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INHALATION INJURY: Pathophysiology, Diagnosis, and Treatment

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Synopsis

The classic determinants of mortality from severe burn injury are age, size of injury, delays of resuscitation, and the presence of inhalation injury. Of the major determinants of mortality, inhalation injury remains one of the most challenging injuries for burn care providers. Patients with inhalation injury are at increased risk for pneumonia – the leading cause of death – and multi-system organ failure. There is no consensus amongst leading burn care centers in the management of inhalation injury. Outlined below are current treatment algorithms and the evidence of their efficacy.

Keywords

Inhalation injury; pneumonia; respiratory failure; bronchodilators; heparin

Introduction

There is no greater trauma than a large burn. No single injury affects more organ systems than a severe burn injury. The subsequent supraphysiologic responses to that injury lead to full body catabolism and increased morbidity and mortality. Advances in critical care management, nutrition, wound coverage, and anti-microbial therapies have substantially improved outcomes for burn survivors regardless of burn size. However, when burns are accompanied by inhalation injury, health care providers and clinical scientists have yet to make major impacts on survival.

Inhalation injury is present in up to one-third of all burn injuries, however it accounts to up to 90% of all burn-related mortality[1–3]. Inhalation injury causes localized damage via direct cellular damage, changes in regional blood flow and perfusion, airway obstruction, as well as toxin and pro-inflammatory cytokine release[2,4]. Inhalation injuries significantly incapacitate mucociliary clearance and impair alveolar macrophages[5]. It predisposes patients to bacterial infection, specifically and primarily pneumonia, a leading cause of death for burn patients[6,7]. In fact burn critical care units have the highest rates of ventilator associated pneumonia in the country, and those patients with concomitant cutaneous injuries with inhalation injury have double the rates of ventilator associated pneumonia[5]. Moreover, the probability of death increases from 40% to 60% when a burned patient with inhalation injury has pneumonia compared to those with just cutaneous injuries[8].

Pathophysiology

The mechanism of destruction can be classified in one of four ways: 1) upper airway injury, 2) lower airway injury, 3) pulmonary parenchymal injury, and 4) systemic toxicity. The extent of damage from an inhalation injury depends on the environment and the host: the source of injury, temperature, concentration, and solubility of the toxic gases generated, and the response to that injury by the individual[9]. Inhalation injuries cause formation of casts, reduction of available surfactant, increased airway resistance, and decreased pulmonary compliance[10], leading to acute lung injury and acute respiratory distress syndrome[11].

The major pathophysiology seen in the upper airway inhalation injury is induced by microvascular changes from direct thermal injury and chemical irritation[6]. The heat denatures protein, which subsequently activates the complement cascade causing the release of histamine[9,12]. Subsequently, there is the formation of xanthine oxidase, and release of reactive oxygen species (ROS) which combines with nitric oxide in the endothelium to induce upper airway edema area by increasing the microvascular pressure and local permeability[9,13,14]. Pro-inflammatory cytokines, ROS and Eicosanoids attract polymorphonuclear cells to the area further amplifying ROS and signaling proteases[15–17]. There is a substantial increase in microvascular hydrostatic pressure, a decrease in interstitial hydrostatic pressure and an increase in interstitial oncotic pressure[9]. The hallmark of burn resuscitation is the administration of large amounts of crystalloid, which reduces plasma oncotic pressure affecting the oncotic pressure gradient in the microcirculation causing significantly more airway edema[9]. Barring steam inhalation injuries and blast injuries, the

upper airway efficiently protects the lower airway via heat exchange to limit distal damage to the lower airway.

Injury to the lower airway is due to the chemicals in smoke. The heat capacity of air is low and the bronchial circulation very efficient in warming or cooling the airway gases, so that most gases are at body temperature as they pass the glottis[18]. In order to induce thermal injury to the airway, flames must be in direct contact[19]. Accelerants, or burned biological materials are caustic to the airways and induce an initial response to trigger pro-inflammatory response. There is a 10-fold increase in bronchial blood flow within minutes of an inhalation injury[20] which is sustained and causes increased permeability and destruction of the bronchial epithelium[9]. There is a subsequent increase in pulmonary transvascular fluid and a fall in $PaO_2/FiO_2 \leq 200$ nearly 24 hours after injury[21]. There is a subsequent hyperemia of the tracheobronchial tree and lower airways and that clinical finding – so prevalent – is used to diagnose the injury[22–25]. Early in the injury, the secretions, from goblet cells, are copious and foamy in nature. In hours to days these secretions solidify forming casts and airway obstruction[9].

Changes to lung parenchyma are delayed, dependent on the severity of injury and the patient's response to the injury. Parenchymal injuries are associated with an increase in pulmonary transvascular fluid which is directly proportional to the duration of exposure of smoke and toxins. As stated previously, injury to the lower airways and lung parenchyma is rarely due to direct thermal contact. Only steam can overcome the very efficient upper airway heat dissipating capabilities[6]. There is a reduction to the permeability of protein, an increase in the permeability to small particles, an increase in pressure in the pulmonary microvasculature pressure, and a loss of hypoxic pulmonary vasoconstriction[9]. The key pathological derangements in inhalation injury are edema, decreased pulmonary compliance from extravascular lung water and pulmonary lymph, and immediate inactivation of surfactant. There is a subsequent ventilation perfusion mismatch that can lead to profound hypoxemia and ARDS[6].

Systemic toxic changes are caused by the inhalation of chemicals and cytotoxic liquids, mists, fumes and gases. Smoke combines with these toxins and increase mortality by increasing tissue hypoxia, metabolic acidosis, and decreasing cerebral oxygen consumption and metabolism[26,27].

Diagnosis

Traditionally, the diagnosis of inhalation injury has rested on both subjective and objective measures. History and physical are important factors as they may help prognosticate the host response and co-morbidities. For example, the elderly population that is unable to escape from danger may have prolonged exposure to smoke and toxins. Key factors in diagnosis from history would be: mechanism (flame and smoke or steam), exposure (duration), location (enclosed space), disability. For the physical exam: facial burns, singed nasal or facial hair, carbonaceous sputum, soot, stridor or edema[6,23]. There are no changes in chest X-ray on admission. Oxygen saturation by pulse oximetry (SpO_2) is usually not initially affected and may be misleading, even in the presence of carbon monoxide poisoning where

the SpO_2 is typically normal. Similarly, arterial blood gases are non-diagnostic. Even in the presence of carbon monoxide poisoning, the PaO_2 will be normal or increased and only the arterial oxygen saturation will be found to be decreased.[9].

Other adjuncts used for confirming inhalation injury include carboxyhemoglobin measurements, chest computed tomography (CT), fiberoptic bronchoscopy (FOB), radionuclide scan with 133 Xenon, and pulmonary function testing[23]. To date, these tools have substantial variability within and between institutions and lack sensitivity. Of the aforementioned studies, FOB prognosticates risk of acute lung injury, resuscitative needs and mortality most accurately and will be the focus of this review[28].

FOB is the standard technique for diagnosis of inhalation injury. It is readily available and allows a longitudinal evaluation. The presence of hyperemia, edema and soot on FOB are diagnostic of inhalation injury but there remains a discordance of determining severity of injury. Severity of injury depends on the material inhaled, length of exposure, and the host response to this trauma. To further underscore the problem with grading inhalation injury, FOB – the most widely accepted diagnostic tool – cannot access distal airways. Hence, damage in the most distal airways is assumed and hypothesized to be the explanation of inconsistent severity of bronchoscopic findings and mortality.

The most widely used approach for grading the severity of an inhalation injury is the Abbreviated Injury Score (AIS), popularized by Endorf and Gamelli[29]. The AIS assigns a severity score from 0 (no injury) to 4 (massive injury) based on the findings at the initial FOB examination. The Abbreviated Injury Score grading scale for inhalation injury on bronchoscopy has shown variable results with respect to predicting outcome. Higher grade injuries have been associated with poorer oxygenation in some studies[30,31] but not others[32–34]. Similarly, a higher (worse) grade of inhalation injury was associated with a longer duration of mechanical ventilation in one study[32], whereas other investigators have not been able to demonstrate this relationship[29,31]. Surprisingly, the AIS grade of inhalation injury severeity has not been found to be associated with fluid resuscitation requirements[29,31,32]. Finally, the grade of inhalation injury severity does not consistently correlate with an increase in mortality[29,31,32]. A recent study has found that clinically relevant trends towards worse oxygenation, more prolonged mechanical ventilation, and higher fluid resuscitation volumes were associated with patients with “high grade” inhalation injuries (former grades 3 and 4) compared to those with “low grade” inhalation injury (former grades 1 and 2)[35]. Further refinement of this approach is required and it is worth noting that serial bronchoscopic evaluations over the 1st 24–48 hours post burn may yield more accurate information than a single examination at burn center admission.[28,31,32].

Laboratory values used to determine severity include PaO2/FiO2 and alveolar-arterial gradients but these can be arbitrarily high or low depending upon ventilation modes and other clinical parameters[23].

Treatment

While mortality rates for inhalation injury has not changed significantly over the last fifty years, the improvements in standards of care for severe burn injuries have. Thus, survival is standard. There is no consensus amongst leading burn centers the optimal treatment protocol for inhalation injury. The fundamental tenet of treatment for inhalation injury is supportive care through the acute hospitalization and rehabilitation. This review will outline key evidence in the literature to common treatment modalities for patients with inhalation injury.

Supportive Care

Inhalation injuries cause formation of casts, reduction of available surfactant, increased airway resistance, and decreased pulmonary compliance[10]. Patients require aggressive pulmonary toilet, chest physiotherapy, airway suctioning, therapeutic serial bronchoscopies, and early aggressive ambulation. This defines our current treatment options.

Bronchodilators

Bronchodilators decrease airflow resistance and improve airway compliance. β2-adrenergic agonists such as albuterol and salbutamol decrease airway pressure by relaxing smooth muscle and inhibiting bronchospasm thereby increasing the PaO2/FiO2 ratio[36].

Muscarinic receptor antagonists

Muscarinic receptor antagonists such as tiotropium decrease airway pressures and mucus secretion and limit cytokine release by causing smooth muscle constriction within the airways, and stimulation of submucosal glands[37,38].

Both beta agonists and muscarinic receptor antagonists decrease the host inflammatory response after inhalation injury. Anatomically, there are muscarinic and adrenergic receptors found lining the respiratory tract. How that impacts the inflammatory response and host response is largely unknown. They have been shown to decrease pro-inflammatory cytokines after stress[39].

Inhaled (nebulized) Mucolytic agents and Anticoagulants

The airway obstruction secondary to mucus, fibrin cast formation, and cellular debris subsequent to inhalation injury are addressed by mucolytic agents, specifically, N-acetylcysteine (NAC)[40]. NAC is an antioxidant and free radical scavenger with anti-inflammatory properties[41]. It is a powerful mucolytic agent that attenuates ROS damage[23].

Inhaled anticoagulants are also used to mitigate airway obstruction from fibrin casts. Heparin has anti-inflammatory properties, it prevents the formation of fibrin and inhibits cast formation. The available evidence from a limited number of human studies[42–45], is somewhat controversial. Some studies suggest that among mechanically ventilated burn patients with inhalation injury, one week of therapy with nebulized heparin (5000 – 10 000 units) alternating with 3 mL of 20% NAC every four hours is beneficial, leading to improved oxygenation and lung compliance, lower re-intubation rates, and higher survival[42,44,45]. Other studies have found no improvements in outcome with this therapeutic intervention[43].

Respiratory support

Without consistent reproducible data to support the use of the above pharmacologic adjuncts, other centers have focused on the risks and benefits of different modes of ventilation. Ideally, aggressive pulmonary toilet without the use of mechanical ventilation improves outcomes. However, there is often such significant upper airway edema from the inhalation injury, or the resuscitation of the cutaneous injury that leads to worsening airway edema. This physiologic consequence can be deadly and may progress expeditiously[6]. It is thus paramount to obtain and sustain a definitive airway early in treatment.

The only mechanical ventilation strategies shown to improve morbidity and mortality from ARDS and ALI come from the ARDSNET trial, which showed in a large randomized controlled trial that lung protective strategies of limited tidal volumes of 6–8mL/kg and plateau pressures of less that 30cm H2O improved outcomes[46]. However, this study excluded burn patients with > 30% total body surface area. Conventional mechanical ventilation modes, to include control mode ventilation, assist-control mode, synchronized intermittent mandatory ventilation, pressure control mode and pressure support mode are limited in the patient with inhalation injury. In a patient with airway obstruction from fibrin casts, decreased airway compliance, extensive chest wall thermal injuries, or high volumes of resuscitative needs, maintaining the recommended tidal volumes of 6–8 ml/kg body weight and plateau pressures of less than 30 cm of water can prove impossible with conventional techniques[10,47]. These conventional settings may be inadequate to appropriately oxygenate and ventilate the patients with inhalation injury and overcome the obstructive and restrictive physiology. Thus, in order to support these patients and apply lung-protective ventilation strategies in patients with inhalation injury, nonconventional ventilator modes are often employed[48]. A recent survey of mechanical ventilation practices in North American burn centers identified wide disparity in ventilation approaches and a lack of consensus with respect to the optimal method of mechanical ventilation, be it conventional or unconventional.

High tidal volume (HTV) versus low tidal volume (LTV)

The efficacy of high tidal volumes compared to low tidal volumes in inhalation injury remains a work in progress. Contrary to the lung protective and mortality findings in the ARDSNET trial[46], one center retrospectively found that pediatric patients treated with high tidal volume ventilation had significantly fewer ventilator days, a lower incidence of atelectasis and ARDS compared to those treated with lower tidal volumes[10]. Of note, strict adherence to a LTV strategy in the burn patient with inhalation injury may not be feasible because of the associated problems of impaired chest wall compliance from restrictive chest wall eschar and edema, along with the problem of bronchospasm and bronchial obstruction related to inhalation injury. In fact, in the only randomized controlled trial in which LTV was assessed, a third of patients failed to meet oxygenation and ventilation goals and two thirds failed when a smoke inhalation injury had occurred[49]. Larger RCTs will need to be completed in order for a consensus to be made.

High-frequency percussive ventilation (HFPV)

High-frequency percussive ventilation (HFPV) was first described by Cioffi et al and Pruitt's group in patients with inhalation injury as a means of assisting with clearance of sloughed respiratory mucosa fibrin casts and mucus plugs, as well as decreasing the incidence of pneumonia[50,51]. It had been classically used as a salvage mode but subsequent studies from this group demonstrated significant benefits from using HFPV preemptively[50–54]. One of the major findings comparing HFPV with conventional and low tidal ventilation is a statistically significant increase in PaO2/FiO2 ratio, a decreased incidence of pneumonia – the leading cause of death, and survival benefit[50]. A randomized controlled trial comparing HFPV to LTV in human burn patients with burns and inhalation injuries found that while there were no significant differences in ventilator-free days, ventilator associated pneumonia, or survival between the two ventilation strategies, subjects receiving LTV required significantly more frequent "rescue" (by crossover to HFPV) to maintain adequate oxygenation and ventilation[49]. Physiologically, HFPV also improves secretion clearance, allows for more gentle (lower) airway pressures, and increased functional reserve capacity[50,51,55,56].

High Frequency Oscillatory Ventilation (HFOV)

HFOV is not a suitable ventilatory modality following inhalation injury, because bronchial obstructive changes likely impair any ability of HFOV to adequately open and recruit the lung[57,58]. Furthermore, enthusiasm for HFOV has waned following recent large RCTs such as the OSCILLATE[59] and OSCAR[60] studies in non-burn patients with the Acute Respiratory Distress Syndrome (ARDS) which found no benefit and potential harm related to HFOV. However, the findings from those studies possibly should not be directly extrapolated to burn patients, where differing etiology for ARDS (e.g. non-pulmonary) and chest wall mechanics (poor chest wall compliance), may affect the relative benefits and risks related to HFOV.

Airway pressure release ventilation (APRV)

APRV is an inverse ratio, pressure controlled mode of ventilation that allows for spontaneous breaths. It has been shown to recruit alveoli, imprve oxygenations and hemodynamics and potentially lung protective[61]. In inhalation injury, PaO2/FiO2 ratios were initially lower APRV compared with conventional mechanical ventilation, but equilibrated in 48 hours. APRV did require higher mean airway pressures to maintain oxygenation and there was no, survival benefit[62].

Extracorporeal membrane oxygenation (ECMO)

A systematic review and meta-analysis on the use of ECMO in inhalation injury is currently limited by the number of available studies. While there is no survival benefit, there is a trend towards increased survival in burn patients with acute hypoxemic respiratory failure treated with ECMO less than 200 hours compared with patients receiving greater than 200 hours. There was no mortality benefit if ECMO is delayed and initiated once the PaO2/FiO2 ratio was <60[63].

Summary

Despite gains in burn critical care, nutrition, our understanding of the hypermetabolic response to burns, burn wound coverage and rehabilitative strategies, we have failed to make significant gains in improving outcomes from inhalation injury. Supportive strategies are promising, but large, multi-centered trials are needed to demonstrate consistent results for many of the pharmacological adjuncts. Unconventional modes of ventilation, primarily HFPV show the most promising results and address the physiologic derangements from inhalation injury. Further studies are needed to better understand the pathophysiology and may help guide future therapeutic options.

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Key Points

- Determinants of mortality in burns are size of burn, age, and the presence of inhalation injury.
- Inhalation injury with or without cutaneous burn increases morbidity and mortality for burn survivors.
- Resuscitation efforts are significantly altered by the presence of inhalation injury.
- There is no consensus amongst leading burn centers on the optimal mechanical ventilation modes for these patients. Supportive care remains the mainstay of treatment.
- Despite research gains in nutrition, and the hypermetabolic response to burn injury, there remains a lack of understanding of the pathophysiology of inhalation injury and the long term physiologic consequences.