A Dose-responsive Model of Smoke Inhalation Injury
Severity-related Alteration in Cardiopulmonary Function

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The dose responsiveness of selected physiologic indices was studied in a sheep model of smoke inhalation injury. In this model, graded severity of injury was achieved by changing the contact time with smoke (defined by "unit"), whereas other variables were kept constant. Blood gas and cardiopulmonary indices were measured in 70 sheep, including 12 controls, either 24 or 72 hours after exposure to 3, 6, 9, 12, 15, or 18 units of smoke. A 12-unit dose of smoke was fatal within 72 hours and an 18-unit dose was fatal within 24 hours. The best correlation between smoke dose and response was observed in arterial oxygen tension 24 hours after exposure. At 24 hours, most of the cardiopulmonary indices showed significant change only after a 12-unit exposure. Although the exact shape of the dose-response curve could not be defined, sigmoid or curved linear shape was suggested, reflecting the progressive deterioration.

Smoke Inhalation Injury is one of the primary determinants of survival after major burns. The significance of pulmonary injury due to smoke inhalation in burn patients was not widely realized until the 1970s, although antecedent work by Phillips had indicated the likelihood that such injury was of consequence. In recent years early diagnosis of smoke inhalation and evaluation of its severity have achieved wide clinical interest, but even now the pathophysiologic mechanisms of the injury are not clear. Although several animal models have been developed to study such mechanisms, they have either been small animal models or failed to permit control of severity. We have developed a sheep model of smoke inhalation injury that is reproducible and dose-responsive.

Sheep are large enough to allow detailed physiologic monitoring and frequent blood sampling. A technique for lung lymph cannulation has also been established for sheep. In this model, dose responsiveness was assessed by changing the duration of smoke exposure to the lung while keeping other factors that influence severity unchanged. The severity of smoke inhalation injury is related to smoke temperature, chemical and physical composition of the smoke (gas, vapor, and particle), contact time (time exposed to smoke), and contact area (depth of breath). In the current system, the smoke was equilibrated at ambient temperature to exclude all possibility of thermal injury to the airway. The animals were exposed to a volume of smoke proportional to their body weight. The severity of injury in a spontaneously breathing animal is also influenced by hyperventilation in response to the carbon monoxide content of the smoke. Spontaneously breathing animals with elongated nasal passages, with epiglottic closure, or with early bronchospasm may show further variability in severity of injury. In this work, smoke exposure was done under general anesthesia using endotracheal intubation to avoid changes in the depth of breath that affect contact area. With respect to smoke...
history of smoke inhalation injury. Twenty-four or 72 hours after smoke inhalation, the sheep were reanesthe-
tized, intubated, and catheterized for the measurement of pulmonary arterial and systemic arterial pressures. After a 2-hour stabilization period, cardiopulmonary indi-
ces were measured under anesthesia, using mechanical ventilation, a state that corresponds to the situation in patients in an intensive care unit setting.

This report describes the dose dependence of alter-
ations in cardiopulmonary function after smoke inhalation.

Materials and Methods

Animals

One- to two-year-old neutered male, commercially available, random source sheep weighing 30.8 ± 4.3 kg (mean ± SD) were used in this study. The animals were housed in covered outdoor runs, treated for parasites, and fed commercial chow and water ad libitum. Baseline complete blood counts, total proteins, and blood chemistries were done 3 weeks before experimental use. The animals were fasted for 24 hours before smoke exposure and experimental use. Twelve sheep were used as controls and 58 were exposed to smoke; 41 sheep were studied 24 hours after smoke exposure and 17 sheep were studied 72 hours after exposure. Immediately after smoke inhalation, the sheep were housed in climate-controlled facilities at 74-76 F (24-25 C) and a relative humidity of 40-50%.

Smoke Generation and Exposure

Smoke was produced by burning 10 disposable under-
pads (45 × 52.5 cm, 40 g each, Hosposable, Inc., Bound Brook, NJ) made of polyethylene, wood pulp, and nonwoven cellulose fabric. The smoke generator was a 32-gallon metal container equipped with an air inlet, a dampered chimney, a window, and smoke outlet (Fig. 1). The smoke passed through a copper pipe (30 × 1.6 cm) into a volume-adjustable metal syringe, which permitted insufflation of either smoke or air. The smoke reached ambient temperature during passage through the pipe and delivery system and contained 10-14% oxygen, 3-8% carbon dioxide, 0.7-2.2% carbon monoxide, and other combustion products (methane, ethylene, propylene, and acetaldehyde), but no cyanide.

The experimental sheep were individually exposed to 3, 6, 9, 12, 15, or 18 units of smoke. One unit of smoke consisted of three successive exposures to smoke with a tidal volume of 30 mL/kg and breath hold of 5 seconds followed by 10 successive ventilations with room air (Fig. 2). The time required per unit was about 50 seconds. Before smoke insufflation, the sheep were intubated, anesthetized with methohexital sodium (9 mg/kg,
Brevital® Sodium, Eli Lilly and Company, Indianapolis, IN) and paralyzed with succinylcholine chloride (0.7 mg/kg). The sheep were extubated after smoke inhalation. Of the 41 sheep studied 24 hours after smoke exposure, six sheep were exposed to 3 units of smoke, eight sheep to 6 units, nine sheep to 9 units, seven sheep to 12 units, seven sheep to 15 units, and four sheep to 18 units. For the 72-hour studies, seven, six, and four sheep were exposed to 6, 9, and 12 units of smoke, respectively.

Monitoring

Sheep were studied 24 or 72 hours after smoke inhalation. On the day of measurement, arterial and central venous lines, a Swan-Ganz catheter (7F, American Edwards Laboratories, Irvine, CA), a lung water catheter (American Edwards Laboratories), and an esophageal balloon were inserted after general anesthesia and intubation. Anesthesia was induced with methohexital sodium (9 mg/kg) and maintained with alpha-chloralose (0.05 g/kg, Calbiochem®, La Jolla, CA) and the sheep were paralyzed with pancuronium bromide (0.03-0.04 mg/kg, Pavulon®, Organon Pharmaceuticals, West Orange, NJ). After the placement of catheters, the animals were positioned prone and artificially ventilated. A volume-limited ventilator (Bear 2TM, Bear Medical Systems, Inc., Riverside, CA) with a tidal volume of 15 mL/kg was used at a respiratory rate of 12 per minute. Sigh ventilation with a tidal volume of 21 mL/kg was applied every 3 minutes to prevent atelectasis. Lactated Ringer’s solution was continuously infused at a rate of 1 mL/kg per hour.

Central venous pressure and pulmonary artery pressure (PAP) were monitored with Statham P23Db transducers (Statham Instruments, Oxnard, CA) and systemic arterial pressure was monitored with a Hewlett-Packard 1290A quartz transducer (Hewlett-Packard Company, Waltham, MA). These pressures were recorded on a Hewlett-Packard four-channel recorder (Model 7754A). Respiratory indices were monitored with a pneumotachograph (Model 17212, Gould, Inc., The Netherlands) for flow rate and tidal volume and a differential transducer (MP-451, Validine Engineering Corporation, Northridge, CA) for transpulmonary pressure, with the pulmonary variables recorded on another Hewlett-Packard four-channel recorder (Model 7754A). Cardiac output was measured in triplicate by thermodilution technique (cardiac output computer, Model 9520A, American Edwards Laboratories) and lung water was measured by thermal-dye double indicator-dilution method (lung water computer, Model 9310, American Edwards Company). Blood gas analysis was performed using an IL 1303 pH/blood gas analyzer and an IL 282 CO-Oximeter (Instrumentation Laboratories, Inc., Lexington, MA). Cardiopulmonary indices and blood gas levels were measured every 30 minutes, and the values measured after 2 hours of stabilization were taken as representative values.

 Necropsies were performed on all sheep dying spontaneously or sacrificed at the end of the experiments. A complete set of tissues was fixed in 10% neutral buffered formalin and processed by standard methods. The locations of the tissue sample collection sites were midtrachea, tracheal bifurcation, right and left proximal and distal bronchi, apical and diaphragmatic lobes, and any other morphologically significant foci.

Data are displayed as mean ± SE. Regression analysis by least-square technique was used to examine the linear relationship between physiologic variables and the number of units of smoke. Linear regression analyses included the control sheep unless otherwise indicated. Survival rate was analyzed by stepwise logistic regression. Multiple comparisons were done by one-way analysis of variance (Tukey student’s range method and the Student-Newman-Keuls multiple range test). Differences were considered significant at p < 0.05.17

Results

Sheep resumed spontaneous breathing soon after smoke exposure, and breathing was supported by an ambu-bag until they were extubated. The sheep usually started walking within 10 minutes after smoke exposure. Sheep exposed to smoke showed symptoms such as coughing, wheezing, and frothing beginning 4–6 hours after smoke exposure. All sheep in which physiologic measurements were made could breathe spontaneously and stand unassisted, although sheep exposed to 12 units or more showed distinct respiratory distress.

Sloughing of the airway epithelium occurred consistently in sheep exposed to smoke (Fig. 3). This pseudo-membrane formation was typically seen in major airways and became progressively thicker in sheep exposed to higher doses of smoke. At autopsy, almost complete occlusion of the trachea was seen in sheep that died spontaneously 12 or more hours after exposure. Histologic changes of the airways included disruption, swelling, and loss of cilia (Fig. 4A). Increased numbers of inflammatory cells were common in the laminae propriae, respiratory mucosae, and airway lumina. Surface accumulation of mucocellular debris, often with obstruction, was associated with parenchymal congestion, edema, and atelectasis (Fig. 4B). These parenchymal changes were most prominent in the dependent areas of the lung.

Mortality at 24 and 72 hours is shown in Figure 5. Six units or less of smoke was not fatal by 72 hours, but 12-unit doses were fatal by 72 hours. Therefore, 15- or
18-unit smoke exposures were not studied for survival or physiologic response at 72 hours. Eighteen-unit doses were fatal by 24 hours; one of the four sheep receiving an 18-unit dose died within 1 hour after exposure and three others died between 5 and 15 hours after exposure. Mortality at 24 hours was well predicted by the logistic model (mortality = exp(y)/(1 + exp(y)), where y = 0.535x − 7.865 and x = number of smoke dose units). According to this equation, the best logistic regression estimation of LD$_{50}$ at 24 hours was 14.7 units of smoke. Data were insufficient for statistical analysis at 72 hours.

Carboxyhemoglobin levels immediately after smoke exposure are shown in Figure 6. Even 3 units of smoke raised the carboxyhemoglobin level over 40%. Eighteen units of smoke elevated the mean blood carboxyhemoglobin level to 85.4 ± 2.6%.

The arterial oxygen tension (PaO$_2$) of each group is shown in Figure 7. Control sheep had an average PaO$_2$ of 88.9 ± 1.2 torr (N = 12, electrode at 37 C). Sheep exposed to 9 units or more had significantly lower PaO$_2$ than the controls at both 24 and 72 hours after smoke exposure. At 24 hours after smoke inhalation, PaO$_2$ (y = torr) was negatively related to the number of units of smoke exposure (x = units): y = 90.0 − 3.24x (r$^2$ = 0.646, N = 44, p < 0.01). The data were insufficient for statistical analysis at 72 hours.

At 24 hours, none of the sheep exposed to 9 units or less of smoke showed significant depression of plasma
The data for mortality and CO-Hb are presented in Table 1. Some of the sheep exposed to 9 units or more had elevated plasma PaCO₂ at 24 hours, but this was not a consistent finding (Table 1). At 72 hours, surviving sheep exhibited no acidosis, but one had hypercapnea (PaCO₂ = 42 torr).

Mean blood pressure (mBP, \( y = \text{torr} \)) also showed dose responsiveness (Fig. 8) between 3 and 15 units of smoke (\( x = \text{smoke units} \)) at 24 hours: \( y = 136.0 - 3.55x \) \( (r^2 = 0.439, \ N = 32, \ p < 0.01) \). Sheep exposed to 3 units of smoke showed highly elevated blood pressure and those exposed to 12 units or more had significantly lower blood pressure than others. The data at 72 hours were not sufficient for such analysis. Sheep exposed to 12 units or more also showed significantly increased PAP at 24 hours (Table 1).

Cardiac index (CI) was higher in the 3-unit and 6-unit groups than in controls at 24 hours, but the difference was not statistically significant (Table 1). At 9- and 12-unit doses, CI decreased progressively, but the CI of the 15-unit group did not differ significantly from control. A significant difference of CI was seen only between the 6-unit and 12-unit dose groups at 24 hours.

Lung static compliance changes were the reciprocal of pulmonary resistance (PR) was significantly elevated at 24 hours in sheep exposed to 9 units or more and at 72 hours in sheep exposed to 9 units of smoke (Fig. 9). Lungs showed higher after temperature correction for their body temperature (39.5-40.0°C).
TABLE 1. Other Cardiopulmonary Indices in Each Group (Mean ± SE)

<table>
<thead>
<tr>
<th>Smoke (units)</th>
<th>Control</th>
<th>24 Hours after Exposure</th>
<th>72 Hours after Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of sheep</td>
<td>12</td>
<td>6 8 9 12 15 18</td>
<td>6 9 12</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.49</td>
<td>7.50 7.52 7.49 7.35 7.46</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>0.02</td>
<td>0.01 0.02 0.02 0.05 0.05</td>
<td>—</td>
</tr>
<tr>
<td>PaCO₂ (torr)*</td>
<td>30.3</td>
<td>30.2 29.1 30.0 40.0 36.8</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td>0.3 0.9 1.4 3.2 1.9</td>
<td>—</td>
</tr>
<tr>
<td>mPAP (torr)</td>
<td>9.3</td>
<td>12.0 10.3 14.7 19.1 20.5</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>1.1</td>
<td>1.7 1.4 2.1 2.1 1.4</td>
<td>—</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>3.4</td>
<td>3.7 4.2 3.7 2.9 3.2</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0.2 0.2 0.3 0.4 0.2</td>
<td>—</td>
</tr>
<tr>
<td>LVSWI</td>
<td>33.3</td>
<td>41.2 35.0 32.3 17.8 31.1</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>3.4</td>
<td>3.3 1.8 2.5 2.7 2.9</td>
<td>—</td>
</tr>
<tr>
<td>TPRI</td>
<td>2627</td>
<td>2704 2110 2516 2519 2515</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>145</td>
<td>163 98 248 375 376</td>
<td>—</td>
</tr>
<tr>
<td>EVLWV (ml/kg)</td>
<td>9.2</td>
<td>12.6 11.4 12.3 18.0 13.4</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>1.1 0.5 1.3 1.5 1.8</td>
<td>—</td>
</tr>
</tbody>
</table>

* PaCO₂ values are direct readings from the electrode set at 37 C. mPAP = mean pulmonary artery pressure; LVSWI = left ventricular stroke work index (g-m/m²); CI = cardiac index; TPRI = total peripheral resistance index (dynes sec/cm²); EVLWV = extravascular lung water volume.

Discussion

In this model, anesthetized sheep were insufflated with smoke, using endotracheal intubation, to inflict a consistent reproducible injury to the lung. After smoke exposure, the sheep were extubated and allowed to breathe spontaneously. Twenty-four or 72 hours after smoke inhalation, the sheep were reanesthetized, intubated, and catheterized for physiologic evaluation. After a 2-hour stabilization period, cardiopulmonary indices were measured under general anesthesia and mechanical ventilation. We used alpha-chloralose as the anesthetic agent because this agent exerts only minimal effects on cardiopulmonary function.18 We returned the sheep to the prone position as soon as the catheters were placed to avoid any adverse effects of the supine position. Prolonged supine positioning causes congestion in the lung, frothing, and cyanosis.19 Sigh ventilation was used to prevent atelectasis, which is likely to develop in sheep, even in the prone position. In exposing the sheep to smoke, a tidal volume of 30 mL/kg was used. This tidal volume did not present a problem for the 24-40-kg sheep used in this study, but such a volume-to-weight ratio might produce hyperinflation of the alveoli in larger sheep.

To understand the significance and limits of the results of this study, several physiologic characteristics of sheep need be pointed out. In sheep, a major difference from humans is seen in the erythrocytes. Sheep not only have low Na-K pump activity, but also have relatively lower blood hemoglobin concentrations, higher P-50...
values, lower 2,3-DPG levels, and a higher body temperature. These differences must be taken into account when analyzing and comparing hemodynamics and oxygen transport in sheep and humans. For example, actual PaO₂ at the sheep's body temperature (39.5–40°C) is usually 7–12 torr higher than the values obtained from blood gas analyzers with the electrode set at 37°C. Sheep also have very low plasma cholinesterase activity. Interestingly, succinylcholine chloride did not have a prolonged effect in the study sheep.

Stephenson et al. have suggested that the severity of smoke inhalation injury is dose-related, but physiologic measurements of dose responsiveness have not been made except for a mortality study in rats. The sheep model of smoke inhalation injury used in these studies is reproducible and manifests dose responsiveness of hemodynamic and pulmonary variables that are most distinct at 24 hours. The lesser number of sheep studied at 72 hours and the narrower range of smoke doses used in the sheep studied at 72 hours may account for the poorer correlations noted at that time.

Mortality at 24 hours was well approximated by the logistic model (mortality = \exp(y)/(1 + \exp(y)), where y = 0.535x - 7.865 and x = number of smoke dose by units). This logistic model predicts mortality of 0.19% and 0.94% for 3 and 6 units of smoke exposure, respectively. Although all sheep given those doses of smoke were sacrificed after physiologic measurements at 24 or 72 hours, the clinical condition of all sheep was consistent with recovery from the inhalation injury and survival. In the sheep exposed to 6 units of smoke, none of the physiologic variables measured at 72 hours showed further deterioration from values measured at 24 hours after smoke exposure. Histologically, tracheal epithelium examined 72 hours after 6 units of smoke exposure showed metaplasia, suggesting early healing. These physiologic and histologic findings suggest that damage from 6 units of smoke is reversible. On the other hand, a 9-unit or greater dose of smoke caused progressive changes resulting in much higher mortality and further deterioration in lung function by 72 hours after exposure. Histologic changes in those sheep were also progressive; the airway epithelium showed further deterioration and congestion and atelectasis of the lung were more severe at 72 hours. The parenchymal changes were most distinct in dependent areas of the lung. This accumulation of occlusive exudate in dependent airways is probably related both to the effect of gravity and to the loss of effective normal elimination of exudate by ciliary action and coughing.

The dose-response patterns of selected physiologic indices were analyzed using the data at 24 hours after smoke exposure. Four patterns were observed (Fig. 11): (1) No apparent smoke dose effect, as exemplified by
DOSE OF SMOKE

C 3 6 9 12 15

1) TPRI

2) pH

3) LVSWI

4) PaO₂

Fig. 11. Four patterns of response in physiologic indices at 24 hours after smoke exposure. Multiple comparisons by the Student-Newman-Keuls multiple range method are described by the underlining method. Groups underlined by the same line are not distinguishable from one another. Typical examples of the four patterns are shown. (1) No apparent smoke dose effect. (2) An apparent threshold effect. (3) A linear relationship ($0.20 < r^2 < 0.40$) over at least a portion of the smoke dosage range. (4) A good linear relationship ($r^2 > 0.40$) over the entire range of doses of smoke. See text for details.

< $r^2 < 0.40$) over at least a portion of the smoke dosage range: PaCO₂, PR, static compliance, lung water, LVSWI, and CI, where LVSWI = between 3 and 15 units and CI = between 6 and 15 units. (4) A good linear relationship ($r^2 > 0.40$) over the entire range of doses of smoke: PaO₂ ($r^2 = 0.646$), mBP ($r^2 = 0.439$), and mPAP ($r^2 = 0.407$), where mBP = between 3 and 15 units.

TPRI was maintained within the normal range in all surviving sheep, suggesting that the TPRI is well protected by homeostatic mechanisms and is not an index of the severity of inhalation injury. Indices showing threshold changes (pH, PVRI, and RVSWI) also appear to be well maintained until a severe insult is incurred. Changes in these indices are indicative of a significant smoke inhalation injury. Once a threshold level was exceeded, no significant further change in these physiologic indices was noted in the 15-unit group compared with the 12-unit group. Indices that manifested the third or fourth patterns showed moderate to good correlation between the number of units of smoke and magnitude of change.

For some variables, a significant difference from the control level was not seen (CI) nor was observed only

after exposure to 12 units of smoke (PaCO₂, LVSWI, PR, static compliance, lung water, mBP, and PAP) when assessed by analysis of variance. PaO₂ showed the highest correlation coefficient ($r^2 = 0.646$), but a significant difference from the control level was observed only in groups exposed to 9 units of smoke or more. The dose-response curve of PaO₂ (Fig. 7) and the fact that changes of most of the cardiopulmonary indices became significant only after 12-unit exposure suggest that the dose-response curve is sigmoid in shape rather than linear, and that the steep portion of the curve is located between 9 and 12 smoke units (Fig. 12). The steep portion of the curve might also be approximated by curved linear (polynomial) functions, reflecting the progressive nature of such injury. Stephenson et al. pointed out that, by inference from the literature, there is no variable to reliably predict lung injury due to smoke inhalation. That failure may be related to the sigmoid nature of the dose-response curve suggested by this study. To describe the sigmoid curve precisely, it will be necessary to assess the physiologic response over a wide range of inhalation injury severity. Several of the indices examined in this

Fig. 12. Schematic presentation of dose-response curve of sigmoid nature and grading of smoke inhalation injury. Ordinate represents physiologic indices and abscissa shows doses of smoke in units. Statistical significance is not detectable at doses below 9 units. Substantial change occurs between 9 and 12 units. The plateau on the right side (shown as an interrupted line) is not clearly observed because those higher doses are fatal. The bars indicate the grading of smoke inhalation injury. See text for details.
logic indices remained normal. In some animals with
combination, mortality was 100% within 24 hours. In
many animals, the severity of smoke inhalation
sequence was evident and when present was minimal. Diagnosis
injury of this degree would be difficult without histologic examination at an appropriate
time. Moderate injury was associated with a mortality of
30% by 72 hours. Pseudomembrane formation in the
major airways was always evident but many physiologic
indices still did not change significantly. Severe inhalation
injury caused 10–14% mortality by 24 hours and
30–100% mortality by 72 hours. A thick pseudomembrane
formed in the airways and physiologic indices showed
significant changes. The variability of changes noted in
the various indices may be attributable to the sigmoid shape of the dose-response curve. Invariably,
fatal injury caused total loss of airway epithelium and
100% mortality. Although this grading is based on an
experimental model of smoke inhalation without cuta-
neous burns, a similar grading for smoke inhalation in
burn patients may be useful in evaluating the severity of
smoke inhalation and assessing treatment outcome.
This dose-responsive sheep model can now be used to
determine the pathogenesis of inhalation injury, to as-
assess the effect of associated burn injury, and to evaluate
the effectiveness of therapeutic interventions.

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References

1. Moylan JA Jr. Inhalation injury—a primary determinant of sur-

vival following major burns. JBCR 1981; 2:78–84.
2. DiVincenti FC, Pruitt BA Jr, Reckler JM. Inhalation injuries. J


176:477–484.
4. Phillips AW, Cope O. Burn therapy: III. Beware the facial burn! Ann

5. Potkin RT, Robinson NB, Hudson LD, et al. An animal model of


natural history of inhalation injury in fire victims: a correlation

110.
7. Thomas WC Jr, O’Flaherty EJ. A system for exposing animals to

smoke generated in a steady-state fashion. Environmental Re-

8. Dresler DP, Skornick WA, Kupersmith S. Corticosteroid treat-

183:46–52.
9. Walker HL, McLeod CG Jr, McManus WF. Experimental inha-


181.
11. Herndon DN, Tubber DL, Niehaus GD, et al. The pathophysi-

ology of smoke inhalation injury in a sheep model. J Trauma
1984; 24:1044–1051.