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Pathophysiology, management and treatment of smoke inhalation injury

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Abstract

Smoke inhalation injury continues to increase morbidity and mortality in burn patients in both the third world and industrialized countries. The lack of uniform criteria for the diagnosis and definition of smoke inhalation injury contributes to the fact that, despite extensive research, mortality rates have changed little in recent decades. The formation of reactive oxygen and nitrogen species, as well as the procoagulant and antifibrinolytic imbalance of alveolar homeostasis, all play a central role in the pathogenesis of smoke inhalation injury. Further hallmarks include massive airway obstruction owing to cast formation, bronchospasm, the increase in bronchial circulation and transvascular fluid flux. Therefore, anticoagulants, antioxidants and bronchodilators, especially when administered as an aerosol, represent the most promising treatment strategies. The purpose of this review article is to provide an overview of the pathophysiological changes, management and treatment options of smoke inhalation injury based on the current literature.

Keywords

acute lung injury; anticoagulants; antioxidants; β_2 -agonists; carbon monoxide; cyanide; nitric oxide; reactive oxygen species

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Smoke inhalation injury is generally defined as the inhalation of thermal or chemical irritants. With more than 23,000 injuries and 5000–10,000 deaths per year in the USA alone, smoke inhalation injury represents a major cause of morbidity and mortality in burn patients [1]. In addition, disasters such as the Station Nightclub Fire in Rhode Island in 2005 [2], or the devastating terrorism attacks on the World Trade Center in New York (NY, USA) [3,4] and the Pentagon in Washington (DC, USA) [5] in 2001 are associated with a high incidence of inhalation injuries. Among the 790 injured survivors from the World Trade Center attack, for example, 49% suffered from inhalation injury caused by toxic compounds in the smoke and dust [3,4]. Compared with isolated burns, a combined injury with smoke inhalation is associated with increases in fluid requirements [6], the incidence of pulmonary complications [7] and mortality [7–9]. It is important to remember however that smoke inhalation injury is not ‘only’ an adjunct to burn trauma; it is an independent injury in and of itself.

According to the WHO, more than 1 billion people develop airway and pulmonary inflammation as a result of inhaled smoke from indoor cooking fires, forest fires and burning of crops [10,11]. In addition, smoke toxicity is increasing because industrial products have shifted from woods and natural materials towards lighter construction materials, synthetics and petrochemicals, which ignite and burn two- to three-times hotter and faster. Thus, the probability that fire victims will breathe in smoke and toxic gases is increased, because they have less time to escape.

While there has been remarkable progress in the treatment of cutaneous burns in recent decades, mortality rates of patients with inhalation injury have changed little in the past 20 years [12]. The heterogeneity of smoke and the resulting differences in clinical symptoms may be one reason why a definition and specific diagnostic criteria of smoke inhalation injury are still lacking. The purpose of this review article is to provide an overview of the pathophysiological changes, management and treatment options of smoke inhalation injury based on the current literature.

Pathophysiology & clinical symptoms

Smoke is composed of a gas phase and a particle phase. Particle size and tidal volume determine their distribution in the lung. Physiologically, the nasopharynx clears the inspiratory air of the majority of particles with a diameter larger than 5 μm [13]. During a fire, however, victims (both conscious and unconscious) breathe through the mouth owing to the nasopharyngeal irritation. As a result, particle deposition in the airway is much greater, causing progressive cellular injury and severe lung injury. The gas phase causes predominantly proximal airway and local damage, although some long-acting oxidants are able to reach distal lung tissues.

Smoke inhalation injury can be divided into three different types of injury [12]:

- Thermal injury, which is mostly restricted to the upper airway (exception: blast injury or steam inhalation)
- Chemical irritation of the respiratory tract
- Systemic toxicity owing to toxic gases

The location of the injury depends on the ignition source, the size of the particles in the smoke, the duration of exposure and the solubility of the gases. Based on the predominant localization, smoke inhalation injury is classified into injuries of [14]:

- The upper airway
- The tracheobronchial system or lower airway
- The lung parenchyma

- Systemic toxicity

This classification will be used in the following sections to represent the different effects of smoke inhalation injury. Figure 1 summarizes the pathogenesis of lung injury following smoke inhalation.

Upper airway

Owing to highly efficient heat exchange in the oro- and nasopharynx [15], the leading injury in the upper airway, above the vocal cords, is caused by thermal injury. In accordance to burns of other body areas, heat destroys the epithelial layer, denatures proteins and activates the complement cascade leading to the release of histamine and the formation of xanthine oxidase [16]. This enzyme catalyses the breakdown of purins to uric acid and thereby releases reactive oxygen species (ROS) such as superoxide [17]. Superoxide represents a highly reactive molecule, which is physiologically stabilized by its formation to hydrogen peroxide catalyzed by superoxide dismutase [18]. At the same time, nitric oxide (NO) formation by endothelial cells is increased by histamine stimulation. In this case, the reaction with NO to form reactive nitrogen species (RNS), such as peroxynitrite, is faster [18]. Both ROS and RNS cause an increased permeability of endothelium for proteins, resulting in edema formation. In addition, eicosanoids and IL-8 are released after injury, leading to the attraction of polymorphonuclear cells [19,20], which amplify the inflammatory process, for example by ROS production. In parallel, activation of pulmonary C-fiber receptors by inflammation and irritants of smoke causes vasodilation by increasing NO production, further aggravating edema formation [21].

While the immediate injury results in erythema, ulceration and edema (Figure 2), clinical symptoms, such as stridor, dyspnea or increased work of breathing might not be obvious until the edema is sufficiently large enough to impair the airway diameter significantly. This time difference can amount up to 18 h or even longer [22]. In the case of combined burn and smoke inhalation injury, however, the aggressive fluid administration necessary to treat the burn shock promotes edema formation [23]. In addition, accompanying face and neck burns might cause anatomic distortion or external compression of the upper airway, further complicating proper airway management [22]. In addition to the inflammation, damage of ciliary function impairs the physiological cleaning process of the airway, resulting in an increased risk of bacterial infections for several weeks. Furthermore, the increased production of viscous secretions causes distal airway obstruction and atelectasis, thereby impairing pulmonary gas exchange [22,24].

Tracheobronchial system

With rare exceptions, such as the inhalation of steam, injury to the tracheobronchial area is usually caused by chemicals in smoke. The airway is richly innervated by vasomotor and sensory nerve endings [25]. Smoke inhalation stimulates these nerves to release neuropeptides [26], which are potent bronchoconstrictors. Under physiological conditions, the mucosa produces neutral endopeptidases, which neutralize these toxic agents. Owing to severe cellular damage, this neutralization is lost [22]. Neuropeptidases also attract and activate neutrophils, resulting in the production of ROS [20]. Simultaneously, the activity of neuronal NO synthases (nNOS, NOS-1) is upregulated by neuropeptides [27]. NOS catalyze the formation of NO and L-citrulline from the amino acid L-arginine in a complex five-electron redox reaction. Three different isoforms of NOS have been identified in mammals: nNOS and endothelial NOS (eNOS, NOS-3) are constitutive isoforms, while the inducible isoenzyme (iNOS, NOS-2) can be upregulated by oxidative stress and systemic inflammation [28]. Notably, in case of substrate (L-arginine) or cofactor limitation, for example under pathophysiological conditions, NOS can also produce superoxide [29]. NO reacts with ROS such as superoxide to form RNS, for example peroxynitrite. Although this highly cytotoxic RNS represents the most cited example,

most of the ROS and RNS are able to interact with proteins, DNA or lipids by oxidation, nitration or nitrosylation, causing the inactivation of key enzymes such as the glycolytic enzyme glyceraldehydes-3-phosphate dehydrogenase or produce a single-strand breakage in DNA [30]. DNA damage leads to the formation of poly(ADP ribose) polymerase (PARP), a nuclear enzyme involved in DNA repair [31,32]. It has been shown that PARP activation can be induced by NO and its toxic products such as RNS [33].

Although the physiological function of PARP is beneficial, PARP activation depletes cellular ATP levels by forming ADP, possibly resulting in cellular dysfunction and apoptosis [32,34]. In addition, PARP activates nuclear factor κ B (NF- κ B), independent of its action to form PAR [35,36]. NF- κ B is known to upregulate IL-8 [37], resulting in the attraction and activation of polymorphonuclear cells and consecutively in the production of ROS. NF- κ B also stimulates iNOS formation [38], thereby accelerating the production of NO. NO and ROS react to form RNS, leading to DNA damage and PARP activation, and thereby a positive feedback loop is established [27].

Histologically, there is evidence of damage to the mucosal lining and peribronchial inflammation [14,22,39–42]. Loss of bronchial epithelium results in a profuse transudate with a high protein content. While these secretions form foam material during the early response, this transudate/exudate mixture solidifies during the pathogenesis, forming obstructive material, which might occlude lower airways. These airway ‘casts’ (Figure 3) are composed of mucus secretions, denuded airway epithelial cells, inflammatory cells and fibrin [24]. Especially when volume-controlled ventilator settings are selected, obstruction can promote a barotrauma of still-ventilated areas. Besides massive airway obstruction, further hallmarks of smoke inhalation injury include bronchospasm, increases in bronchial circulation and transvascular fluid flux [43]. A tenfold increase in bronchial blood flow within 20 min after smoke inhalation was reported in an experimental study. In addition, the same animals demonstrated a sixfold increase in pulmonary transvascular fluid flux [44]. Both of these changes promote the development of airway edema. Further clinical symptoms include persistent coughing and wheezing, soot-containing airway secretions, increased work of breathing resulting in hypoventilation, erythema, hyperemia and increased pulmonary shunting [22]. The latter is caused by the loss of hypoxic pulmonary vasoconstriction owing to high NO production [14].

Lung parenchyma

The damage of lung parenchyma following smoke inhalation injury is delayed. The time difference between the initial trauma and a decrease in arterial oxygen tension to inspiratory oxygen fraction ($\text{PaO}_2:\text{FiO}_2$) is correlated with the severity of the lung injury, and represents a consequence of changes described for the upper airway and the tracheobronchial system [14]. Alveolar injury is characterized by alveolar collapse and atelectasis owing to increased transvascular fluid flux, a lack of surfactant and a loss of hypoxic pulmonary vasoconstriction, resulting in impaired oxygenation. In addition, a severe imbalance in alveolar hemostasis, increased procoagulatory and decreased antifibrinolytic activity, leads to massive fibrin deposition in the airway, which prevents regular ventilation and causes a ventilation/perfusion mismatch [43]. By inhibiting surfactant, fibrin itself leads to atelectasis [45] and can attract inflammatory cells [46].

Activated neutrophils play a central role in the pathogenesis of smoke inhalation injury. First, they initiate and continuously support the pathological pathway described previously by producing ROS and releasing proteases, such as elastase [27]. Second, neutrophils activated in the bronchial circulation are drained into the pulmonary microvasculature [14]. Since activated neutrophils are stiff owing to F-actin activation, they are not able to traverse the pulmonary capillaries as usual by changing their shape [14]. Instead, they adhere to the alveolar

capillary membrane via L-selectin [47], causing direct damage by releasing proteases and ROS. Our group and our colleagues in Boston (MA, USA) were able to demonstrate that ligation of the bronchial artery reduces parenchymal injury following smoke inhalation [48–52]. The important role of activated neutrophils in the pathogenesis of smoke inhalation injury was verified by Basadre *et al.* [53]. In leucocyte-depleted sheep, a high percentage of the described response to smoke inhalation was prevented from occurring. However, since patients with smoke inhalation injury are at high risk for pulmonary infections, the depletion of leukocytes represents only a mechanistic rather than a therapeutic approach.

Systemic response & toxicity

Systemic response—The systemic response to smoke inhalation injury is characterized by a systemic inflammatory response syndrome (SIRS), caused at least in part by systemic circulation carrying proinflammatory mediators via the lung through the bronchial and pulmonary vasculature to systemic organs [48–52]. The reduction in systemic oxygen delivery owing to elevated carboxyhemoglobin (COHb) levels and a decreased cardiac function might represent further potential mechanisms [54]. After combined burn and smoke inhalation injury, the hypermetabolic state is characterized by increased oxygen consumption and a shift of arterial blood flow from the intestine to soft tissues or muscles, thereby increasing the risk of organ failure owing to bacterial translocation [55]. In addition, inflammatory mediators released in the lung lead to increased systemic vascular permeability and oxidative stress [56]. In the absence of burn injury, these systemic effects might occur with a delay of 24–48 h [22].

The interaction between burn and smoke inhalation injury was investigated by our research group in an established ovine model [57]. Pulmonary vascular permeability as represented by increases in lung lymph flow and bloodless lung wet-to-dry ratio was caused by smoke inhalation injury. The combination with burn injury increased permeability, while isolated burn injury showed no statistically significant differences compared with sham animals. Another interesting observation of this study was that burn injury caused an immediate myocardial depression, which was also seen in combined burn and smoke inhalation injury and is probably related to hypovolemia owing to fluid losses through the burned area. By contrast, myocardial dysfunction occurred approximately 18–24 h after isolated smoke inhalation and is mostly part of the SIRS.

The increased amounts of ROS after smoke inhalation injury originate from various origins [58]:

- Metabolism of adenosine monophosphate in ischemic tissues to hypoxanthine and its subsequent reaction with xanthine oxidase, leading to excessive production of superoxide and hydrogen peroxide;
- During oxidative phosphorylation in the mitochondrial respiratory chain;
- From the nicotinamide adenine dinucleotide phosphate oxidase system in several different cell types; for example, in neutrophils;
- Breakdown of arachidonic acid to form prostaglandins and leukotrienes [59].

Simultaneously, antioxidative protection mechanisms may be adversely affected by the disease process. Accordingly, we reported a marked reduction in antioxidant levels in severely burned patients [60]. Antioxidant deficiency potentially occurs for multiple reasons, including redistribution of antioxidants to immunoreactive tissues, dilution owing to fluid administration, insufficient intake and losses through biological fluids (exudates, drains and chyle) [61].

Systemic toxicity—A direct systemic effect of smoke inhalation injury is caused by inhalation of toxic gases during the combustion of organic and inorganic substances. With respect to morbidity and mortality, the two most relevant gases are carbon monoxide (CO) and cyanide. Other toxic gases and their symptoms are listed in Table 1.

Carbon monoxide—Carbon monoxide is not only one of the most frequent immediate causes of death following smoke inhalation injury, but also of poisoning deaths in the USA. It accounts for approximately 15,000 emergency room visits and 500 unintentional deaths each year [62]. CO is an odorless, colorless gas with an affinity for hemoglobin more than 200-times higher than that of oxygen [63]. Accordingly, inhalation of only 0.1% CO mixture can result in a life-threatening COHb level of 50% [14]. Oxygen delivery to organs is further decreased by a left shift of the oxygen–hemoglobin dissociation curve, impairing tissue oxygen availability [64]. In addition, CO inhibits hepatic cytochromes, leading to mitochondrial oxidative stress and membrane damage owing to lipid peroxidation [63].

Clinical symptoms vary depending on the concentration of CO, the duration of exposure and pre-existing morbidity of the patient. Generally, a COHb level of more than 90% may lead to immediate cardiac arrest [65]. Clinical symptoms mainly involve neurological and cardiovascular manifestations. Owing to a lack of alternatives, diagnosis of CO poisoning is still based on the measurement of COHb levels. However, the strength of the correlation between COHb levels and the severity of poisoning, the prognosis or the choice of therapy is discussed controversially [66]. Cellular mechanisms, such as caspase-mediated apoptosis, may play an additional role in CO poisoning [67]. Importantly, it has to be taken into account that the usual pulse oximeter can not differentiate between COHb and oxyhemoglobin and that venous blood underestimates the arterial COHb content [68]. However, there are now devices available (Masimo Set[®] Rad 57[™]) enabling physicians or paramedics to determine COHb levels noninvasively at the injury scene. In contrast to usual pulse oximeters, Masimo Set Rad 57 measures seven or more instead of two wavelengths.

Cyanide—Hydrogen cyanide (HCN) represents the gaseous form of cyanide (CN), which is a colorless gas with the odor of bitter almonds; however, HCN is difficult to detect at the site of a fire, as most inhalation injuries represent mixed intoxications. Notably, CN is a normal human metabolite as reflected by plasma levels of 0.3 mg/l in nonsmokers and 0.5 mg/l in smokers [69]. All cells, but mostly those in the liver, are able to convert CN into thiocyanide, which is excreted in the urine via the enzyme rhodanase. In case of large amounts of CN, this system can be overcome, especially in burned or traumatized patients who are hypovolemic [22]. Toxicity of CN is based on hypoxic states owing to the reversible inhibition of cytochrome c oxidase, which is the terminal oxidase of the respiratory chain. The definition of fatal blood levels, however, varies from 1–3 to 5 mg/l [70]. The lack of a precise definition may be one reason for controversial discussions regarding the role of CN poisoning within smoke inhalation injury. Advocates cite studies reporting increased CN plasma levels in nonsurvivors as compared with survivors of fire disasters [71,72]. By contrast, opponents argue that CN is likely to be rapidly consumed in fires. Davies and colleagues described CN concentrations in the smoke of 250 ppm, which went down to below 10 ppm at 8 min [73]. Neither the short-term exposure limit (15 ppm), nor the short-term lethal concentration (350 ppm) were exceeded [70]. Nevertheless, CN originates from numerous compounds during combustion (Table 1), resulting in an increased probability of CN intoxication in a fire victim. At the same time, diagnosis of CN poisoning represents a challenge at the injury scene, as generally described symptoms (e.g., increased lactate levels and base deficit, or metabolic acidosis) may also be caused by asphyxiation, under-resuscitation, CO poisoning or associated traumatic injury. However, owing to the high probability of its presence at a fire scene (especially in case of combustion of certain materials such as plastics), in combination with the difficult diagnosis

and its lethal potential, CN intoxication should be carefully considered in every patient with smoke inhalation injury.

Management

At the injury scene

The first priority at the injury scene is rescue of the victim from the source of fire to stop the exposure time. This is usually the responsibility of firefighters. In order to reduce COHb levels as soon as possible, a high flow of 100% oxygen should be administered via facemask immediately. The next step includes a short but careful body check to estimate the extent of smoke inhalation and to assess accompanying injuries such as burns and/or trauma. In addition, it is important to determine whether the victim has been exposed to an explosion, since this can cause barotrauma to the lung. If possible, information about comorbidities should be obtained. Indications of inhalation injury are summarized in Box 1. Usual cardiopulmonary monitoring (electrocardiogram, pulse oxymeter and noninvasive blood pressure) should be established.

Box 1

Indications and symptoms of inhalation injury

- Facial and neck burns
- Burned lips and vibrissae
- Soot-containing airway secretions
- Pathological respiration patterns (coughing, stridor and hoarseness)
- Dyspnea
- Cyanosis
- Neurological symptoms (current or past unconsciousness, dizziness, nausea and vomiting)

After these basic measures, a decision needs to be made on how best to secure the airway of the patient. On the one hand, the risk of a rapidly developing airway edema has to be taken into account even if no dyspnea is present. On the other hand, endotracheal intubation itself, especially at the injury scene, is associated with undeniable risks such as esophageal intubation, aspiration, barotrauma or laryngeal trauma. Therefore, in the authors' opinion, prophylactic endotracheal intubation is not generally advised in every patient and, depending on the technical skills, for every physician or paramedic. Nevertheless, it is important to consider that airway management will only become more difficult over time. Patients with heat and smoke inhalation injury combined with extensive face or neck burns definitely have to be intubated. In the case of oral burn without inhalation injury, an airway secured early represents the safest approach. However, victims with smoke inhalation injury but no facial or neck burns can be carefully observed and later be intubated, if necessary [22].

If the patient is endotracheally intubated, the tube should be carefully secured. Accidental removal of the endotracheal tube is easy and may be lethal. In cases of vocal cord damage, tracheostomy may be necessary to prevent further damage. The patient's head should be elevated to minimize facial and airway edema. As a matter of course, hemodynamic stability is a prerequisite. Aerolized epinephrine or corticosteroids may be beneficial to reduce upper airway edema [22]. However, there is no conclusive evidence for the efficacy of these treatment strategies. After initial stabilization of the patient, it might be very helpful for further treatment

to obtain information about the fire source, combustion products and the estimated duration of exposure. In case of specific intoxications, for example, HCN poisoning, recommended therapies should be started (please see the section entitled 'Mechanical ventilation strategies').

In-hospital treatment

After adequate airway management and arrival in the emergency room, the treatment of accompanying burn injuries or trauma usually represents the first, most immediate priority. Inhalation injury, by comparison, often develops with a latency of several hours. Nevertheless, airway management and oxygenation status of the patient, regardless if intubated or not, need to be reevaluated frequently to allow clinicians to react to the dynamic development of smoke inhalation injury [22]. After stabilization of cardiopulmonary hemodynamics and pulmonary gas exchange, the assumed diagnosis of smoke inhalation injury needs to be verified. However, as there are currently no uniform criteria available, diagnosis of smoke inhalation injury is usually a subjective decision based on a combination of history (please see the section entitled 'At the injury scene') and physical examination, which are confirmed by diagnostics [12]. The bronchoscopic examination of the airway represents the gold standard to detect a pathognomonic mucosal hyperemia. Chest radiographs may show signs of diffuse atelectases, pulmonary edema or bronchopneumonia. However, during the initial period, the degree of injury is usually underestimated based on the chest x-ray, as the injury is mainly confined to the airways [74].

Although many observational studies compared outcomes with various grading systems [75–77], there is still no uniform algorithm for assessing inhalation injury. As a result, no reliable indicators of progressive respiratory failure in patients with smoke inhalation injury have been identified so far [78,79]. This failure is largely explained by the extreme heterogeneity of the clinical presentation. In addition, the delay in the manifestation and development of acute lung injury (ALI) as a consequence of SIRS, initiated by accompanying burns or trauma, complicate the evaluation of the isolated effects of smoke inhalation. Useful tools to monitor smoke inhalation injury include frequent blood gas and sputum analyses [22].

Appropriate fluid resuscitation of patients with smoke inhalation injury is still subject to controversial debates. It has been demonstrated that smoke inhalation injury increases fluid requirements in burned patients [6,80]. This, of course, does not inevitably indicate that isolated smoke inhalation injury is associated with increased fluid requirements. By contrast, over-resuscitation may increase pulmonary microvascular pressures and might thereby lead to increased edema formation under the high permeability conditions in early lung injury [57, 81]. In a retrospective study of more than 2346 trauma patients, Plurad *et al.* found an increased incidence of late post-traumatic acute respiratory distress syndrome (ARDS) with rising volumes of administered crystalloids and packed red blood cells [82]. Unfortunately, there is currently no evidence for the specific patient population of isolated smoke inhalation injury. Against the background of no proven benefit and the potential risk of detrimental effects, however, increased amount of fluids should be avoided in patients with isolated smoke inhalation injury. Instead, fluid resuscitation should be guided by urine output and hemodynamic parameters of the individual patient. Thereby, rather dynamic parameters, such as changes in pulse pressure, rather than static parameters, such as central venous or pulmonary artery occlusion pressures, might be helpful.

After acute therapy, treatment is mainly focused on three cornerstones: first, maintenance and restoration of a sufficient gas exchange. Thus, respiratory ventilator settings have to be adjusted frequently to guarantee the most efficient ventilatory support and to minimize ventilation-associated side effects, such as baro- or volutrauma (please see section entitled 'Nebulized treatments'). Second, vigorous bronchial toilet should be performed to clear the airway and avoid airway occlusion. Mucociliary action is extensively impaired owing to the extensive

structural damage of heat and chemicals in the smoke [22]. In combination with an impaired cough reflex and increased tenacious secretions, this injury bears a high risk of occlusion of smaller airways, leading to atelectasis and infection [83]. Third, therefore, very careful infection surveillance is advised. Impairment of alveolar macrophage function and post-traumatic immunodeficiency also represent important risk factors, but a prophylactic administration of antibiotics is not recommended to avoid the development of resistant organisms [84].

Treatment

The following section provides a brief overview of current therapeutic strategies in respect to smoke inhalation injury. These recommendations are based on limited evidence from clinical and experimental trials as well as expert opinions resulting from clinical experience.

Mechanical ventilation strategies

Several years ago, mechanical ventilation was performed by using high inspiratory oxygen concentrations and tidal volumes of 10–15 ml/kg in a volume-controlled mode. However, “this approach may have violated the injunctive, first to do no harm (*Primum non nocere*)” [85]. During the last two decades, mechanical ventilation has been investigated extensively. Low tidal volume ventilation with associated permissive hypercapnia has been shown to effectively reduce ventilator-induced lung injury, and currently represents the standard of care [86]. The Assessment of Low Tidal Volume and Elevated End Expiratory Pressure to Obviate Acute Lung Injury (ALVEOLI) trial revealed no effects of higher positive end-expiratory pressure (PEEP) levels in ARDS patients [87]. In addition, prone positioning has been shown to have no beneficial effect on mortality, despite a transient improvement in oxygenation [88].

Although smoke inhalation predisposes patients to ALI and ARDS, especially in combination with burns, it remains to be determined if these results also apply to the specific patient population after smoke inhalation. In the ARDS Network Study concerning low tidal volume ventilation, for example, patients with burns of more than 30% total body surface area (TBSA) have been excluded. A direct transfer of these approaches may be limited in clinical practice owing to the unique clinical and pathophysiological features of smoke inhalation. Ventilation protocols differ not only between different burn centers but also between individual physicians. Apart from conventional pressure-controlled low tidal volume ventilation, multiple strategies for mechanical ventilation are currently used for the treatment of smoke inhalation injury, isolated as well as in combination with burns.

Airway pressure release ventilation (APRV), first described in 1987 by Stock and colleagues [89], is a time-triggered, pressure-limited, time-cycled ventilation mode [90]. It provides two levels of airway pressures during two time periods: a long, high-level and a short, low-level period. In this way, lower peak but higher mean airway pressures are produced compared with conventional ventilation strategies, resulting in lower tidal volumes and more effective alveolar recruitment. In addition, APRV allows spontaneous breathing during the whole inspiration–expiration cycle. Possible side effects include higher intrinsic PEEP, secondary to increased airway resistance and short expiratory times, resulting in hyperinflation of the lungs [90]. Two randomized, controlled trials in mechanically ventilated patients – not patients with smoke inhalation injury – revealed beneficial effects on oxygenation and lower end-inflation pressures [91,92]. However, there was no reduction in mortality. In conclusion, further research is necessary to determine whether APRV represents a beneficial approach for the ventilation of patients suffering from smoke inhalation injury.

The volumetric diffusive ventilator (VDR; Percussionaire Corp., Sandpoint, ID, USA) is a pneumatically powered, pressure-limited ventilator that stacks oscillatory breaths to a selected

peak airway pressure by means of a sliding venturi called Phasitron[®], resulting in low tidal volumes. Exhalation is passive and a level of continuous positive airway pressure can be selected. In addition, VDR re-establishes physiologic diffusive gas exchange, while standard ventilation modes induce a convective gas exchange [93]. In contrast to APRV, the effects of VDR have been studied in patients with smoke inhalation injury. A prospective clinical analysis revealed an improved gas exchange and a decrease in peak pressures [94]. In addition, a retrospective study in 330 patients with inhalation injury even reported a lower mortality rate [95]. While these studies compared the VDR to high-volume ventilatory strategies, data regarding a comparison with modern low tidal volume ventilation are still lacking. This may represent one reason why VDR is not universally accepted. Another factor might be that the VDR differs from other ventilators, and therefore requires special training. In addition, tidal and minute volumes cannot be monitored and humidified air, as well as nebulized saline, are necessary to prevent airway desiccation [93].

High-frequency oscillatory ventilation (HFOV) uses extremely low tidal volumes of 1–2 ml/kg applied with high frequencies of 3–15 Hz and mean airway pressures of 30–40 cmH₂O. This ventilation regime prevents alveolar trauma [96] and leads to improved lung recruitment, thereby improving oxygenation, allowing lower inspiratory oxygen concentrations and consequently limiting oxygen toxicity [97]. However, its use after smoke inhalation injury may be limited by copious secretions and small airway obstruction. In addition, gas trapping and hypercapnia will be hard to control using HFOV [97]. Accordingly, HFOV failed to improve PaO₂:FiO₂ ratios in patients with combined burn and smoke inhalation injury, while it improved oxygenation in isolated burn patients within 8 h [97,98]. Furthermore, the administration of nebulized adjunctive therapies is not possible with this ventilation strategy.

Taken together, all these ventilation modes, with the HFOV as an extreme, apply low tidal volumes and high mean airway pressures or PEEP, respectively, to improve oxygenation and airway recruitment. Patients with inhalation injury suffer from increased mucous secretions and even airway cast formation to a greater extent than ARDS patients in general. Therefore, clearance of secretions represents an essential factor within the therapeutic regime. However, airway clearance is best supported by high tidal volumes and low PEEP [81], thereby contradicting the ventilation strategies for improved oxygenation. As a consequence, physicians need to balance these competing objectives based on the individual situation of the patient until future studies might provide more evidence.

External arterial venous CO₂ removal represents a unique form of CO₂ removal, which is driven by endogenous arterial pressure [99]. Several studies in animal models of smoke inhalation injury revealed a reduction in morbidity and mortality [100–102]. However, clinical evidence is lacking.

In conclusion, mechanical ventilation of patients after smoke inhalation injury will further represent a tightrope walk between providing sufficient oxygenation and causing as little collateral harm as possible. While there are several specific ventilation devices and strategies available, large, randomized, controlled multicenter studies are warranted to clarify their potential usefulness in patients with smoke inhalation injury.

Nebulized treatments

Against the background that the lung is the primary injured organ following smoke inhalation injury and that mechanical ventilation is frequently necessary, the administration of therapeutic compounds via nebulization directly to the affected organ seems to be more than reasonable. Based on the complex pathogenesis of smoke inhalation injury, drugs with different mechanisms of action, such as bronchodilators, anticoagulants, antioxidants and

corticosteroids have been investigated. In each case, however, the key to any successful aerosol therapy is the consistent delivery into the lung and to the distal airways.

Bronchodilators, such as β_2 -agonists, improve respiratory mechanics by decreasing airflow resistance and peak airway pressures. This results in improved dynamic compliance [103]. In addition, β_2 -agonists provide anti-inflammatory properties, represented by a decrease in inflammatory mediators such as histamine, leukotrienes and TNF- α [104,105]. Finally, β_2 -agonists are associated with improved airspace fluid clearance and stimulation of epithelial repair [106]. While clinical evidence for ALI/ARDS in general is present [107,108], the literature discussing smoke inhalation is limited. Using an established ovine model of combined burn (40% cutaneous third-degree burn) and smoke inhalation injury (48 breath of cotton smoke, average COHb of 75% injury), our research group was able to show a reduction of pulmonary vascular permeability, pulmonary edema and airway pressures, as well as an improvement of the PaO₂:FiO₂ ratio by continuous administration of nebulized albuterol at 20 or 40 mg/h compared with placebo treatment [109]. Clinical evidence is restricted to retrospective data in children. Continuous nebulized albuterol (10–40 mg/h) in children with smoke inhalation injury and a PaO₂:FiO₂ ratio less than 200 mmHg led to improved oxygenation and lung compliance in the first 72 h after treatment. No serious adverse events (e.g., tachycardia or hypokalemia) have been reported [110].

Inhaled NO is thought to improve oxygenation and to reduce increased pulmonary vascular resistance by reversing the ventilation-perfusion mismatch in ARDS owing to selective vasodilation in well-ventilated lung areas. Experimental studies in animals with smoke inhalation injury revealed a consistent reduction in pulmonary hypertension but variable results regarding pulmonary shunting [111,112]. Single-center case studies in patients with combined burn and smoke inhalation injury demonstrated a significant increase in the PaO₂:FiO₂ ratio, with no additional advantage of doses exceeding 20 ppm [113,114]. Several randomized, controlled trials as well as recent meta-analyses in the general population of ARDS patients revealed only a positive effect on the patient's oxygenation for 24 h (in some studies until 48 h) [115–117], but no advantages in respect to mortality, ventilator-free days, duration of ventilation or pulmonary hypertension could be verified. On the contrary, there was even a strong trend towards increased mortality in patients receiving NO as compared with placebo treatment [115].

Against the evidence of beneficial effects of NO synthesis inhibition [27,29,118], inhaled administration of NO for the treatment of smoke inhalation injury seems questionable. While a possibly increased production of RNS is only hypothetical at this time point, there are several known, unwanted effects of nebulized NO administration. Long-term treatment might lead to the diffusion of NO into poorly ventilated areas, abolishing the selective pulmonary vasoconstriction and consecutively increasing pulmonary shunt volume. In addition, surfactant inhibition, edematous changes and continuing fibrosis may over-ride any benefit of inhaled NO therapy. Although findings are controversial, renal dysfunction and methemoglobinemia have also been described [115]. Based on the current literature, the standard treatment of smoke inhalation injury with inhaled NO cannot be recommended. However, short-term inhaled administration of NO might be considered as a rescue treatment to improve oxygenation for a short period in patients with acute, life-threatening hypoxemia [116].

Owing to increased procoagulatory activity following smoke inhalation injury [43], the aerolized administration of anticoagulants seems to be more than promising. In an ovine model, Brown *et al.* first described a reduction of mortality after smoke inhalation induced ARDS by aerolized heparin in 1988 [119]. Interestingly, Murakami and colleagues reported that heparin nebulization had only partial or no beneficial effects in ovine ARDS after combined burn and smoke inhalation injury [120]. This might be explained by the lower levels of antithrombin in

bronchoalveolar lavage fluid after combined burn and smoke inhalation injury, as the effects of heparin depend on the binding to antithrombin, thereby enhancing the ability of antithrombin to inhibit fibrin and factor Xa by 2000–6000-fold [114]. In accordance, combined nebulization of heparin and recombinant human antithrombin (rhAT) in the same model significantly improved pulmonary function by reducing airway obstruction [121]. However, heparin binding to antithrombin inhibits the anti-inflammatory effects of antithrombin [43]. In addition, aerolized antithrombin administration did not affect the reduced systemic plasma levels of antithrombin [121]. Recently, our research group was able to demonstrate that the combination of intravenous rhAT and nebulized heparin effectively attenuated pulmonary injury following combined burn and smoke inhalation injury [122]. In children with combined burn and smoke inhalation injury, nebulization of heparin and *N*-acetylcysteine significantly decreased re-intubation rates, the incidence of atelectasis and mortality [123]. Notably, these children also received transfusions of fresh frozen plasma, a rich source of antithrombin. These promising results, however, need to be verified in randomized, controlled multicenter trials.

As mentioned earlier, following combined burn and smoke inhalation injury, the oxidative–antioxidative balance is disturbed by an increase in ROS and a parallel decrease in antioxidants [124]. Accordingly, the antioxidant Vitamin E or α -tocopherol is markedly reduced in patients with major burns (>50% TBSA) and combined smoke inhalation injury [60]. Our study group reported that prophylactic administration of α -tocopherol (5 mg/kg orally) 24 h prior to injury attenuated the decrease in pulmonary function and the increase in vascular permeability that occurs after combined burn and smoke inhalation injury in sheep [125]. Of special interest are two studies in sheep after combined 40% TBSA burn and smoke inhalation injury, showing the practicability and efficacy of local antioxidant administration to the lung by nebulization [126,127]. Both α - and γ -tocopherol attenuated the progressive decrease in pulmonary function represented by higher PaO₂:FiO₂ ratios compared with control animals. In addition, nebulized γ -tocopherol decreased lung lymph flow, lung wet-to-dry weight ratio, and markers of oxidative and nitrosative tissue injury more effectively than α -tocopherol. Plasma levels of γ -tocopherol were not increased, suggesting a successful local administration potentially avoiding systemic side effects. The superiority of γ -tocopherol over α -tocopherol might be based on the higher ability of γ -tocopherol to scavenge RNS as well as ROS [128].

Intravenous treatments

While the efficacy of aerolized compounds always depends on consistent delivery into the lung and to the distal airways, the intravenous injection of a compound represents a relatively sure way of administration. Accordingly, the following section discusses some of the intravenous, therapeutic approaches of smoke inhalation injury.

The progressively developing upper airway edema induced by smoke inhalation injury represents one of the major indications for endotracheal intubation. Aerolized epinephrine or corticosteroids as therapeutic approaches have been proposed [22]; however, conclusive evidence for these treatment strategies is still missing. One of the reasons might be the varying efficacy of the aerolized drug delivery, especially in emergency situations. Therefore, intravenous administration of corticosteroids should be the treatment of choice.

Vitamin C has been shown to decrease oxidative damage in several experimental [129,130] and clinical [131,132] trials in different critical diseases. Unfortunately, to the best of our knowledge, there are no studies investigating the effects of Vitamin C administration on isolated smoke inhalation injury. However, Tanaka and colleagues revealed very impressive results in a randomized, controlled trial by adding 66 mg/kg/h Vitamin C to the continuous infusion in patients who had over 30% TBSA burns [132]. Fluid requirements, body weight gain, wound edema and duration of mechanical ventilation were significantly reduced. Notably, 73% of the included patients in this study were diagnosed with inhalation injury after

admission to the hospital, with equal distribution between groups. A subgroup analysis revealed improved oxygenation, represented by higher PaO₂:FiO₂ ratios, beginning at 18 h after injury. In addition, duration of mechanical ventilation was reduced in patients receiving Vitamin C (12 ± 9 days) as compared with the control group (21 ± 16 days). No differences were seen in PEEP level, inspiratory oxygen fraction or the incidence of pneumonia. Nevertheless, it must be explicitly stated that no direct data exist to confirm a beneficial effect of intravenous Vitamin C treatment on patients with smoke inhalation injury.

As mentioned in the section 'Nebulized treatments', combined burn and smoke inhalation injury causes an acquired antithrombin deficiency, which represents an independent predictor of length of hospital stay and mortality [133,134]. In addition to its anticoagulatory properties, antithrombin provides anti-inflammatory effects. Antithrombin inhibits the inflammatory signal transduction in and promotes prostacyclin release from endothelial cells. Thereby, antithrombin directly attenuates lung inflammation and edema after combined burn and smoke inhalation injury [135]. Murakami *et al.* reported decreased airway obstruction by casts, higher urine outputs and mean arterial pressures after/or during the continuous administration of 100 µg/kg rhAT over 24 h as compared with control animals in an ovine model of smoke inhalation injury and pneumonia [136]. In a small clinical study of Kowal-Vern and colleagues, patients with 20% or more TBSA burn and smoke inhalation injury who received rhAT had increased PaO₂:FiO₂ ratios and significantly fewer episodes of pneumonia compared with standard therapy alone [113]. In conclusion, restoring physiological antithrombin levels in patients with smoke inhalation injury has the potential to improve survival and to decrease inflammation. Again, however, clinical evidence regarding isolated smoke inhalation injury is missing.

Specific intoxications

Carbon monoxide—Current treatment recommendations of CO poisoning include cessation of exposure, administration of 100% oxygen and supportive care [67]. Hyperbaric oxygenation therapy (HBO) is sometimes used to encourage rapid displacement of CO from hemoglobin and to reduce the duration of the hypoxic state. Administration of 100% oxygen at 3 atmospheres reduces the CO half-life from 250 min at ambient pressure to 30 min [14]. In spite of this efficiency, the use of HBO remains controversial [67] owing to the questioned correlation between COHb levels and outcomes [66] in combination with limited access to the patient during HBO therapy, which has a severe impact on treatment quality of combined burn injuries.

Key issues

- Smoke inhalation injury continues to increase morbidity and mortality in burn patients not only in the third world, but also in industrialized countries.
- Smoke inhalation injury can cause thermal and chemical injuries, as well as systemic toxicity.
- The ignition source, the size of the particles in the smoke, the duration of exposure and the solubility of the gases all determine the location and the severity of smoke inhalation injury.
- The formation of reactive oxygen and nitrogen species, as well as the procoagulant and antifibrinolytic imbalance of alveolar homeostasis, play a central role in the pathogenesis of smoke inhalation injury.
- Massive airway obstruction owing to cast formation, bronchospasm, the increase in bronchial circulation and transvascular fluid flux represent further hallmarks of smoke inhalation injury.

- The development of clinical symptoms, such as erythema, dyspnea or massive airway edema, may be delayed, but are ultimately fatal.
- Specific intoxications such as cyanide or carbon monoxide need to be considered critically and treated, if necessary.
- Clinical management consists preponderantly of supportive care.
- Clinical evidence for specific therapeutic approaches is lacking.
- Anticoagulants, antioxidants and bronchodilators currently represent the most promising treatment strategies.
- Aerolized administration of compounds seems to be feasible, safe and effective.
- The optimal ventilation protocol still needs to be defined.
- Establishing clear criteria for the diagnosis and grading of smoke inhalation injury is essential for the design and success of randomized, controlled multicenter trials.

A second potential argument for HBO is that CO binds not only to hemoglobin, but also to cytochrome oxidase, and thus delayed neurological sequelae may be prevented by HBO. A Cochrane database review of six randomized, controlled trials, however, did not reveal a beneficial effect of HBO compared with standard treatment with respect to neurological sequelae [137]. These results should be interpreted with care, however, because flaws in design and analyses were evident in all the included trials. In summary, all patients with CO intoxication should be treated with 100% oxygen. HBO might be a useful therapeutic option in patients with severe neurological symptoms and high COHb concentrations (>50%), but without major burns and severe pulmonary injury.

Cyanide—The adequate treatment of HCN poisoning following smoke inhalation injury is currently under discussion. Several antidotes are available: the ‘cyanide antidote kit’ includes amyl nitrite, thiosulfate and sodium nitrite [70], and is based on the classic treatment approach by Chen and Rose [138]. As these substances are methemoglobin generators, which may additionally impair oxygen transport, they should only be used in case of proven diagnosis (increased plasma levels of CN) and under continuous monitoring in an intensive care unit. Methemoglobin chelates CN to form cyanomethemoglobin, which, as it dissociates, allows free CN to be converted to thiocyanite by liver mitochondrial enzymes (rhodanase) using thiosulfate as a substrate. Thiocyanate is then excreted into the urine [138]. In contrast to these antidotes, hydroxycobalamin, a Vitamin B12 derivative, actively binds CN by forming cyanocobalamin, which will be directly excreted via the kidney [139,140]. In case of intoxication with 1 mg CN, 50 mg/kg hydroxycobalamin is recommended [141]. Because it averts methemoglobin production, hydroxycobalamin can even be used in the preclinical setting. Accordingly, hydroxycobalamin represents the active compound of the ‘cyanokit’, which is used in the prehospital management of smoke inhalation injury in Europe with a reported improvement in mortality [140].

Aggressive restoration of cardiopulmonary function augments the hepatic clearance of CN via the enzyme rhodanase [142], and has been reported to be successful in severe CN poisoning (blood levels 5.6–9 mg/l) as well as after ingestion [143–145] or smoke inhalation [146], even without the use of antidotes. Therefore, the standard care of CN poisoning should combine the aggressive supportive therapy with the causal treatment using hydroxycobalamin.

Expert commentary

Against the background of the current literature, there was a remarkable increase in our knowledge regarding the pathogenesis of smoke inhalation injury during the last 10–15 years. There are several promising therapeutic approaches, such as the β_2 -agonists, antioxidants or anticoagulants, and nebulization of the use of different ventilation modes. In addition, the trend goes to a combination of different compounds rather than a single ‘magic bullet’. Bearing in mind the complex pathophysiology and different clinical presentations of smoke inhalation injury, this is more than justifiable.

At the same time, however, we cannot be satisfied with the clinical progress made. The fact that mortality rates of smoke inhalation injury did not change is a more than obvious indicator for the lacking success of our current efforts. The future challenge, then, will exist largely in transferring our expanding theoretical knowledge adequately into daily clinical practice. Owing to the relatively small patient population, however, no single-center study will be able to recruit enough patients for a randomized, controlled trial with enough power to prove or disprove the efficiency of a therapeutic approach in an adequate time period. To achieve this goal, the cooperation and communication between burn centers should be intensified.

Five-year view

During the recent Consensus Conference for Inhalation Injury (Couer d’Alene, ID, USA), invited experts in the field of smoke inhalation injury met to “define what basic research elements are lacking and what additional information/definitions/technology is needed to advance inhalation injury research” [147]. Definition of criteria for the diagnosis and grading of inhalation injury received the highest ranked priority. These would represent the basis for uniform data acquisition, enabling the evaluation of short- and long-term efficiency of current as well as new therapeutic approaches. Therefore, the authors fully agree and hope that this goal will be achieved within the next 5 years.

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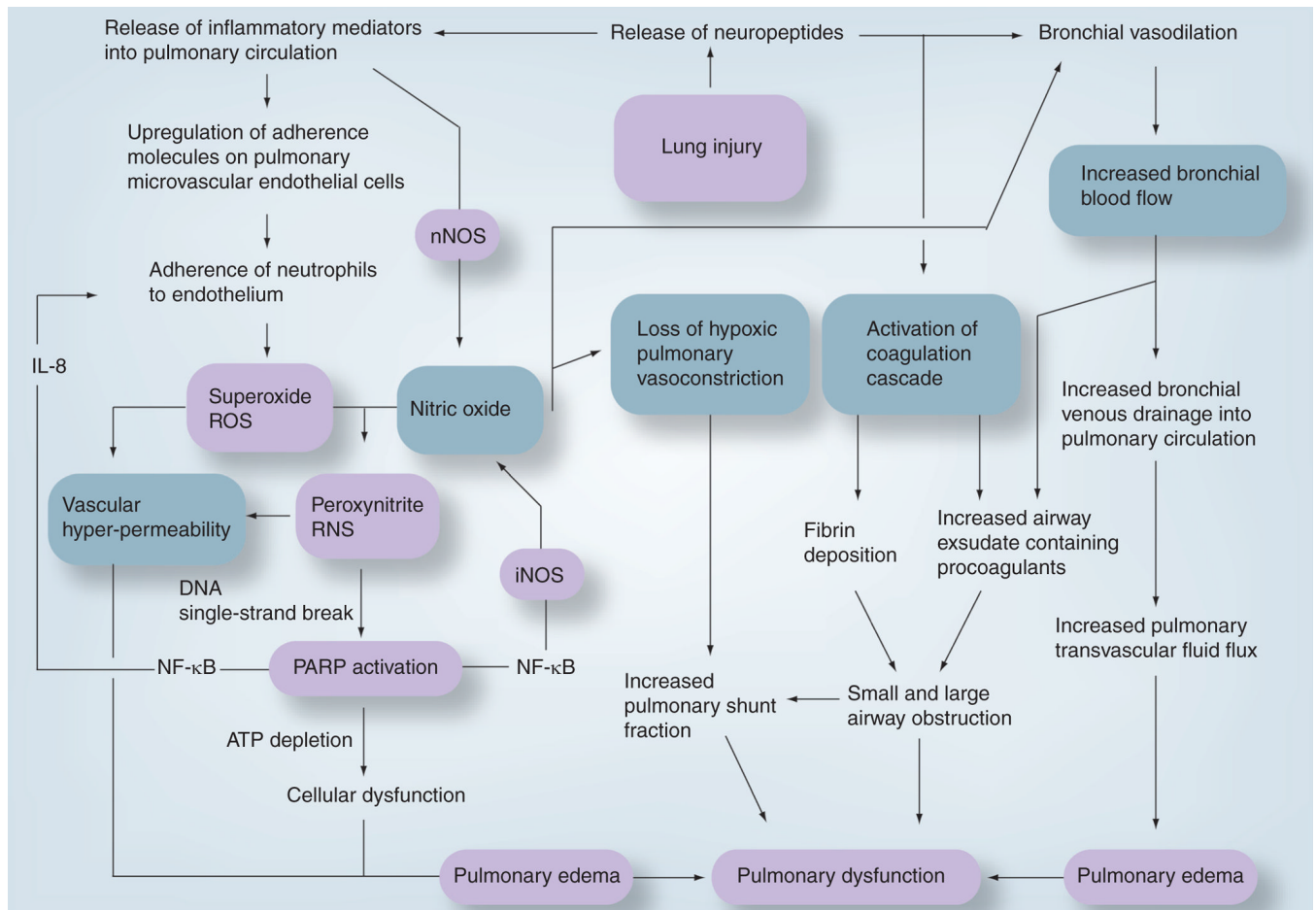


Figure 1. Proposed pathophysiology of smoke inhalation injury

iNOS: Inducible nitric oxide synthase; NF: Nuclear factor; nNOS: Neuronal nitric oxide synthase; PARP: Poly(ADP ribose) polymerase; RNS: Reactive nitrogen species; ROS: Reactive oxygen species.

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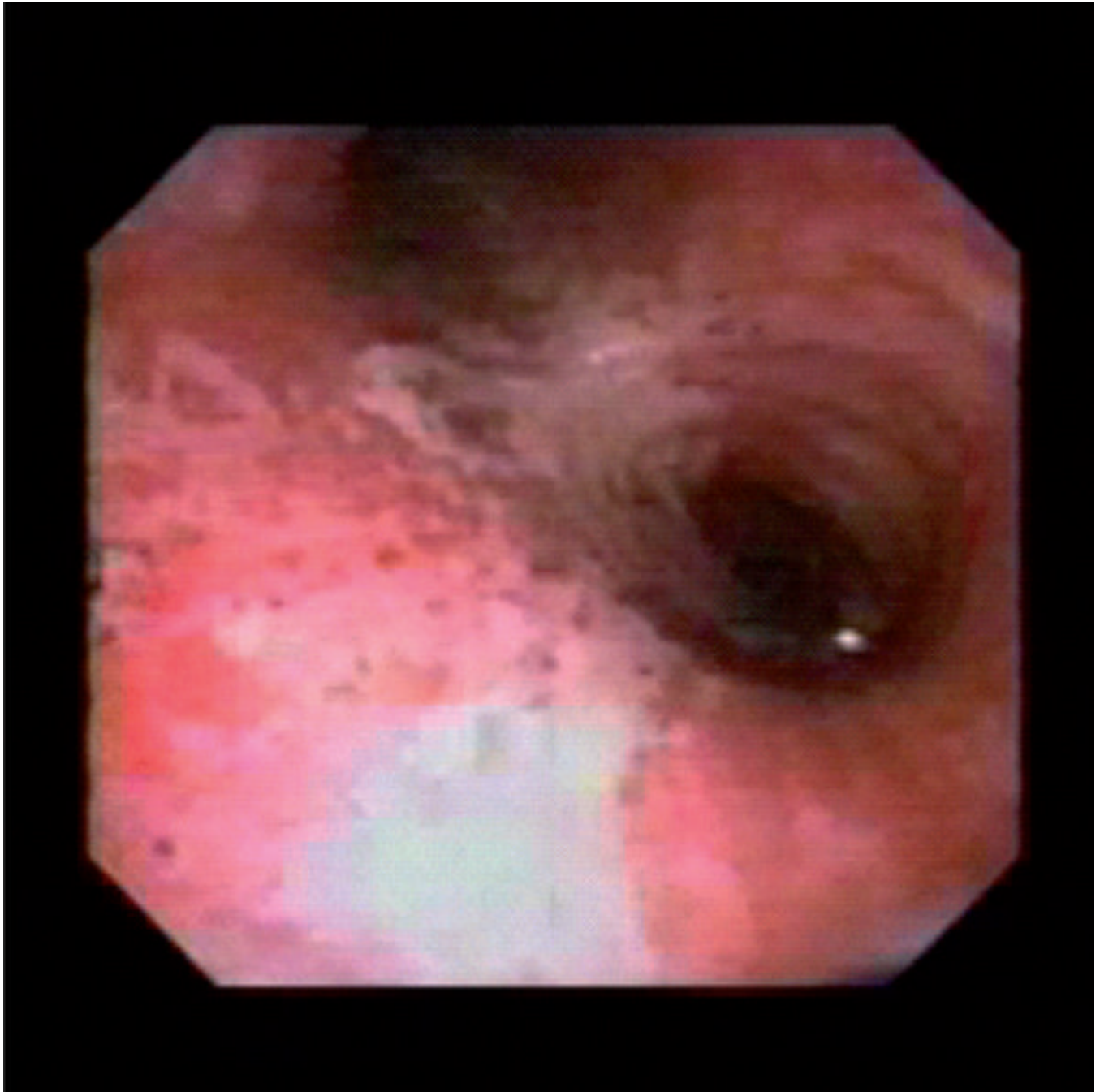


Figure 2. Bronchoscopic finding after smoke inhalation injury
Erythema, edema and ulceration (view into the left and right main bronchi).



Figure 3. Isolated airway cast

The formation of mucus secretions, denuded airway epithelial cells, inflammatory cells and fibrin leads to subtotal or total occlusion of distal as well as main airways.

Table 1

Selected toxic compounds of smoke: materials, sources and their pathophysiological effects.

Toxic compound	Material	Source	Pathophysiology
Arolein/propenal	Acrylics	Aircraft windows, textiles, wall coverings	Severe irritation of upper respiratory tract, mucosa necrosis and death within 10 min with concentrations over 50 ppm [22]
	Cellulose	Cotton, jute, paper, wood	
	Polypropylene	Carpeting, upholstery	
Aldehydes	Acrylics	Aircraft windows, textiles, wall coverings	Corrosive, denatures proteins; formaldehyde: denatures ribonucleic acid
	Cellulose	Cotton, jute, paper, wood	
	Polyamine resins	Household, kitchen goods	
Ammonia	Polyamide	Carpeting, clothing	Airway irritant leading to cough, increasing secretions and bronchoconstriction; ammonium hydroxide: tissue necrosis
	Polyamine resins	Household, kitchen goods	
	Polyurethane	Insulation, upholstery	
	Silk, wool	Blankets, clothing, fabrics, furniture	
Carbon monoxide	All materials	All combustible products	Tissue hypoxia, organ failure, death within 1 h with concentrations of 80–90% [14]
Hydrogen chloride	Polyester	Clothing, fabrics	Mucosa necrosis and acute bronchitis
	Polyvinyl chloride	Floor, furniture, upholstery, wall, wire/pipe coating	
Hydrogen cyanide	Fire retardants	Polymeric material	Tissue hypoxia, organ failure, death; death possible with concentrations over 1 µg/ml [14]
	Polyacrylonitrile	Appliances, engineering, plastics	
	Polyamide	Carpeting, clothing	
	Polyamine resins	Household, kitchen goods	
	Polyurethane	Insulation, upholstery	
	Silk, wool	Blankets, clothing, fabrics, furniture	
Hydrogen sulfide	Rubber	Tires	Airway irritant, corrosive
	Silk, wool	Blankets, clothing, fabrics, furniture	

Toxic compound	Material	Source	Pathophysiology
Phosgene	Polyvinyl chloride	Floor, furniture, upholstery, wall, wire/pipe coating	Mucosa necrosis, primary in the small airways and alveoli
Sulfur dioxide	Rubber	Tires	Strong irritant to eyes and airways, lower airway injury and pulmonary edema