Clinical Science

New Developments in the Pathogenesis of Smoke Inhalation-Induced Pulmonary Edema

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Smoke inhalation causes most of the deaths in fire-related injuries, with pulmonary edema as a major determinant in the outcome of smoke-inhalation injury. The pathophysiology of pulmonary edema is thought to be related to the products of incomplete combustion. Damage to the integrity of the alveolar epithelium is one of the determinants of the development of smoke-induced pulmonary edema. In recent studies using lung clearance of aerosolized pentetic acid (DTPA [diethylenetriaminepentaacetic acid]) labeled with technetium Tc 99m to assess the permeability of the alveolar epithelium, several factors were identified that may increase a person's susceptibility to smoke-induced acute lung injury. These are increased initial alveolar permeability and alterations in the number and activity of alveolar macrophages. Clinical measurement of ^{99m}TcDTPA clearance may provide a sensitive and convenient method for the early detection and serial assessment of smoke-induced alveolar epithelial permeability changes.

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Each year in the United States about 2 million people suffer burns that require medical attention.[1] Of these, 130,000 need hospital treatment and more than 50% require intensive care. Although each year 8,000 to 12,000 persons die of fire-related injuries, most deaths are not due to cutaneous burns but are caused by inhaling the toxic products of combustion.[2] The illness resulting from smoke inhalation can be divided into two major processes: the systemic effects of toxic gases such as carbon monoxide that are absorbed from the respiratory tract and the direct local effects of the inhaled substances on the respiratory system.[3] In this review we will focus on the pathophysiology of parenchymal lung injury produced by smoke inhalation.

Inhalation injuries are usually produced by gaseous or particulate products of incomplete combustion and are rarely due to heat unless steam is inhaled.[4] The combination of burning material and an enclosed space is a major determinant that can cause smoke inhalational injury. Recent incidents such as the takeover of an Egyptian airliner in Malta, the Air Canada airliner fire, and the Las Vegas MGM Hotel fire show the catastrophic combination of fire and an enclosed space. Additionally, increasingly more homes and public buildings are being built and furnished with flammable synthetic materials that yield copious smoke and gases when burned.

Numerous toxic gases are generated from the combustion and thermal degradation of synthetic materials such as polyvinyl chloride and polyurethane. Polyvinyl chloride is commonly used in furnishings and building fixtures. It does not burn until it reaches 475°C; from a temperature of 225°C until it burns at 475°C, however, it loses 60% of its weight by thermal degradation.[3] More than 75 known toxic products are formed in the process, including hydrogen chloride, chlorine, and phosgene.[5] Polyurethane combustion can result in the formation of isocyanate and hydrogen cyanide.[6]

Combustion of natural materials such as wood, cotton, paper, and so forth can result in the generation of numerous organic acids, aldehydes, and other noxious gases, including oxides of sulfur and nitrogen. Aldehydes, especially acrolein, can cause irritation of exposed mucous membranes and pulmonary edema.[7] Irritant gases such as ammonia and sulfur dioxide combine with water present in the lungs to form strong acids and alkalis.[2] Smoke particulate matter can absorb toxic gases, such as nitrous oxide and sulfur dioxide, and transport them to alveolar areas where they cause further damage.[8] Mucosal edema, bronchorrhea, and sloughed mucosa caused by chemical injury increase airway resistance and cause obstruction of airways.[3] Inhaled smoke particulate matter can cause bronchoconstriction, possibly by stimulating irritant receptors in the airways.[9]

In addition to airway injury, there is damage to the gas-exchanging areas of the lung. Within seconds surfactant activity in the lung is diminished, resulting in congestion followed by atelectasis.[2] When lung injury occurs, clinical and physiologic evidence is apparent soon after smoke inhalation. In the absence of surface burns, well-documented cases of pulmonary disease following smoke inhalation with a latency to onset of greater than 24 hours have not been reported.[10,11]

The trachea and upper airways have good heat-exchange properties. Consequently, the efficient cooling of the upper air passages makes thermal injury below the vocal cords uncommon, occurring in less than 5% of patients admitted to hospitals with surface burns.[12,13]

Inhaling the toxic constituents of smoke may damage both alveolar epithelium and capillary endothelium and result in an

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ABBREVIATIONS USED IN TEXT

BAL = bronchoalveolar lavage
DTPA = United States Pharmacopeial Convention, Inc, code designation for pentetic acid
LT = leukotriene
PG = prostaglandin
PGI_2 = prostacyclin
TX = thromboxane

increased permeability of the alveolar-capillary barrier. Edema forms by filtration of fluid across a damaged and excessively permeable membrane even when pulmonary capillary hydrostatic pressure is normal.

The diagnosis of pulmonary edema resulting from smoke inhalation is made on the basis of respiratory distress, impairment of oxygenation, and roentgenographic evidence of pulmonary edema in the absence of pulmonary venous hypertension. A study of 239 patients admitted to a hospital burn unit found that of 76 patients in whom pulmonary edema developed, 75% (57) died.[14] Patients involved in a closed-space fire conducive to producing large amounts of smoke and those with burns covering 50% of their surface area seemed to be at the greatest risk for the development of pulmonary edema. Another clinical study showed that 35 of 56 patients with smoke-inhalation injury had radiographic findings of pulmonary edema, such as perivascular fuzziness and peribronchial cuffing. Furthermore, these radiographic signs of pulmonary edema appeared in the first 24 hours after the injury.[15]

Other clinical studies have shown that the development of pulmonary edema occurs without a concomitant increase in the pulmonary capillary wedge pressure.[16,17] Measuring the extravascular lung water volume in burn patients with and without inhalation injury showed that, on admission, patients with parenchymal inhalation injury had elevated extravascular lung water volumes (10.1 ± 3.4 ml per kg body weight), whereas patients without parenchymal injury had significantly lower lung water values (3.9 ± 1.5 ml per kg). The accumulation of extravascular lung water and ventilation-perfusion scan abnormalities in the group with parenchymal inhalation injury occurred within hours of smoke inhalation. The normal hydrostatic pressures in these patients suggest that there was an increase in the pulmonary capillary membrane permeability. These clinical observations have been confirmed in sheep where smoke generated from burning cotton cloth caused changes in microvascular permeability to protein.[18] The inhalation injury produced a substantial change in lung lymph flow concomitant with an elevation in the lymph to plasma oncotic pressure ratio. These clinical and experimental findings provide evidence that the formation of pulmonary edema may be caused by an increase in the permeability of the alveolar-capillary barrier. Increased permeability allows fluid to leave the capillary and traverse the endothelial and epithelial layers of the alveolar-capillary barrier, resulting in pulmonary edema.

There is considerable evidence that the epithelial layer of the alveolar-capillary barrier is less permeable to solute than is the endothelial layer. The relatively greater resistance of the alveolar epithelium to solute movement is an important factor in understanding the probable sequence of events in the formation of smoke-induced pulmonary edema. Fluid fills the loose alveolar interstitium before it ruptures the epithelial layer and floods the alveolar spaces (Figure 1). Consequently, the permeability of the alveolar epithelium may be the most critical determinant leading to the development of pulmonary edema.

Several investigators believe that the pulmonary clearance of pentetic acid (United States Pharmacopeial Convention, Inc, code designation DTPA [diethylenetriaminepentaacetic acid]) labeled with technetium Tc 99m (molecular weight, 492 daltons) reflects permeability of the epithelial layer of the alveolar-capillary barrier.[19,20] Long-term exposure to cigarette smoke and the smoke of wood and diesel fires increases the ^{99m}TcDTPA alveolar clearance in humans.[21,22] Intense, short-term exposure to large amounts of smoke in rabbits also can increase the alveolar clearance of ^{99m}TcDTPA.[23] The amount of smoke required to increase the epithelial uptake of ^{99m}TcDTPA varied (5 to 35 tidal volume breaths). A tidal volume smoke breath is equivalent to smoking two cigarettes in a normal manner.[24] Rabbits pretreated with ibuprofen (25 mg per kg per day given intramuscularly), a cyclooxygenase eicosanoid inhibitor, for seven days before smoke exposure will have rapid increases in the alveolar clearance of ^{99m}TcDTPA, severe injury to type I alveolar cell epithelium (Figure 2), pulmonary edema, and a mortality rate of 61%.[25,26] Blockade of the arachidonic acid cyclooxygenase pathway could cause shunting of arachidonic metabolites to the lipoxygenase pathway. The death rate in these studies is comparable to the human experience after severe smoke inha-

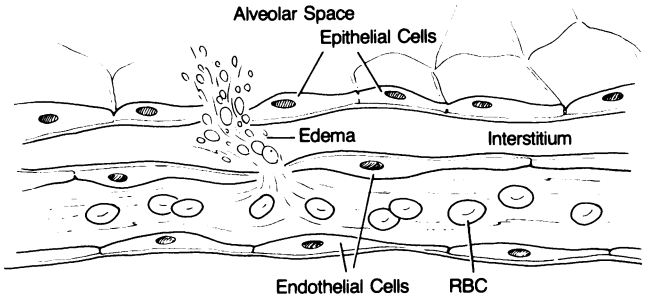

Figure 1.—A theory of the formation of smoke-induced pulmonary edema is that fluid fills the loose alveolar interstitial space before it ruptures the epithelial layer and floods the alveolar spaces. RBC = erythrocyte

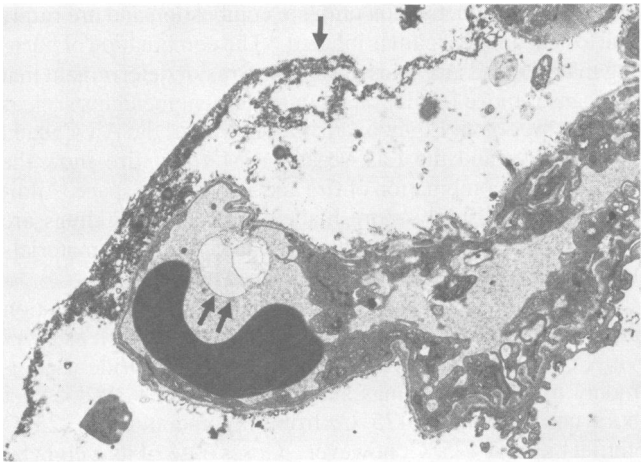

Figure 2.—The electron micrograph shows an alveolar septum in a rabbit treated with ibuprofen before smoke exposure. Smoke inhalation causes type I alveolar cell epithelium to form a membrane that is lifted off the alveolar wall **(single arrow).** A pale bleb of capillary endothelium is adjacent to an erythrocyte **(double arrows)** (uranyl acetate-lead citrate, original magnification × 9,540) (from Witten et al[25]).

lation. These experimental observations would tend to support the hypothesis that a critical determinant in edema formation after smoke inhalation is the integrity of the alveolar epithelium.

The particulate matter in smoke may be the constituent responsible for the development of increased alveolar epithelial permeability after smoke inhalation. Minty and Royston recently used a rat model to study the effects of cigarette smoke on alveolar epithelial permeability as measured by the clearance of ^{99m}TcDTPA.[20] Rats exposed twice a day to 90 puffs of cigarette smoke for seven days showed an increase in ^{99m}TcDTPA uptake. Filtered smoke did not cause increases in the ^{99m}TcDTPA uptake. These investigators suggested that particulates in cigarette smoke were responsible for the recruitment and activation of alveolar macrophages.

The contribution of inflammatory cells, such as alveolar macrophages, to the increase in alveolar permeability produced by smoke has been studied by bronchoalveolar lavage (BAL). In comparison to other smoke-exposed groups, ibuprofen-pretreated rabbits that died during smoke inhalation had a decreased number of alveolar macrophages and decreased leukotriene (LT) B_4 levels in addition to a more rapid rate of ^{99m}TcDTPA clearance.[26] In contrast, other studies have shown that alveolar macrophages are activated by smoke exposure. Long-term cigarette smokers can have a fivefold increase in alveolar macrophages compared with nonsmokers.[27] Rabbits with exposure to wood smoke had an increase in alveolar macrophages in both cell counts of BAL fluid and on electron micrographs.[28] Furthermore, smoke-exposed alveolar macrophages showed significant changes in surface features, possibly indicating activation. These studies suggest that changes in the alveolar macrophage number and activity are important in the development of the increase in alveolar permeability induced by smoke inhalation.

The mechanism by which changes in alveolar macrophage activity result in an increase in alveolar epithelial permeability after smoke inhalation is still not completely defined. It is possible, however, that chemical mediators released from inflammatory cells modulate the permeability of the alveolar epithelium.

Leukotriene B_4 is the major lipoxygenase metabolite of human alveolar macrophages.[29] Both in sheep lung lymph and alveolar fluid, a small increase in protein clearance occurred after LTB_4 (2 nmol per ml, 50 ml total) was administered in the alveoli of a caudal lung lobe through a fiber-optic bronchoscope. Staub and co-workers speculated that some of this effect may have been caused by a direct action of LTB_4.[30] When lung injury is induced by the administration of smoke, rabbits, including those pretreated with ibuprofen, had significant decreases in BAL LTB_4 concentration compared with controls. These data suggest that smoke exposure may have altered alveolar macrophage activity as evidenced by decreased LTB_4 production. Because, however, LTB_4 levels were reduced after smoke exposure, it is unlikely that LTB_4 was responsible for the increased lung permeability in the smoke-exposed rabbits. Other eicosanoids, such as thromboxane (TX) A_2, can modulate lung vascular permeability during complement and endotoxin injury processes.[31] Smoke inhalation, however, did not increase TXA_2 levels in BAL fluid or plasma.[26]

Chemical mediators released from lung parenchymal cells also might modulate alveolar epithelial permeability. It has recently been shown that levels of sheep lung lymph 6-keto prostaglandin (PG) $F_{1\alpha}$—a stable metabolite of prostacyclin (PGI_2)—increase after smoke exposure.[18] Prostacyclin is the major eicosanoid released by the endothelial cells of the alveolar-capillary barrier.[32(pp183-184)] In rabbits exposed only to smoke, 6-keto-$PGF_{1\alpha}$ levels are significantly increased in both BAL fluid and plasma. These rabbits had several focal areas of alveolar edema. Several investigators have postulated a protective role of prostacyclin in the lung,[33,34] but a recent observation fails to support this hypothesis. Rabbits pretreated with ibuprofen that survive smoke exposure have 6-keto-$PGF_{1\alpha}$ levels that are not increased and there is no pathologic evidence of lung injury.[26] Consequently, increased PGI_2 levels may be nothing more than a marker of endothelial cell injury. It is not known whether other eicosanoids may be released from lung parenchymal cells in response to smoke inhalation. Therefore, it appears that there is little evidence at this time to support a primary injurious or protective role for chemical mediators in the maintenance of alveolar epithelial permeability after smoke inhalation.

The initial permeability of the alveolar epithelial layer may play a role in the development of acute lung injury after smoke inhalation. Rabbits pretreated with ibuprofen that died during smoke inhalation had a significantly faster baseline alveolar clearance of ^{99m}TcDTPA than did ibuprofen-pretreated rabbits that survived smoke exposure.[25,26] Thus, it is possible that smoke particulate matter could have had greater access to lung parenchyma in these rabbits and could have caused acute lung injury. Humans also have shown a degree of variation in alveolar clearance of ^{99m}TcDTPA, and, consequently, there is a wide range of normal epithelial permeability. In the absence of a potentially injurious event such as smoke inhalation, there are probably no clinical consequences to a slight increase in the alveolar epithelial permeability. After smoke inhalation, however, an initial increased epithelial permeability could facilitate the development of pulmonary edema by increasing fluid flux across the alveolar-capillary barrier as well as allowing smoke particulate matter into lung parenchyma. There is a poor correlation clinically between the severity of smoke inhalational injury and the amount of pulmonary edema. Therefore, this observation may be explained by differences in susceptibility to smoke inhalational injury as determined by the permeability of the alveolar epithelium.

As suggested by recent experimental studies, measurement of alveolar epithelial permeability using ^{99m}TcDTPA offers a possible means of rapidly detecting smoke-induced injury to the alveolar-capillary barrier.[23,25,26] The use of ^{99m}TcDTPA in humans is becoming increasingly prevalent, although it is not yet a standard clinical procedure.[21,35-38] In addition, lung clearance of ^{99m}TcDTPA is sensitive to changes in alveolar permeability and is a relatively fast (less than 20 minutes) test to administer. Furthermore, serial periodic measurement of alveolar permeability with ^{99m}TcDTPA might be useful in following changes in a patient's condition with therapy. Therefore, in the future, the pulmonary clearance of ^{99m}TcDTPA may provide additional information to clinicians in the diagnosis and treatment of smoke-inhalation injury.

Lung scanning using xenon Xe 133 and bronchoscopy are other diagnostic methods used to determine the extent of smoke-induced lung injury. False-positive findings of xenon lung scans may occur, however, in patients with preexisting bronchitis, bronchiectasis, asthma, or pneumonia.[39] Unfortunately, no studies have yet been done comparing xenon lung

scans with ^{99m}TcDTPA lung clearance studies to determine the most effective method of detecting lung injury. Upper airway injury is diagnosed bronchoscopically when laryngeal or tracheobronchial erythema or edema and carbonaceous material or bronchorrhea are observed.[40] Therefore, bronchoscopy may provide information about upper airway injury that might be missed if only ^{99m}TcDTPA lung clearance studies were done. It is likely that ^{99m}TcDTPA lung clearance studies and bronchoscopy together give the most complete assessment of the extent of smoke inhalation injury.

In summary, research has identified several factors that may play crucial roles in determining the severity of lung injury and pulmonary edema after smoke inhalation. The permeability of the epithelial layer of the alveolar-capillary barrier and the number and activity of alveolar macrophages available as a defense against smoke particulate matter could determine the ultimate outcome for a smoke-inhalation victim. In addition, clinical measurement of the ^{99m}TcDTPA clearance may provide a sensitive and convenient method for detecting changes in alveolar epithelial permeability induced by smoke exposure.

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