Wood Smoke Inhalation Causes Alveolar Instability in a Dose-Dependent Fashion

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BACKGROUND: Wood smoke inhalation causes severe ventilation and oxygenation abnormalities. We hypothesized that smoke inhalation would cause lung injury by 2 mechanisms: (1) direct tissue injury by the toxic chemicals in the smoke and (2) a mechanical shear-stress injury caused by alveolar instability (ie, alveolar recruitment/derecruitment). We further postulated that alveolar instability would increase with the size of the cumulative smoke dose. METHODS: Anesthetized pigs were ventilated and instrumented for hemodynamic and blood-gas measurements. After baseline readings, the pigs were exposed to 5 separate doses of wood smoke, each dose lasting 1 min. Factors studied included hemodynamics, pulmonary variables, and in vivo photomicroscopy of alveolar mechanics (ie, the dynamic change in alveolar size with ventilation). RESULTS: Smoke inhalation significantly increased alveolar instability with 4 min and 5 min of smoke exposure. Significant rises in carboxyhemoglobin levels and in pulmonary shunt were also observed at 4 min and 5 min of smoke exposure. Lung histology demonstrated severe damage characteristic of acute lung injury. CONCLUSIONS: We demonstrated that wood smoke inhalation causes alveolar instability and that instability increases with each dose of smoke. These data suggest that smoke inhalation may cause a "2-hit" insult: the "first hit" being a direct toxic injury and the "second hit" being a shear-stress injury secondary to alveolar instability. *Key words: smoke inhalation injury, alveoli, microscopy, dose response.* [Respir Care 2005;50(8):1062–1070. © 2005 Daedalus Enterprises]

Introduction

Patients who suffer severe smoke inhalation during a structure fire can develop serious pulmonary lesions that may progress into acute respiratory distress syndrome (ARDS).[1] Currently, the treatment for ARDS is only supportive, in the form of mechanical ventilation and general critical care.[2] However, if mechanical ventilation is improperly used, it can cause ventilator-induced lung injury (VILI) that exacerbates the primary injury and significantly increases mortality in ARDS patients.[3] It is postulated that there are 3 basic mechanisms of VILI: volutrauma, atelectrauma, and biotrauma.[4] Surfactant deactivation is central to the pathogenesis of ARDS and can cause a heterogeneous injury, resulting in areas of atelectatic and noncompliant lung directly adjacent to healthy areas of lung. Volutrauma is caused when healthy areas of lung are overstretched because of the high airway pressure needed to ventilate noncompliant ARDS lungs. Loss of surfactant function causes alveoli to become unstable and to recruit and derecruit with each breath.[5] Alveolar recruitment/derecruitment results in a shear-stress induced injury known as atelectrauma.[6] Both volutrauma and atelectrauma cause mechanical injury to the lung, resulting in release of inflammatory cytokine and chemokines.[7] These inflammatory mediators cause recruitment of neutrophils that release toxic oxygen radicals and proteases that cause further lung injury, called biotrauma.

Since surfactant deactivation is a primary component in ARDS pathophysiology and is also a key factor in the subsequent VILI, any type of lung injury that directly deactivates surfactant would render the lung susceptible

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to VILI. It has been shown that wood smoke is a very potent surfactant deactivator.[8,9] In this study we hypothesized that the known effect of wood smoke on the deactivation of pulmonary surfactant would cause alveolar instability (ie, alveolar recruitment/derecruitment). We further postulated that the increase in alveolar instability would directly correlate with increases in the cumulative dose of smoke inhalations.

Methods

Surgical Preparation

Three Yorkshire female pigs (Keystone Farms, Romulus, New York) weighing 23–30 kg were anesthetized with 30 mg/kg of sodium pentobarbital, intubated with a cuffed endotracheal tube (ETT), and ventilated with 100% oxygen, using a volume-cycled ventilator (Harvard Medical Supplies, Reno, Nevada) and 5 cm H_2O of positive end-expiratory pressure (PEEP). The initial tidal volume was set at 15 mL/kg, and the respiratory rate was 15 breaths/min. The left femoral artery and vein were cannulated with lengths of 2-mm inner diameter polyethylene tubing for drug administration, blood-gas sampling, and arterial pressure measurement. All pressures, cardiac output, arterial and mixed venous blood gas samples (model ABL2, Radiometer, Westlake, Ohio) and carboxyhemoglobin concentration and oxyhemoglobin saturations (model OSM2, Radiometer, Westlake, Ohio) were recorded at baseline and immediately following each smoke dose.

Hemodynamics

A 7 French flow-directed Swan Ganz thermodilution catheter was passed through the external jugular vein into the pulmonary artery for pulmonary arterial pressure, pulmonary artery wedge pressure, mixed venous blood sampling, and cardiac output determinations (Baxter Explorer, Medford, Massachusetts). All pressures, including central venous pressure and mean arterial pressure, were measured using disposable transducers (model 049-992-000A, Argon Medical, Princeton, New Jersey) leveled at the heart and recorded on an 8-channel recorder (7754A, Hewlett Packard, Palo Alto, California).

Pulmonary Variables

Peak airway pressure and PEEP were measured from a side port 10 cm from the end of the tracheal tube. Static pulmonary compliance was measured by disconnecting the ventilator and injecting twice the tidal volume into the lung with a Collins 1-L syringe and held until pressure became constant (plateau airway pressure, which was recorded and used to calculate static pulmonary compliance,

calculated as the injected volume divided by the plateau airway pressure). The respiratory rate was adjusted to maintain a P_{aCO_2} between 35 and 45 cm H_2O. Pulmonary shunt ($\dot{Q}s/\dot{Q}t$) was calculated utilizing the equation

$$\dot{Q}s/\dot{Q}t = (C_{cO_2} - C_{aO_2})/(C_{cO_2} - C_{\bar{v}O_2})$$

where C_{aO_2} is the oxygen content of arterial blood, C_{cO_2} is the oxygen content of the capillary blood, and $C_{\bar{v}O_2}$ is the oxygen content of the mixed venous blood.

In Vivo Microscopy

A left thoracotomy was performed for access of the in vivo microscope to the lung surface, and the exposed lung surface was kept moist with saline. In order to minimize evaporative water loss, a single layer of plastic was placed on the exposed lung. In vivo videomicroscopy was performed at baseline and again at the time of smoke exposure. The in vivo microscope technique has been described in detail elsewhere.[10] Briefly, the microscope (M50, Wild Heerbrugg, Switzerland) and halogen light source (15Y and 150W, Bellaphot) focused on a ring-mounted coverslip that was lowered onto the pleural surface of the lung. Fields of the pleural surface were filmed with the in vivo microscope at baseline and again after each smoke exposure. The field was viewed with a video camera (CCD SSC-S20, Sony, Tokyo, Japan) and recorded (VO-9500 MD recorder, Sony, Taiwan). Subpleural alveoli were analyzed with a computerized image-analysis software package (Image Pro, Media Cybernetics, Carlsbad, California) and alveolar areas were calculated.

Alveolar Mechanics

We analyzed the dynamic change in alveolar size during ventilation. Still images of alveoli were captured from the video at peak inspiration and end expiration, and alveolar area at both peak inspiration and end expiration were measured by computer analysis. Alveolar area measurements were made by tracing the outer walls of individual alveoli at both peak inspiration and end expiration by a blinded observer. The change in alveolar size during tidal ventilation was used to assess the degree of alveolar instability and was measured by subtracting the alveolar area at end expiration (E) from that at peak inspiration (I) and calculating an alveolar stability index (I-EΔ), with an increase in I-EΔ demonstrating an increased alveolar instability. The number of alveoli visualized per microscopic field (range 3–20) varied with the degree of microatelectasis.

Histology

The right middle lobe was removed and 6 tissue cubes (2 cm per side) were fixed for a minimum of 2 days in
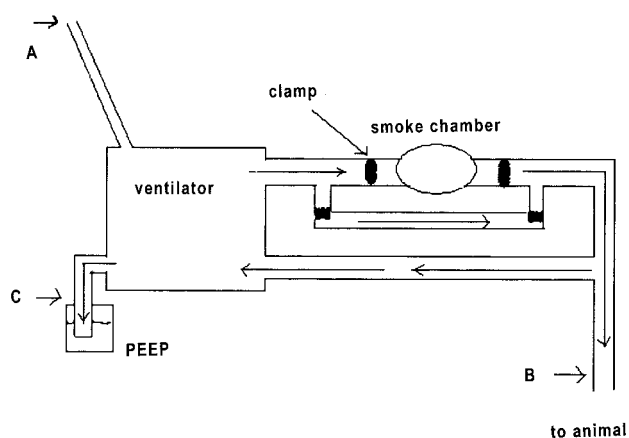
Fig. 1. Diagram of physical set-up. Room air enters the ventilator at A and is selectively channeled through or around the smoke chamber. By cutting off the appropriate channels with tubing clamps, air passes through the appropriate channel. Airway pressure is measured at B. The end-expiratory pressure is varied by placing the expiratory line C under different levels of water.

10% buffered formalin. Subsequently, one block from each animal was processed for routine paraffin histology and stained with standard hematoxylin and eosin. Qualitative assessment of the tissues was carried out on high-resolution photomicrographs obtained at random locations throughout each preparation.

Protocol

Following baseline measurements, the pigs were exposed to 5 individual doses of wood smoke, each dose lasting 1 min. The 1-min doses were of the same intensity, but the time in between each smoke exposure ranged from 15 min to 30 min. The method of smoke delivery is described in detail elsewhere.[10] Briefly, a standard mixture of sawdust (124 g of fir plywood) and kerosene (50 mL) was burned to generate the smoke. Nine grams of the mixture was placed in a burning chamber and ignited for each episode of smoke exposure. The burning chamber was a metal cylinder without weld, with an inner sleeve of copper screen. The chamber was placed in series with the ventilator and ETT and parallel to a bypass line (Fig. 1). After the sawdust was ignited, the chamber was connected to a vacuum line so as to draw air through the burning mixture until combustion was brisk and uniform before smoke was released to the animal. The duration of the smoke exposure was controlled by clamping the tube connecting the smoke chamber to the inspiratory line. The total exposure time for each dose of smoke was 1 min. After smoke exposure the animals were again ventilated with room air at the original ventilator settings. The length of the tubing from the smoke source to the ETT was 52 cm; this distance was such that the temperature of the

inspired smoke averaged 37°C at the ETT.[10] Brown, tar-like deposit slowly collected in this tubing. At the end of the experiment, the animal was sacrificed with an infusion of sodium pentobarbital (6 g/4.54 kg body weight) given via the peripheral vein.

Vertebrate Animals

The above experiments were performed in accordance with National Institute of Health guidelines for the ethical use of animals in research. The protocol was approved by the Committee for the Humane Use of Animals at our institution.

Statistics

All values expressed are mean $\pm$ SD. Significant differences between each smoke exposure were determined by analysis of variance. Whenever the F ratio indicated significance, a post hoc Tukey's Honest Significant Difference test was performed. Significance is reported if the probability of the null hypothesis being true was less than 5% ($p < 0.05$).

Results

Hemodynamics

Hemodynamic results are found in Table 1. With increasing smoke exposure, cardiac output was mildly depressed, while mean arterial pressure, pulmonary arterial pressure, and central venous pressure decreased, although these changes were not statistically significant.

Pulmonary Variables

The pulmonary physiological data are reported in Table 2. Peak airway pressures increased and static compliance decreased after 5 min of smoke exposure, but these changes were not significant. As smoke exposure increased, both P_{aO_2} and base excess progressively decreased, although this change was not significant. Acidemia occurred after 5 min of smoke exposure. Significant rises in carboxyhemoglobin levels were observed at 4 min and 5 min of smoke exposure (Fig. 2). There was a significant increase in pulmonary shunt 4 min and 5 min after smoke exposure, as compared to baseline (Fig. 3).

Alveolar Mechanics

The images of alveoli extracted from the video film at peak inspiration and end expiration expressed alveolar stability. Stability was expressed by the change in alveolar area between inspiration and expiration (I-EΔ). Alveoli at baseline (pre-smoke) were stable, with minimal change in

Table 1.   Hemodynamic Variables*

Variable	Baseline	Smoke Exposure (min)				
		1	2	3	4	5
Cardiac output (L/min)	6.1 ± 2.4	7.0 ± 3.4	6.5 ± 2.4	5.8 ± 2.9	5.5 ± 2.0	4.7 ± 1.2
Mean arterial pressure (cm H_2O)	99.7 ± 14.1	87.3 ± 8.8	92.7 ± 13.3	82.7 ± 14.8	83 ± 6.0	83 ± 8.7
Pulmonary artery pressure (cm H_2O)	29 ± 7.7	26 ± 3.4	25.7 ± 2.6	24.3 ± 2.2	23.3 ± 3.9	25 ± 3.4
Pulmonary artery wedge pressure (cm H_2O)	9 ± 1.7	8 ± 1.0	7.3 ± 2.6	8.3 ± 0.5	7 ± 2.0	6 ± 2.9
Central venous pressure (cm H_2O)	6.7 ± 1.5	6.7 ± 1.5	6.3 ± 1.5	6.3 ± 1.5	6 ± 2.6	5 ± 2.6
Pulmonary venous resistance (dyn·s·cm^{-5})	275.3 ± 99.8	258 ± 177.1	242.3 ± 69.8	244.3 ± 69.9	242 ± 19.9	321.7 ± 40.8
Systemic venous pressure (dyn·s·cm^{-5})	1,329 ± 428.7	1,141.7 ± 468.0	1,161.7 ± 358.9	1,209.3 ± 524.6	1,208.7 ± 334.2	1,399.7 ± 398.5

*Values are mean ± SD

Table 2.   Pulmonary Variables*

Variable	Baseline	Smoke Exposure (min)				
		1	2	3	4	5
pH	7.42 ± 0.03	7.42 ± 0.03	7.42 ± 0.05	7.37 ± 0.05	7.35 ± 0.08	7.32 ± 0.09
P_{aO_2}	616.3 ± 21.1	582.7 ± 44.7	589.3 ± 70.4	377.3 ± 254.3	243.7 ± 218.4	198 ± 202.0
P_{aCO_2}	40.3 ± 6.5	44.7 ± 11.6	28.3 ± 8.5	32.3 ± 16.8	39 ± 9.0	34.7 ± 7.5
Base excess	2 ± 3.6	4 ± 8.5	−4.3 ± 6.5	−5 ± 11.6	−3.7 ± 1.5	−7.3 ± 4.6
Mean airway pressure (cm H_2O)	10.23 ± 0.7	10.7 ± 1.2	10.7 ± 0.5	11 ± 1.0	11.7 ± 0.5	12.3 ± 0.5
Plateau airway pressure (cm H_2O)	21.3 ± 3.2	22.7 ± 2.6	22.3 ± 2.9	24 ± 2.6	24.7 ± 0.5	27 ± 1.0
Peak airway pressure (cm H_2O)	15.7 ± 13.6	24 ± 3.6	23.7 ± 2.6	26 ± 3.4	28 ± 2.9	30 ± 1.0
Static compliance (mL/cm H_2O)	21.3 ± 2.0	19.6 ± 1.4	19.6 ± 2.2	17.3 ± 2.4	17 ± 2.0	15.1 ± 3.2

*Values are mean ± SD.
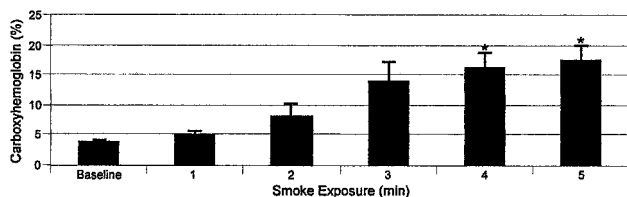
Fig. 2. Carboxyhemoglobin values following 5 consecutive 1-min smoke exposures. Data are mean ± SD. * p < 0.5 versus baseline.
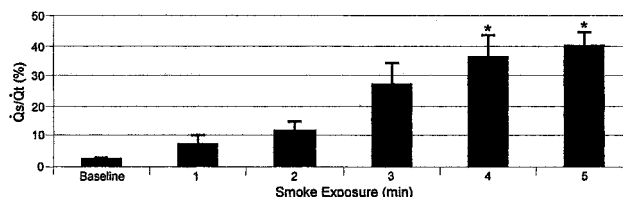

Fig. 3. Effect of 5 consecutive 1-min smoke exposures on pulmonary shunting ($\dot{Q}s/\dot{Q}t$). Data are mean ± SD. * p < 0.05 versus baseline.

area between peak inspiration and end expiration. After each additional minute of smoke exposure, a further increase in alveolar instability was observed. An increase in I-EΔ was representative of increased alveolar instability. There was a significant increase in alveolar instability 4 min and 5 min after smoke exposure, as compared to baseline (Fig. 4).

In Vivo Microscopy

In vivo photomicrographs depict individual alveoli (dots) at peak inspiration (Figs. 5A and 5B) to end expiration (Figs. 5C and 5D) during tidal ventilation in the normal and smoke-injured lung. Normal alveoli at baseline change
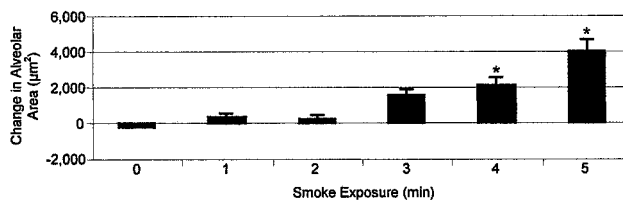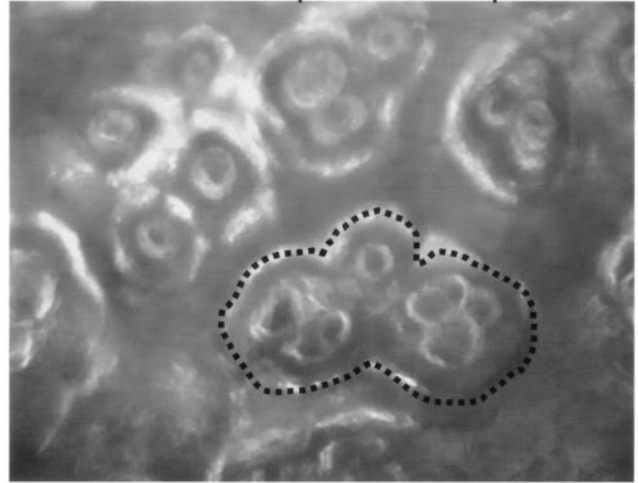

Fig. 4. Effect of 5 consecutive 1-min smoke exposures on alveolar stability. Alveolar stability is defined as the degree of change in alveolar area between peak inspiration and end expiration. Alveolar stability was assessed on individual alveoli at baseline and after each minute of smoke delivery. Data are mean ± SD. * p < 0.05 versus baseline.
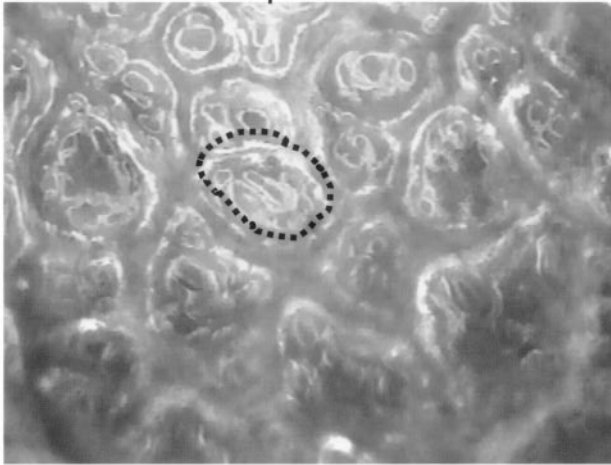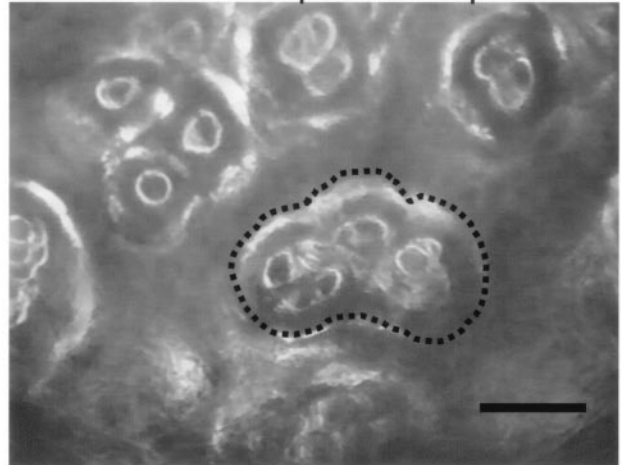
Fig. 5. In vivo photomicrographs (10× objective, bar = 100 μm) depict individual alveoli (dots) at peak inspiration (A and B) to end expiration (C and D) during tidal ventilation in the normal and smoke-injured lung. Alveoli at baseline change size very little from peak inspiration to end expiration (A and C). After five 1-min smoke exposures, alveoli become unstable and change volume substantially from peak inspiration to end expiration (B and D).

volume very little during ventilation. This is consistent with previous results from our laboratory.[11] Five 1-min doses of smoke caused alveoli to become very unstable (Figs. 5B and 5D). Alveolar instability is measured by an elevation in I-EΔ (see Fig. 4).

Histology

Smoke inhalation is caused by substantial cellular infiltration of lung parenchyma and prevalent thickening of alveolar septa, enlargement of interstitial spaces, and dilation of the microvasculature (Fig. 6). Interlobular septa were marked by dilated lymphatic vessels and interstitial mononuclear infiltration. In contrast, the peribronchovascular interstitium showed no obvious signs of edema.

There was strong histological evidence of influx, sequestration, and heavy infiltration of inflammatory cells. The presence of large numbers of leukocytes within small pulmonary vessels was consistent with the interstitial accumulation of mononuclear and polymorphonuclear leukocytes. Most alveolar capillaries appeared distended with erythrocytes as well as leukocytes, in a pattern of acute lung injury. Leukocyte adhesion in the microvasculature and leukocyte accumulation in the parenchyma were uniformly distributed in all specimens.

The effects of smoke inhalation were most conspicuous at the alveolar level, as focal areas of fibrin deposition were indicative of varying extents of intra-alveolar edema. Most alveoli exhibited at least scant strands of fibrin, although in some alveoli fibrin deposition was extensive
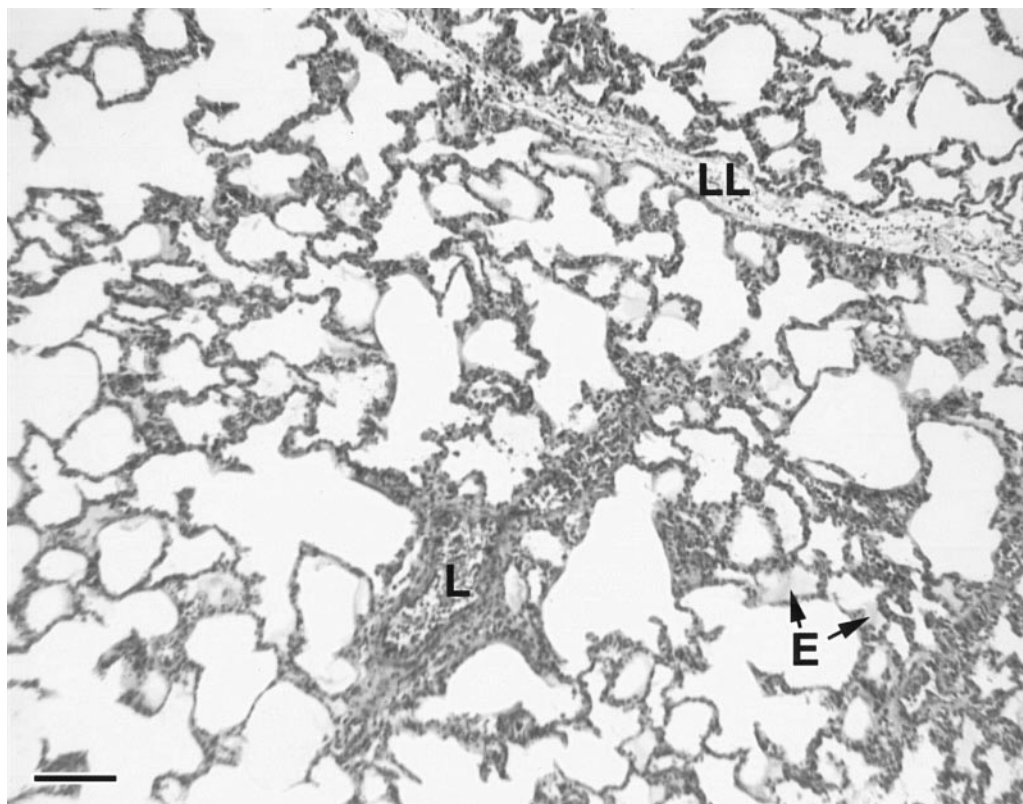
Fig. 6. Low-magnification photomicrograph (10× objective, bar = 100 μm) of pig lung shows leukocytes in the lumen of a pulmonary venule (L) and within the connective tissue of an interlobular septum (LL). Amorphous alveolar edema (E) is frequent, albeit inconsistent at this magnification.

(Fig. 7). Amorphous alveolar edema and patchy interstitial edema were widely distributed in all the histological preparations (see Fig. 6).

Focal alveolar wall widening was often coupled with red-cell congestion, and most commonly accompanied by a marked increase in alveolar wall cellularity, mainly mononuclear cells. Because of the marked increase in cell numbers within the parenchyma, most alveoli had a thickness of 2 or more cells (see Fig. 7). This was a distinct departure from the thickness of the healthy alveolar septum. There was no additional loss of alveolar architecture beyond the thickening of septa associated with cellular infiltration and interstitial edema, which was consistent with the short-term nature of the insult.

Discussion

The most important finding of this study is that alveolar instability increases with increasing cumulative doses of smoke exposure. In previous studies from our laboratory, alveolar mechanics were studied following a single insult and thus could not measure a dose-response relationship (ie, increased injury causes increased alveolar instability). We utilized multiple models of surfactant deactivation,

including Tween instillation and a single large dose of wood smoke. In a study conducted with dogs, administration of one dose of 5% Tween 20 immediately produced unstable alveoli, with marked cross-sectional-area change during a respiratory cycle. However, alveoli stabilized throughout the 4 hours of the experiment.[5] A single large dose of wood smoke caused instantaneous alveolar instability as well as decreased pulmonary compliance and increased shunt, as demonstrated by Clark et al.[12]

Data from this study demonstrate that, with repetitive insults, alveoli become progressively unstable. From a clinical perspective this suggests that the more severe smoke inhalation is, the more likely that alveolar instability will be present in the patient. Thus smoke-induced alveolar instability is not an all-or-none phenomenon, but, rather, dependent on the time of exposure.

Pathophysiology of Smoke Inhalation

Smoke inhalation is very harmful because it delivers "2 hits" to the pulmonary parenchyma. Smoke damages the lung tissue directly, due to exposure of toxic compounds in the smoke (hit #1), and also causes repetitive alveolar collapse and expansion to occur (hit #2).
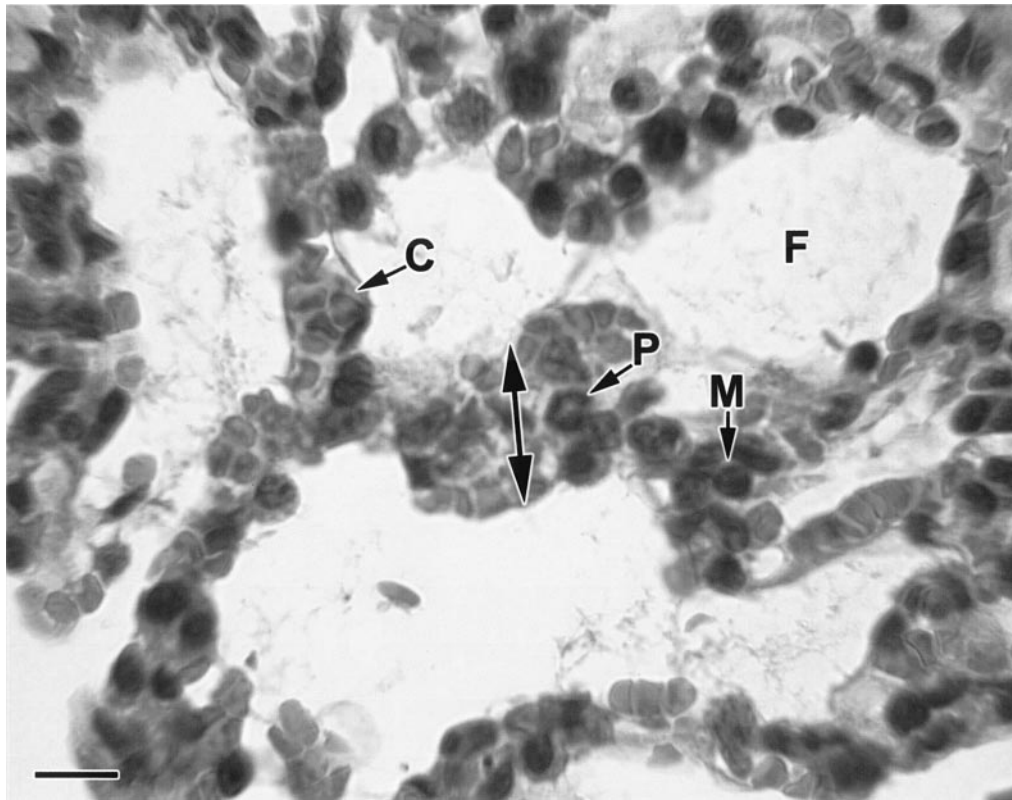
Fig. 7. High-magnification photomicrograph (oil immersion, bar = 10 μm) of pig lung shows alveolar lumina with fibrin deposition. At this level of resolution, discrete fibrin strands (F) are conspicuous and widespread. Alveolar septa commonly exceed one cell in thickness (double arrow) as they are infiltrated by polymorphonuclear (P) and mononuclear (M) leukocytes, and accommodate congested capillaries (C).

Direct Injury to Lung Tissue by Toxic Compounds (Hit #1). Smoke inhalation causes severe ventilation and oxygenation abnormalities by damaging airways and air spaces. Many mechanisms have been proposed as the basis for pathological consequences of smoke inhalation, including increased permeability and epithelial damage.[13,14] Increased microvascular permeability due to chemical injury leads to deterioration of respiratory function.[15] In response to smoke inhalation, observations following smoke exposure were loss of cilia, epithelial attenuation, and ulceration of respiratory mucosa.[16] Studies have demonstrated that after smoke inhalation, lung injury was evidenced by an increase in alveolar capillary permeability as well as total injury of both airway and pulmonary parenchymal tissues. Studies have also shown that smoke inhalation causes injury to both alveolar epithelial barrier and lung endothelium.[17] In animal models, a few hours after smoke inhalation there is an increase in lung lymph flow, extravascular lung water content, and pulmonary vascular permeability.[17,18] Morphologic damage to alveolar epithelium such as denudation of basal lamina and swelling of alveolar epithelial type I cells occurs after 24 hours.[18] After moderate to severe smoke inhalation, more than 50%

of the tracheal mucosa is denuded, and large sections of the airway are covered with inflammatory exudates that limit mixing of gases in breathing.[19] Inhalation injury to the tracheobronchial tree results in bronchoconstriction and obstruction of small airways. It has been hypothesized that the changes in airway pressure and compliance may be due to the destruction of surfactant.[20] The loss of surfactant results in alveoli instability. Progressive atelectasis develops as alveoli collapse. The law of Laplace, where p = 2 T/r (in which p is pressure, T is the surface tension on the alveolar surface, and r is the radius of the alveolus), states that a small alveolus will have a high collapsing pressure and require most pressure to keep it open. Surfactant reduces the alveolar surface tension and the collapsing pressure for a given radius. It also increases lung compliance. In alveoli, expansion can occur in inspiration, and atelectasis is prevented from occurring in expiration. Long-term complications of smoke inhalation injury range from increases in airway pressure to destruction of the small airways.

Lung Injury Induced by Repetitive Alveolar Collapse and Expansion (Hit #2). In a study performed by Schiller et al,[21] it was demonstrated that acute lung injury results in

a continuum of abnormal alveolar mechanics that may cause substantial shear-stress-induced lung injury and play a major role in the development of VILI. Schiller and his colleagues observed abnormal alveolar mechanics following surfactant deactivation, which they termed repetitive alveolar collapse and expansion. These complex mechanics include a type of alveoli with minimal size change during ventilation (normal ventilation), a type that changes volume significantly with ventilation but does not collapse at end expiration, and a type of alveoli that totally collapses and reinflates with each breath. After surfactant deactivation, histological sections taken from areas with repetitive alveolar collapse and expansion reveal alveoli that are reduced in volume or collapsed and have thickened alveolar walls. A large number of leukocytes are also found in the pulmonary parenchyma. Alveolar mechanics are altered in the acutely injured lung, demonstrated by the development of alveolar instability (repetitive alveolar collapse and expansion) and the increase in alveolar size at peak inspiration. Schiller also speculates that the mechanism of ventilator-induced lung injury may involve altered alveolar mechanics, such as repetitive alveolar collapse and expansion and alveolar overdistension.[21]

Does the increase of alveolar instability shown by Schiller et al[21] actually cause injury to pulmonary tissue? Mead et al, using a mathematical model, demonstrated that a heterogeneous collapse of alveoli (ie, alveolar instability) could induce a shear stress of approximately 140 cm H_2O.[6] Peak airway pressure of a mere 40–75 cm H_2O has been shown to cause severe VILI.[21–23] Thus, a shear pressure of as great as 140 cm H_2O, in theory, could cause tremendous lung-tissue damage. Indeed, it has been shown that shear stresses can cause lung injury experimentally.[11]

Steinberg et al caused repetitive alveolar collapse and expansion by intratracheal Tween instillation in pigs, and separated them into 2 groups.[11] Group I was ventilated at low PEEP, and alveoli were unstable (repetitive alveolar collapse and expansion) for 4 hours. In Group II, PEEP was increased immediately after Tween instillation, to stabilize alveoli. Tween caused a heterogeneous lung injury, with areas of unstable alveoli directly adjacent to normal stable alveoli. Increasing PEEP stabilized alveoli and significantly reduced histologic evidence of lung injury. In vivo videomicroscopy was used to directly assess alveolar stability and to positively identify alveoli with abnormal alveolar mechanics. Alveolar instability was associated with no significant increase in neutrophil or protease activity. This suggests that the histopathologic changes observed were due largely to the mechanical shear stresses, and not to neutrophil-released proteases. This experiment demonstrates that the alveolar instability can mechanically injure the lung, independent of inflammatory damage.[11]

The lung injury due to the smoke inhalation can be further demonstrated with the histological study. Significant infiltration of inflammatory cells was found in the lung parenchyma, as well as enlargement of interstitial spaces and dilation of the microvasculature. The interlobular septa thickened and contained dilated lymph vessels. Entrapped leukocytes were present in the pulmonary circulation. Focal areas of alveolar fibrin deposition were evidence of intra-alveolar edema. Alveolar walls were thickened because of cellular infiltration and interstitial edema. The histological data demonstrate the acute short-term insult of smoke inhalation.

In conclusion, one model of the progression in sepsis-induced ARDS is a cycle beginning with an inciting inflammatory stimulus, leading to elevated expression and activity of inducible nitric oxide synthase and other agents that result in a high-permeability pulmonary edema. This edema, at the alveolar level, disrupts normal surfactant function. This surfactant deactivation causes a pathologic change in alveolar mechanics. This change in alveolar mechanics makes the lung vulnerable to additional VILI. Pulmonary epithelial cells subjected to VILI elaborate additional inflammatory cytokines that feed back into the cycle. The current study demonstrates that smoke inhalation (presumably through surfactant deactivation) results in changes in alveolar mechanics that set the lung up for VILI and entry into the cycle of progressive lung failure. The clinical implication of this finding is that an early and aggressive protective ventilation strategy for the smoke-exposed patient with hypoxemia may arrest this cycle.

Critique of Methods

The major limitation of our study is the small sample size. The intent of the study was to interrogate the changes in alveolar mechanics when exposed to smoke inhalation. We have previously demonstrated that surfactant deficiency resulted in alveolar instability. Our central hypothesis was that smoke inhalation (as we previously demonstrated) causes surfactant deactivation and should thus result in patterns of alveolar instability, as observed by in vivo microscopy. Because of the universal and rapid development of alveolar instability in the study animals, we terminated the study with the minimal number of animals for ethical concerns. The 3-animal sample size used in our experiment was the smallest number of animals considered to reach statistical significance. This limited sample size does limit the extrapolation of our numerical data outside of the experimental model. This limitation does not take away from the fact that a consistent pathologic change in alveolar mechanics was observed with smoke inhalation.

Measurements are restricted to analysis of subpleural alveoli, and only 2-dimensional changes in alveolar size can be measured. The limited depth of field prohibits us from observing and analyzing the dynamic changes of the

entire air sac. There is a concern that subpleural alveolar mechanics differ from those of alveoli in the lung interior, secondary to pleural influences. Another concern is that subpleural alveolar mechanics differ from those of pleural influences. If subpleural alveoli are tethered to the pleura, alveolar size change could be exaggerated with lung inflation.[21] However, even with the above limitation, to our knowledge, in vivo microscopy is the only technique that directly visualizes and measures individual alveoli throughout tidal ventilation and thus remains an important tool in the investigation of VILI.

There are 2 other limitations of our study. First, clinical smoke inhalation is very complex, and modeling it is difficult. We know that all smoke-inhalation victims do not inhale only plywood smoke. However, we had to standardize the model and choose a common constituent of most houses (ie, plywood) as our smoke source. Second, we assumed that smoke-induced alveolar instability was caused by surfactant deactivation without directly measuring surfactant function. However, we used our established smoke model in this study, which has been shown by direct measurement to deactivate surfactant.[5,8–10]

Conclusions

We conclude that wood smoke inhalation causes: (1) a dose-dependent decrease in alveolar stability that is probably caused by progressive surfactant deactivation, and (2) alveolar instability causes a significant increase in pulmonary shunt fraction. Direct deactivation of surfactant resulting in immediate alveolar instability predisposes the lung of patients with severe wood smoke inhalation to VILI.

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