

## Animal models of smoke inhalation induced injuries

Poon David<sup>1</sup>, Denny Dunsford<sup>1</sup>, Jia Lu<sup>1</sup>, Shabbir Moochhala<sup>1</sup>

<sup>1</sup>Combat Care Laboratory, Combat Care and Performance Programme, Defence Medical & Environmental Research Institute, DSO National Laboratories (Kent Ridge), 27 Medical Drive #09-01, Singapore 117510

### TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Pathophysiology of Smoke Inhalation
  - 3.1. Pulmonary edema
  - 3.2. Blood Flow
  - 3.3. Lung lymph flow
  - 3.4. Airway obstruction
  - 3.5. Metabolic changes
  - 3.6. Oxidative stress
  - 3.7. Mucin
  - 3.8. Cytokines
4. Clinical characteristics of smoke inhalation
5. Animal models used to study smoke inhalation induced injuries
6. Current therapy for smoke inhalation
7. Potential therapeutics
  - 7.1. Surfactants
  - 7.2. Leukotriene antagonist
  - 7.3. Antioxidants
  - 7.4. Anti-inflammatory drugs
  - 7.5. Anti-epileptic drug
  - 7.6. Inducible nitric oxide synthase inhibitor
  - 7.7. Nitric oxide
  - 7.8. Poly(adp-ribose) polymerase inhibitor
  - 7.9. Reducing cast formation
  - 7.10. Mechanical ventilation
  - 7.11. Bronchial circulation
  - 7.12. Endothelin-1 receptor blockade
  - 7.13. Protease inhibitor
  - 7.14. Antibiotics
  - 7.15. Thromboxane  $\alpha_2$  synthase inhibitor
  - 7.16. Activated protein c
8. Summary and perspective
9. References

## 1. ABSTRACT

Smoke inhalation injury is the leading cause of mortality from structural fires, as a result of complications such as systemic inflammatory response syndrome and chronic obstructive pulmonary disease, which can be caused by a localized or systemic response. In this review, the pathophysiology of smoke inhalation injury, along with the characteristics found in clinical settings, common animal models, current treatment methods and future potential therapeutics are discussed.

## 2. INTRODUCTION

Smoke inhalation injury is initiated by the uninhibited absorption of inhaled smoke and toxicants in the respiratory system, and is the leading cause of mortality from structural fires. In combat situations, inhalation injury is particularly common during armour engagements, shipboard fires, and military operations in an urban environment. For the civilian population, there is the possibility of terrorists employing conventional fuels and explosives or toxic industrial chemicals. The inhalation of

## Animal models of smoke inhalation induced injuries

these compounds would produce injuries similar in several aspects to the inhalation of smoke.

Smoke inhalation injury can be caused by primary thermal burns due to inhalation of hot vapours, inhalation of toxic gases and particulates, or in combination. The pathophysiology and severity of inhalation injury varies with the aerosolized toxins emitted with the smoke. Lung damage from smoke inhalation injury generally occurs in two stages. The first stage is characterized by neutrophilic influx, production of reactive oxygen and nitrogen species, generation of inflammatory mediators and release of products from degradation of complement. The second stage is characterised by fibrosis, cellular hyperplasia and formation of hyaline membrane. Smoke inhalation injury can be divided into three parts, the upper airways, the lower airways and system toxicity.

The level of mortality, progression of lung injury and increase in inflammatory markers and the subsequent deterioration of lung function was similarly observed in both human victims of smoke inhalation as well as in animal models of smoke inhalation injury. Animal models are fundamental in providing an understanding of the mechanisms and progression of inhalation injury along with the subsequent development of appropriate therapies.

### 3. PATHOPHYSIOLOGY OF SMOKE INHALATION

Cytotoxic particles causes initial damage to the upper air passages, which can lead to an inflammatory response. Inflammation and pulmonary edema causes increased resistance in airflow and breathing becomes more difficult. Further increase in airway resistance can be caused by reflex bronchoconstriction. Bronchiolitis and alveolitis causes reduced gaseous exchange efficiency and reduces blood oxygenation. Reduced surfactant or trapped air may cause atelectasis (partial or completely collapsed lung) which leads to secondary airway blockages.

A report on cotton smoke inhalation in sheep shows that lung lesions formed are due to localized injury and not a generalised pulmonary response (1). Rats challenged with concentrated ambient particles are found to be affected by the chemical composition of the particles instead of their mass (2). In fire victims in the US, progressive pulmonary failure and cardiovascular dysfunction are important determinants of morbidity and mortality (3).

The analysis of smoke inhalation in rabbits was used to determine that cigarette smoke inhalation leads to significantly increased intraparenchymal vascular congestion and thrombosis, intraparenchymal haemorrhage, respiratory epithelial proliferation, heightened numbers of macrophages in alveolar and bronchial lumen, alveolar destruction, emphysematous changes and bronchoalveolar haemorrhage scores. Dried dung smoke inhalation results in considerably increased respiratory epithelial proliferation, alveoli destruction and emphysematous change scores (4).

Second-hand smoke exposure lengthens stimulated apnoea, increases the number of stimulated

coughs and increases the degree of stimulated bronchoconstriction as a result of the increased reactivity of the peripheral sensory neurones and second-order neurones in the nucleus tractus solitarius. This suggests that cough and wheeze caused by exposure to second-hand smoke could be related to plasticity in the nervous system (5).

Smoke inhalation without burns precedes a fall in arterial oxygenation that is caused by increased pulmonary fluid flux, loss of pulmonary vasoconstriction and airway obstruction, which is mediated in part by reactive oxygen and nitrogen species. The reactive nitrogen species can be detected by measuring reaction products such as 3-nitrotyrosine, a tissue injury indicator, which is elevated in the airway after smoke/burn injury. Additionally, the blockade of bronchial blood flow aids in minimizing pulmonary injury, suggesting that cytotoxins and activated cells are formed in the airway and carried to the parenchyma, leading to pulmonary edema and reduction in blood oxygenation (6).

#### 3.1. Pulmonary edema

Pulmonary edema is the main determinant to mortality and the pathophysiology of lung injury from smoke inhalation (7). An ovine cotton smoke-inhalation model showed an increase in capillary permeability, proposed to be caused by cytotoxic agents found in the smoke, polymorphonuclear leukocytes and eicosanoids (8). Another study suggested that the increase in microvascular permeability is caused by an increase in circulating leukocytes and release of oxygen radicals and proteolytic enzymes (9). Another study in ovine smoke-inhalation model shows that pulmonary edema is formed as a result of significant increase in both capillary pressure and capillary permeability (10).

Airway blood flow is increased due to selective vasodilation in the airway, which may account for increased capillary filtrate from the bronchial circulation, culminating in pulmonary edema (11). Another study in ovine shows that bronchial artery ligation led to increased attenuation of pulmonary edema as compared to pulmonary artery ligation. This suggests that the bronchial artery significantly contributes to pulmonary edema when compared to the pulmonary artery (12).

#### 3.2. Blood flow

The analysis of sheep models is used to establish the relationship between smoke inhalation and blood flow. An increase in systemic blood flow to the lower trachea and intrapulmonary central airways accompanies smoke inhalation (13). After 48 h of exposure to cotton smoke, blood flow to the trachea increases significantly, blood flow to the kidneys remains at pre-exposure levels, whilst blood flow to the ileum, colon, spleen and pancreas decreases markedly. These changes are independent of cardiac output and systemic oxygen delivery. The alteration of microvascular blood flow leads to the development of nonpulmonary organ dysfunction after smoke inhalation injury (14). When one side of the lung is exposed to smoke inhalation injury while the other side is exposed to air, damage also occurs in the air-exposed side, alluding to a mediatory response via blood flow (15).

### 3.3. Lung lymph flow

Sheep that are exposed to cotton smoke without bronchial artery occlusion display a sevenfold increase in lung lymph flow compared to controls. Moreover, sheep exposed to cotton smoke with bronchial artery occlusion reveal a threefold increase in lung lymph compared to controls. A wet-to-dry weight ratio of the aforementioned lung samples without bronchial artery occlusion is 23% higher than those with bronchial artery occlusion. These data illustrates that pulmonary fluid flux plays a role in the formation of pulmonary edema (16). However, an earlier paper published by the same group suggests that there is no correlation between an increase in bronchial blood flow and lung lymph flow after cotton smoke inhalation (17).

### 3.4. Airway obstruction

Combustion products like particulates, oxidants and toxic gases cause damage to the respiratory tract, which can lead to its closure or partial collapse (18). The patency of the airway is also affected by the accumulation of cast material which usually occurs in multiple sites. Cast material consists of fibrin, neutrophils, bronchial epithelial cells and mucus secretions, which is recruited, shed or secreted by the victim exposed to smoke inhalation injury. As the ciliary transport system is impaired due to damage of the ciliated epithelium by smoke inhalation, the cast material remains uncleared in the airway. More cast materials are found in smoke inhalation victims with pneumonia than those with burns, indicating that airway coagulopathy is worse in smoke inhalation victims with pneumonia.

### 3.5. Metabolic changes

Smoke inhalation injury leads to a change in metabolism of arginine in the lung. A day after combined smoke with burn injury, arginine metabolism is significantly higher than control animals and animals administered with a nonspecific NOS inhibitor (19).

### 3.6. Oxidative stress

Nitric oxide is produced endogenously by macrophages and neutrophils as an immune response against bacterial pathogens. Nitric oxide is also used by vascular endothelial cells as a signalling molecule acting on the smooth muscle cells as a potent vasodilator. At high levels, nitric oxide behaves as a free radical and increases inflammation response.

During inflammatory stress, heme is not available to scavenge nitric oxide, which accumulates and binds with cellular superoxide to form peroxynitrite, a strong oxidant which can cause damage to cells and DNA. High levels of peroxynitrite causes extensive tissue damage, leading to increased capillary permeability, subsequently pulmonary edema and impaired gaseous exchange (20).

Cardiac depression as a result of burn/smoke inhalation injury in sheep, is observed to consist of 2 phases (immediate and 24h), with the later phase mediated by nitric oxide synthesized by inducible nitric oxide synthase (iNOS) (21). Sheep, when exposed to combined burn and smoke inhalation exhibits increasing expression

of iNOS, elevation of plasma nitrate/nitrite (NOx) levels, and an increase of 3-nitrotyrosine in lung tissue, indicating heightened peroxynitrite levels. Pulmonary shunting, a progressive decrease in PaO<sub>2</sub>/FiO<sub>2</sub> ratio, loss of hypoxic pulmonary vasoconstriction, pulmonary edema, airway obstruction and an increase in airway pressure occurred in parallel. It is suggested that the sudden physiological deterioration of blood gas parameters is caused by airway obstruction and loss of hypoxic pulmonary vasoconstriction (22).

Sheep exposed to wood smoke demonstrate an increase in myeloperoxidase activity in lung tissue, which leads to dose-dependent injury of tracheal epithelium and lung parenchyma. This indicates that wood smoke inhalation leads to an increase in oxidative stress (23).

Substantial research conducted on the effects of cigarette smoke on oxidative stress in humans established that smokers have significantly lower alpha-tocopherol and gamma-tocopherol in lymphocytes, and lower alpha-tocopherol in platelets. In addition significantly higher excretion of urinary gamma-tocopherol metabolite, gamma-carboxyethyl-hydroxychroman (CEHC) is deduced. Measurement of lymphocyte and platelet vitamin E is suggested as a biomarker of vitamin E status in relation to oxidative stress conditions (24). Cigarette smoking causes oxidative stress in humans, increases alpha-tocopherol disappearance and decreases plasma and urinary CEHC. CEHC is suggested to be an excellent marker of vitamin E status and smokers may have a higher need for vitamin E (25).

The increase in disappearance of alpha-tocopherol and reduction of plasma ascorbic acid concentrations, which suggests increased oxidative stress, accompanies cigarette smoking. It is suggested that smokers have a heightened need for alpha-tocopherol and ascorbic acid (26). Smokers have 60% lower alpha-tocopherol and 40% lower gamma-tocopherol levels than non-smokers. This measured reduction of alpha-tocopherol is not a result of P450-mediated tocopherol metabolism, implying that the decrease in alpha-tocopherol is due to oxidative stress (27).

Chronic obstructive pulmonary disease is caused by local and systemic inflammation, due to an increase in inflammatory cell count, increased production of cytokines, oxidative stress caused by an imbalance between reaction oxygen species formation and antioxidant capacity (28).

### 3.7. Mucin

Rats that are exposed to wood smoke show tracheal epithelium deterioration, cilia reduction and submucosal edema. From the correlation of Muc4 upregulation and the improvement in histological results, Muc4 gene is shown to be a likely marker for repair of the tracheal epithelium (29).

In a clinical setting, smoke victims presents with an upper airway gland specific mucus, mucin 5B, in the bronchioles in all cases, and in the parenchyma in all but

## Animal models of smoke inhalation induced injuries

two subjects. The results illustrate that an increase in mucus production or impairment of mucociliary function may be the cause of lung injury in smoke inhalation (30).

### 3.8. Cytokines

The rabbit model of smoke inhalation injury demonstrates that exposure to cotton smoke leads to alveolar macrophages priming the release of TNF-alpha and reduced antimicrobial activities like phagocytosis (31-32). Furthermore studies have proven that IL-8 mediates injury to the alveolar epithelial barrier and the lung endothelium (33).

Victims of smoke inhalation assessed 6 months after exposure revealed that serum and bronchoalveolar lavage fluid significantly increased TNF-alpha and IFN-gamma, while IL-2 increased did not see a significant increase. Airway hyper-responsiveness to methacholine was observed in all but one patient. Inflammatory reactions in the airways and peripheral blood continued for at least 6 months after smoke inhalation (34).

Inhalation of advanced composite material (ACM) consisting of carbon, graphite and epoxy was compared to a rodent model of paraquat-induced acute lung injury (ALI). Rats exposed to ACM smoke show no change in lung function indicative of ALI. Expression of TNF-alpha increases in the lavage fluid after 1 day, MIP-2 significantly increase from day 2, 3 and 7 while IFN-gamma levels significantly increases on day 7. Changes related to ALI include a decrease in lung compliance, lung volumes/capacities, distribution of ventilation and gas exchange capacity. The expression of TNF-alpha and MIP-2 is seen to increase in lung tissue and lavage fluid. The temporal relationship may account for differences in lung function between paraquat treated and ACM smoke exposed rats (35). Smoke inhalation and burn injury induces a large influx of alveolar leukocytes, increases levels of TNF-alpha, IL-6, and IL-8 cytokine response after LPS stimulus, compared to burn injury alone or with normal controls (36).

Smoke inhalation and burn injury in sheep leads to an obstruction of the bronchial airways in the first 24 hours. At 4 h after injury, the obstructive material consists mostly of mucus, with neutrophils clustered around and within gland acini. At 8-24 h, the obstruction is caused by increased inflammatory cell accumulation. Gland cells constitutively express and secrete IL-1beta. After injury, there is an increase in number of gland cells secreting IL-1alpha, IL-8 and TNF-alpha instead (37).

## 4. CLINICAL CHARACTERISTICS OF SMOKE INHALATION

Victims of smoke inhalation can be classified based on clinical presentations. Victims with nasal soot, singed facial hair, facial burns or with breathing difficulty can be classified as high risk. They are more likely to have depressed mental status, low blood pH of 7.2, respiratory failure, cardiac failure, high COHb of 38 % and above, lower body temperature of 35 °C and have a higher

mortality rate (38). Victims with no surface burns but with altered mental status, sore throat, hoarseness, cough, dyspnea, chest pain, sooty sputum, wheezing or stridor have lower mortality (39).

Mild (<20% COHb) CO poisoning causes headache and dizziness. Moderate (20-40%) CO poisoning causes nausea, convulsions and impaired motor function. Severe (40-60%) CO poisoning causes altered mental status, loss of muscle coordination and coma. Lethal (>60% COHb) CO poisoning leads to death within 3 min (40). Acute exposure to high levels of CO can lead to brain injury, delayed encephalopathy, hemorrhagic leukoencephalopathy, hemorrhagic infarction, myocardial infarction and hearing loss (41-56). Cognitive sequelae, depressed mental status and anxiety is suggested to be independent of the severity CO exposure from 6 weeks to 1 year after CO poisoning (57). These delayed neurological symptoms can be treated if recognised early (58).

Respiratory distress can be due to bronchial obstruction by soot or cast materials. Fiberoptic bronchoscopy can be conducted on victims of smoke inhalation to aid in the removal of the airway obstructions by bronchoscopic lavage or grasping forceps (39). Intubation and pulmonary toilet (deliberate clearing of mucus from trachea and bronchial tree via deep breathes, percussion, postural drainage and incentive spiratomy) can be beneficial to remove the bronchial obstructions (59).

Four soldiers exhibited severe dyspnea after being exposed to fumes from smoke bombs. CT scans of the chest revealed bilateral ground-glass attenuation (appearance of dark regions in the lung radiographs despite clear visualization of embedded vessels) with peripheral lung sparing. With steroid therapy, gradual recovery of the soldiers was noted. CT is found to be useful for determining severity of lung injury and diagnosis of inhalation pulmonary edema (60). Additionally, data obtained from 1057 older adults shows that lifetime exposure to second-hand smoke results in a greater decline in lung function and risk of cardiovascular mortality, accounting for confounders, mediating effect of FEV1 and baseline cardiovascular diseases (61).

## 5. ANIMAL MODELS USED TO STUDY SMOKE INHALATION INDUCED INJURIES

The first animal models developed in smoke inhalational studies are described in Table 1, categorised into small animals, large animals and non-human primates.

## 6. CURRENT THERAPY FOR SMOKE INHALATION

Immediate administration of humidified oxygen should be performed to address carbon monoxide poisoning. Oxygen can be administered via nose tube, face mask or tracheal intubation. Patients showing symptoms of upper airway problems should be intubated to ensure oxygenation and to prevent atelectasis. Patients with breathing difficulty or altered psychological state due to

## Animal models of smoke inhalation induced injuries

**Table 1.** Animals used in smoke inhalation injury studies, exposed to various smoke types

Animal Category	Animal Type	Smoke Type (year)	Findings
Small animals	Rat	White pine (1976)	Administration of large doses of methylprednisolone and dexamethasone 1 h after smoke exposure was able to reduce mortality and interstitial edema levels, while administration of cortisone and hydrocortisone increased mortality. An increase of methylprednisolone from 10 mg to 20 mg resulted in a decrease in mortality from 22.6 % to 76.7 % (65).
	Rabbit	Pine wood (1982)	Pulmonary epithelium remained intact although infiltrated with inflammatory cells within 6 h after injury. The ciliated and secretory lining cells were destroyed and high levels of cytokines were present within 24 h after injury. A nonciliated, stratified reparative epithelium was present 72 h after injury. The response seen in this model resembles the injuries in the lungs of victims exposed to smoke inhalation injury (103).
	Mini-pig	Cigarette smoke (1986)	Cigarette smoke and carbon monoxide caused the aggregation of platelets to the arterial endothelium, which potentiates the beginning of atherogenesis (104).
	Guinea pig	Cigarette smoke (2007)	Codeine, DNK333 (selective NK(1)/NK(2) antagonist), terbutaline and atropine were shown to inhibit cough stimulated by citric acid or capsaicin. VR1 antagonists capsaizine and iodo-resiniferatoxin were not able to inhibit stimulated cough. Codeine and terbutaline are currently used clinically for treatment of cough (105).
Large animals	Goat	Byproducts of incomplete combustion (1981)	Smoke inhalation caused necrotic tracheobronchitis, bronchiolitis with pseudomembrane and cast formation, mild multifocal atelectasis and bronchopneumonia, which is an appropriate model to evaluate pathophysiology and treatment of inhalation injury (106).
	Sheep	Cotton smoke (1984, 1986, 1988, 2002)	Anaesthetized sheep exposed to smoke were monitored for lung lymph flow and cardiopulmonary levels for 72 h, with significant decrease in arterial oxygen tension and development of dyspnea within 24 h after exposure (107). An ovine smoke-inhalation model showed an increase in lung lymph flow and an increase in the lymph:plasma ratio of protein, suggesting increased permeability of the alveolar capillary membrane (8). Another study in ovine smoke-inhalation model shows that pulmonary edema is formed as a result of significant increase in capillary pressure and capillary permeability (10). A model of sepsis following inhalation injury in sheep was found to resemble closely the condition of hyperdynamic sepsis in humans (108).
	Mongrel dog	Wood smoke (1991)	Administration of methylprednisolone (30 mg/kg before smoke exposure did not ameliorate haemodynamics, gas exchange, lung compliance, lung edema, pulmonary vascular permeability or pulmonary surfactant function (66).
Non-human primates	Stumptailed macaque	Cigarette smoke (1982)	No significant changes in plasma cholesterol and lipoprotein cholesterol concentration were observed between the control group, low-dose group and high-dose group (109).
	Baboon	Polyethylene, wood pulp and nonwoven cellulose fabric (1993)	After 7 days of mechanical ventilation, high-frequency flow interruption was found to have significantly reduced barotraumas and parenchymal damage, compared to high-frequency oscillatory ventilation (110).

smoke inhalation should be intubated to remove build-up of mucus and to prevent choking on secretions. Mechanical ventilation may be considered to increase oxygen intake. A bronchodilator could be used to allow smoother breathing if airway is constricted.

Bronchoscopy can be performed to allow a better prognosis of the type and amount of damage sustained, to identify and remove mucus, secretions and debris. Bronchoscopy should be done during atelectasis to prevent apoxia. Victims presenting with >10 mmol/L plasma lactate are highly likely to have cyanide poisoning and should be treated with cyanide antidote (Taylor, Lilly or Pasadena Kit) (62). Patients should also be tested for other toxic substances in the blood. If any are detected, the respective antidote should be administered immediately. Antibiotics should only be given after confirmation of sputum or blood cultures.

For patients with severe carbon monoxide or hydrogen cyanide poisoning, hyperbaric oxygenation treatment (HBOT) can be considered. In HBOT, the patients are given concentrated oxygen in a pressurised chamber of about 1.5 to 3 atm. Studies have shown that HBOT prevents loss of consciousness, reduces symptoms of altered mental state, prevents long term (6 weeks and 1 year) cognitive sequelae, cardiovascular dysfunction, ameliorates pulmonary edema and attenuates neurological

damage (63). However, the use of HBOT in smoke victims still remains controversial as the methods for treating adults can not be used in children or pregnant women (64). More clinical studies are needed to validate HBOT as a therapy for smoke inhalation injury.

Bronchodilators should be administered to patients with prior lung conditions like asthma to address reflex bronchoconstriction due to irritation by inhaled smoke. Where possible, deep breathing, coughing and clearing of mucus is beneficial to prevent atelectasis and to the removal of airway debris. In victims with tracheal intubation, pulmonary toilet can be done to remove airway debris. Corticosteroids like methylprednisolone and hydrocortisone are found to have no significant effect or ineffective (65-66).

A 67 year old woman who lived 35 years with her husband, who was a heavy smoker, presented with pulmonary over-inflation via chest roentgenogram, but chest CT scans did not show emphysematous changes. Her respiratory functions improved after beta2-agonist inhalation, anti-cholinergic drug inhalation, steroid drug (HFA-BDP) inhalation, and salmeterol. One year after treatment, FEV1.0 increased by 450 ml (67). Beta2-agonist was also suggested by another group as a possible therapy for acute inhalational lung injury (68).

### 7. POTENTIAL THERAPEUTICS

In various animal models of smoke inhalation, the benefits of exogenous surfactant, antagonists, antioxidants, anti-inflammatories, anti-epileptics, inhibitors, nitric oxide, fibrinolytics, antibiotics, recombinant proteins, mechanical ventilation and bronchial circulation suggest that these compounds or clinical interventions may have a future therapeutic role in smoke-induced injury.

#### 7.1. Surfactants

Mongrel dogs that are exposed to wood smoke inhalation and immediately administered with an exogenous surfactant, show improvement of pulmonary function and gaseous exchange (69). Adult male Sprague Dawley rats shows that the co-administration of intratracheal surfactant and dexamethasone, an anti-inflammatory steroid, improves pulmonary gaseous exchange, attenuates lung inflammation, and reduces lung damage after paraquat-induced lung injury (70).

#### 7.2. Leukotriene antagonist

Sheeps that are exposed to acrolein smoke and treated with BW-755C (a combined cyclooxygenase and lipoxygenase inhibitor) prevents pulmonary edema and pulmonary hypertension. Treatment with indomethacin (a cyclooxygenase inhibitor) prevents pulmonary hypertension but not pulmonary edema, indicating that leukotriene B4 is responsible for formation of pulmonary edema (71).

#### 7.3. Antioxidants

The effects of antioxidants on smoke inhalation injury have been detailed in numerous studies based on ovine model. Antioxidants protects against oxidative damage which occurs in smoke inhalation injury. Aerosolised deferoxamine-pentastarch but not aerosolised deferoxamine alone prevents lung injury in an ovine smoke-inhalation model, either directly or indirectly as an antioxidant (72).

Manganese superoxide dismutase (Mn-SOD), which increases lung microvascular permeability coefficient, reduces filtration coefficient, reduces lymph flows and improves arterial  $O_2$ -to-inspired  $O_2$  ratio (73). Moreover, when treated with nebulised Mn-SOD, which attenuates the increase in filtration coefficient and filtration sigma, significantly decreases lung tissue conjugated dienes and attenuates loss of protein in the animal. Mn-SOD did not moderate the increase in lung lymph flow, failed to reduce the fall in  $PaO_2/FiO_2$  ratio, did not prevent pulmonary edema and thus shows modest clinical potential (74).

Nebulised vitamin E is acknowledged to increase lung alpha-tocopherol concentrations and significantly improve pulmonary gas exchange in a burn and cotton smoke inhalation injury model (75). Furthermore, when sheep are given alpha-tocopherol orally 24h prior to injury, it doubles plasma alpha-tocopherol levels, preventing an increase in pulmonary permeability index, attenuating the increase in lung lymph flow, increases the  $PaO_2/FiO_2$  ratio,

reduces both peak and pause airway pressure increases and decreases plasma conjugated dienes and nitrotyrosine. Vitamin E can thus be utilized as a prophylactic to protect against smoke inhalation injuries (76).

Sheep that are exposed to combined cotton smoke and skin burn injury demonstrate a depletion of tissue alpha-tocopherol. Administration of vitamin E is found to alleviate this depletion and protect against oxidative stress (77). In addition, when subjects are treated with L-arginine, the decline in plasma arginine is softened. A reduction in decline of the  $PaO_2/FiO_2$  ratio, reduction of airway obstruction, lessening of histopathological injuries, and a significant decrease in nitrotyrosine, which indicates reduced lung tissue damage, is associated with L-arginine. Administration of L-arginine is able to prevent formation of peroxynitrite by iNOS, lessening oxidative stress levels (78-79).

Smokers are characterized by increased rates of disappearance in levels of alpha-tocopherol and gamma-tocopherol. Ascorbic acid is able to double plasma ascorbic acid concentrations and attenuate the increased rate of disappearance by reducing oxidative stress, hence reducing vitamin E disappearance (80).

#### 7.4. Anti-inflammatory drugs

After exposure to concentrated ambient particles, rats show slight bronchiolar inflammation and thickened vessels at the bronchiole, which is ameliorated by prophylactic treatment with N-acetylcysteine (81). Treatment of sheep subjected to burn and smoke inhalation injury with continuous nebulised albuterol, a bronchodilator and anti-inflammatory drug, leads to lower pause and peak inspiratory pressures, a decrease in pulmonary transvascular fluid flux, significantly higher  $PaO_2/FiO_2$  ratio, a lower shunt fraction 48 h postinjury, a decrease in lung wet-to-dry weight ratio and bronchial obstruction scores (82). Furthermore, cotton smoke inhalation injury is attenuated by alpha-Trinositol, by reducing pulmonary microvascular permeability and transvascular fluid change (83).

#### 7.5. Anti-epileptic drug

Smoke inhalation studies on sheep shows that phenytoin, an anti-convulsant, attenuates the increase in pulmonary artery pressure and pulmonary vascular resistance index and the decrease in cardiac index (84).

#### 7.6. iNOS inhibitor

The majority of nitric oxide is produced by macrophages and neutrophils as an immune response against foreign pathogens through iNOS. The sustained levels of nitric oxide can lead to formation of peroxynitrite, a potent oxidant which can cause extensive tissue and DNA damage. Inhibition of iNOS by BBS-2, a selective iNOS dimerisation inhibitor ameliorates the decrease in pulmonary function and gaseous exchange, attenuates pulmonary edema, reduces airway obstruction, reduces the increase in bronchial blood flow and plasma nitric oxide in an ovine model of combined smoke with burns (85).

## Animal models of smoke inhalation induced injuries

A study on a combined smoke and burn model of sheep shows that mercaptoethylguanidine, an iNOS inhibitor, is able to attenuate the increase in plasma and lymph NO<sub>x</sub> concentration, prevent depressed hemodynamics, and reducing fluid requirements compared to the control group. Inhibition of iNOS significantly minimizes changes in pulmonary microvascular permeability (86).

### 7.7. Nitric oxide

Studies show that the inhalation of 40 ppm nitric oxide, which is reported to decrease microvascular permeability to protein, 22 h after cotton smoke inhalation injury in sheep, reduces lung lymph flow and pulmonary edema and prevents a marked increase in pulmonary microvascular resistance (87).

### 7.8. PARP inhibitor

Poly(ADP-ribose) polymerase (PARP) inhibitor, INO-1001, attenuates pulmonary edema, airway blood flow and pressure, lung histological injury and systemic vascular leakage in an ovine burn and smoke-inhalation model (88).

### 7.9. Reducing cast formation

Combustion products like particulates, oxidants and toxic gases cause damage to the respiratory tract, which can lead to its closure or partial collapse (89). The patency of the airway is also affected by the accumulation of cast material which usually occurs in multiple sites. Cast material consists of fibrin, neutrophils, bronchial epithelial cells and mucus secretions, which is recruited, shed or secreted by the victim exposed to smoke inhalation injury. As the ciliary transport system is impaired due to damage of the ciliated epithelium by smoke inhalation, the cast material remains uncleared in the airway. More cast materials are found in smoke inhalation victims with pneumonia than those with burns, indicating that airway coagulopathy is worse in smoke inhalation victims with pneumonia.

Cast material consists of fibrin, neutrophils, epithelial cells and mucus in multiple sites in the respiratory tract causes airway obstruction. Tissue plasminogen activator (TPA), which breaks apart fibrin clots, was nebulized and inhaled in an ovine smoke with burn model. Nebulized 2 mg TPA has been shown to attenuate decrease in pulmonary function and gaseous exchange, reduce pulmonary edema and airway obstruction. Nebulized 1 mg TPA showed similar results compared to nebulized saline (90).

Continuous infusion of heparin leads to a reduction in cast formation, improves blood oxygenation, attenuates barotrauma and reduces pulmonary edema (91). Additionally, it is shown that inhalation of nebulized heparin is able to reduce sepsis-induced cast formation, pulmonary edema, congestion, macrophage infiltration and attenuates hyperdynamic cardiovascular flux and a decrease in blood oxygenation (92). It is also noted that high-dose heparin does not improve lung function in a sepsis-induced smoke inhalation injury model (93).

### 7.10. Mechanical ventilation

Immediate initiation of positive pressure ventilation with positive end-expiratory pressure significantly increases survival, decreases cast formation and does not alleviate hypoxia following smoke inhalation injury in a sheep model (94). Additionally, volume controlled mechanical ventilation with systemic heparin achieved 50% survival, while high-frequency percussive ventilation with systemic heparin achieved 100% survival 60 hours after the onset of acute respiratory distress syndrome in a cotton smoke/burn induced LD100 sheep model (95).

### 7.11. Bronchial circulation

A study of cotton smoke inhalation in sheep indicates that inhalation injury leads to a slow increase in pulmonary vascular resistance and lung lymph flow, linked to deteriorating tissue oxygenation. A drop in bronchial blood flow attenuates these pathophysiological effects and the attenuation is increased when 70% ethanol is injected into the ligated bronchial artery than when only the artery was ligated. These data suggest that bronchial circulation contributes to the formation of pulmonary edema after smoke inhalation injury (96).

### 7.12. Endothelin-1 receptor blockade

Tezosentan (an ETA and ETB receptor antagonist) is unable to protect against smoke inhalation injury in a sheep model (97).

### 7.13. Protease inhibitor

Intravenous administration of gabexate mesilate, a synthetic protease inhibitor, significantly reduces transvascular fluid and protein flux, and eliminated gas exchange degradation in an ovine cotton smoke-inhalation model (98).

### 7.14. Antibiotics

Gentamicin stabilizes cardiac index, attenuates the decrease in mean arterial pressure and systemic vascular resistance index in an ovine septic shock model following cotton smoke inhalation injury (99).

### 7.15. Thromboxane A<sub>2</sub> synthase inhibitor

OKY-046, a selective thromboxane A<sub>2</sub> synthase inhibitor, is shown in an ovine smoke model to significantly inhibit pulmonary thromboxane B<sub>2</sub> delivery, reduces early increase in pulmonary vascular resistance, prevents increase in systemic vascular resistance, diminishes and delays decrease in cardiac output and prevents an increase in lung lymph flow. OKY-046 was noted to ameliorate cardiovascular and pulmonary dysfunction caused by smoke inhalation injury (100).

### 7.16. Activated protein C

Activated protein C (APC) is a serine protease that has anti-inflammatory and anti-coagulant activities. The effects of recombinant human APC (rhAPC) in ALI based on a sheep model shows that infusion of rhAPC attenuates a fall in PaO<sub>2</sub>/FiO<sub>2</sub> ratio, moderates an expected increase in pulmonary microvascular shunt fraction,

increases peak airway pressure and limits an increase in 3-nitrotyrosine. rhAPC fails to ameliorate lung edema formation. Treatment with rhAPC does not alter activated clotting time or platelet count but causes reduced fibrin degradation products (101). Intravenous administration of APC into Wistar rats significantly reduced inflammatory cell sequestration and attenuated lung reperfusion injury by increasing antioxidative and decreasing oxidative enzyme activity levels (102).

## 8. SUMMARY AND PERSPECTIVE

Studies are needed to evaluate the safety and efficacy of these potential therapies before they can be used clinically. Through a better understanding of the pathophysiology of the various kinds of smoke inhalation injury and the lung's response to them, more effective and specific therapies may be discovered for improving the outcomes of people with various types of smoke-induced lung injury. As each case of smoke-induced lung injury is unique, it would be ideal to tailor the therapy to the condition of the victim using combinatory therapeutics.

## 9. REFERENCES

1. Prien T, H. A. Linares, L. D. Traber, D. N. Herndon, D. L. Traber: Lack of hematogenous mediated pulmonary injury with smoke inhalation. *J Burn Care Rehabil* 9(5), 462-466 (1988)
2. Harkema JR, G. Keeler, J. Wagner, M. Morishita, E. Timm, J. Hotchkiss, F. Marsik, T. Dvonch, N. Kaminski, E. Barr: Effects of concentrated ambient particles on normal and hypersecretory airways in rats. *Res Rep Health Eff Inst* 120, 1-79 (2004)
3. Enkhbaatar P, D. L. Traber: Pathophysiology of acute lung injury in combined burn and smoke inhalation injury. *Clin Sci (Lond)* 107(2),137-143 (2004)
4. Fidan F, M. Unlu, M. Sezer, O. Sahin, C. Tokyol, H. Esme: Acute effects of environmental tobacco smoke and dried dung smoke on lung histopathology in rabbits. *Pathology* 38(1), 53-57 (2006)
5. Joad JP, S. Sekizawa, C. Y. Chen, A. C. Bonham: Air pollutants and cough. *Pulm Pharmacol Ther* 20(4), 347-354 (2007)
6. Traber DL, H. K. Hawkins, P. Enkhbaatar, R. A. Cox, F. C. Schmalstieg, J. B. Zwischenberger, L. D. Traber: The role of the bronchial circulation in the acute lung injury resulting from burn and smoke inhalation. *Pulm Pharmacol Ther* 20(2), 163-166 (2007)
7. Witten ML, S. F. Quan, R. E. Sobonya, R. J. Lemen: New developments in the pathogenesis of smoke inhalation-induced pulmonary edema. *West J Med* 148, 33-36 (1988)
8. Traber DL, D. N. Herndon, M. D. Stein, L. D. Traber, J. T. Flynn, G. D. Niehaus: The pulmonary lesion of smoke

- inhalation in an ovine model. *Circ Shock* 18, 311-323 (1986)
9. Basadre JO, K. Sugi, D. L. Traber, L. D. Traber, G. D. Niehaus, D. N. Herndon: The effect of leukocyte depletion on smoke inhalation injury in sheep. *Surgery* 104(2), 208-215 (1988)
10. Isago T, S. Noshima, L. D. Traber, D. N. Herndon, D. L. Traber: Analysis of pulmonary microvascular permeability after smoke inhalation. *J Appl Physiol* 71, 1403-1408 (1991)
11. Kramer GC, D. N. Herndon, H. A. Linares, D. L. Traber: Effects of inhalation injury on airway blood flow and edema formation. *J Burn Care Rehabil* 10(1), 45-51 (1989)
12. Efimova O, A. B. Volokhov, S. Iliaifar, C. A. Hales: Ligation of the bronchial artery in sheep attenuates early pulmonary changes following exposure to smoke. *J Appl Physiol* 88(3), 888-893 (2000)
13. Stothert JC Jr, K. D. Ashley, G. C. Kramer, D. N. Herndon, L. D. Traber, K. Deubel-Ashley, D. L. Traber: Intrapulmonary distribution of bronchial blood flow after moderate smoke inhalation. *J Appl Physiol* 69(5), 1734-1739 (1990)
14. Schenarts PJ, H. G. Bone, L. D. Traber, D. L. Traber: Effect of severe smoke inhalation injury on systemic microvascular blood flow in sheep. *Shock* 6(3), 201-205 (1996)
15. Kikuchi Y, L. D. Traber, D. N. Herndon, D. L. Traber: Unilateral smoke inhalation in sheep: effect on left lung lymph flow with right lung injury. *Am J Physiol* 271(6 Pt 2), R1620-1624 (1996)
16. Abdi S, D. N. Herndon, L. D. Traber, K. D. Ashley, J. C. Stothert Jr, J. Maguire, R. Butler, D. L. Traber: Lung edema formation following inhalation injury: role of the bronchial blood flow. *J Apl Physiol* 71(2), 727-734 (1991)
17. Abdi S, D. Herndon, J. McGuire, L. Traber, D. L. Traber: Time course of alterations in lung lymph and bronchial blood flows after inhalation injury. *J Burn Care Rehabil* 11(6), 510-515 (1990)
18. Haponick E, W. Summer: Respiratory complications in burned patients: pathogenesis and spectrum of inhalation injury. *J Crit Care* 2, 49-54 (1987)
19. Murakami K, D. L. Traber: Pathophysiological basis of smoke inhalation injury. *News Physiol Sci* 18, 125-129 (2003)
20. Soejima K, L. D. Traber, F. C. Schmlstieg, H. Hawkins, J. M. Jodoin, C. Szabo, E. Szabo, L. Varig, A. Salzman, D. L. Traber: Role of nitric oxide in vascular permeability after combined burns and smoke inhalation injury. *Am J Respir Crit Care Med* 163, 745-752 (2001)

## Animal models of smoke inhalation induced injuries

21. Soejima K, F. C. Schmalstieg, L. D. Traber, C. Szabo, A. Salzman, D. L. Traber: Role of nitric oxide in myocardial dysfunction after combined burn and smoke inhalation injury. *Burns* 27(8), 809-815 (2001)
22. Westphal M, R. A. Cox, L. D. Traber, N. Morita, P. Enkhbaatar, F. C. Schmalstieg, H. K. Hawkins, D. M. Maybauer, M. O. Maybauer, K. Murakami, A. S. Burke, B. B. Westphal-Varghese, H. E. Rudloff, J. R. Salisbury, J. M. Jodoin, S. Lee, D. L. Traber: Combined burn and smoke inhalation injury impairs ovine hypoxic pulmonary vasoconstriction. *Crit Care Med* 34(5), 1428-1436 (2006)
23. Park MS, L. C. Cancio, B. S. Jordan, W. W. Brinkley, V. R. Rivera, M. A. Dubick: Assessment of oxidative stress in lungs from sheep after inhalation of wood smoke. *Toxicology* 195(2-3), 97-112 (2004)
24. Jeanes YM, W. L. Hall, A. R. Proteggente, J. K. Lodge: Cigarette smokers have decreased lymphocyte and platelet alpha-tocopherol levels and increased excretion of the gamma-tocopherol metabolite gamma-carboxyethyl-hydroxychroman (gamma-CEHC). *Free Radic Res* 38(8), 861-868 (2004)
25. Leonard SW, R. S. Bruno, R. Ramakrishnan, T. Bray, M. G. Traber: Cigarette smoking increases human vitamin E requirements as estimated by plasma deuterium-labeled CEHC. *Ann N Y Acad Sci* 1031, 357-360 (2004)
26. Bruno RS, R. Ramakrishnan, T. J. Montine, T. M. Bray, M. G. Traber: alpha-Tocopherol disappearance is faster in cigarette smokers and is inversely related to their ascorbic acid status. *Am J Clin Nutr* 81(1), 95-103 (2005)
27. Bruno RS, S. W. Leonard, J. Li, T. M. Bray, M. G. Traber: Lower plasma alpha-carboxyethyl-hydroxychroman after deuterium-labeled alpha-tocopherol supplementation suggests decreased vitamin E metabolism in smokers. *Am J Clin Nutr* 81(5), 1052-1059 (2005)
28. Dourado VZ, S. E. Tanni, S. A. Vale, M. M. Faganello, F. F. Sanchez, I. Godoy: Systemic manifestations in chronic obstructive pulmonary disease. *J Bras Pneumol* 32(2), 161-171 (2006)
29. Bhattacharyya SN, M. A. Dubick, L. D. Yantis, J. I. Enriquez, K. C. Buchanan, S. K. Batra, R. A. Smiley: *In vivo* effect of wood smoke on the expression of two mucin genes in rat airways. *Inflammation* 28(2), 67-76 (2004)
30. Cox RA, R. P. Mlcak, D. L. Chinkes, S. Jacob, P. Enkhbaatar, J. Jaso, L. P. Parish, D. L. Traber, M. Jeschke, D. N. Herndon, H. K. Hawkins: Upper airway mucus deposition in lung tissue of burn trauma victims. *Shock* 29(3), 356-361 (2007)
31. Bidani A, C. Z. Wang, T. A. Heming: Cotton smoke inhalation primes alveolar macrophages for tumor necrosis factor-alpha production and suppresses macrophage antimicrobial activities. *Lung* 176(5), 325-336 (1998)
32. Bidani A, C. Z. Wang, T. A. Heming: Early effects of smoke inhalation on alveolar macrophage functions. *Burns* 22(2), 101-106 (1996)
33. Laffon M, J. F. Pittet, K. Modelska, M. A. Matthay, D. M. Young: Interleukin-8 mediates injury from smoke inhalation to both the lung endothelial and the alveolar epithelial barriers in rabbits. *Am J Respir Crit Care Med* 160(5 Pt 1), 1443-1449 (1999)
34. Park GY, J. W. Park, D. H. Jeong, S. H. Jeong: Prolonged airway and systemic inflammatory reactions after smoke inhalation. *Chest* 123(2), 475-480 (2003)
35. Whitehead GS, K. A. Grasman, E. C. Kimmel: Lung function and airway inflammation in rats following exposure to combustion products of carbon-graphite/epoxy composite material: comparison to a rodent model of acute lung injury. *Toxicology* 183(1-3), 175-197 (2003)
36. Wright MJ, J. T. Murphy: Smoke inhalation enhances early alveolar leukocyte responsiveness to endotoxin. *J Trauma* 59(1), 64-70 (2005)
37. Cox RA, A. S. Burke, G. Oliveras, P. Enkhbaatar, L. D. Traber, J. B. Zwischenberger, M. G. Jeschke, F. C. Schmalstieg, D. N. Herndon, D. L. Traber, H. K. Hawkins: Acute bronchial obstruction in sheep: histopathology and gland cytokine expression. *Exp Lung Res* 31(9-10), 819-837 (2005)
38. Chou KJ, J. L. Fisher, E. J. Silver: Characteristics and outcome of children with carbon monoxide poisoning with and without smoke exposure referred for hyperbaric oxygen therapy. *Pediatr Emerg Care* 16(3), 151-155 (2000)
39. Cha SI, C. H. Kim, J. H. Lee, J. Y. Park, T. H. Jung, W. I. Choi, S. B. Han, Y. J. Jeon, K. C. Shin, J. H. Chung, K. H. Lee, Y. J. Kim, B. K. Lee: Isolated smoke inhalation injuries: Acute respiratory dysfunction, clinical outcomes, and short-term evolution of pulmonary functions with the effects of steroids. *Burns* 33, 200-208 (2007)
40. Mellins RB, S. Park: Respiratory complications of smoke inhalation in victims of fires. *J Pediatr* 87, 1-7 (1975)
41. Lo CP, S. Y. Chen, K. W. Lee, W. L. Chen, C. Y. Chen, C. J. Hsueh, G. S. Huang: Brain injury after acute carbon monoxide poisoning: early and late complications. *AJR Am J Roentgenol* 189(4), W205-211 (2007)
42. Zagami AS, A. K. Lethlean, R. Mellick: Delayed neurological deterioration following carbon monoxide poisoning: MRI findings. *J Neurol* 240(2), 113-116 (1993)
43. Werner B, W. Bäck, H. Akerblom, P. O. Barr: Two cases of acute carbon monoxide poisoning with delayed neurological sequelae after a "free" interval. *J Toxicol Clin Toxicol* 23(4-6), 249-265 (1985)

44. Hsiao CL, H. C. Kuo, C. C. Huang: Delayed encephalopathy after carbon monoxide intoxication--long-term prognosis and correlation of clinical manifestations and neuroimages. *Acta Neurol Taiwan* 13(2), 64-70 (2004)
45. Chang KH, M. H. Han, H. S. Kim, B. A. Wie, M. C. Han: Delayed encephalopathy after acute carbon monoxide intoxication: MR imaging features and distribution of cerebral white matter lesions. *Radiology* 184(1), 117-122 (1992)
46. Seet RC, E. P. Wilder-Smith, E. C. Lim: Hemorrhagic leukoencephalopathy following acute carbon monoxide poisoning. *Eur J Neurol* 15(6), e49-50 (2008)
47. Finelli PF, F. J. DiMario Jr: Hemorrhagic infarction in white matter following acute carbon monoxide poisoning. *Neurology* 63(6), 1102-1104 (2004)
48. Varol E, M. Ozaydin, S. M. Aslan, A. Dogan, A. Altinbas: A rare cause of myocardial infarction: acute carbon monoxide poisoning. *Anadolu Kardiyol Derg* 7(3), 322-323 (2007)
49. Sorodoc L, C. Lionte, V. Laba: A rare cause of non-Q myocardial infarction--acute carbon monoxide poisoning. *Rev Med Chir Soc Med Nat Iasi* 108(4), 782-785 (2004)
50. Mokaddem A, W. Sdiri, K. Selmi, B. Darghouth, H. Mahjoub, K. Bachraoui, H. Makni, S. Kachboursa, M. R. Boujnah: A rare cause of myocardial infarction: carbon monoxide intoxication. *Tunis Med* 82(3), 320-323 (2004)
51. Tan ES, D. J. van Veldhuisen, K. I. Lie: Carbon monoxide poisoning as a trigger for myocardial infarction. *Ned Tijdschr Geneesk* 137(44), 2266-2268 (1993)
52. Wierzbicka-Chmiel J, A. Chmiel, T. Dzielski: Myocardial infarction after carbon monoxide exposure--a case report. *Pol Arch Med Wewn* 116(1), 683-686 (2006)
53. Skrzypczak W, K. Galecka, A. Shorek: Sensorineural hearing loss as a consequence of carbon monoxide poisoning. *Otolaryngol Pol* 61(4), 479-483 (2007)
54. Shahbaz Hassan M, J. Ray, F. Wilson: Carbon monoxide poisoning and sensorineural hearing loss. *J Laryngol Otol* 117(2), 134-137 (2003)
55. Michalska-Piechowiak T, M. Miarzyńska, I. Perlik-Gattner: Sudden unilateral sensorineural hearing loss after carbon monoxide intoxication. *Przegl Lek* 61(4), 374-376 (2004)
56. Baker SR, D. J. Lilly: Hearing loss from acute carbon monoxide intoxication. *Ann Otol Rhinol Laryngol* 86(3 Pt 1), 323-328 (1977)
57. Chambers CA, R. O. Hopkins, L. K. Weaver, C. Key: Cognitive and affective outcomes of more severe compared to less severe carbon monoxide poisoning. *Brain Inj* 22(5), 387-395 (2008)
58. Raj RS, P. Abdurahiman, J. Jose: Delayed syndrome in carbon monoxide poisoning. *J Assoc Physicians India* 54, 955-956 (2006)
59. Herndon DN, F. Langner, P. Thompson, H. A. Linares, M. Stein, D. L. Traber: Pulmonary injury in burned patients. *Surg Clin North Am* 67, 31-46 (1987)
60. Masaki Y, K. Sugiyama, H. Tanaka, Y. Uwabe, M. Takayama, M. Sakai, T. Hayashi, M. Otsuka, S. Suzuki: Effectiveness of CT for clinical stratification of occupational lung edema. *Ind Health* 45(1), 78-84 (2007)
61. Eisner MD, Y. Wang, T. J. Haight, J. Balmes, S. K. Hammond, I. B. Tager: Secondhand smoke exposure, pulmonary function, and cardiovascular mortality. *Ann Epidemiol* 17(5), 364-373 (2007)
62. Baud FJ, P. Barriot, V. Toffis, B. Riou, E. Vicaut, Y. Lecarpentier, R. Bourdon, A. Astier, C. Bismuth: Elevated blood cyanide concentrations in victims of smoke inhalation. *N Engl J Med* 325(25), 1761-1766 (1991)
63. Weaver LK, R. O. Hopkins, K. J. Chan, S. Churchill, E. C. Gregory, T. P. Clemmer, J. F. Orme Jr, F. O. Thomas, A. H. Morris: Hyperbaric oxygen for acute carbon monoxide poisoning. *New Engl J Med* 347(14), 1057-1067 (2002)
64. Liebelt EL: Hyperbaric oxygen therapy in childhood carbon monoxide poisoning. *Curr Opin Pediatr* 11(3), 259-264 (1999)
65. Dressler DP, W. A. Skornik, S. Kupersmith: Corticosteroid treatment of experimental smoke inhalation. *Ann Surg* 183(1), 46-52 (1976)
66. Nieman GF, W. R. Clark, T. Hakim: Methylprednisolone does not protect the lung from inhalation injury. *Burns* 17(5), 384-390 (1991)
67. Yamazoe M, H. Tanaka, C. Takezawa, Y. Yamada, S. Abe: A case of severe airflow limitation markedly improved by inhalation therapy in non-smoking woman with chronic obstructive pulmonary disease. *Nihon Kokyuki Gakkai Zasshi* 44(2), 122-127 (2006)
68. Wiener-Kronish JP, M. A. Matthay: Beta-2-agonist treatment as a potential therapy for acute inhalational lung injury. *Crit Care Med* 34(6), 1841-1842 (2006)
69. Nieman GF, A. M. Paskanik, R. R. Fluck, W. R. Clark: Comparison of exogenous surfactants in the treatment of wood smoke inhalation. *Am J Respir Crit Care Med* 152(2), 597-602 (1995)
70. Chen CM, C. L. Fang, C. H. Chang: Surfactant and corticosteroid effects on lung function in a rat model of acute lung injury. *Crit Care Med* 29(11), 2169-2175 (2001)
71. Janssens SP, S. W. Musto, W. G. Hutchison, C. Spence, M. Witten, W. Jung, C. A. Hales: Cyclooxygenase and

lipoygenase inhibition by BW-755C reduces acrolein smoke-induced acute lung injury. *J Appl Physiol* 77(2), 888-895 (1994)

72. LaLonde C, K. Ikegami, R. Demling: Aerosolized deferoxamine prevents lung and systemic injury caused by smoke inhalation. *J Appl Physiol* 77, 2057-2064 (1994)

73. Nguyen TT, C. S. Cox Jr, D. N. Herndon, N. A. Biondo, L. D. Traber, P. E. Bush, A. Zophel, D. L. Traber: Effects of manganese superoxide dismutase on lung fluid balance after smoke inhalation. *J Appl Physiol* 78(6), 2161-2168 (1995)

74. Maybauer MO, Y. Kikuchi, M. Westphal, D. M. Maybauer, K. Nishida, L. D. Traber, B. B. Westphal-Varghese, N. Morita, P. Enkhbaatar, D. N. Herndon, D. L. Traber: Effects of manganese superoxide dismutase nebulisation on pulmonary function in an ovine model of acute lung injury. *Shock* 23(2), 138-143 (2005)

75. Morita N, M. G. Traber, P. Enkhbaatar, M. Westphal, K. Murakami, S. W. Leonard, R. A. Cox, H. K. Hawkins, D. Herndon, L. D. Traber, D. L. Traber: Aerosolized alpha-tocopherol ameliorates acute lung injury following combined burn and smoke inhalation injury in sheep. *Shock* 25(3), 277-282 (2006)

76. Morita N, K. Shimoda, M. G. Traber, M. Westphal, P. Enkhbaatar, K. Murakami, S. W. Leonard, L. D. Traber, D. L. Traber: Vitamin E attenuates acute lung injury in sheep with burn and smoke inhalation injury. *Redox Rep* 11(2), 61-70 (2006)

77. Traber MG, K. Shimoda, K. Murakami, S. W. Leonard, P. Enkhbaatar, L. D. Traber, D. L. Traber: Burn and smoke inhalation injury in sheep depletes vitamin E: kinetic studies using deuterated tocopherols. *Free Radic Biol Med* 42(9), 1421-1429 (2007)

78. Murakami K, P. Enkhbaatar, Y. M. Yu, L. D. Traber, R. A. Cox, H. K. Hawkins, R. G. Tompkins, D. Herndon, D. L. Traber: L-arginine attenuates acute lung injury after smoke inhalation and burn injury in sheep. *Shock* 28(4), 477-483 (2007)

79. Souza-Costa DC, T. Zerbini, I. F. Metzger, J. B. T. Rocha, R. F. Gerlach, J. E. Tanus-Santos: L-Arginine attenuates acute pulmonary embolism-induced oxidative stress and pulmonary hypertension. *Nitric Oxide* 12(1), 9-14 (2005)

80. Bruno RS, S. W. Leonard, J. Atkinson, T. J. Montine, R. Ramakrishnan, T. M. Bray, M. G. Traber: Faster plasma vitamin E disappearance in smokers is normalized by vitamin C supplementation. *Free Radic Biol Med* 40(4), 689-697 (2006)

81. Rhoden CR, J. Lawrence, J. J. Godleski, B. Gonzalez-Flecha: N-acetylcysteine prevents lung inflammation after short-term inhalation exposure to concentrated ambient particles. *Toxicol Sci* 79(2), 296-303 (2004)

82. Palmieri TL, P. Enkhbaatar, R. Bayliss, L. D. Traber, R. A. Cox, H. K. Hawkins, D. N. Herndon, D. G. Greenhalgh, D. L. Traber: Continuous nebulised albuterol attenuates acute lung injury in an ovine model of combined burn and smoke inhalation. *Crit Care Med* 34(6), 1719-1724 (2006)

83. Nakazawa H, T. O. Gustafsson, L. D. Traber, D. N. Herndon, D. L. Traber: Alpha-Trinositol decreases lung edema formation after smoke inhalation in an ovine model. *J Appl Physiol* 76(1), 278-282 (1994)

84. Nishida K, N. Matsumoto, Y. Kikuchi, D. N. Herndon, L. D. Traber, D. L. Traber: Effect of phenytoin on smoke inhalation injury in sheep. *Shock* 4(3), 211-215 (1995)

85. Enkhbaatar P, K. Murakami, K. Shimoda, A. Mizutani, L. D. Traber, G. B. Phillips, J. F. Parkinson, R. Cox, H. Hawkins, D. N. Herndon, D. L. Traber: The inducible nitric oxide synthase inhibitor BBS-2 prevents acute lung injury in sheep after burn and smoke inhalation injury. *Am J Respir Care Med* 167, 1021-1026 (2003)

86. Soejima K, L. D. Traber, F. C. Schmalstieg, H. Hawkins, J. M. Jodoin, C. Szabo, E. Szabo, L. Virag, A. Salzman, D. L. Traber: Role of nitric oxide in vascular permeability after combined burns and smoke inhalation injury. *Am J Respir Crit Care Med* 163(3Pt1), 745-752 (2001)

87. Enkhbaatar P, Y. Kikuchi, L. D. Traber, M. Westphal, N. Morita, M. O. Maybauer, D. M. Maybauer, D. N. Herndon, D. L. Traber: Effect of inhaled nitric oxide on pulmonary vascular hyperpermeability in sheep following smoke inhalation. *Burns* 31(8), 1013-1019 (2005)

88. Shimoda K, K. Murakami, P. Enkhbaatar: Effect of poly(ADP ribose) synthetase inhibition on burn and smoke inhalation injury in sheep. *Am J Physiol Lung Cell Mol Physiol* 285, 240-249 (2003)

89. Haponick E, W. Summer: Respiratory complications in burned patients: pathogenesis and spectrum of inhalation injury. *J Crit Care* 2, 49-54 (1987)

90. Enkhbaatar P, K. Murakami, R. Cox, M. Westphal, N. Morita, K. Brantley, A. Burke, H. Hawkins, F. Schmalstieg, L. D. Traber, D. N. Herndon, D. L. Traber: Aerosolized tissue plasminogen inhibitor improves pulmonary function in sheep with burn and smoke inhalation. *Shock* 22, 70-75 (2004)

91. Cox CS Jr, J. B. Zwischenberger, D. L. Traber, L. D. Traber, A. K. Haque, D. N. Herndon: Heparin improves oxygenation and minimizes barotrauma after severe smoke inhalation in an ovine model. *Surg Gynecol Obstet* 176(4), 339-349 (1993)

92. Murakami K, R. McGuire, R. A. Cox, J. M. Jodoin, L. J. Bjertnaes, J. Katahira, L. D. Traber, F. C. Schmalstieg, H. K. Hawkins, D. N. Herndon, D. L. Traber: Heparin nebulization attenuates acute lung injury in sepsis following smoke inhalation in sheep. *Shock* 18(3), 236-241 (2002)

93. Murakami K, P. Enkhbaatar, K. Shimoda, A. Mizutani, R. A. Cox, F. C. Schmalstieg, J. M. Jodoin, H. K. Hawkins, L. D. Traber, D. L. Traber: High-dose heparin fails to improve acute lung injury following smoke inhalation in sheep. *Clin Sci (Lond)* 104(4), 349-356 (2003)
94. Cox C. S. Jr, J. B. Zwischenberger, D. L. Traber, P. K. Minifee, N. Navaratnam, A. K. Haque, D. N. Herndon: Immediate positive pressure ventilation with positive end-expiratory pressure (PEEP) improves survival in ovine smoke inhalation injury. *J Trauma* 33(6), 821-827 (1992)
95. Wang D, J. B. Zwischenberger, C. Savage, L. Miller, D. J. Deyo, S. Alpard, V. J. Cardenas Jr: High-frequency percussive ventilation with systemic heparin improves short-term survival in a LD100 sheep model of acute respiratory distress syndrome. *J Burn Care Res* 27(4), 463-471 (2006)
96. Sakurai H, R. Johnigan, Y. Kikuchi, M. Harada, L. D. Traber, D. L. Traber: Effect of reduced bronchial circulation on lung fluid flux after smoke inhalation in sheep. *J Appl Physiol* 84(3), 980-986 (1998)
97. Cox RA, P. Enkhbaatar, A. S. Burke, J. Katahira, K. Shimoda, A. Chandra, L. D. Traber, D. N. Herndon, H. K. Hawkins, D. L. Traber: Effects of a dual endothelin-1 receptor antagonist on airway obstruction and acute lung injury in sheep following smoke inhalation and burn injury. *Clin Sci (Lond)* 108(3), 265-272 (2005)
98. Niehaus GD, R. Kimura, L. D. Traber, D. N. Herndon, J. T. Flynn, D. L. Traber: Administration of a synthetic antiprotease reduces smoke-induced lung injury. *J Appl Physiol* 69, 694-699 (1990)
99. Maybauer MO, D. M. Maybauer, L. D. Traber, M. Westphal, P. Enkhbaatar, N. Morita, J. M. Jodoin, J. P. Heggers, D. N. Herndon, D. L. Traber: Gentamicin improves hemodynamics in ovine septic shock after smoke inhalation injury. *Shock* 24(3), 226-231 (2005)
100. Westphal M, S. Noshima, T. Isago, K. Fujioka, M. O. Maybauer, D. M. Maybauer, L. D. Traber, J. T. Flynn, B. B. Westphal-Varghese, D. L. Traber: Selective thromboxane A2 synthase inhibition by OKY-046 prevents cardiopulmonary dysfunction after ovine smoke inhalation injury. *Anesthesiology* 102(5), 954-961 (2005)
101. Maybauer MO, D. M. Maybauer, J. F. Fraser, L. D. Traber, M. Westphal, P. Enkhbaatar, R. A. Cox, R. Huda, H. K. Hawkins, N. Morita, K. Murakami, A. Mizutani, D. N. Herndon, D. L. Traber: Recombinant human activated protein C improves pulmonary function in ovine acute lung injury resulting from smoke inhalation and sepsis. *Crit Care Med* 34(9), 2432-2438 (2006)
102. Teke Z, M. Sacar, C. Yenisey, A. O. Atalay, T. Bicakci, E. Erdem: Activated protein C attenuates intestinal reperfusion-induced acute lung injury: an experimental study in a rat model. *Am J Surg* 195(6), 861-873 (2008)
103. Thorning DR, M. L. Howard, L. D. Hudson, R. L. Schumacher: Pulmonary responses to smoke inhalation: morphologic changes in rabbits exposed to pine wood smoke. *Hum Pathol* 13(4), 355-364 (1982)
104. Marshall M: Ultrastructural findings on platelet deposition in initial atherogenesis. *Wien Klin Wochenschr* 98(7), 212-214 (1986)
105. Lewis CA, C. Ambrose, K. Banner, C. Battram, K. Butler, J. Giddings, J. Mok, J. Nasra, C. Winny, C. Poll: Animal models of cough: literature review and presentation of a novel cigarette smoke-enhanced cough model in the guinea-pig. *Pulm Pharmacol Ther* 20(4), 325-333 (2007)
106. Walker HL, C. G. McLeod Jr, W. F. McManus: Experimental inhalation injury in the goat. *J Trauma* 21(11), 962-964 (1981)
107. Herndon DN, T. Adams Jr, L. D. Traber, D. L. Traber: Inhalation injury and positive pressure ventilation in a sheep model. *Circ Shock* 12(2), 107-113 (1984)
108. Murakami K, L. J. Bjertnaes, F. C. Schmalstieg, R. McGuire, R. A. Cox, H. K. Hawkins, D. N. Herndon, L. D. Traber, D. L. Traber: A novel animal model of sepsis after acute lung injury in sheep. *Crit Care Med* 30(9), 2083-2090 (2002)
109. Raymond TL, A. J. Delucia, L. R. Bryant: Failure of chronic cigarette smoke exposure to alter plasma lipoproteins of stump-tailed macaques (*Macaca arctoides*). *Atherosclerosis* 41(1), 27-33 (1982)
110. Cioffi WG, R. A. deLemos, J. J. Coalson, D. A. Gerstmann, B. A. Pruitt Jr: Decreased pulmonary damage in primates with inhalation injury treated with high-frequency ventilation. *Ann Surg* 218(3), 328-335 (1993)

**Abbreviations:** NOS: nitric oxide synthase; DNA: deoxyribose nucleic acid; iNOS: inducible nitric oxide synthase; NOx: nitric nitrate oxide ratio; CEHC: gamma-carboxyethyl-hydroxychroman; TNF: tumour necrosis factor; IFN: interferon; IL: interleukin; ACM: advanced composite material; ALI: acute lung injury; MIP: macrophage inflammatory protein; COHb: carboxyhaemoglobin; CO: carbon monoxide; CT: chest tomography; FEV: forced expiratory volume; HBOT: hyperbaric oxygen therapy; Mn-SOD: manganese superoxide dismutase; PARP: Poly(ADP-ribose) polymerase; TPA: tissue plasminogen activator; APC: activated protein C; rhAPC: recombinant human activated protein C

## **Animal models of smoke inhalation induced injuries**

**Key Words:** Smoke inhalation, Acute lung injury, Animal models, Pathophysiology, Treatment, Therapeutics, Review

**Send correspondence to:** Shabbir Moochhala , Programme Director, Combat Care and Performance Programme, Defence Medical and Environmental Research Institute, DSO National Laboratories (Kent Ridge), 27 Medical Drive, Singapore 117510, Tel: 65-6485-7201, Fax: 65-6485-7226, E-mail: [mshabbir@dso.org.sg](mailto:mshabbir@dso.org.sg)

<http://www.bioscience.org/current/vol14.htm>