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The Effects of Pentoxifylline on Pulmonary Function Following Smoke Inhalation[1,2]

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Bronchopulmonary injury secondary to smoke inhalation is a significant comorbid factor following major thermal trauma. The present study evaluates the effects of pentoxifylline (PTX) on pulmonary function in an ovine model of inhalation injury. Following smoke exposure to produce a moderate inhalation injury, 16 animals were divided into two groups. Group 1 animals ($n = 8$) were untreated; Group 2 animals ($n = 8$) were treated continuously with pentoxifylline following smoke exposure. The animals were observed in the unintubated, awake state for 48 hr. Cardiopulmonary variables and blood gases were measured serially. Ventilation perfusion distribution ($\dot{V}_A/\dot{Q}$), analyzed using the multiple inert gas elimination technique, and bronchoalveolar lavage (BAL) were performed at 48 hr. The wet to dry lung weight ratio was measured following necropsy. In Group 2, the progressive hypoxemia observed following smoke inhalation was attenuated with less $\dot{V}_A/\dot{Q}$ mismatching than in Group 1 ($P < 0.05$). Pulmonary hypertension secondary to increased vascular resistance was also attenuated in Group 2 ($P < 0.05$). In BAL fluid, polymorphonuclear leukocytes, total protein content, and conjugated dienes were less in Group 2 than in Group 1 ($P < 0.05$). Plasma-conjugated diene levels were also lower in Group 2 at 48 hr. Extravascular lung water and decrease in lung compliance were greater in Group 1. There was less morphologic evidence of airway injury in Group 2 compared to Group 1. The improvement of pulmonary function following treatment with PTX suggests that this agent may be useful in the management of smoke inhalation injury.

INTRODUCTION

Smoke inhalation injury is a significant comorbid factor in patients with major thermal injury [1]. Smoke inhalation causes airway inflammation in the early phase, with subsequent pulmonary edema and infection [2]. Medical interventions that decrease airway inflammation may attenuate the later deleterious consequences of inhalation injury.

Pentoxifylline [3,7-dimethyl-1-(5-oxohexyl)xanthine, PTX] has been advocated for use in patients with chronic peripheral vascular insufficiency [3]. PTX appears to increase the deformability of erythrocytes and leukocytes, to decrease plasma fibrinogen levels, to increase the secretion of tissue plasminogen activator, to inhibit platelet aggregation, and to increase prostacyclin production from endothelial cells [4–6]. These effects result in the hemorheologic and antithrombotic properties of PTX, potentially decreasing blood viscosity and improving microcirculatory blood flow. Recently, the effects of PTX on cytokine production and leukocyte activation have been investigated [7]. In *in vitro* studies, PTX has been reported to block TNF mRNA expression in macrophages and to inhibit TNF, IL-1, and PAF activity on neutrophils, leading to decreased leukocyte adhesion to endothelium, superoxide production, degranulation, and phagocytosis, as well as increased leukocyte migration and chemotaxis [8–12]. In animal models, beneficial effects of PTX have been reported following peritonitis, septicemia, ischemia–reperfusion, and hemorrhagic shock [13–18]. Also, acute lung injury induced by TNF, chymotrypsin, and *Escherichia coli* have been significantly attenuated with PTX therapy [19–21].

Polymorphonuclear leukocytes (PMNs) have been implicated as a source of oxygen radicals and proteases which participate in the cascade of events leading to pulmonary damage following smoke exposure. In the present study we evaluated the pulmonary effects of PTX following smoke inhalation injury in an ovine model.

METHODS AND MATERIALS

Twenty random source male sheep, 1 to 2 years old, weighing 25.4 ± 0.5 kg were used in this study. The animals were housed in covered outdoor runs, treated for parasites (ivermectin, 0.2 mg/kg, im), and fed commer-

[1] The views of the authors do not purport to reflect the positions of the Department of the Army and the Department of Defense.

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cial chow and water *ad libitum*. The animals were divided into three groups. Group 1 (n = 8) animals received only saline after smoke exposure. Group 2 (n = 8) animals received a continuous intravenous infusion of pentoxifylline (Hoechst–Roussel Pharmaceuticals, Inc., Somerville, NJ) after smoke exposure. Normal control animals (n = 4) were used for the analyses of normal ventilation–perfusion distributions in lung, bronchoalveolar lavage fluids, and wet to dry lung weight ratios.

The animals in Groups 1 and 2 were instrumented while under sodium pentobarbital (25 mg/kg, iv; Sigma Chemical Co.) general anesthesia the day prior to smoke exposure. Silastic cannulae were placed in a femoral artery and vein. One radiopaque sheath introducer, through which a Swan Ganz catheter was placed, was inserted into an external jugular vein.

The following day, the animals were anesthetized with sodium pentobarbital and intubated with a 7.5-mm orotracheal tube. Before smoke exposure, the animals were paralyzed with succinylcholine chloride (0.5 mg/kg, iv; Abbott Laboratories). Smoke was generated by thermolysis of pine woodchips (50 g) in a crucible furnace (Furnace Model 56622 and Control Console Model 58114; Lindberg, Watertown, WI) at a constant temperature of 400°C and a constant airflow of 3 liters/min. Smoke exposure was accomplished using a circuit equipped with a volume-controlled pump and a breathhold valve. Moderate smoke inhalation injury was produced by alternating 7 units of smoke with 7 units of air; 1 unit consisting of five breaths at a constant tidal volume of 30 ml/kg with a constant breathhold of 4 sec.

After smoke exposure, the animals were housed in individual cages in climate controlled facilities and observed for 48 hr while breathing spontaneously, in the awake state. Group 1 animals received a maintenance infusion of lactated Ringer's solution (1.5 ml/kg/hr, iv). Group 2 animals received a bolus injection of pentoxifylline (20 mg/kg, iv) immediately following smoke exposure, followed by a continuous infusion of pentoxifylline (2 mg/kg/hr, iv) mixed in lactated Ringer's solution (1.5 ml/kg/hr).

Cardiopulmonary variables and blood gases were measured before smoke exposure and at 1, 3, 6, 12, 24, 36, and 48 hr following exposure. Pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP), and systemic artery pressure were measured using a pressure monitor (Model 78354A; Hewlett–Packard Company). Cardiac output was measured by thermodilution technique (Cardiac Output Computer Model 9520A; American Edwards Laboratory). Blood gas analyses were performed using an IL 1303 pH/blood gas analyzer and an IL 282 CO-oximeter (Instrumentation Laboratories, Inc.). Plasma samples for the measurement of conjugated dienes were stored at −70°C until measurement.

Forty-eight hours following smoke exposure the animals were anesthetized with sodium pentobarbital, intubated, paralyzed with pancuronium bromide (0.03 mg/kg, iv; Organon Pharmaceuticals), and mechanically ventilated. During mechanical ventilation, tidal volume was set at 15 ml/kg, respiratory rate at 10/min, and positive end-expiratory pressure (PEEP) at 5 cm H_2O. After 30 min, ventilation perfusion distribution ($\dot{V}_A/\dot{Q}$) using the multiple inert gas elimination technique (MIGET) was measured according to the method developed by Wagner *et al.* [22]. Lactated Ringer's solution containing six inert gases (sulfur hexafluoride, ethane, cyclopropane, halothane, diethylether, and acetone) was infused at a rate of 0.1 ml/kg/min. After 30 min, when equilibrium of gas exchange occurred, samples of arterial and mixed venous blood (10 ml each) were drawn anaerobically into preweighed heparinized syringes. Mixed expired gas was collected through a temperature-controlled copper coil (o.d. = 3.5 cm, L = 550 cm) 1 min after blood sampling. Duplicate blood and expired gas samples were immediately analyzed on a Hewlett–Packard 5890 Series 2 gas chromatograph (Hewlett–Packard Company). $\dot{V}_A/\dot{Q}$ distribution was analyzed utilizing a computer program designed specifically for the analysis of $\dot{V}_A/\dot{Q}$ using MIGET.

After the MIGET study, bronchoalveolar lavage (BAL) was performed. Twenty milliliters of 0.9% sterile saline was injected into the left lower lobe and the fluid was immediately aspirated. This process was repeated three times. The collected fluid was centrifuged and aliquots of the supernatent were stored at −70°C until measurement of total protein content and conjugated dienes. The cell pellet was resuspended with the same amount of saline as the supernatant and the total white blood cell count was determined using a hemocytometer. Differential cell counts were performed on Wright–Giemsa-stained cytocentrifuge preparations. Total protein in the BAL fluid supernatant was measured using a spectrophotometric dye-binding protein assay (Bio-Rad) [23].

Conjugated diene levels in the plasma and BAL fluid supernatant were measured by the method reported previously [24]. One-half milliliter of plasma or BAL fluid was mixed with 7.0 ml of a chloroform/methanol (2:1) solution which was preheated to 45°C. The mixture was vortexed vigorously for 2 min and then centrifuged for 5 min at 1500g. The lower chloroform layer was carefully removed and mixed with 2 ml of acidified water (pH 2.5). After the same agitation and centrifugation procedure was repeated, the lower level was aspirated and dried under nitrogen gas. The residue was reconstituted with 2 ml of heptane and the absorbance was measured spectrophotometrically at 233 nm. Results are expressed as absorbance at 233 nm against a blank consisting of heptane alone.

The wet to dry lung weight ratio (W/D) was determined by a modification of the gravimetric method of Drake *et al.* [25]. The right lung was removed after the bronchi and vessels were ligated. The entire right lung was homogenized with an identical weight of distilled water. Duplicate samples of the homogenate and blood

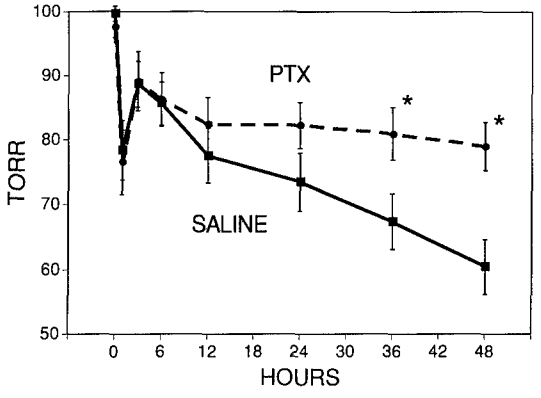

FIG. 1. Serial P_aO_2 in two groups following smoke inhalation. Group 1 (SALINE) is represented by the solid line, Group 2 (PTX) by the dotted line. The progressive hypoxemia observed in Group 1 was significantly attenuated in Group 2 during the second 24 hr (*$P < 0.05$, Student's t test at equivalent time).

were weighed and dried at a constant temperature of 80°C. Dry weights were measured and the wet to dry ratios of the homogenate and blood were calculated. A sample of the homogenate was centrifuged at 14,500 rpm for 1 hr, and a blood sample was diluted with the same volume of distilled water. To determine the hemoglobin levels in the homogenate and blood, 20 μl of the homogenate supernatant or the diluted blood was added to 2.5 ml of Drabkin's solution. The absorbance of both solutions was measured spectrophotometrically at 540 nm. Then, the blood weight in the wet lung was calculated. From these data, blood-free wet and dry weights of the right lung were calculated, and the W/D ratio was determined.

Static lung compliance was measured before smoke exposure and 48 hr after smoke exposure, while the animals were mechanically ventilated. Using an esophageal balloon, transpulmonary pressure was measured with a differential transducer (MP-415; Validine Engineering Corporation) and recorded. Inspiratory tidal volume was measured with a Wright spirometer. Static lung compliance was calculated by dividing the tidal volume by the transpulmonary pressure difference between the plateaued end-inspiratory-pause phase and the PEEP phase.

Respiratory index (RI), an oxygenation capacity index, was calculated by the formula

$$RI = (P_AO_2 - P_aO_2)/P_aO_2$$

$$P_AO_2 = 149 - 1.2 * P_aCO_2$$

P_AO_2 (mm Hg), alveolar O_2 pressure

P_aO_2 (mm Hg), arterial O_2 pressure

P_aCO_2 (mm Hg), arterial CO_2 pressure.

Bronchoepithelial damage of each animal was determined by histological light microscopic evaluation using the following epithelial damage score criteria:

0, normal
1, normal height of epithelium with some loss of cilia
2, superficial erosion of epithelium with complete loss of cilia
3, severe erosion of epithelium
4, complete ulceration of epithelium.

Statistical analysis of the data was performed, using Student's t test between Group 1 and Group 2 at equivalent times and analysis of variance to compare Groups 1 and 2 and a normal control group. Data are shown as mean ± standard error of the mean; significance was assigned at $P < 0.05$.

RESULTS

The arterial carboxy-hemoglobin levels just after smoke exposure were 71.8 ± 2.2% in Group 1 and 65.1 ± 4.0% in Group 2. This difference was not statistically significant. All animals survived the 48-hr observation period.

Figure 1 depicts the serial P_aO_2 following smoke exposure. The progressive hypoxemia measured in Group 1 was significantly attenuated in Group 2 during the second 24 hr ($P < 0.05$).

Figure 2 depicts the serial mean pulmonary artery pressure for the two groups. The elevation of mean pulmonary artery pressure in Group 1 was attenuated in Group 2. The difference between groups was significant during the entire second 24 hr.

Other physiologic parameters are shown in Table 1. The respiratory index in Group 2 was significantly lower 48 hr following smoke exposure compared to that in Group 1. The PCWP was significantly lower in Group 2 during the second 24 hr. The elevation of pulmonary vascular resistance observed in Group 1 was not present in Group 2 at 48 hr. P_aCO_2, mean systemic arterial pres-

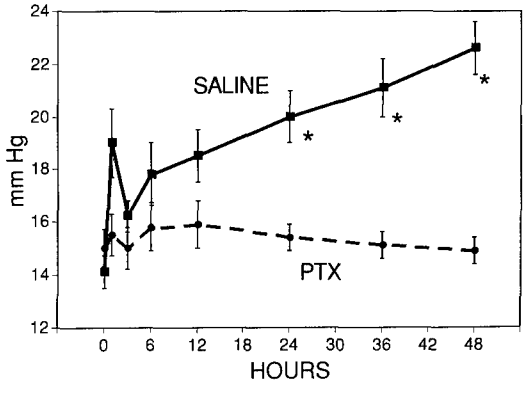

FIG. 2. Serial mean pulmonary artery pressures in two groups following smoke inhalation. Group 1 (SALINE) is represented by the solid line, Group 2 (PTX) by the dotted line. The progressive pulmonary artery hypertension observed in Group 1 was significantly attenuated in Group 2 during the entire second 24 hr (*$P < 0.05$, Student's t test at equivalent time).

TABLE 1

Other Cardiopulmonary Variables

		Time (hr)						
		PRE	3 hr	6	12	24	36	48
RI	G1	0.07 ± 0.02	0.22 ± 0.04	0.24 ± 0.03	0.36 ± 0.05	0.42 ± 0.05	0.55 ± 0.08	0.66 ± 0.09
	G2	0.06 ± 0.02	0.24 ± 0.09	0.28 ± 0.07	0.34 ± 0.08	0.31 ± 0.06	0.37 ± 0.07	0.29 ± 0.06*
PCWP	G1	7.3 ± 0.3	7.8 ± 0.3	8.5 ± 0.5	9.0 ± 0.6	9.0 ± 0.7	9.9 ± 1.0	10.8 ± 0.8
	G2	7.1 ± 0.4	6.8 ± 0.5	7.1 ± 0.4	7.9 ± 0.4	7.6 ± 0.3	7.0 ± 0.2*	7.5 ± 0.4*
PVR	G1	134 ± 13	144 ± 12	173 ± 18	178 ± 12	203 ± 15	206 ± 21	218 ± 11
	G2	162 ± 15	146 ± 14	162 ± 14	162 ± 18	167 ± 13	159 ± 15	152 ± 11*
PaCO2	G1	35.8 ± 1.3	34.7 ± 1.8	36.2 ± 1.6	37.4 ± 2.2	36.9 ± 1.9	38.6 ± 2.7	39.3 ± 2.5
	G2	38.2 ± 1.6	34.2 ± 0.7	33.7 ± 1.1	34.3 ± 0.4	35.3 ± 1.3	33.8 ± 0.7	38.1 ± 1.4
MSAP	G1	97 ± 3	101 ± 3	98 ± 4	101 ± 3	97 ± 5	98 ± 2	102 ± 3
	G2	92 ± 3	92 ± 3	93 ± 4	90 ± 2	91 ± 3	94 ± 3	94 ± 4
TPR	G1	1885 ± 131	1725 ± 140	1792 ± 130	1870 ± 118	1773 ± 197	1779 ± 107	1797 ± 64
	G2	1850 ± 99	1589 ± 105	1719 ± 110	1782 ± 123	1918 ± 165	1813 ± 176	1910 ± 136
CI	G1	5.6 ± 0.4	6.6 ± 0.5	6.0 ± 0.5	5.9 ± 0.4	6.0 ± 0.4	6.3 ± 0.6	5.9 ± 0.1
	G2	5.4 ± 0.4	6.6 ± 0.7	6.1 ± 0.4	5.7 ± 0.4	5.3 ± 0.5	5.9 ± 0.4	5.5 ± 0.3

Note. RI, respiratory index; PCWP (mm Hg), pulmonary capillary wedge pressure; PVR (dyne · sec/cm^5) = pulmonary vascular resistance; MSAP (mm Hg), mean systemic arterial pressure; TPR (dyne · sec/cm^5), total peripheral resistance; CI (liters/min/m^2), cardiac index; G1, Group 1; G2, Group 2; PRE, presmoke measurement. Values are means ± SEM. * $P < 0.05$, Student's t test at equivalent time.

sure, total peripheral resistance, and cardiac index did not differ significantly between the two groups throughout the entire study.

Table 2 shows the results of the MIGET analysis. The mean $\dot{V}_A/\dot{Q}$ of blood flow distribution, one index of $\dot{V}_A/\dot{Q}$ mismatching, was significantly decreased in Group 1 compared to normal. In Group 2, the decrease in mean $\dot{V}_A/\dot{Q}$ was less than that in Group 1, but the difference was not statistically significant. The logarithmic standard deviation of blood flow distribution, another index of $\dot{V}_A/\dot{Q}$ mismatching, was significantly increased in Group 1 compared to normal. In Group 2, the increase in the log SD $\dot{Q}$ was significantly less than that in Group 1. In addition, the percentage of blood flow to the shunt and very low $\dot{V}_A/\dot{Q}$ area ($\dot{V}_A/\dot{Q} < 0.1$) was greater in Group 1 than in Group 2 or normal animals.

Figure 3 shows the total WBC and PMN counts in bronchoalveolar lavage effluent. The recovery of BAL fluid in this study was approximately 60%. Total WBC and PMN counts were significantly greater in Group 1 than in controls or Group 2.

Figure 4 displays the conjugated diene levels in the BAL fluid from Groups 1 and 2 and normal controls. The level in Group 1 was significantly greater than that in normal controls or Group 2.

Figure 5 shows the serial conjugated diene levels in plasma for both experimental groups. At 48 hr the difference between Group 1 and Group 2 was statistically significant.

Figure 6 depicts the total protein content in BAL fluid

TABLE 2

$\dot{V}_A/\dot{Q}$ Distribution by MIGET Analysis

	Normal ($N = 4$)	Group 2	Group 1
Mean $\dot{V}_A/\dot{Q}$ of $\dot{Q}$	0.99 ± 0.09	0.89 ± 0.09	0.65 ± 0.06*
Log SD $\dot{Q}$	0.48 ± 0.03	0.71 ± 0.10	1.26 ± 0.10*,**
$\dot{V}_A/\dot{Q} < 0.1$ area (%)	0.1 ± 0.1	2.1 ± 1.5	11.5 ± 2.5*,**

Note. Mean $\dot{V}_A/\dot{Q}$ of $\dot{Q}$, mean ventilation perfusion ratio of blood flow distribution; log SD $\dot{Q}$, logarithmic standard deviation of blood flow distribution; $\dot{V}_A/\dot{Q} < 0.1$ area, total percentage of blood flow to shunt and very low $\dot{V}_A/\dot{Q}$ area. Values are means ± SEM. * $P < 0.05$ versus Normal; ** $P < 0.05$ versus Group 2 (ANOVA Tukey).

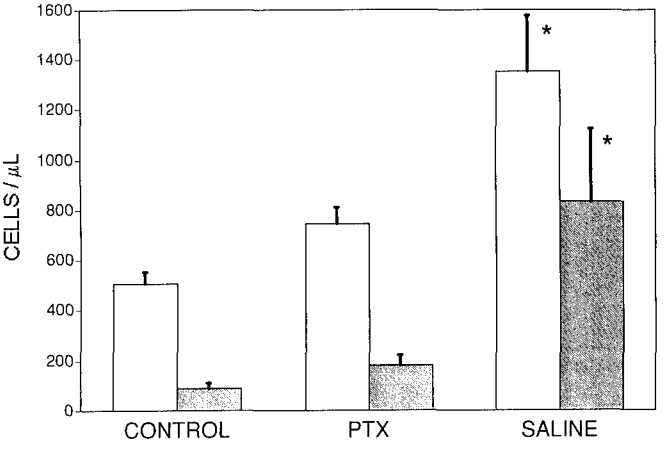

FIG. 3. Total WBC and PMN counts in BAL fluid in Group 1 (SALINE), Group 2 (PTX), and normal controls (CONTROL, $n = 4$). The left bars represent total WBC counts and the right bars represent PMN counts. Both numbers were significantly greater in Group 1 compared to Group 2 or normal controls (*$P < 0.05$, ANOVA Tukey).

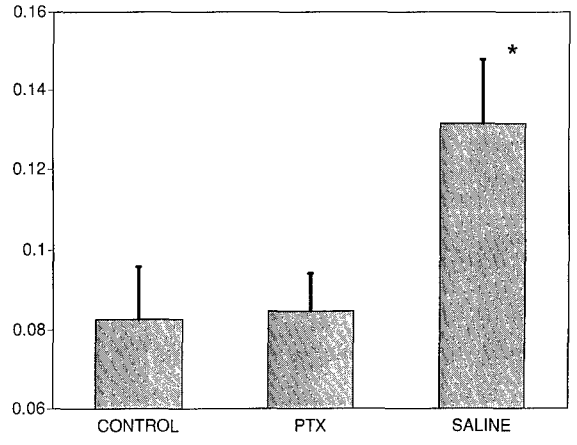

FIG. 4. Conjugated diene levels in BAL fluid in Group 1 (SALINE), Group 2 (PTX), and normal controls (CONTROL, $n = 4$). The levels are expressed as absorbance at 233 nm. The conjugated diene levels in Group 1 were significantly greater compared to Group 2 or normal controls ($^*P < 0.05$, ANOVA Tukey).

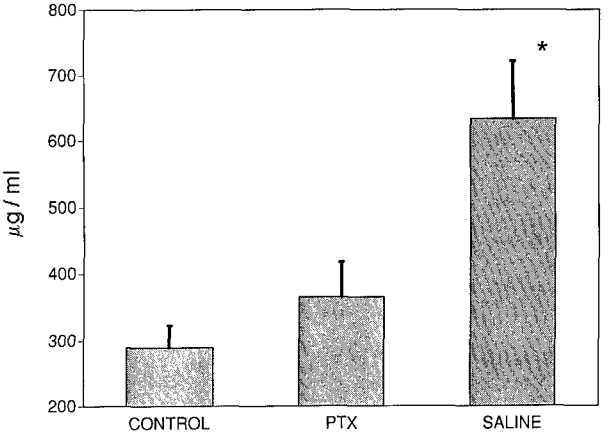

FIG. 6. Total protein content in BAL fluid in Group 1 (SALINE), Group 2 (PTX), and normal controls (CONTROL, $n = 4$). The protein content in Group 1 was significantly greater compared to Group 2 or normal controls ($^*P < 0.05$, ANOVA Tukey).

from Groups 1 and 2 and normal controls. BAL protein content was significantly greater in Group 1 compared to Group 2 or normal controls.

Figure 7 portrays the wet to dry lung weight ratios at 48 hr following smoke exposure. *W/D* in Group 1 was significantly greater than that in normal or Group 2.

The decrease in static lung compliance at 48 hr, compared to the preinjury value, was significantly lower in Group 2 than in Group 1 ($-9.5 \pm 3.4\%$ vs $-32.3 \pm 6.3\%$, $P < 0.05$).

The epithelial damage score at the bronchus level was significantly higher in Group 1 than in Group 2 (2.0 ± 0.2 vs 1.4 ± 0.1, $P < 0.05$). Figure 8 shows the morphologic changes in the two groups at the level of left segmental bronchus by light and electron microscopy.

DISCUSSION

Smoke inhalation injury is initiated by noxious chemicals generated from incomplete combustion of various kinds of materials [26]. These stimulants not only directly injure the exposed airways, but appear to activate chemotactic factors which may result in macrophage activation [27]. Although the precise mechanism has not been clarified, PMNs appear to be modulated by signals from activated macrophages [28]. In a granulocyte-depleted sheep model, smoke inhalation injury was significantly attenuated compared to controls, supporting the role of granulocytes in such injury [29]. Activated polymorphonuclear cells, which demonstrate enhanced adhesiveness to endothelium, superoxide production, and degranulation may cause the progressive airway inflamma-

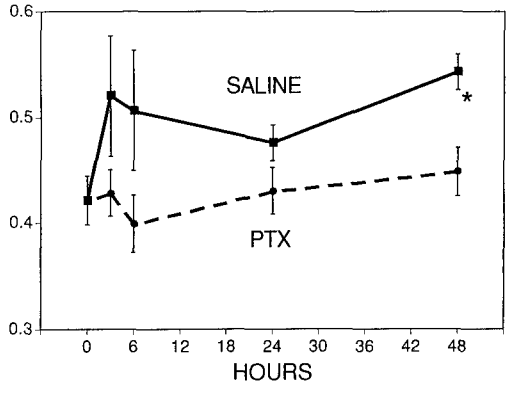

FIG. 5. Serial conjugated diene levels in plasma in two groups following smoke inhalation. The levels are expressed as absorbance at 233 nm. Group 1 (SALINE) is represented by the solid line, Group 2 (PTX) by the dotted line. The elevated cojugated diene levels in Group 1 were attenuated in Group 2, and the difference between the two groups was significant at 48 hr ($^*P < 0.05$, Student's t test at equivalent time).

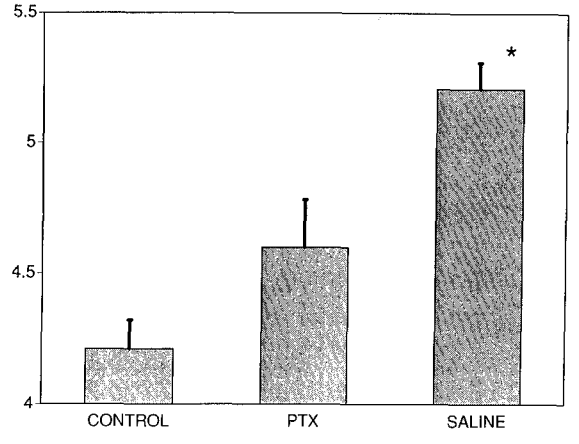

FIG. 7. Wet to dry lung weight ratios in Group 1 (SALINE), Group 2 (PTX), and normal controls (CONTROL, $n = 4$). *W/D* in Group 1 was significantly greater compared to Group 2 or normal controls ($^*P < 0.05$, ANOVA Tukey).

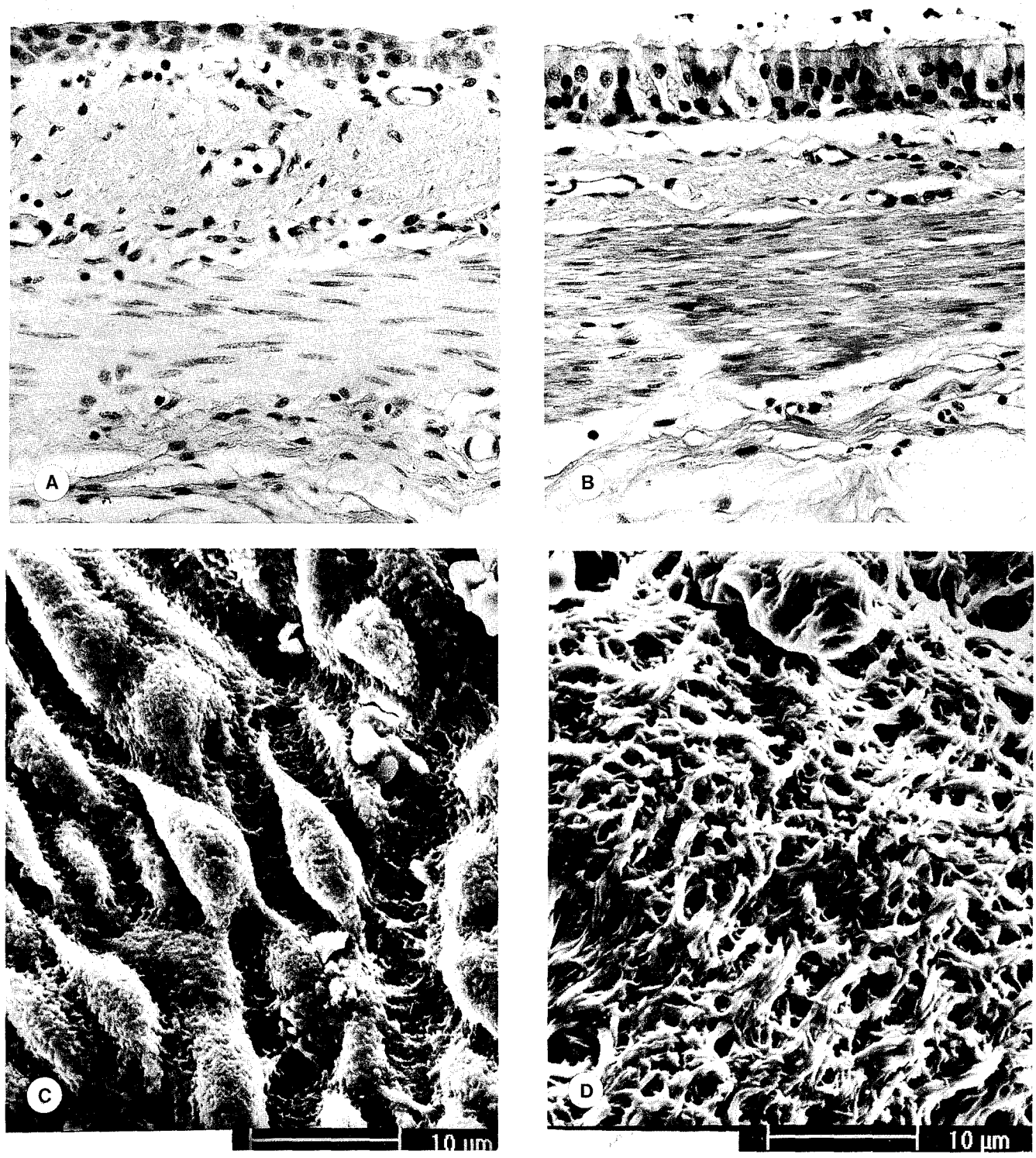

FIG. 8. Morphologic changes in two groups at the level of segmental bronchus. (A) A representative light micrograph (×114) in Group 1 shows a significant loss of cilia and erosion of bronchoepithelial cells. (B) A representative light micrograph (×114) in Group 2 shows preservation of epithelial cells with cilia. (C) A scanning electron micrograph (×1900) in Group 1 shows a complete loss of cilia on the bronchoepithelial surface. (D) A scanning electron micrograph (×1900) in Group 2 shows a preservation of cilia on the epithelial cells although they are matted and distorted.

tion which follows smoke exposure. During this inflammatory process, thromboxane production is increased, leading to platelet aggregation in the lung [30], antiprotease activity is inhibited [31], surface tension in the alveoli is reduced [32], and both pulmonary capillary permeability and hydrostatic pressure are increased [33]. In addition, the denuded cilia and epithelial cells of the injured airway form pseudomembranes consisting of cellular debris, mucus, and leukocytes, which may cause occlusion of small airways [2]. This mechanical obstruction, together with deficient alveolar surface tension and pulmonary edema secondary to increased capillary permeability, can significantly increase shunt and low $\dot{V}_A/\dot{Q}$ area in the lung [34]. Increased $\dot{V}_A/\dot{Q}$ mismatching results in hypoxemia following smoke inhalation. Damage and occlusion of small airways increase the susceptibility to pulmonary infection, enhancing morbidity, and mortality in the later phase of injury [1]. Medical interventions which might attenuate the acute airway inflammatory response have the potential to diminish these deleterious pulmonary changes.

Several studies have been published concerning the effects of anti-inflammatory drugs following smoke exposure in ovine models. Treatment with a platelet activating factor antagonist has been reported to attenuate smoke inhalation injury through modulation of lipid peroxidation [35]. The administration of ibuprofen and the nebulization of DMSO with heparin have been reported to decrease lung lymph flow and antiprotease activity following smoke exposure [36, 37]. Furthermore, the administration of a synthetic antiprotease (gabexane mesilate) has been reported to decrease lung lymph flow and preserve pulmonary function [38].

Pentoxifylline appears to have two major pharmacologic effects. One involves its hemorheologic and antithrombotic effects, which may improve microcirculatory blood flow and tissue oxygenation [17, 18]. The other is its potential inhibitory effect on cytokine release and leukocyte activation, which may attenuate the inflammatory process induced by activated leukocyte/endothelial complex [15–21]. The mechanisms by which pentoxifylline exerts these effects has not been thoroughly delineated. Pentoxifylline, a methylxanthine, inhibits cyclic AMP phosphodiesterase and delays the inactivation of cyclic AMP in cells. Increased intracellular cyclic AMP appears to decrease monokine expression, inhibit PMN adhesion, and depress superoxide production and degranulation of activated PMNs [39]. Increased cyclic AMP has also been reported to decrease vascular permeability and vascular smooth muscle vasoconstriction [40, 41]. Pentoxifylline has also been reported to regulate signal transduction through modulation of cell surface receptors. In *in vitro* studies, pentoxifylline downregulated CD11b/CD18 expression on leukocytes [42]. Pentoxifylline also blunted the increase in intracellular calcium in PMNs stimulated by FMLP, which served to decrease superoxide production [9]. Further, pentoxifylline is reported to decrease the F-actin content of PMNs and lymphocytes, leading to an increased membrane skeleton flexibility [43].

Pentoxifylline has also been reported to inhibit macrophage TNF production and to inhibit the activity of TNF, IL-1, PAF, and GM-CSF on PMNs [8–10, 44]. In addition, pentoxifylline inhibits the function of preactivated PMNs, which themselves synthesize and secrete cytokines [45]. These *in vitro* inhibitory effects of pentoxifylline on cytokine production and activity might attenuate the inflammatory reaction induced by smoke exposure.

In the present study, a continuous infusion of pentoxifylline following smoke exposure exerted significant anti-inflammatory effects. Progressive postexposure hypoxemia was significantly decreased with treatment, a finding consistent with the observed smaller increase in $\dot{V}_A/\dot{Q}$ mismatching. The smaller change in shunt and low $\dot{V}_A/\dot{Q}$ area in the treated animals indicates that treatment preserved airway and alveolar patency. The significant attenuation of airway epithelial damage and interstitial edema with PTX might account for this beneficial effect. The smaller rise in PMN counts and conjugated dienes in the BAL fluid from treated animals compared to the nontreated group suggest a decrease in PMN adhesion and oxidant production in the lung.

The smaller increase in extravascular lung water in pentoxifylline-treated animals may be explained by two mechanisms. The first is a smaller increase in pulmonary microvascular permeability following smoke exposure. In the present study, the decreased total protein in the BAL fluid in treated animals supports this mechanism. Pentoxifylline may inhibit intercellular gap formation in capillary endothelial and pulmonary epithelial cells by increasing cyclic AMP levels. In addition, PTX may decrease the cell membrane damage produced by activated PMNs. Another mechanism that may have contributed to the smaller increase in extravascular lung water is attenuation of pulmonary capillary hypertension following smoke exposure. In this study, both mean pulmonary artery pressure and pulmonary capillary wedge pressure were significantly lower in the treated animals, compared to the nontreated animals; a resultant decrease in pulmonary capillary pressure could result in decreased lung water accumulation. Although the treatment with PTX blunted the increase in pulmonary vascular resistance following smoke inhalation, systemic vascular resistance was not influenced by PTX administration. This is consistent with a previous report in which the vasodilatory effects of pentoxifylline were observed only in vessels which were previously vasoconstricted [46]. The attenuation of the pulmonary vascular response could also be secondary to a decrease in hypoxic pulmonary vasoconstriction; in addition, the hemorheologic effect of PTX might result in a reduction of pulmonary capillary vascular resistance.

During this study, no significant adverse cardiopulmonary effects of pentoxifylline were noted. PTX has been reported to be well tolerated [3]. In one study, a continuous infusion (1.5 mg/kg/hr) for 6 days resulted in no significant adverse effect in ARDS patients [47]. In our study, the significant physiologic advantages associated with pentoxifylline administration appeared during the second 24 hr, indicating a potential superiority of continuous prolonged infusion over short-duration bolus therapy. Continuous infusion has been noted to be more effective when compared to bolus administration in septic animals [21].

The beneficial effects of pentoxifylline therapy following smoke exposure in this study are probably a result of multiple mechanisms. *In vitro,* PTX has been noted to improve PMN chemotactic migration, which may enhance the host defense against bacterial infections [12, 13]. In animal models of peritonitis or septicemia, survival rates were significantly improved with PTX [13, 14]. Although the effects of PTX on the systemic hemodynamic response to injury in the early postburn period have yet to be clarified, these results suggest that PTX treatment may be feasible in thermally injured patients.

In summary, PTX significantly improved $\dot{V}_A/\dot{Q}$ mismatching in this ovine model of smoke inhalation injury. These effects appear to be the result of a decrease in airway damage and pulmonary edema. The improvement in pulmonary function following PTX treatment suggests that this agent may be useful in the management of smoke inhalation injury.

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