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Inhalation injury

John C. Fitzpatrick, M.D., and William G. Cioffi, Jr., M.D.
U.S. Army Institute of Surgical Research,
Fort Sam Houston, Texas, U.S.A.

Inhalation injury is defined as acute respiratory tract damage of variable severity caused by inspiration of steam or toxic inhalants such as fumes, gases, and mists. Fumes consist of small particles dispersed in air, usually with various irritants or cytotoxic chemicals adherent to the particles. Mists consist of aerosolized irritants or cytotoxic liquids. Smoke consists of a combination of fumes, gases, mists, and hot air. The level and degree of injury are broadly determined by the physicochemical properties of the causative agent, the amount inhaled, and any preexisting diseases of the victim. Inhalation injury is notable for its inhomogeneity both within and between patients and may occur independently from cutaneous burn injury, although they usually occur together. Inhalation injury may occur at any location along the respiratory tract. The airway may conveniently be divided into three anatomical areas which are differentially affected by inhalation injury: the supraglottic, tracheobronchial (major airways), and lung parenchymal regions.

DIAGNOSIS

Patients with inhalation injury usually present with a history of exposure to smoke in a closed space. Pertinent facts to be obtained include characteristics of the site of injury (closed space injury suffered in a structural fire, industrial gas exposure, etc.), duration of exposure, the type of toxic inhalant, type of materials and fuels ignited, transport time, and significant past medical history. Many patients admit to ethanol or drug use immediately prior to the time of injury, and an even larger proportion appear intoxicated and have confirma-

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Address correspondence and reprint requests to Dr. J. C. Fitzpatrick at U.S. Army Institute of Surgical Research, SGRD-US, 2322 Harney Road, Fort Sam Houston, TX 78234-6315, U.S.A.

tory laboratory data. Depressed sensorium exacerbates the inhalation injury by increasing the length of exposure to the toxic environment of the fire. Most patients with an inhalation injury present with some combination of the symptoms and signs listed in Table 1. Routine arterial blood gas determination and a carboxyhemoglobin level are essential in the initial screening.

The classic historical details or physical findings have a poor predictive value in either assuring or excluding an inhalation injury (1). This inadequacy has led to the routine use of fiberoptic bronchoscopy or i.v. ^{133}xenon ventilation scanning at many burn centers to establish the diagnosis. Fiberoptic bronchoscopy allows detailed examination of the supraglottic area. Supraglottic injuries may result from either thermal or chemical means and may be so severe that rapidly developing upper airway obstruction necessitates endotracheal intubation. Such proximal injuries are not, however, a reliable index of the presence or severity of more distal damage. If the bronchoscope is placed through an endotracheal tube prior to the procedure, any patients with marked upper airway edema or respiratory failure may be intubated under direct visualization over the bronchoscope. Examination of the major airways for the presence of soot and early inflammatory changes (hyperemia, edema, superficial mucosal sloughing, and ulceration) confirms the diagnosis of inhalation injury. The technique of performing fiberoptic bronchoscopy is the same as that used for standard diagnostic bronchoscopy. Spray bottles of lidocaine or similar agents are convenient for anesthetizing the supraglottic area. If available, the use of video endoscopy equipment, especially in teaching institutions, allows many to learn proper technique and the gross pathologic appearance of the injury. In any institution, video allows support personnel to anticipate the needs of the endoscopist, thus directly benefiting the patient. When experienced personnel perform bronchoscopy in an appropriately monitored setting, complications such as airway obstruction or aspiration are rare. The accuracy of the examination approaches 100% under ideal conditions: in general use, the accuracy is ~87% (2).

TABLE 1. *Symptoms and signs suggesting possible inhalation injury*

Symptoms	Signs
Lacrimation	Conjunctivitis
Severe cough	Carbonaceous sputum
Hoarseness	Facial burns
Dyspnea	Singed nasal vibrissae
Tachypnea	Stridor
Anxiety	Bronchorrhea
Wheezing	Disorientation
	Obtundation
	Coma

Intravenous ^{133}xenon ventilation–perfusion scanning is a means of identifying regions of incomplete tracheobronchial obstruction secondary to small airway injury. After injection of the radionuclide, serial scans demonstrate respiratory exchange and excretion of xenon via the lungs. Areas retaining isotope >90 s are indicative of segmental airway obstruction presumptively due to inhalation injury. False positive examinations may occur in patients with chronic obstructive pulmonary disease, aspiration injury, or pneumonia prior to smoke exposure. Although not as frequently performed as bronchoscopy, ^{133}xenon scanning is still useful as a complementary examination, particularly when clinical suspicion is high for the presence of inhalation injury but the bronchoscopic examination is negative. The accuracy of ^{133}xenon scanning is

86% in the diagnosis of smoke inhalation injury (2).

Although pulmonary function tests are useful for long-term follow-up of inhalation injury, they are of little efficacy in confirming the acute diagnosis of inhalation injury because they are effort dependent. Thus pain, weakness, dyspnea, and narcotic administration all adversely affect the ability of the patient to comply with testing. However, normal pulmonary function tests essentially rule out the possibility of significant inhalation injury since the FEV_1/FVC percentage is a sensitive early marker for airway obstruction. Thus, despite the compliance problems, such tests are useful for their negative predictive value (94–100%) when triaging large numbers of victims for further treatment (3).

MANAGEMENT

Although there are many disparate causes of inhalation injury, initial therapy consists of a few common sense measures to stabilize the patient and confirm the diagnosis. Subsequent therapy (with the exception of specific treatments for poisonings) is largely supportive. Initial stabilization follows the principles garnered from the general management of trauma, with airway integrity as the top priority. After adequate respiration and circulation are assured (spontaneously or assisted), supplemental 100% oxygen should be administered during patient transport to the nearest appropriate medical treatment facility. Intravenous access should be secured and fluid resuscitation initiated as appropriate. The patient should be assessed for other life-threatening injuries while a pertinent history is obtained and a physical examination is expeditiously performed.

If respirations are labored or inadequate, the airway should be protected and ventilatory support provided by endotracheal intubation. Nasotracheal intubation using fiberoptic bronchoscopy, if possible, is preferred. If the patient is breathing spontaneously yet has a history and physical findings indicative of inhalation injury, then direct inspection of the airway by bronchoscopy should be performed to confirm the diagnosis. The natural history of upper airway injury is that edema and airway narrowing peak at 12 to 24 h postinjury. Thus, if a significant injury is evident on initial inspection, early prophylactic intubation to protect the airway is preferable to observation. Erroneously observing the patient until upper airway occlusion is imminent significantly complicates intubation and reduces the size of the endotracheal tube that can be placed. If the injury initially appears insignificant, then ICU observation is warranted. At the earliest sign of upper airway constriction (i.e., stridor), however, prompt intubation is mandatory. For victims with simple asphyxiation, little else need be done except to assure oxygenation and provide ventilatory support needed. Serial examinations should carefully document any neurologic changes.

For all patients with an inhalation injury, serial carbon monoxide levels should be obtained. Patients should receive 100% oxygen until their COHb level $<10\%$ since the elimination half-life ($t_{1/2}$) for COHb is dependent on oxygen tension. For example, the $t_{1/2}$ for COHb is 250 min in room air, 40 to 50 min with 100% oxygen (4,5), and 27 min in 100% oxygen at 2 atm pressure (6). Thus, supplemental oxygen accelerates elimination of the carbon monoxide.

Specific therapy for cyanide poisoning in patients with inhalation injury is also controversial, as there is no consensus on the incidence of clinically important

cyanide exposure. Proponents of therapy point out the increased incidence of fires involving polyurethanes, which produce large amounts of hydrogen cyanide. Opponents cite the lack of correlation between cyanide levels and mortality in fire victims. Cyanide uncouples oxidative phosphorylation by binding to mitochondrial cytochrome a-a_3. Therefore, for patients with unexplained severe metabolic acidosis, tachycardia, tachypnea, elevated central venous oxygen content, and normal arterial oxygen content, treatment should be considered. The goal of therapy is to create a sink of ferric iron that traps the cyanide until it can be converted to thiocyanate through the actions of the hepatic enzyme rhodanese. The most convenient sink is hemoglobin and the administration of amyl and sodium nitrite, which convert the ferrous iron in heme to the ferric form, accelerates the formation of cyanhemoglobin. Sodium thiosulfate is administered to ensure that sufficient sulfur substrate is available to rhodanese for the conversion of cyanate to thiocyanate. The thiocyanate ion is then excreted by the kidneys to complete the process.

Except for carbon monoxide or cyanide poisoning there is no specific treatment for toxins associated with most inhalation injuries. Once the airway is secure and the patient oxygenated, priority should be given to minimizing airway edema, maintaining pulmonary toilet, relieving mechanical restriction of chest wall motion, and treating any bronchospasm. Elevation of the head of the bed may help decrease airway edema and minimizes the effect of the abdominal pressure on diaphragmatic excursion. Appropriate fluid resuscitation must be carried out regardless of its potential to exacerbate airway edema. Respiratory failure is much easier to treat and much less morbid than persistent hypovolemic shock and renal failure. Chest physiotherapy to stimulate cough and clear secretions is very helpful. Adequate humidification of inspired gas may help reduce inspissation of mucus in the injured airways. Circumferential full thickness burns of the thorax may require escharotomies placed along the anterior axillary lines bilaterally and connected by a transverse incision anteriorly to prevent constrictive limitation to chest wall excursion. If wheezing occurs, a trial of standard $beta_2$ agonist (albuterol or equivalent) via a nebulizer may decrease bronchospasm. If this therapy is not successful, i.v. aminophylline should be instituted. Steroids should be avoided unless the patient was steroid dependent before injury or has persistent bronchospasm unresponsive to other therapy.

If the above measures are insufficient and respiratory failure ensues, mechanical ventilation is necessary. Airway resistance is often increased following inhalation injury secondary to edema, debris within the airway, or bronchospasm. Thus, increased airway pressures often result if minute ventilation is fully supported by conventional "volume controlled" mechanical ventilation. High airway pressures decrease tracheobronchial mucosal blood flow, potentiating mucosal ischemia. Therefore, short of developing significant respiratory acidosis, elevated levels of carbon dioxide physiologically are well tolerated. The goal of mechanical ventilation should be to accept a slightly acidic ($pH_a \geq 7.32$) environment in order to minimize the mean airway pressure required for ventilation; so-called "permissive hypercapnia." Similarly, "normal" levels of pO_2 may require high levels of positive end expiratory pressure, which may further elevate airway pressures. Since oxygen satura-

tions >93% or pO_2 >70 are sufficient to maintain an adequate oxygen concentration gradient in peripheral tissues, maneuvers to increase oxygenation in excess of these requirements may be detrimental if they result in higher airway pressures. To keep airway pressures to a minimum, ventilator settings may need to be adjusted to slightly higher respiratory rates (16–20 breaths/min) and smaller tidal volumes (7–8 ml/kg). While PEEP of 5 cm H_2O may minimize alveolar collapse and reduce opening pressures, additional PEEP should be avoided if feasible. Experimental evidence reported by Cioffi et al. (7) has shown in a baboon model of moderate smoke inhalation that the barotrauma index (rate pressure product) was significantly increased during conventional ventilation in comparison to high-frequency flow interruption ventilation. There was also significantly greater histologic damage of pulmonary parenchyma in the group treated with conventional ventilation. The utility of this mode of ventilation appears to be its ability to recruit damaged collapsed alveoli and maintain these alveoli in an open state during expiration. Maintaining alveolar recruitment at low mean airway pressures helps to minimize barotrauma and allows improved distribution of ventilation. Two retrospective clinical studies (8,9) have demonstrated a significant decrease in the incidence of pneumonia and mortality in patients with inhalation injury when high-frequency percussive ventilation was used in comparison to conventional "volume limited" ventilation.

COMPLICATIONS

Early complications of inhalation injury are usually mechanical or infectious in etiology. Barotrauma underlies the majority of mechanical complications and most commonly presents as a pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumoperitoneum. Patients at risk for barotrauma complications are those that require high mean airway pressures to maintain alveolar recruitment following severe inhalation injury. Occasionally barotrauma may occur in unintubated patients as the result of vigorous coughing and presents as a spontaneous pneumothorax. Infectious complications may present as tracheobronchitis or pneumonia. Respiratory tract infection has been shown to be the most common complication following inhalation injury (10). The incidence of pneumonia appears to be relatively stable (38%) in patients with inhalation injury although the mortality rate in these patients decreased from 46.6 to 29.4% (8). Because many of the natural airway defenses are bypassed in intubated patients, colonization of the respiratory tract with pathogenic organisms is rapid (11). Most bacterial pathogens originate from either the oropharynx, burn wound, or the GI tract.

The diagnosis of tracheobronchitis or pneumonia rests on the presence of fever, leukocytosis, productive cough, organisms and white blood cells in the sputum, and, for pneumonia, parenchymal infiltrates on chest roentgenogram. However, inhalation injury itself, without a superimposed infection, is characterized by fever, leukocytosis, productive cough, the presence of white blood cells in the sputum, and patchy perivascular and peribronchial infiltrates on chest roentgenogram. Thus the diagnosis of an infectious complication can be difficult to exclude simply on clinical findings. Any substantial change in the quantity and purulence of the patient's sputum, a change in the fever

pattern, a need for increased ventilatory support, a change in the pattern of infiltrates on chest roentgenogram, and the confirmation of organisms by Gram's stain and culture strongly support the diagnosis of an infectious complication.

Treatment consists of empiric i.v. antibiotics based initially on the Gram's stain of the sputum and later adjusted as dictated by subsequent sputum culture and antibiotic sensitivity results. Therapy should usually be administered for 10 to 14 days for common pulmonary pathogens, and both clinical parameters and serial sputum cultures should be followed to verify effectiveness of treatment. When available, serum antibiotic levels should be monitored to ensure that effective but not toxic quantities are being administered. Meticulous pulmonary toilet is also necessary to clear secretions and prevent atelectasis.

Other complications of inhalation injury may be related to prolonged mechanical damage or the consequences of an uncontrolled inflammatory process. Delayed mechanical complications occur most often as the result of tracheal or laryngeal damage from the endotracheal tube or tracheostomy tube cuff. Prolonged contact and excessive cuff pressure may cause erosion of the tracheal wall. Cartilaginous damage may allow the tracheal wall to collapse during negative airway pressures during inspiration (tracheomalacia). This complication manifest clinically as stridor and greatly increases the work of breathing. Erosion into adjacent structures (innominate artery or esophagus) may result in exsanguinating hemorrhage or severe mediastinitis. Injuries to the tracheal epithelium may result in fibrosis and stenosis of the trachea (subglottic stenosis) as the wound contracts. Tube instability, high cuff pressures (>20 cm H_2O), and prolonged time of intubation all contribute to the respiratory tract damage. These injuries are difficult to treat satisfactorily once they occur, emphasizing the importance of prevention (e.g., stabilization of the tube and careful surveillance of the cuff pressure). Expedient extubation when feasible or conversion to a tracheostomy for patients in whom prolonged ventilatory support is anticipated may help avoid these complications.

Inflammatory complications (bronchiectasis and bronchial stenosis) probably occur as a result of extensive neutrophil activation in a localized area of airway damaged by inhalation. Activated neutrophils produce both protease and oxygen radicals that may severely damage the already injured bronchial mucosa and extracellular matrix. Although most proteases are produced by neutrophils, alveolar macrophages, mast cells, basophil, eosinophil, and fibroblasts may also participate in protease secretion. Oxidants secreted by neutrophils are known to inhibit the function of $alpha_1$-antitrypsin resulting in prolonged action of proteases such as neutrophil elastase, collagenase, cathepsin, and gelatinase (12). Because normal host defense mechanisms protecting mucosal integrity (antiproteases and antioxidants) have been shown to function poorly after inhalation injury (13), uncontrolled degradation of extracellular matrix proteins may occur. The ravages of this inflammatory process may manifest in acute disease such as adult respiratory distress syndrome and chronic lung dysfunction such as emphysema and bronchiectasis.

PATHOPHYSIOLOGY

Etiology

The specific causes of inhalation injury may be conveniently divided into two

classes: thermal and chemical. Although injuries caused exclusively by either thermal or chemical means are uncommon, an example of a pure thermal injury would be steam and a pure chemical injury may occur from the fumes, gases, or mists of a chemical spill. Smoke from a fire is by far the most common etiology of inhalation injury: particles with adherent toxic chemicals and toxic gases are primarily responsible for the injury. Heat also contributes to the insult by increasing perfusion, absorption, and local distribution of the toxins within the airway (14).

Thermal

Although damage to respiratory mucosa may occur at sustained air temperatures of as low as 150°C (15), temperatures encountered during fires may range from 250 to >1100°C (16). The number of calories transferred to the respiratory mucosa or the pulmonary parenchyma determines the severity of injury (see Table 2). Steam due to its high thermal capacity (specific heat of water + heat of vaporization + specific heat of steam) is the main caloric source for the thermal injury. In contrast, the thermal capacity of hot dry air is only 0.24 cal/g/°C. As temperatures decrease toward 100°C, the disparity increases in magnitude; 1 L of hot dry air at 100°C releases only 15.6 cal, but 1 L of steam releases 782.6 cal. The supraglottic area (nasopharynx) is a very efficient thermal exchange surface. Therefore, hot air is usually cooled sufficiently by the time it reaches the trachea so that there is little heat available for transfer and resultant damage. Steam, however, due to its greater thermal capacity can overwhelm the supraglottic protection and create tremendous lower airway damage.

This pathophysiology is supported clinically by Pruitt (17) who reported in a review of 697 burn patients that only one patient demonstrated subglottic injury related to hot air alone. In this patient, the injury extended only a few centimeters below the glottis. Thus, damage caused by hot air usually affects only the supraglottic area. Steam, because of its greater thermal capacity, usually carries sufficient heat to the glottis, major airways, and pulmonary parenchyma to cause significant tissue damage (Table 3).

Chemical

Toxic inhalants consisting of fumes, gases, and mists may cause severe inhalation injuries, an effect primarily related to chemical exposure (14). The total toxic effect of the inhalant is also related to the systemic toxicity of the inhaled agent because many irritant agents are well absorbed across the respiratory mucosa. The level at which the injury oc-

TABLE 2. *Relative amounts of heat transferred by air and steam*

Both air and steam have approximately the same density (1.3 g/L). The amount of heat transferred by 1 L of either substance cooled from 1000°C to 37°C (body temperature):

Air $(1000 - 37)°C \times 1.3\ g \times 0.24\ cal/g/°C = 300.5\ cal$

Steam $[(1000 - 100)°C \times 1.3\ g \times 0.48\ cal/g/°C] + [1.3\ g \times 539\ cal/g] + [(100 - 37)°C \times 1.3\ g \times 1\ cal/g/°C] = 1344.2\ cal$

0.24 cal/g/°C = thermal capacity of hot dry air
0.48 cal/g/°C = thermal capacity of steam
539 cal/g = heat of vaporization of water
1 cal/g/°C = thermal capacity of water

TABLE 3. *Sites and severity of thermal inhalation injury indexed by causative agent*

Agent	Upper trachea	Lower trachea	Parenchyma
Hot air	Mild	None	None
Flame	Moderate	Mild	None
Steam	Severe	Severe	Moderate

Mild - erythema
Moderate - edema, patchy mucosal erosion
Severe - edema, severe erosion with ulceration

curs is determined by physicochemical properties of the inhaled substance, its concentration, and the duration of exposure to the substance (see Table 4). In general, as particle size, irritant properties, and water solubility decrease, the site of injury moves distally toward the pulmonary parenchyma. Toxins of larger particle size, marked irritant properties, or high water solubility more characteristically affect the major upper airways or nasopharynx.

Water solubility (19), concentration, and warning properties, e.g., irritation or odor, determine the site where a gas causes injury. Gases that are highly water soluble (HCl, SO_2, NH_3) are highly irritating and most damage occurs in the upper airways. Gases with low solubility and less irritation (phosgene, nitrogen oxides) result in deep penetration and greater pulmonary parenchymal damage.

TABLE 4. *Determinants of site and severity of respiratory tract injury (18)*

I. Toxic inhalant
  A. Physicochemical properties
    1. Particle size
    2. Water solubility
    3. Reactivity
    4. pH
    5. Warning properties (odor, irritation)
  B. Amount inhaled
    1. Concentration
    2. Duration of exposure
    3. Depth of breathing
    4. Minute ventilation
II. Host
  A. Ability to escape exposure
  B. Preexisting lung diseases
  C. Olfactory senses
  D. Status of host defense mechanisms

Particle size is very important in determining the site of injury when fumes or mists are inhaled. Suspended large particles moving in the region of laminar flow (as air passes through the respiratory tract) develop significant inertia. Turbulent airflow, such as at bifurcations of the airway, separates the particles from the laminar flow as a consequence of their inertia and promotes their deposit. This mechanism is responsible for removal in the nasopharynx of nearly all particles >10 μm in diameter and the deposition of particles between 5 and 10 μm in the upper airways. For particles between 0.5 and 5 μm in diameter, sedimentation occurs in progressively smaller airways of the pulmonary parenchyma and finally in the alveoli. Particles with diameters <0.5 μm are primarily deposited in the alveoli.

The injury resulting from inhalation of a fume is related not only to the presence of the particles but also to the inherent toxicity of the particle. The number and amount of toxic chemicals produced in the fire environment is dependent on the types of fuel, temperature, and amount of oxygen present.

Toxic inhalants may be classified by their mechanism of toxicity. Several agents, particularly the simple asphyxiants and neurotoxin, are noted to have no significant local toxicity, yet have profound systemic toxicity. Asphyxiants cause injury by replacing oxygen in the ambient atmosphere (simple asphyxiants), occupying oxygen binding sites on hemoglobin (carbon monoxide), or by uncoupling electron transport in cellular oxidative phosphorylation (met-

abolic asphyxiants). Simple asphyxiants include products of combustion such as carbon dioxide, nitrogen oxide, and the fire environment itself. The mechanism of action of all simple asphyxiants is to decrease the partial pressure of oxygen in the ambient atmosphere. At critically incapacitating levels of pO_2 (<40 mm Hg), unconsciousness generally occurs in 120 to 150 s, and rational thought processes are lost much sooner (20). Even if the anoxic injury itself is not immediately fatal, the patient's ability to escape may be impaired. The fire environment is often overlooked as a cause of asphyxiation: decreased atmospheric oxygen tensions to as low as 15 mm Hg (equivalent to an altitude of 56,000 ft) have been reported (16).

Carbon monoxide (CO) is an odorless, colorless, nonirritating gas produced by incomplete combustion of organic material. The toxic effect of CO is related to its impairment of oxygen transport by occupying oxygen-binding sites on the hemoglobin molecule. While CO combines with hemoglobin at one tenth the rate of oxygen, it dissociates at 1/2200 the rate of oxygen. This yields a net affinity for hemoglobin 220 times greater than that of oxygen (21). Thus, toxicity relates to two factors: reduction in oxygen-carrying capacity and interference with hemoglobin–oxygen dissociation in the tissues. Decreases in the oxygen-carrying capacity are proportionate to the amount of carboxyhemoglobin formed. Also, the normal cooperative property of the heme–globin–oxygen interaction to unload O_2 in peripheral tissues is disrupted by CO, resulting in the oxygen dissociation curve to shift to the left decreasing oxygen release to the tissues. CO concentrations of just 0.5 to 1.0% (5000–10,000 ppm) lead to blood carboxyhemoglobin levels of 70 to 80% after 1 to 2 min of exposure (22). A postmortem carboxyhemoglobin level >50% is usually considered evidence of a CO-induced death (23). It is one of the most dangerous constituents of smoke.

Metabolic asphyxiants bind to cytochrome enzymes in the electron transport chain and uncouple oxidative phosphorylation. The prototypical metabolic asphyxiant is hydrogen cyanide. Uncoupling of the oxidative phosphorylation pathway prevents aerobic metabolic generation of ATP, forcing a conversion to anaerobic metabolism. Consequently, lactic acidosis results. CO is also a potential metabolic asphyxiant because of its ability to bind to cytochrome oxidase and thus prevent cellular utilization of oxygen. Clinically this effect is a minor aspect of carbon monoxide poisoning.

Inflammatory Response

The primary effects of inhalation injury include direct damage to the respiratory epithelium and impairment of mucociliary function, which reduces the clearance of foreign material from the respiratory tract. The extent of the inflammatory response is also directly proportional to the dose of smoke (24). Shorter exposures result in disorientation, clumping, and loss of cilia with blebbing and superficial epithelial erosion. Prolonged toxic exposure results in severe injury with necrosis and sloughing of epithelium. Inflammatory changes are noted within 2 h after injury and include interstitial edema, neutrophil invasion, and pseudomembrane formation. Mucus production is markedly increased within 12 h of injury. The peak neutrophil response occurs at 24 h, with bacterial colonization present by 72 h. Mucociliary dysfunction, edema, and epithelial injury of the major airways cause secondary injury in the dependent

areas of pulmonary parenchyma. Occlusion of the terminal airways from debris and edema causes atelectasis and, subsequently, bronchopneumonia. With increasing smoke severity, prominent alveolar interstitial edema and marked damage to type I pneumocytes may also occur (25).

Temporal examination in an ovine model for smoke inhalation have categorized four overlapping phases of injury and repair (26). The first phase is an exudative phase occurring during the first 48 h postexposure. This phase is characterized by formation of interstitial edema and accumulation of neutrophils in the pulmonary interstitium. The second phase is degenerative, lasting from 12 to 72 h postexposure. Progressive epithelial necrosis and formation of pseudomembranous casts are seen. This debris may partially or completely obstruct small bronchi. Necrosis of type I alveolar cells also occurs, producing areas of exposed alveolar basement membrane and forming fibrinous, debris-laden pseudomembrane. Type II pneumocytes appear to be more resistant to injury and remain intact. The third phase, extending from the second to seventh day postinjury, is proliferative; macrophages infiltrate and phagocytize necrotic debris. This is accompanied by hyperplasia of type II pneumocytes to cover denuded basement membranes in alveoli; surviving basal epithelial attach mucosal integrity in the airways. The last phase is reparative; mild injuries return to normal morphology. More severe injuries may progress to fibroblast proliferation with subsequent interstitial or intraalveolar fibrosis.

The exact factors responsible for orchestrating the response to inhalation injury remain obscure. Oxygen radicals present in smoke directly damage epithelial cells and stimulate pulmonary macrophages to release chemotactic factors. Activation of the arachidonic acid pathway is also activated and may contribute to edema formation (27) and bronchoconstriction (26). Preinjury induction of leukopenia, oxygen free radical scavengers (28), and cyclooxygenase inhibitors (29) have been noted to ameliorate but not eliminate the adverse effects of smoke inhalation.

The initial release of vasoactive substances from the damaged epithelium produces pulmonary arterial hypertension and bronchospasm that exacerbate V/Q mismatch. Interstitial edema decreases pulmonary compliance. The mucociliary function is disabled postinjury. This results in poor clearance of necrotic debris and toxins from the airway. The net result is a prolonged bronchorrhea and cough. Sloughed necrotic epithelium, inflammatory exudate, and mucus form casts that perpetuate the atelectasis and exacerbate both V/Q mismatching and hypoxia (30), and may result in barotrauma and pneumonia.

During mechanical ventilation, mean airway pressure may exceed mucosal perfusion pressure, and the resultant ischemic injury may compound the existing inhalation injury. Perpetuation or exacerbation of the inflammatory process may result in increasing mucosal slough, interstitial edema, and decreasing compliance. This scenario may lead to worsening barotrauma, as well as increased likelihood of pneumonia. Eventually, adult respiratory distress syndrome and multiple organ system failure may arise.

Current work in the field of lung injury centers on the following areas: modification of existing ventilator therapy to reduce the incidence and severity of barotrauma, mechanisms of neutrophil recruitment and activation, modulation of extracellular protease and oxygen rad-

icals, the role of deficient surfactant function, prevention of tracheobronchial cast formation, reduction of pulmonary hypertension, and the role of numerous inflammatory mediators (TNF, IL-1, IL-8, prostaglandin, and leukotriene) in propagation of local injury.

Numerous cells residing in the lung have the ability to produce chemotactic and inflammatory activating substances, notably alveolar macrophages (TNF, IL-1, IL-8, platelet activating factor, platelet-derived growth factor), endothelial cells (IL-1 and IL-8) (31,32), and possibly epithelial cells (IL-8 and leukotriene) (33,34). Many of these substances are also under investigation for their contributions to the pathogenesis of adult respiratory distress syndrome and multiorgan system failure. Identification of the roles of these substances in amplification of the initial injury response may in the future provide an excellent opportunity to intervene and modulate the inflammatory cascade and thus minimize airway damage and hasten recovery. Extracellular protease and oxidants are the direct mediators of neutrophil induced injury. Protease inhibitors such as $alpha_1$-antitrypsin and $alpha_2$-macroglobulin are the primary antiproteases present in the lung under normal circumstances. Extensive neutrophil activation and release of large amounts of oxidant species result in inactivation of antiproteases. Therapy that increases the quantity of free radical scavengers and functional antiproteases, or controls the synthesis and secretion of oxygen radicals and proteases, may be effective in preventing secondary injury to normal lung. Experimentally, free radical scavengers such as dimethylsulfoxide have been shown to improve survival (in one study) and decrease lung microvascular permeability following inhalation injury in an ovine model (28,35). Also in an animal study, pentoxifylline has been demonstrated to significantly reduce leukocytosis, polymorphonuclear cell counts and total protein content of bronchoalveolar lavage fluid following inhalation injury (36). In addition, pulmonary compliance, respiratory index (a measure of oxygenation efficiency), V_A/Q mismatching, and pulmonary vascular resistance were all significantly improved following administration of pentoxifylline. A recent study investigating the effects of nitric oxide insufflation following inhalation injury found that while pulmonary vascular resistance could be reduced, nitrous oxide had no apparent effect on the magnitude of inflammation (37). In an ovine model of inhalation injury, the administration of a platelet-activating factor antagonist decreased leukocytosis and lipid peroxidation (38). In experimental models of inhalation injury, heparin has proved effective alone (39) and in combination with dimethylsulfoxide (28,35) in reducing airway obstruction by decreasing the cast formation of sloughed epithelial cells and protein-rich exudate that commonly obstruct the airways. Significant reductions in the magnitude of ventilatory pressure needed to attach adequate minute ventilation were noted. Although these initial animal studies are promising, prospective randomized studies will be necessary to document whether these various agents favorably influence morbidity and mortality in patients with inhalation injury.

Deficient surfactant function has been demonstrated in many animal models of lung injury as well as in studies of acute respiratory disease syndrome (ARDS) patients (40). The deficiency results from inactivation of existing surfactant via lipid peroxidation and apoprotein cleavage, as well as decreased production from

type II pneumocytes. Inactivation of surfactant results in loss of hysteresis in the lung, encourages alveolar collapse, markedly increases peak and mean airway pressures, worsens V/Q mismatch, increases extravascular lung water, and greatly decreases ventilatory efficiency (41). Despite the theoretical advantage, clinical research trials in patients with ARDS have demonstrated no efficacy with exogenous surfactant administration. Trials of adjuvant surfactant therapy in patients following smoke inhalation are ongoing.

CONCLUSION

At present, care of the patient with inhalation injury is supportive, with an emphasis on prevention or early recognition of complications. Efforts to minimize barotrauma are important to decrease the incidence of mechanical complications and minimize the inflammatory response. Further research into the pathogenesis of inhalation injury may lead to the development of specific therapies to minimize the insult and to prevent the exaggerated inflammatory sequelae.

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