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## Review

# Inhalation injury: Pathophysiology and clinical care Proceedings of a Symposium Conducted at the Trauma Institute of San Antonio, San Antonio, TX, USA on 28 March 2006

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## 1. Introduction

Despite advances in critical care in general and in mechanical ventilation in particular, inhalation injury continues to impose an unacceptable burden of morbidity and mortality on burn patients. The recent conflict in Iraq has produced an increase in the number of patients with inhalation injury treated here at the U.S. Army Burn Center, and has led to new observations concerning the many complications of inhalation injury such as the risk of laryngeal sequelae. Meanwhile, ongoing research has continued to expand our understanding of the pathophysiology of inhalation injury. In March 2006, we conducted a multi-disciplinary conference under the auspices of the Trauma Institute of San Antonio (TRISAT) which was broadcast from this center at the U.S. Army Institute of Surgical Research, via videoteleconference, to our sister institutions, Wilford Hall Medical Center and the University of Texas Health Science Center at San Antonio. Our purpose was to review both current clinical practice and recent laboratory investigations.

## 2. Ventilation-perfusion changes following lung injury (Andriy Batchinsky, MD)

### 2.1. Ventilation-perfusion (V/Q) heterogeneity

Attempts to investigate ventilation-perfusion (V/Q) heterogeneity have been made for about 100 years and initially were

based on calculations of the pulmonary venous admixture [1] and dead space ventilation [2], and assessment of regional distribution of blood flow and ventilation by radioactive tracer techniques [3,4]. These methods unveiled considerable information on V/Q relationships, but were limited in resolution both at the lower and upper scales of the V/Q ratios [5].

### 2.2. Multiple Inert Gas Elimination Technique (MIGET)

With the introduction of the Multiple Inert Gas Elimination Technique (MIGET) in 1974 by Peter Wagner [6], a comprehensive tool in respiratory physiology emerged that became the gold standard in distinguishing among the different intrapulmonary causes of hypoxia, i.e. true shunt, V/Q mismatch, alveolar hypoventilation and diffusion limitation. For details on MIGET, please see [Appendix A](#). In a normal lung the blood flow is fully contained within the range of  $V/Q = 0.1$  and  $V/Q = 10$ . Abnormally low V/Q is  $< 0.1$  and abnormally high is  $V/Q > 10$ . Shunt is specified as blood flow in units with  $V/Q < 0.005$  and dead space as ventilation in units with  $V/Q > 100$ .

### 2.3. Acute lung injury (ALI): V/Q mismatch or shunt?

Early MIGET findings suggested that the predominant cause of hypoxia in chronic diseases is V/Q mismatch, whereas in acute lung injury (ALI) it is shunt [7]. However, recent evidence suggests that subtle differences in pathophysiologic distinction among various forms of ALI may also be made based on

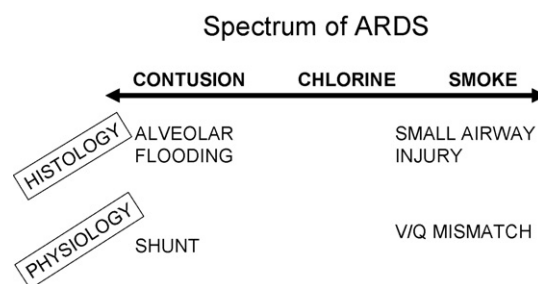
MIGET analysis. Shimazu et al. at the U.S. Army Institute of Surgical Research used MIGET to investigate of smoke inhalation [8]. MIGET sampling was performed before and 24 h after smoke exposure. They concluded that 24 h post-exposure, smoke inhalation causes small airways injury and hypoxia, instigated predominantly by V/Q mismatch rather than shunt. Histologically, smoke inhalation caused small-airway injury [8] as well as large-airway injury with ciliary disorientation and cast formation [9].

#### 2.4. MIGET for V/Q relationships in acute respiratory distress syndrome (ARDS)

In a recent study, we applied MIGET to investigate V/Q relationships in ARDS secondary to inhalation of chlorine gas in sheep and implicated both shunt and transient V/Q mismatch as causative factors for development of hypoxia in the first 2-24 h after inhalation injury [10]. On histology, both small-airway and alveolar-capillary membrane injuries were identified. We also investigated the V/Q relationships 6 h after right-sided pulmonary contusion (PC) followed by 12 cm<sup>3</sup>/kg hemorrhage and resuscitation in swine. We found that shunt and increased dead space ventilation caused the depressed P<sub>a</sub>O<sub>2</sub> values 6 h after pulmonary contusion. Histologically, PC was characterized by evidence of alveolar-capillary membrane injury. In addition, when dynamic assessment of V/Q changes was conducted in two additional animals, minutes to hours after PC, we found a transient shift in blood flow to low but non-zero V/Q compartments (unpublished data). Similar MIGET findings have been implicated in other animal [11] and human ARDS studies [12,13]. These investigators interpreted the transient channeling of blood flow to low V/Q but other-than-shunt compartments as MIGET evidence for existence of partially flooded but oxygenating alveoli. Furthermore, it is possible that these units may then become fully engaged in gas exchange or, with disease progression, be lost to the shunt fraction.

#### 2.5. The etiology of hypoxia in ARDS varies with mechanism of injury

In conclusion, accumulating data suggests that the perception of ALI and ARDS as a purely "shunt" phenomenon may be erroneous. Together with the other lung-injury studies employing MIGET, the studies presented here suggest that the etiology of hypoxia in different forms of ARDS varies with mechanism of injury (Fig. 1). An improved understanding of the differences among various types of ARDS, as revealed by MIGET, may better our clinical management of these patients. For example, those forms of ARDS which feature V/Q mismatch and small-airway injury may be amenable to interventions that maintain airway patency, such as high-frequency percussive ventilation and nebulized anticoagulants [14]. On the other hand, forms of ARDS that feature disruption of the alveolar-capillary membrane may be particularly vulnerable to overzealous fluid resuscitation. The latter was observed by us in the pulmonary contusion study as well as in the chlorine inhalation study. In both cases, vigorous fluid loading worsened the hypoxia. Finally, in those models of ARDS in which the existence of



**Fig. 1 – Spectrum of ARDS. Smoke inhalation injury is caused by small airway injury, primarily featuring V/Q mismatch by MIGET. On the other end of the spectrum is pulmonary contusion caused by disruption of the alveolar capillary membrane and featuring shunt. Chlorine inhalation injury occupies a middle ground between the two, featuring both V/Q mismatch and an increase in shunt.**

unstable and partially atelectatic or flooded alveoli can be inferred, moderate PEEP [15] or other lung-recruitment maneuvers may be indicated in an effort to minimize expansion of the shunt compartment and prevent further atelectasis.

### 3. Smoke inhalation injury of the lung and airways: role of oxidants (Michael A. Dubick, PhD)

#### 3.1. Oxidants affect the lining fluid of the respiratory tract where antioxidant concentrations vary

As it is currently understood, oxidants, such as inhaled components of smoke, gaseous air pollutants, particulate matter, or other toxicants, react first with the lining fluid that covers the surfaces of the respiratory tract. This lining fluid contains a number of compounds with antioxidant properties, both enzymatic and non-enzymatic, that serve as a major line of defense against oxidative injury [16]. However, the concentrations of these antioxidants vary along the respiratory tract such that they are not distributed uniformly throughout the respiratory system. In addition, compounds with antioxidant activities are found in cells of the respiratory tract and lung parenchyma, as well as in the blood that perfuses these tissues.

#### 3.2. Antioxidants function as reducing agents

These compounds are labeled as antioxidants based on their function as reducing agents, chelating agents, detoxifying enzymes or cofactors to enzymes. As examples, reducing agents such as glutathione (reduced form) and uric acid are considered important water-soluble antioxidants. In addition, a number of metalloenzymes such as superoxide dismutase, glutathione peroxidase and catalase have well-described antioxidant function, as do dietary components such as Vitamin C, Vitamin E, carotenoids and various polyphenolic substances. Certain B Vitamins have also been included as dietary antioxidants. It should also be

mentioned that the ability of the cell to compartmentalize function is an important component of its antioxidant defense system. The various antioxidants are distributed differently in different compartments of the cell such as in the cytoplasm, incorporated into the membranes and in the sub-cellular organelles. Many antioxidants are found in multiple cellular compartments, but their concentrations may differ with location and function. For example, it is well established that with exercise, injury or other stress, mitochondria can generate 10 times the amount of oxygen radicals that it generates under resting conditions. Thus, the cell must have sufficient antioxidants in the appropriate compartment to handle this oxidant burden. The key is for cells to maintain their oxidant and antioxidant balance in favor of antioxidants. When this balance shifts in favor of oxidants, the antioxidant defense system gets overwhelmed and oxidant-induced injury can occur.

### **3.3. Wood smoke is a complex mixture of gases and particulates**

Evidence suggests that wood smoke is a complex mixture of chemical substances that exist as gases and particulates with various chemical and physical properties. Previous studies reported that smoke contains oxidants in both the gaseous and particle phases, in addition to other toxicants, and smoke inhalation generates an inflammatory process associated with the development and progression of hypoxia. Traber et al. hypothesized that chemicals in smoke, such as aldehydes, damage epithelial cells, releasing chemotactic factors and inflammatory mediators, and prime neutrophils [17]. They postulated that neutrophil-generated oxygen radicals and inflammatory mediators initiate bronchial constriction, formation of exudate, and airway casts that are common in smoke inhalation injury [17]. In support of this hypothesis, we demonstrated that the wood smoke itself contains oxidants. In a study done in collaboration with colleagues at NIOSH in West Virginia, pine or fir smoke extract incubated with hydrogen peroxide for 3 min generated hydroxyl radicals as determined by conventional electron spin resonance [18]. Further analysis determined that the wood itself contained iron. Iron is known to react with hydrogen peroxide to form hydroxyl radicals through the Fenton reaction. Incubating the smoke extract longer (30 or 90 min) resulted in the detection of stable carbon-centered radicals that are long-lived [18]. We observed similar results with smoke generated from the thermolysis of Douglas fir. In general, most oxygen radicals are very reactive and have half-lives determined in fractions of a second. In contrast, these long-lived radicals have the potential to propagate the injury process after inhalation of wood smoke. In addition, we observed that the smoke extract activated NF $\kappa$ B, and induced lipid peroxidation and TNF- $\alpha$  release by macrophages, *in vitro* [18]. Taken together, these data support the hypothesis [17] that wood smoke induces a direct oxidant effect based on its components, as well as generate a secondary oxidant effect related to activation of inflammatory cells and processes. It is likely that this may be a common mechanism related to inhalation injury of the lung and airways.

### **3.4. The effects of wood smoke inhalation on antioxidants in the lung**

In other studies we investigated the effects of wood smoke inhalation on antioxidants in the lung. Rats were exposed to wood smoke for 16 min. Other animals received a 20% total body surface area scald burn or were subjected to a combined burn injury and smoke inhalation. Evaluation of bronchoalveolar lavage fluid (BALF) collected 24 h after initial injury found that ascorbic acid and glutathione concentrations were markedly reduced in the smoke-exposed animals compared with controls [19]. Concentrations of these antioxidants in BALF from the combined injury group were intermediate between these levels. These changes were accompanied by elevated thiobarbituric acid reactive substances (TBARS) levels in lungs from animals subjected to smoke inhalation or combined burn and smoke compared with controls, suggesting increased lipid peroxidation in these groups [20]. Elevated TBARS were also seen in lung tissue from sheep that were exposed to wood smoke. A dose-dependent effect was observed in all the lung lobes evaluated [21]. In this study sheep were subjected to mild, moderate or severe smoke injury, defined as exposure to 5, 10 or 16 units of wood smoke, respectively, and lung tissues were analyzed 48 h after exposure. To determine the possible role of neutrophils in inducing oxidative injury in this study, we determined myeloperoxidase activity in lung as an index of neutrophil infiltration [21]. A dose-dependent effect of wood smoke inhalation on the elevation of myeloperoxidase activity in most lung lobes was observed, with a marked increase in activity after the 16 units of smoke dose [21].

### **3.5. Reactive oxygen species are a major factor in the development of ALI after smoke exposure**

Thus, the generation of reactive oxygen species has been considered a major factor in the development of acute lung injury after smoke exposure. As mentioned, the long-lived carbon-centered radicals generated by wood smoke can be deposited in the airways and lung, and have sufficient time to migrate to critical sites and decompose into free radicals, initiating tissue damage at multiple sites. To illustrate the evidence that oxidant generation and lipid peroxidation in the lung were related to the degree of injury, tissues from smoke-exposed sheep were analyzed histologically. We observed a dose-dependent effect of wood smoke inhalation on the injury profile in both the airways and the lung parenchyma [21]. Injury in the airway was associated with loss of cilia, ulceration of the respiratory mucosa and cast formation. The predominant effects of wood smoke inhalation on lung parenchyma were edema and infiltration of inflammatory cells [20,21].

### **3.6. Nitrogen species and nitric oxide in tissue following inhalation injury**

Most recently, we began to investigate reactive nitrogen species and nitric oxide as part of our assessment of antioxidant status of tissue following inhalation injury. In preliminary data from sheep exposed to chlorine gas, we did

not see a significant change in nitric oxide levels in lung in response to any dose of chlorine. In contrast, chlorine gas exposure resulted in elevated TBARS and myeloperoxidase activity, and reduced levels of antioxidant enzymes at the higher levels of exposure.

### 3.7. *In inhalation injury the role of oxidants is not fully understood*

In summary, reactive oxygen, nitrogen, and halogenated species are well documented as actors in lung injury associated with inhalation of wood smoke or other air pollutants and toxicant gases. However, the role of oxidants in the initiation or progression of the disease is not fully understood. There are a number of antioxidants that are distributed throughout the airway and lung parenchyma as protective mechanisms, but as mentioned, they are not evenly distributed throughout the respiratory system, and they have different roles related to their location within the cellular compartments. At present, evidence is scant that current strategies to counteract these oxidants directly are clinically beneficial. For example, short-term studies with antioxidant supplements, such as Vitamins C and E in healthy individuals, did not raise the levels of these antioxidants within the respiratory tract and the clinical benefit of such supplementation has been controversial. As we better understand mechanisms of oxidant-induced lung injury and that not all cellular compartments are responsive to standard antioxidant supplementation practices, the future should see more attempts at targeted delivery of antioxidants (e.g., aerosols) as part of more comprehensive treatment strategies.

## 4. **Assessment of the severity of inhalation injury by CT scan (Myung S. Park, MD)**

### 4.1. *Evaluation of CT scan in inhalation injury in an animal model*

The presence of inhalation injury is currently diagnosed by bronchoscopy or by xenon lung scan. No method, however, is available for grading the severity of injury. The objective of this study [22] was to evaluate the utility of CT scan in assessing the severity of injury. Twenty anesthetized sheep evenly divided into 4 groups, consisting of controls, mild, moderate, and severe injuries, underwent inhalation of wood bark smoke. After injury, the sheep were mechanically ventilated for 48 h in the animal ICU. The sheep underwent CT scans at 6, 12 and 24 h after injury. CT scans were analyzed by two methods. First, a thoracic radiologist, blinded to group and timepoint, graded each quadrant in each slice, as follows: 0 = normal, 1 = increased interstitial markings, 2 = ground-glass appearance and 3 = consolidation. Second, commercially available vector-based software (3D Doctor, Lexington, MA) was used to perform semi-automated three-dimensional reconstruction and analysis. Each scan was segmented into objects based on the Hounsfield-unit ranges established by Gattinoni et al. [23] (air: hyperinflated, normal, poorly aerated, and non-aerated lung). The fraction of the abnormal lung tissue (FALT) was then calculated from the volumes of poorly

aerated and non-aerated lung. The mean gray scale density of the lungs was also calculated.

### 4.2. *CT scan is potentially useful in gauging the severity of inhalation injury non-invasively*

Blood-gas data in this study were significant in that only in the severe group did the alveolar-arterial gradient differ significantly from controls. This phenomenon suggests that the lungs are able to compensate for mild to moderate injuries, establishing a threshold effect in oxygenation [24]. The radiologist's score was linearly related to severity of injury at 24 h and it outperformed computerized analysis with respect to detecting abnormalities, particularly in the mild and moderately injured groups. By ordinal logistic regression, the radiologist's score at 24 h was retained in a model for severity of injury, whereas the FALT and mean gray scale density scores were rejected. Thus, CT scan is potentially useful in gauging the severity of inhalation injury non-invasively. Failure of computerized indices based on the gray-scale density to detect more subtle injury features indicates the role of small airway injury, as opposed to alveolar-capillary membrane disruption and alveolar flooding, in the pathophysiology of this model of smoke inhalation injury [8]. Human trials are needed to establish the clinical utility of the method, as well as to determine the effect of various modes of mechanical ventilation on the pulmonary parenchyma.

## 5. **Emergency ventilation with insufflated oxygen (Ian H. Black, MD)**

Insufflation of oxygen has been used as a rescue technique for airway obstruction and as an adjunctive technique for acute lung injury (ALI). What is the rationale for tracheal gas insufflation, the efficacy of tracheal gas insufflation, and some of its problems in a clinical setting? Before addressing these questions it is important to clarify some nomenclature. *Apneic oxygenation* (AO) usually refers to supraglottic airway delivery. *Tracheal insufflation of oxygen* (TRIO) is either supra- or infraglottic insufflation. *Tracheal gas insufflation* (TGI) commonly refers to infraglottic insufflation [25]. There is also *expiratory washout*. Investigators have also explored reverse-thrust catheters and catheter insufflation during the expiratory phase to provide ventilatory benefit [26,27].

### 5.1. *Delivering air via tracheotomy is not a new idea*

Delivering air via tracheotomy is not a new idea. Tracheotomy is one of the oldest surgical procedures on record and was found in Egyptian hieroglyphics. In 1956, Jacoby published a fascinating article in JAMA [28]. He induced patients who he thought were going to become obstructed. These patients had large tracheal or oral tumors, and when they became cyanotic, Jacoby inserted tracheal catheters. Interestingly, it worked. Boyce has successfully used pre-emptive vessel dilator cricothyrotomy for over 20 years [29]. Frumin in 1959 observed a similar benefit using pure apneic oxygenation instead of a tracheal catheter [30]. These

patients tolerated 30–40 min of apneic oxygenation without any ventilation. The arterial pH reached nadirs of 6.8 before they were ventilated and none suffered any negative effects. In the 1980s Slutsky did studies in dogs that showed that as little as 91 ml of oxygen per minute could keep them alive for at least 5 h [31].

## 5.2. Tracheal gas insufflation (TGI)

Currently we use tracheal gas insufflation (TGI). Scoop catheters can be placed intratracheally for oxygen conservation and to reduce the work of breathing in patients with chronic obstructive pulmonary disease (COPD). There have also been some studies of cardiopulmonary resuscitation (CPR) using TGI, in which positive-pressure ventilation is not performed, producing similar outcomes [32].

We recently performed a study in uninjured swine, in which we allowed the animals to desaturate to an SpO<sub>2</sub> of 50% or lower [33]. We then initiated TGI via a tracheal catheter at 2 l/min, without jet ventilation. Within 25 s the vast majority of these animals attained an SpO<sub>2</sub> above 90%. No animals took more than 50 s to get above 90%. We then kept these animals alive for 1 h with TGI at 2 l/min, without ventilation. TGI can produce an auto-PEEP (positive end-expiratory pressure) phenomenon, which may explain the decreased levels of atelectasis observed in CT scans of these animals.

To determine whether TGI may be feasible in patients with acute lung injury (ALI), airway pressure release ventilation (APRV), TGI, or both were performed in an oleic-acid-injury model. Ventilatory PEEP was adjusted to account for any auto-PEEP. With TGI, peak inspiratory pressures were reduced dramatically by over 18 cm H<sub>2</sub>O. The mean airway pressures were the same [34]. Though there are practical difficulties in executing this concept, we think there may be a role for TGI when it is combined with best mechanical ventilation practices. TGI in combination with mechanical ventilation improves ventilation by reducing the dead space, subsequently reducing the P<sub>a</sub>CO<sub>2</sub>. Thus, the minute volume and the work of breathing are actually decreased. Additionally, peak airway pressure is reduced, and there is evidence of less inflammation.

TGI disadvantages [35] include drying of secretions. Auto-PEEP has to be accounted for. We do not have a good, commercially available mechanism for delivery. Neither do we have a fail-safe pressure-relief valve. In the APRV study there was a pressure-relief valve that in case of obstruction would help prevent pneumothorax. Right now there is a commercial FDA-approved endotracheal tube, the Bousignac tube (Vygon SA, Encouen, France), that has a separate port for insufflation. A tube designed for continuous aspiration of subglottic secretions can also be used for this purpose. The Bousignac tube has 6 different micro-channels that can be used to deliver oxygen at the carina [36].

In summary, TGI does work as an emergency rescue method. It seems to improve CO<sub>2</sub> elimination and to have added benefit over conventional ventilation alone in an ALI model. Improved methods for accessing the trachea, however, are needed.

## 5.2.1. Questions

- Dr. Cancio: Can TGI be delivered effectively through any plastic cannula inserted percutaneously into the trachea?
- Dr. Black: Yes.
- Dr. Cancio: I take it you don't need a high-pressure oxygen-powered device.
- Dr. Black: Absolutely not. In fact, that is one of the misconceptions—that you need a special high-pressure delivery system. You need a high-pressure delivery system in order to ventilate effectively. But you still get some CO<sub>2</sub> elimination with low-pressure flow.
- Dr. Cancio: Operationally, how easy is it to place the catheter into the trachea under emergency conditions? It sounds simple, but is it simple?
- Dr. Black: It is as easy as it is performing a cricothyroidotomy, and we expect medics to perform cricothyroidotomies in emergency situations.

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## 6. Clinical care of patients with inhalation injury (Rubén Gómez, MD, PhD)

This section reviews the clinical care of patients with inhalation injury. Where appropriate, a rating for the quality of evidence is provided. Inhalation injury is present in 8–15% of burn-center admissions [37], was associated with a mean mortality of 56% in two large series [37,38], and, when suspected, is considered one of the major criteria for burn-center referral according to the American Burn Association and the American College of Surgeons [39]. Inhalation injury below the glottis is what is meant by “inhalation injury” in reports from this and many other burn centers [40]. Most of these injuries are actually chemical injuries caused by products of combustion, which are often adherent to smoke particles. These chemicals cause direct damage to the epithelium of the airways. The smaller the size of the smoke particle, the deeper its penetration into the lung.

### 6.1. Fiberoptic bronchoscopy (FOB) for diagnosis and treatment

The threshold for intubation should be low when inhalation injury is suspected. Fiberoptic bronchoscopy (FOB) is performed for diagnosis and treatment. Mild injury gives rise to erythema and edema of the mucosa. In severe inhalation injury FOB may show gray-colored mucosa, erosions, ulcerations, and/or desquamation. What on the first FOB looks like mild inhalation injury, on repeated FOB may reveal a more severe injury. Therefore, it is often useful to repeat FOB 1–2 days after burn. Inhalation injury is a dynamic disease [14]. FOB is essential to follow the disease and to remove debris and casts of large size as they form. The more severe the inhalation injury, the more frequently FOB may be necessary. The presence of an on-site, dedicated respiratory therapy (RT) team is an essential component of this burn center's multidisciplinary approach. RTs provide the treating physicians with the ability to perform emergent FOB, as well as to employ advanced ventilators such as the VDR-4<sup>®</sup> (see below).

## 6.2. Negative effects of fluid restriction

Fluid restriction will not prevent pulmonary edema [41]. In fact, under-resuscitation leads to polymorphonuclear cell sequestration in the lungs, thus making pulmonary damage worse [42]. At this burn center, the modified Brooke formula is utilized as for patients without inhalation injury, recognizing that patients with inhalation injury usually require more fluid than predicted [43].

## 6.3. Bronchodilators and inhaled heparin may be helpful in inhalation injury

Bronchodilators may be helpful in the treatment of bronchospasm following inhalation injury. In animal models, intravenous heparin was shown to decrease cast formation, minute ventilation and peak inspiratory pressures [44]. Nebulized *n*-acetyl-cysteine and heparin decreased reintubation rates and mortality in children with inhalation injury [45] (Class III evidence). In view of this, nebulized porcine heparin (5000–10,000 units every 4–6 h) is currently used in this burn center to decrease cast formation [46].

## 6.4. Lung-protective strategies for mechanical ventilation

As with other forms of ARDS, a lung-protective strategy should be employed when mechanically ventilating patients with inhalation injury [47] (Class II evidence). At this time, no specific ventilator or method has rigorously been shown superior to any other. At the U.S. Army Burn Center, a high-frequency percussive ventilator, Volumetric Diffusive Respiration (VDR 4<sup>®</sup>, Percussionaire, Sandpoint, ID), is used for patients with inhalation injury. In addition to providing improved oxygenation and ventilation at lower pressures than conventional ventilators, the VDR-4<sup>®</sup> is highly effective at secretion clearance and reversal of inhalation-injury-induced small airway obstruction and atelectasis [42,48,49] (Class III evidence). Like airway-pressure release ventilation (APRV), the VDR-4<sup>®</sup> also permits spontaneous negative-pressure breathing by the patient throughout the respiratory cycle, potentially improving gas distribution, maintaining diaphragmatic function, and reducing sedation requirements. Another device used at this burn center primarily for the treatment of intubated patients with pneumonia, atelectasis, or copious secretions is Intrapulmonary Percussive Ventilation (IPV<sup>®</sup>, Percussionaire, Sandpoint, ID), which provides additional capabilities for removal of secretions following inhalation injury.

## 6.5. Patients with inhalation injury are at high risk for bronchopneumonia

Patients with inhalation injury are at high risk for bronchopneumonia beginning 3–10 days after burn. In the first week, the causative agents of bronchopneumonia are predominantly Gram-positive organisms. After the first week, Gram-negative organisms come to the fore. Prophylactic antibiotics have not been shown to prevent the development of pneumonia [50].

## 6.6. Tracheostomy

The role of tracheostomy is far from unequivocally established [51]. At this center, a tracheostomy is customarily performed after 14 days of tracheal intubation, or earlier if necessary to facilitate pulmonary toilet. More importantly, the fact that ventilator days and sepsis, to include pneumonia, independently predict mortality in burn patients [52] underscores the importance of aggressive weaning of these patients from the ventilator.

In brief, high-frequency percussive ventilation, nebulized heparin and bronchodilators, thorough pulmonary toilet, timely diagnosis and treatment of pneumonia, and early liberation from the ventilator are the mainstays of treatment for inhalation injury. More work, to include prospective, randomized, controlled trials, is required to optimize the treatment of these patients, particularly with respect to mechanical ventilation strategies.

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## 7. Laryngeal and upper airway sequelae of inhalation injury (Jeffrey A. Faulkner, MD, and Travis A. Pfannenstiel, MD)

### 7.1. Vocal cord paresis in lung injury

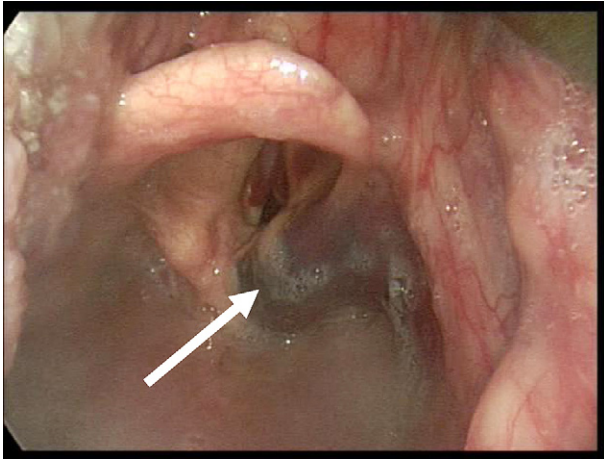
We present results of a recent evaluation of the laryngeal sequelae seen in burn patients. Upon request by burn-center surgeons, a total of 52 patients underwent evaluation by a speech pathologist at the U.S. Army Burn Center. Twenty-five of these were diagnosed with vocal-cord paresis. Patients who were intubated overseas (mostly patients from the current conflict in Iraq) had a 4.5-fold increase in the incidence of vocal-cord paresis. In addition, the risk of vocal-cord paresis increased with increasing burn size. Thus, adjusting for total body surface area burned, this risk increased to 9.8. Factors unrelated to the occurrence of paresis included central-line placement and the use of vasopressors.

### 7.2. Etiology of vocal cord paresis

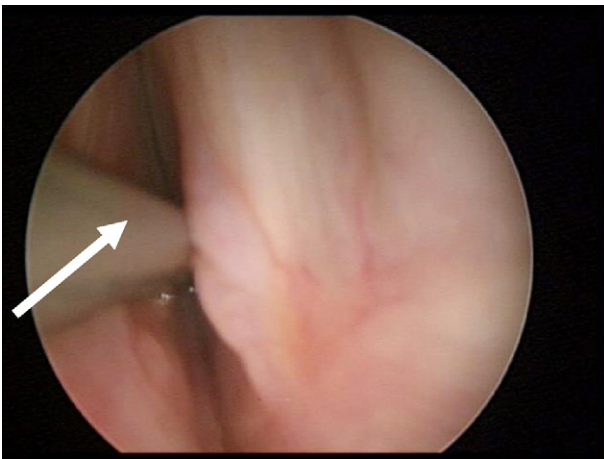
The etiology of these findings is uncertain. However, it is known that an air-filled endotracheal tube balloon will expand during flight. This could cause pressure at the cricothyroid joint, causing injury to the recurrent laryngeal nerve as it enters the larynx. Two approaches are currently used by U.S. military aeromedical evacuation teams to prevent this.

U.S. Air Force teams (who transport non-burn patients) replace the air in the balloon with saline solution; U.S. Army teams (who transport the majority of intubated burn patients) monitor the balloon pressure and reduce the air content as needed. This may explain, in part, the observed relationship between burn and paresis, although no causal relationship has been proven. Further studies in an altitude chamber are planned. Electromyography would be useful in the diagnosis of nerve injury.

Other possible etiologies include traumatic intubation. This can cause cord avulsion, arytenoid dislocation, or mucosal injury leading to anterior webbing or posterior stenosis. Fig. 2 shows an arytenoid dislocation. Long-term intubation can



**Fig. 2 – Arytenoid dislocation, manifested by hematoma around the arytenoid (arrow), and medial displacement of the arytenoid. This resolved after resolution of the hematoma.**



**Fig. 3 – Vocal-cord fixation secondary to arytenoid dislocation. The cord itself is unscarred in appearance, but it is fixed such that a spatula (arrow) cannot move it.**

cause subglottic stenosis (hence our practice of performing tracheostomy after about 2 weeks of endotracheal intubation), tracheal stenosis, or vocal-cord paresis. In a recent review, intubation was the cause of up to 11% of cases of unilateral recurrent-nerve paralysis [53].

Three patients at our center have been seen with vocal-cord fixation secondary to cricoarytenoid joint dislocation rather than paresis. Fig. 3 shows one such patient. The etiology of cricoarytenoid arthritis is unknown due to insufficient data, but possible causes include prolonged intubation, the effect of inhalation injury, or a systemic inflammatory response.

Recently, Casper et al. reported follow up at 16–25 years postburn of 10 patients [54]. Seventy percent had dysphonia and 100% had abnormal laryngeal findings. Earlier identification of these abnormalities, for example by stroboscopic exam, may make surgical or behavioral treatment possible. In conclusion, we seem to have a higher than expected incidence of vocal-cord immobility after burn. The pathophysiology may

be nerve injury, joint fixation, or soft-tissue injury, and the etiology may be cuff pressures, prolonged intubation, or intubation trauma. Prospective evaluation of all burn and non-burn trauma patients who have undergone field intubation is warranted. Vocal physical therapy is indicated for many of these patients, and helps prevent arytenoid arthritis resistant to therapy. In addition, mobilization of the arytenoid, with concomitant steroid injection, may be therapeutic.

#### 7.2.1. Question

- A physician: Do you know the incidence of emergency re-intubation during transport that might lend itself to this kind of injury?
- Dr. Faulkner: Zero in these patients.

## 8. Artificial lung technology (Leopoldo C. Cancio, MD)

### 8.1. Extracorporeal membrane oxygenation (ECMO)

Extracorporeal membrane oxygenation (ECMO) has been available for many years, but is costly and cumbersome. ECMO has a significant complication rate, and is labor- and equipment-intensive. Increasingly, instead of ECMO for the treatment of patients with ARDS, simpler technologies are being proposed. These include intravenous devices such as the Hattler catheter, and extracorporeal devices such as those for arteriovenous CO<sub>2</sub> removal (AVCO<sub>2</sub>R) and the venovenous Paracorporeal Respiratory Assist Lung (PRAL).

### 8.2. The efficiency of gas exchange in artificial lung devices

The efficiency of gas exchange in these devices is affected by several factors. First, the partial pressures of oxygen (PO<sub>2</sub>) and of carbon dioxide (PCO<sub>2</sub>) in the inflow blood are important. For example, if the PO<sub>2</sub> is low in the inflow blood then the amount of oxygen that will be transferred into that blood will be high because of a high gradient. Similarly, if the PCO<sub>2</sub> is high in the inflow blood, then more CO<sub>2</sub> will come out of the blood and into the device. These facts affect device placement, i.e. on the venous or arterial side, and decisions about patient management, such as permissive hypercapnia. Second, the membrane surface area affects the efficiency of gas exchange. Finally, the blood flow rate influences gas exchange.

### 8.3. Design considerations

What are the design considerations? First, if an extracorporeal device is placed on the arterial side, the arterial blood pressure can be used to drive blood through the system. Given a low-resistance circuit, a pump can be avoided and with it the potential damage done to the blood by the pump. On the other hand, if the device is placed on the venous side, there are advantages with respect to PCO<sub>2</sub> and PO<sub>2</sub> gradients. Next, much effort has gone into developing low-resistance external devices. The earlier ECMO devices had relatively high resistances; thus, a pump was mandatory. The newer

low-resistance systems, like the Novalung<sup>®</sup> and the AVCO<sub>2</sub>R, can simply rely on arterial blood pressure to drive blood through the circuit.

#### 8.4. Efficient rates of oxygen consumption and CO<sub>2</sub> removal

Intracorporeal and extracorporeal systems provide different levels of efficiency with respect to the rates of oxygen consumption (VO<sub>2</sub>) and CO<sub>2</sub> removal (VCO<sub>2</sub>). A hyperdynamic septic patient may require a VO<sub>2</sub> of 315 ml/min (i.e., 170 ml/min/m<sup>2</sup>), whereas a normal resting human has a VO<sub>2</sub> of about 210–280 ml/min. Assuming a respiratory quotient of 1, VCO<sub>2</sub> rates are about the same. Thus, a reasonable target for artificial lung technologies is a little over 200 ml/min for VO<sub>2</sub> and VCO<sub>2</sub>. At present, no extracorporeal or intravenous systems achieve these targets, but substantial reductions in the level of mechanical ventilatory support are possible.

#### 8.5. Intravenous venous oxygenator (IVOX)

Artificial lung devices may be intravenous or extracorporeal. One of the early intravenous devices was the intravenous oxygenator (IVOX) [55]. It provided a VO<sub>2</sub> and VCO<sub>2</sub> of about 40–70 ml/min. The IVOX went to phase II clinical trials in ARDS patients. It improved oxygenation in these patients but it failed to cause an improvement in mortality; there has been no further development done on the IVOX.

#### 8.6. Hattler catheter or intravenous membrane oxygenator (IMO)

The Hattler catheter or intravenous membrane oxygenator (IMO) is an intravenous device currently in development at the University of Pittsburgh [56]. The IMO fibers are arranged in a constrained bundle around a helium-powered balloon. The balloon inflates and deflates at up to 300 beats/min. This improves blood flow across the fibers, thus improving gas exchange. Gas exchange plateaus at about 250–300 beats/min. It is inserted via the internal jugular vein (external jugular vein in the sheep) and lies across the right atrium. This device is currently in trials in our animal lab in an ovine model of inhalation injury.

#### 8.7. Arteriovenous CO<sub>2</sub> removal (AVCO<sub>2</sub>R)

Zwischenberger in Galveston has developed a method of AVCO<sub>2</sub>R using a low-resistance Affinity<sup>®</sup> oxygenator (Medtronic, Inc., Minneapolis, MN) [57]. This device primarily removes CO<sub>2</sub> rather than delivers O<sub>2</sub>. A pump is not used, and the inflow cannula is placed in the femoral artery. Moderate systemic anticoagulation is required. The system is dependent on blood flow through the device in order to remove CO<sub>2</sub>, so that hypotension and low cardiac output will decrease device performance. In the ovine studies, a smoke inhalation injury and burn model is used. AVCO<sub>2</sub>R makes it possible to dramatically decrease minute ventilation while maintaining a reasonable PCO<sub>2</sub>. Interestingly, the PO<sub>2</sub> tends to increase in AVCO<sub>2</sub>R-treated animals, probably because of a decrease in secondary lung injury. This experience

indicates the utility of such devices in allowing gentle mechanical ventilation in patients who otherwise might be difficult to ventilate adequately. The AVCO<sub>2</sub>R system is currently in clinical trials.

The Novalung<sup>®</sup> iLA (Novalung GmbH, Hechingen, Germany) is an AVCO<sub>2</sub>R device which is commercially available in Europe [58]. The European data are currently being reviewed by the U.S. Food and Drug Administration (FDA). The Novalung<sup>®</sup> is an arteriovenous system, which is powered by the patient's own blood pressure.

#### 8.8. Paracorporeal respiratory assist lung (PRAL)

The PRAL is currently in development at the University of Pittsburgh [59]. This venovenous device uses one dual-lumen catheter, although two catheters in different veins can also be employed. It has a rotating hollow-fiber bundle, which serves both to increase gas exchange and to pump the blood. At a rotation rate of 1500 rpm, this device draws about 750 ml/min, i.e. half the blood flow of a typical AVCO<sub>2</sub>R device. Hemolysis is reportedly negligible. This device will be tested in our animal lab this year.

AVCO<sub>2</sub>R operates ideally at blood flow rates of about 1500 ml/min, as does the Novalung<sup>®</sup>. The PRAL requires about half that. CO<sub>2</sub> removal for the extracorporeal devices is currently about 100 ml/min. None of these devices are designed primarily to oxygenate, with VO<sub>2</sub> rates of about 30–60 ml/min. We believe, however, that we will be able to oxygenate casualties by an apneic technique such as that described above by Dr. Black.

In conclusion, artificial lung technologies continue to advance, and may revolutionize how we care for our sickest casualties with ARDS secondary to inhalation injury or other causes.

##### 8.8.1. Questions

- A physician: Do all of these devices require anticoagulation?
- Dr. Cancio: All of the systems require some degree of anticoagulation. A lot of work has gone into developing coatings for the fibers that would help reduce the activated clotting time required. Clearly, the continued need for anticoagulation is a disadvantage in our combat casualties.
- A physician: There has been some recent re-examination of some acute respiratory distress syndrome (ARDS) data that says that the hypercapnia is what gives a survival benefit, and not the low-volume strategy. Are you concerned that you may be missing the boat taking away that survival benefit by using this technology?
- Dr. Cancio: I frankly, find it hard to believe that hypercapnia is truly beneficial and I recall data that suggest that respiratory acidosis is not beneficial. In any event, I believe that injurious levels of mechanical ventilation cause inflammation and secondary lung injury, if not overt barotrauma. I think that sometimes it is difficult for us to perform lung-protective ventilation under actual clinical conditions, and that devices like this might help that minority of patients who truly are very difficult to ventilate. We also don't know whether 2 ml/kg tidal volume or no ventilation at all might be even more beneficial.

## 9. Inhalation injury: summary and conclusions (Steven E. Wolf, MD)

Inhalation injury is associated with increased mortality in burn patients [60]. Thus, inhalation injury is often included in multivariate predictors of burn mortality, along with factors such as burn size and age [61]. Clinically, however, the diagnosis of inhalation injury is very difficult. Dr. Park's data summarize what we know from clinical experience: that inhalation injury is readily managed unless the injury is severe, in which case mortality increases substantially [22].

Dr. Gomez gave a review on inhalation injury, its diagnosis and treatment, and pointed out that care at this point is primarily supportive. There is a need for more randomized, controlled, multicenter trials in the burn community, a need which the multicenter trials group of the American Burn Association has begun to address [62].

Dr. Faulkner brought up some interesting data that we typically don't consider—that there is a laryngeal problem. Subglottic injury is the real problem with respect to mortality. Now, however, we are also finding an increasing incidence of laryngeal problems. Long-term follow-up is warranted to assess the true impact of these problems.

Dr. Batchinsky presented data from the Multiple Inert Gas Elimination Technique, comparing pulmonary contusion, smoke inhalation, and chlorine inhalation along a pathophysiological spectrum [8,10].

Dr. Dubick addressed oxidants and antioxidants and their role in smoke inhalation. These intriguing data suggest a potential treatment approach for the injury. This is but one of the areas of productive research in inhalation injury. For example, Bhattacharyya et al. at the William Beaumont Army Medical Center demonstrated increased expression of the Muc 5B and Muc 5AC genes in rats subjected to smoke inhalation injury [63]. Nebulized antisense oligomers inhibited mucin secretion by over 50%. This novel therapy would address the mucus hypersecretion which typifies many models of inhalation injury [64]. Traber and colleagues at the University of Texas Medical Branch at Galveston have recently reported the efficacy of recombinant activated protein C, and of an inducible-nitric-oxide-synthase inhibitor, in an ovine model of combined inhalation injury and sepsis [65,66].

Dr. Park presented a very interesting study employing CT scans, but the knowledge we gained from that experiment has not been well publicized in the burn community. More studies, employing human patients, will be needed in order to establish the role of this technology in clinical practice [22]. Other methods of diagnosing and quantifying inhalation injury would be helpful. One such technology is endoscopic optical coherence tomography (OCT) [67,68], currently under evaluation in our laboratory.

Dr. Black addressed tracheal gas insufflation [33], and Dr. Cancio reviewed some of the artificial lung technologies [69]. We can dramatically change what we do, and we can look forward to performing extracorporeal support of lungs, kidneys and liver all in the same machine.

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## Appendix A

The MIGET is based on measurement of steady-state transpulmonary exchange of six inert gases (sulfur hexafluoride [SF<sub>6</sub>], ethane, cyclopropane, halothane, ether, and acetone). These gases are dissolved in saline and infused into a peripheral vein. Next, the retention (level of each gas in the arterial blood leaving the alveolus) and excretion (level of each gas in the expired air) are calculated by determining the partial pressures of gases in the arterial blood (assessment of blood flow, Q) and mixed expired air (assessment of ventilation, V) by means of gas chromatography.

Since the inert gases have a wide range of solubility in blood, covering from 0.008 to 300 ml gas/100 ml blood/mm Hg for SF<sub>6</sub> and acetone, respectively, they span a wide range of possible retention and excretion values in the lung. Assessment of retentions and excretions for each gas as a function of their solubility is computed on a 50-compartment scale. Distribution of the gas with the lowest solubility (SF<sub>6</sub>) predicts existence of compartments with V/Q ratios approximating zero. The retention/excretion dynamics of the gas with the highest solubility (acetone) describe V/Q ratios of 100 or more. The other 3 gases lie between these two with respect to solubility and describe compartments with intermediate V/Q ratios. From the six discrete excretion and retention data points calculated for each gas, the unit-by-unit description of how V and Q are distributed to units of different V/Q ratios across the lung is extrapolated on a 50 compartment model by means of mathematical smoothing [6]. The projected fractional distributions of blood flow and ventilation across the lung are obtained and lumped into arbitrary ranges for ease of interpretation.

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