen tension (PaO_2), carbon dioxide tension, and pH using ABL2 (Radiometer, Copenhagen, Denmark), and the number of peripheral leukocytes with a Coulter counter (Coulter Electronics, Harkenden, UK) and the Bürker-Türk method.³⁸ Immediately after the start of mechanical ventilation (before infusion of saline or lidocaine) and immediately before killing the rabbits (after the period of observation), lung mechanics were measured by the passive expiratory flow-volume technique as described by LeSouef *et al.*³⁹ The airflow was measured with a Fleish OO pneumotachograph and a differential pressure transducer (model MP-45, Validyne Engineering, Northridge, CA). Airway pressure was measured at the proximal end of the pneumotachometer with a semiconductor pressure transducer (model P-300 501G Copal Electronics, Tokyo, Japan). The volume was determined for each breath by digital integration of airflow using a respiration monitor (Aivision, Tokyo, Japan) and a personal computer (PC9801 VM11, NEC, Tokyo, Japan). The lungs were inflated and the airflow

was interrupted at $20 \text{ cmH}_2\text{O}$. The occlusion was rapidly released after airway pressure reached a plateau. Compliance and resistance of total respiratory system were then calculated by means of the personal computer.

At the end of the experiment, after the thorax was opened, blood (15 ml) was drawn into a heparinized syringe ($20 \text{ U} \cdot \text{ml}^{-1}$) from the pulmonary artery for chemiluminescence assay (see below). The sampling of blood was completed before administration of thiamylal, by which the rabbits were killed. Then, the heart and lungs were removed en bloc by observers blinded to the nature of experiment.

Lung Wet- to Dry-weight Ratio. The left upper lobe was weighed and then dried to constant weight at 60°C for 24 h in an oven. The ratio of wet weight to dry weight was calculated to assess tissue edema.

Preparation of Bronchoalveolar Lavage Fluid and Measurements. Through the right mainstem bronchus 40 ml saline with EDTA (ethylenediamine-tetraacetic acid)- 2Na at 4°C was slowly infused and withdrawn. This procedure was repeated five times. Indomethacin was added to the bronchoalveolar lavage fluid (BALF) to inhibit further metabolism of arachidonic acid to prostaglandins during analysis. The BALF was analyzed for cell count and cell differentiation. A cytocentrifuged preparation (Cytospin 2, Shandon Southern Products, UK) of the BALF was stained with Wright-Giemsa for cell differentiation. The cells present in the fluid were counted by the Coulter counter (Coulter Electronics, Harkenden, UK) and the Bürker-Türk method.³⁸

The fluid was centrifuged at 250 g at 4°C for 10 min to remove the cells. The cell-free supernatant was divided into several aliquots and stored at -70°C until assayed. The following substances, metabolites, and mediators in the BALF were then measured: (1) activated components of the complements, C3a and C5a, quantified by radioimmunoassay (Amersham, Bucks, UK); (2) albumin concentrations, determined by nephelometry with immunoglobulin G fraction of goat anti-rabbit albumin (Cappel, PA); (3) concentrations of tumor necrosis factor α ($\text{TNF}\alpha$) and interleukin- 1β ($\text{IL-1}\beta$), determined by enzyme immunoassay (Amersham, Bucks, UK); and (4) concentration of thromboxane A_2 (TxA_2), quantified by radioimmunoassay (Amersham, Bucks, UK) as TxB_2 , the stable metabolite of TxA_2 .

Chemiluminescence Assay. Reagents. *Cypridina* luciferin analog (CLA) (2-methyl-6-phenyl-3,7-dihy-

droimidazo [1,2-a]-pyrazin-3-one), dimethyl sulfoxide, Hank's balanced salt (HBSS), Histopaque-1119, Histopaque-1077, N-formyl-L-methionyl-L-leucyl-L-phenylalanine (FMLP), and zymosan A were obtained from Sigma Chemical Co. (St. Louis, MO).

CLA was dissolved to 56 $\mu\text{g}/\text{ml}$ in distilled water. The solution was stored in 1-ml aliquots at -80°C . CLA concentrations were based on $\epsilon 410 \text{ nm} = 8,900 \cdot \text{mol} \cdot \text{l}^{-1} \cdot \text{cm}^{-1}$.⁴⁰ FMLP 5 mg was dissolved in 1.14 ml DMSO. The solution was stored at -80°C until assayed. Just before usage, the stored solution was diluted with 50% dimethyl sulfoxide–50% HBSS to 100 μM . Zymosan was opsonized by the method of Nishida *et al.*⁴¹ with modification. Zymosan A was suspended in HBSS at a concentration of 2 $\text{mg} \cdot \text{ml}^{-1}$ and heated in a boiling water bath for 100 min, washed twice with HBSS, and opsonized with pooled serum in a shaking water bath for 30 min at 37°C . The opsonized zymosan was then washed twice, resuspended in HBSS to a concentration of 20 $\text{mg} \cdot \text{ml}^{-1}$, and stored at -80°C until use.

Isolation of Neutrophils. Histopaque-1119, Histopaque-1077, and whole blood were layered and centrifuged at $700 \times g$ for 30 min at room temperature. The layer containing granulocytes (at the interphase between Histopaque-1077 and Histopaque-1119) was transferred to another tube. The cells were washed in HBSS and centrifuged twice at $200 \times g$ for 10 min. The resultant leukocytes were suspended to 1×10^7 cells/ml in HBSS and were kept at 0°C for no longer than 3 h before use. The cell analysis showed that more than 98% of the cells were neutrophils, and the trypan blue dye exclusion test confirmed that more than 97% of the cells were viable.

Measurement of Chemiluminescence. Measurement of chemiluminescence was based on the method by Sugioka *et al.*⁴² The incubation mixture contained WBC 4×10^5 , FMLP 20 μL or opsonized zymosan 80 μL , 40 μM CLA 50 μL and HBSS in a total volume of 2 ml. Cells and HBSS were preincubated for 3 min and the reaction initiated by the simultaneous addition of the other two components. CLA-dependent luminescence, which is thought to represent mostly O_2^- production, was monitored with a luminescence reader (Lumicounter-1000, Nichion, Chiba, Japan). During luminescence measurement, the incubation mixture was agitated at 37°C in the luminescence reader.

Histopathologic Examination. Shortly after killing (<5 min) the rabbits, the left lower lobe was fixed by instillation of 10% formaldehyde solution through the

left lower bronchus at 20 cmH_2O . The specimens were embedded in paraffin wax, and stained with hematoxylin and eosin and examined under a light microscope. Lung injury was scored 0 (minimal (little) damage) to 4+ (maximal damage) according to combined assessments of alveolar congestion, hemorrhage and edema, infiltration or aggregation of neutrophils in airspace or vessel wall, thickness of alveolar wall, and hyaline membrane formation by a blinded observer outside the group assignment of the animal.

Implications of Variables Measured

Various immunocytes (*e.g.*, polymorphonuclear cells [PMNs] and macrophages), platelets, and inflammatory chemical mediators are involved in the pathogenesis of endotoxin-induced lung injury. These phagocytes and the inflammatory mediators have been shown to constitute a complex cascade and network to enhance inflammatory responses to various stimuli leading to the acute lung injury.^{6,13,44} Lidocaine probably has its many targets in the cascade-network of these pathogenic factors.

Therefore, in the current study, we measured many variables, which can be divided into two categories: "result" (effect) and "cause" (pathogenesis). "Result" variables included (1) wet- to dry-weight ratio (pulmonary edema), (2) albumin concentrations in BALF (permeability), (3) lung injury score (pathology), (4) compliance and resistance (function: mechanics), (5) PAP (hemodynamics), and (6) PaO_2 (function: gas exchange), and "cause" variables (possible mechanism of lung injury) included (7) total leukocytes and percentage of PMNs in BALF (chemotaxis), (8) peripheral platelets (coagulation disorder), (9) peripheral leukocytes (chemotaxis), (10) C3a and C5a concentrations in BALF (chemotaxis) (11) $\text{TNF}\alpha$ and $\text{IL-1}\beta$ in BALF, (12) TxB_2 , and (13) CLA-dependent chemiluminescence (O_2^-). Some of these "cause" variables are thought to be "result" ones. We consider that "result" variables are clinically more important than "cause" variables. Among "result" variables ((1)–(6)) of lung injury, we believe that (4), (5), and (6) are more important than any other variables because these are readily evaluable clinically and are relevant to pulmonary function and signs. In particular, (6) PaO_2 is likely to represent general assessment of the severity of lung injury. On the other hand, of "cause" variables ((7)–(16)) of lung injury, we believe that (7) and (13) are relatively more important because the inhib-

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itory effect of lidocaine on leukocytes' function is well-known.

Statistical Analysis

Data except lung injury score are expressed as mean \pm SEM whereas data on lung injury score are given as median (range). The degree of attenuation of lung injury by lidocaine was calculated from the following formula: percent attenuation = $100 \times (b - c)/(b - a)$, where a = value in the S group; b = value in the E group; and c = value in the E-L group. Statistical analysis was performed by analysis of variance for continuous variables, except for lung injury score, for which the Kruskal-Wallis rank test was used. $P < 0.05$ was deemed significant. When analysis of variance indicated a significant difference, the Bonferroni multiple-comparisons test was used to identify the groups significantly different from each other.

Results

Changes in Arterial Oxygen Tension, Hemodynamics, and Peripheral Leukocyte Counts

Results are presented in table 1. No rabbits died of endotoxemia. In group E-L, plasma lidocaine concentrations were maintained between 1.3–2.2 $\mu\text{g} \cdot \text{ml}^{-1}$. As shown in figure 1, Pa_{O_2} in group S remained at a level exceeding 160 mmHg, whereas Pa_{O_2} in group E gradually decreased to 91 mmHg during the experiment. In group E-L, however, this decrease was attenuated (by 57%). The AP did not differ among the three groups at any point. Infusion of endotoxin rapidly increased PAP, and lidocaine pretreatment attenuated (by 53%) this increase. There was no difference in central venous pressure among the three groups. Peripheral leukocyte counts abruptly decreased with infusion of endotoxin, reached the lowest level 2 h after the end of endotoxin infusion, and remained low during the experiment. Lidocaine slightly (by 13%) attenuated the decrease in peripheral leukocyte counts. Endotoxin infusion but not endotoxin plus lidocaine decreased the platelet count in peripheral blood. However there was no difference in the platelet count decrease between groups E and E-L.

Lung Mechanics

Neither compliance nor resistance immediately after the start of mechanical ventilation was different among

the three groups (table 2). Compliance 6 h after treatment with endotoxin was less group E than in group E-L. Resistance after endotoxin was greater in group E than in group E-L but not significantly.

Lung Wet- to Dry-weight Ratio

The lung wet- to dry-weight ratio was calculated as a parameter of lung edema. The ratio increased in rabbits receiving endotoxin compared with those receiving saline (table 3). Lidocaine treatment attenuated the increase in wet- to dry-weight ratio.

Analysis of Bronchoalveolar Lavage Fluid

Recovery percentage of BALF in the three groups was 83–88%, indicating no difference among the three groups (fig. 2 and table 3). Figure 2A shows that the total number of leukocytes recovered in BALF was significantly higher in group E compared with that in group S. Total BALF leukocyte counts were also significantly increased in group E-L. However, figure 2A indicates that the leukocyte counts were less in group E-L than in group E (attenuation 45%). Differential counts revealed that BALF leukocytes in group S were mostly macrophages. PMNs accounted for 1.3% of the white blood cells (WBC) in BALF obtained from group S. In contrast, the PMN/total WBC ratio increased to 11% in group E. As shown in figure 2B, lidocaine pretreatment reduced the increase in the ratio to 3.9% (attenuation by 72%).

Albumin concentrations in the supernatant of BALF were higher in endotoxin-treated rabbits than in the control rabbits. Lidocaine decreased the albumin concentrations in endotoxin-treated rabbits (table 3). Table 3 indicates that the concentrations in BALF of C3a and C5a, which are known to be chemotactic factors, were less in group E-L than in group E but not significantly. The concentrations of $\text{TNF}\alpha$ and $\text{IL-1}\beta$ significantly increased in endotoxin-treated rabbits. They were less in group E-L than in group E but not significantly (table 3). The TxB_2 concentration in BALF increased in group E compared with group S whereas it was not greater in group E-L than in group S.

Chemiluminescence

The CLA-dependent chemiluminescence (representing O_2^- production) by neutrophils isolated from the pulmonary artery in group E was significantly higher compared with that in group S when stimulated by opsonized zymosan or FMLP (fig. 3). Pretreatment with lidocaine attenuated the increase in chemilumines-

Table 1. Changes in Hemodynamics and Peripheral Leukocyte and Platelet Counts in the Three Groups

	Time after the Start of Endotoxin or Saline							
	0h	0.5 h	1 h	2 h	3 h	4 h	5 h	6 h
MAP (mmHg)								
Group S	98 ± 3	102 ± 4	101 ± 4	97 ± 4	98 ± 4	103 ± 4	102 ± 4	101 ± 4
Group E	96 ± 3	96 ± 4	95 ± 4	94 ± 3	96 ± 4	94 ± 4	93 ± 4	93 ± 4
Group E-L	93 ± 3	94 ± 4	95 ± 4	95 ± 3	93 ± 3	95 ± 4	96 ± 4	94 ± 3
MPAP (mmHg)								
Group S	20 ± 1	20 ± 1	19 ± 1	19 ± 1	21 ± 1	20 ± 1	20 ± 1	20 ± 1
Group E	20 ± 1	31 ± 1*	34 ± 1*	30 ± 1*	26 ± 2	25 ± 2	23 ± 2	24 ± 2
Group E-L	19 ± 1	24 ± 1†	26 ± 1*†	24 ± 1†	21 ± 1	20 ± 1	20 ± 1	20 ± 1
HR (beats/min)								
Group S	217 ± 5	212 ± 6	219 ± 6	216 ± 6	211 ± 5	218 ± 6	221 ± 6	219 ± 6
Group E	226 ± 4	218 ± 6	224 ± 6	222 ± 5	215 ± 5	212 ± 6	210 ± 6	209 ± 5
Group E-L	221 ± 4	223 ± 6	217 ± 6	214 ± 5	217 ± 6	211 ± 5	213 ± 5	215 ± 5
CVP (cmH ₂ O)								
Group S	2.9 ± 0.2	2.8 ± 0.2	2.8 ± 0.2	2.7 ± 0.2	2.8 ± 0.3	2.9 ± 0.3	2.8 ± 0.2	2.7 ± 0.2
Group E	2.7 ± 0.2	2.5 ± 0.2	2.4 ± 0.2	2.4 ± 0.3	2.5 ± 0.2	2.4 ± 0.3	2.4 ± 0.2	2.4 ± 0.3
Group E-L	2.7 ± 0.2	2.6 ± 0.2	2.6 ± 0.2	2.5 ± 0.2	2.7 ± 0.3	2.6 ± 0.2	2.6 ± 0.2	2.6 ± 0.2
Leukocytes (× 10 ² cells/mm ³)								
Group S	42 ± 4	41 ± 4	37 ± 5	40 ± 4	43 ± 3	37 ± 4	35 ± 3	39 ± 4
Group E	39 ± 4	14 ± 0.8*	9 ± 0.7*	5 ± 0.2*	5 ± 0.2*	6 ± 0.2*	8 ± 0.2*	10 ± 0.7*
Group E-L	42 ± 4	25 ± 2*†	12 ± 0.8*†	9 ± 0.6*†	8 ± 0.2*†	10 ± 0.3*†	11 ± 0.3*†	15 ± 0.6*†
Platelets (× 10 ⁴ cells/mm ³)								
Group S	32 ± 3	34 ± 3	31 ± 2	30 ± 3	29 ± 3	29 ± 3	28 ± 3	27 ± 3
Group E	34 ± 3	32 ± 3	28 ± 4	25 ± 3	20 ± 2	18 ± 3	18 ± 2*	16 ± 3*
Group E-L	33 ± 2	30 ± 3	29 ± 2	30 ± 3	31 ± 2	27 ± 4	22 ± 3	23 ± 3

Values are mean ± SEM.

MAP = mean arterial pressure; HR = heart rate; CVP = central venous pressure; MPAP = mean pulmonary arterial pressure.

* $P < 0.05$ versus group S.† $P < 0.05$ for group E-L versus group E.

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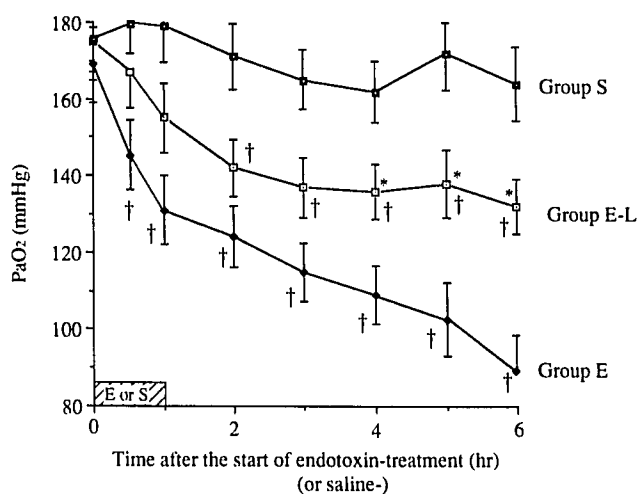


Fig. 1. Changes in arterial oxygen tension (PaO_2) (mean \pm SEM) in the three groups. Infusion of endotoxin (E) or saline (S). † $P < 0.05$ versus group S; * $P < 0.05$ group E-L versus group E.

cence (by 83% for opsonized zymosan and by 65% for FMLP). Ketamine used as an anesthetic in the current study has been shown to have no effect on O_2^- production by neutrophils at doses used in the clinical setting.⁴⁵

Histopathologic Grading

The results of the grading of lung damage are summarized in table 4. Infusion of endotoxin caused extensive morphologic lung damage in group E and less damage in group E-L. The score for E-L group was statistically less than for group E (table 4). Light microscopic findings in group E included hemorrhage and edema, thickened alveolar septum, and existence of inflammatory cells in alveolar spaces (fig. 4A). In contrast, these changes were far less pronounced in group E-L (fig. 4B).

Discussion

Postulated Pathogenesis of Endotoxin-Induced Lung Injury

Circulating endotoxin causes complement activation,⁴³ which results in liberation of active fragments, particularly C3a and C5a.⁴³ These activated fragments are chemotactic and are aggregating factors for neutrophils⁴³; they lead to pulmonary capillary leukostasis and promote granulocyte migration into interstitial alveolar spaces.⁴³ Dramatic reductions in WBC

concentration have been reported in the early phase of ARDS in animals,⁴³ corresponding to pulmonary trapping of leukocytes. Endotoxin also activates alveolar macrophages,⁵ which release cytokines (TNF α and IL-1 β).⁵ These mediators promote neutrophil chemotaxis⁵ and adherence of neutrophils to pulmonary vascular endothelium⁴⁶ by enhancing the expression of adhesive molecules on endothelial membranes.⁴⁶ Activated neutrophils can injure the capillary endothelium by releasing oxygen radicals, proteinases (elastase, collagenase, and cathepsins), and arachidonic acid metabolites (particularly TxA₂), which mediate bronchoconstriction and pulmonary vasoconstriction and increase capillary permeability and pulmonary edema,⁴⁷ and platelet-activating factor (PAF),⁴³ which appears to cause TxA₂ release from platelets⁴³ and platelet-mediated lung edema in isolated rabbit lungs.⁴⁸ The arachidonic acid metabolites may act as markers of lung injury and may aid in lung adaptation to injury.^{49,50} However, controversy exists over the role of neutrophils in the pathogenesis of ARDS. Ognibene *et al.* reported that ARDS can occur in the presence of severe neutropenia, without pulmonary neutrophil infiltration.¹⁸ They speculated that direct endothelial cell injury caused by activated complement or other mediators might be involved in the causation of pathologic changes observed in ARDS.

Postulated Mechanism of Attenuation of the Lung Injury by Lidocaine

In the current study, lidocaine slightly attenuated the decrease in peripheral leukocytes counts occurring in

Table 2. Lung Mechanics before and after Endotoxin or Saline

	Time after the Start of Endotoxin or Saline	
	0 h	6 h
Compliance (ml/cmH ₂ O)		
Group S	2.87 \pm 0.09	2.75 \pm 0.18
Group E	2.82 \pm 0.08	1.68 \pm 0.14*
Group E-L	2.96 \pm 0.09	2.23 \pm 0.15*† (45)
Resistance (cmH ₂ O \cdot L ⁻¹ \cdot s ⁻¹)		
Group S	102 \pm 5	105 \pm 10
Group E	103 \pm 4	126 \pm 6*
Group E-L	99 \pm 5	117 \pm 7 (43)

Values are mean \pm SEM. Values in parentheses are the percent attenuation of the variables by lidocaine.

* $P < 0.05$ versus group S.

† $P < 0.05$ for group E-L versus group E.

Table 3. Wet/Dry Weight Ratio and Analysis of Bronchoalveolar Lavage Fluid

Variables	Group			% Attenuation \ddagger
	S	E	E-L	
Wet/dry weight ratio	4.9 \pm 0.1	5.5 \pm 0.2*	5.1 \pm 0.1 \ddagger	67
Albumin (mg/dl)	1.1 \pm 0.3	8.7 \pm 1.1*	2.3 \pm 0.6 \ddagger	84
C3a (ng/dl)	29 \pm 3	49 \pm 8*	35 \pm 3	70
C5a (ng/dl)	8 \pm 1	17 \pm 2*	11 \pm 2	68
TNF α (fmol/ml)	2 \pm 1	22 \pm 4*	10 \pm 3*	60
IL-1 β (fmol/ml)	3 \pm 1	23 \pm 6*	13 \pm 3*	54
TxB $_2$ (pg/ml)	104 \pm 36	193 \pm 51	167 \pm 38	29

Values are mean \pm SEM.

* $P < 0.05$ versus group S.

$\ddagger P < 0.05$ for group E-L versus group E.

\ddagger % attenuation = (group E - group E-L) \times 100/(group E - group S).

endotoxin-treated rabbits. The number of alveolar neutrophils recovered in BALF decreased in rabbits receiving lidocaine. These observations indicate inhibition by lidocaine of accumulation of leukocytes in the alveolar spaces. This effect of lidocaine may be due to decreased neutrophil response to the stimulus. Lidocaine is known to inhibit chemotaxis¹⁵ and adherence of human neutrophils to endothelial monolayers or nylon fiber.³¹ In the current study, no significant differences were observed between rabbits receiving lidocaine and those not receiving lidocaine in chemotaxis (C3a, C5a, TNF α , and IL-1 β in BALF).

Incipient pulmonary hypertension frequently observed in ARDS is likely to exacerbate lung injury. This increase in PAP is thought to be mediated by vasoconstrictors (e.g. TxA $_2$, leukotrienes, and serotonin).⁵¹ In

the current study, lidocaine attenuated this pulmonary hypertension 15–120 min after the start of endotoxin. However, it is indeterminable whether the attenuation of pulmonary hypertension was a cause or a result of lessened lung damage. Furthermore, lack of "lidocaine control group (group Saline-Lidocaine)" did not allow us to determine whether the ameliorating effect of lidocaine on pulmonary hemodynamics was direct or indirect. From the previous investigations,^{53,52} we speculate that lower PAP observed in the first 2 h in group E-L compared with group E is likely to be due to an indirect hemodynamic effect of lidocaine rather than a direct one. Lidocaine, 2 mg \cdot kg⁻¹ intravenously, has been shown to have little effect on PAP whereas the drug at doses of 5–10 mg \cdot kg⁻¹ increases PAP in animals.⁵² Infusion of lidocaine at 1 mg \cdot kg⁻¹ \cdot h⁻¹ has

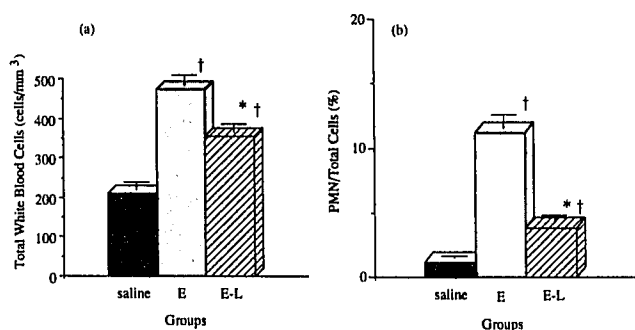


Fig. 2. Leukocyte counts and cell differentiation in bronchoalveolar lavage fluid. (A) Ration of polymorphonuclear cells to total cells (mean \pm SEM). (B) Count of total white blood cells. Filled columns = group S; dotted columns = group E; cross-hatched columns = group E-L. $\ddagger P < 0.05$ versus group S; * $P < 0.05$ group E-L versus group E.

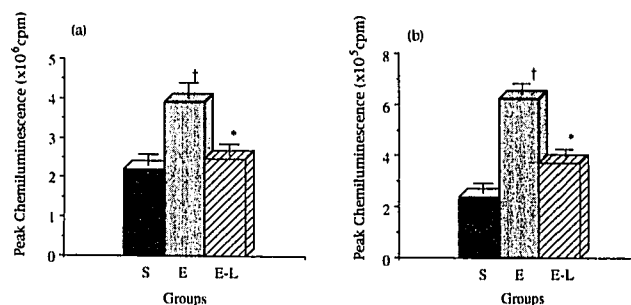


Fig. 3. *Cypridina* luciferin analogue-dependent chemiluminescence (peak) by neutrophils isolated from pulmonary artery (mean \pm SEM). (A) Opsonized zymosan-stimulated chemiluminescence (mean \pm SEM). (B) Chemiluminescence (mean \pm SEM) stimulated by N-formyl-L-methionyl-L-leucyl-L-phenylalanine. Filled columns = group S; dotted columns = group E; cross-hatched columns = group E-L. $\ddagger P < 0.05$ versus group S; * $P < 0.05$ group E-L versus group E.

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Table 4. Mean Lung Injury Score

	n	Lung Injury Score
Group S	9	0 (0-1)
Group E	9	3 (2-4)*
Group E-L	9	2 (1-4)*†

Values are medians (with range in parentheses).

Score of 0 = minimal (little) damage; 1+ = mild damage; 2+ = moderate damage; 3+ = severe damage; 4+ = maximal damage.

* $P < 0.05$ versus group S.

† $P < 0.05$ for group E-L versus group E.

no effect on PAP.³³ These reports suggest that lidocaine at doses used in clinical practice does not decrease PAP at least.

It is also of importance that lidocaine pretreatment lessened the increases in the lung wet- to dry-weight ratio and albumin concentrations in BALF after endotoxin. These are indexes of endothelial permeability leading to pulmonary edema. The beneficial actions of lidocaine on endotoxin-induced vascular permeability include an action to lessen impairment of O_2^- production by neutrophils. Lidocaine has been shown to reduce O_2^- release from neutrophils,¹⁵⁻¹⁷ and lessen endothelial damage. In the current study, neutrophils isolated from rabbits receiving lidocaine produced less O_2^- than did those not receiving lidocaine. Furthermore, reactive oxygen species indirectly contribute to edematous lung injury by inactivating antiproteases, thereby enhancing the susceptibility of microvasculature to neutrophil elastase.⁴³ Thus, reduction of O_2^- production by lidocaine may be critical for attenuation of cellular damage. Lidocaine has been also demonstrated to diminish thiourea-induced increases in pulmonary vascular protein leak through an unknown mechanism that is independent of their effects on neutrophil O_2^- metabolite-dependent toxicity.¹⁶

Possible Clinical Relevance and Implication

We investigated whether lidocaine pretreatment has a prophylactic effect on endotoxin-induced lung injury because the effect, if it exists, was thought to be elicited more easily than a therapeutic effect (posttreatment) of the drug. Further studies are required to assess the therapeutic effect of lidocaine from a practical viewpoint. Lidocaine may prove effective in attenuating lung injury even when given after administration of endotoxin: Fletcher *et al.* reported that posttreatment with the drug for only 3 h successfully decreased mortality

(as assessed 72 h after endotoxin) due to endotoxin shock in baboons and dogs.⁵³ In their report, however, the effect on lung injury was not evaluated. Furthermore, their report encourages us to expect the effectiveness of lidocaine in the later phase of lung injury (24-72 h after endotoxin). On a theoretical basis, we can expect the effect of early posttreatment with lidocaine on endotoxin-induced lung injury although the degree to which lung injury is mitigated would be smaller compared with pretreatment. The pathogenesis of endotoxin-induced lung injury is complicated and the final step is thought to be that activated leukocytes, macrophages, and platelets attack endothelium or epithelium by releasing reactive oxygen species, proteases, or arachidonic acid metabolites, leading to high

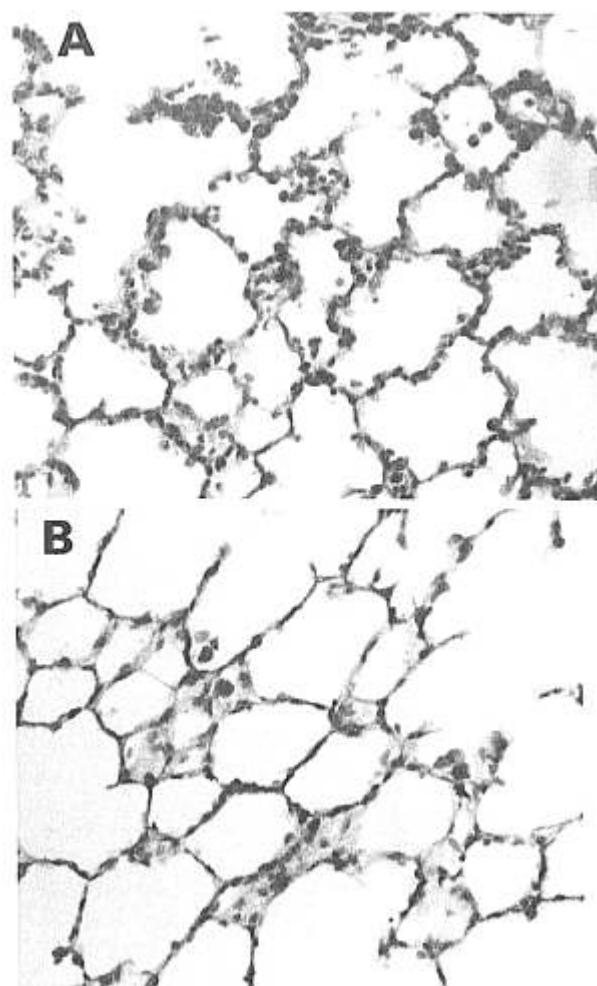


Fig. 4. Light micrograph (hematoxylin and eosin, $\times 100$) of the lung. (A) Group E. (B) Group E-L.

permeability edema. According to some *in vivo* animal studies, it would take several hours to activate macrophages, PMNs, platelets, endothelial cells, and other cells by humoral chemical mediators such as cytokines and activated complements. Early posttreatment with lidocaine possibly targets this final step to attenuate the lung injury.

Lidocaine, which is used extensively in Intensive Care Unit and Coronary Care Unit, is less costly, has relatively high safety, and may be able to be given in advance to critically ill patients who are at increased risk of ARDS such as those with sepsis, major trauma, and shock. In this context, we believe that the current study, which explored the effect of lidocaine pretreatment on the lung injury, has clinical relevance.

Possible Adverse Effects of Lidocaine Treatment

A potential negative aspect of lidocaine-induced impairment of neutrophil function is a possible increase in susceptibility to infection. Several studies have shown local anesthetics to possess potent antimicrobial properties *in vitro* and *in vivo*.^{54,55} However, the current study is unable to provide an obvious solution to this problem because the effect of lidocaine on the bactericidal system in this setting was not investigated. Whether lidocaine would enhance susceptibility to infection deserves further studies.

Conclusions

Intravenous lidocaine had a prophylactic effect on endotoxin-induced lung injury in rabbits. This effect may be due, in part, to inhibition of the function of neutrophils. However, further studies are required to investigate the therapeutic (early posttreatment) effect of the drug on this lung injury because rabbits in the current study received lidocaine before endotoxemia.

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