News Release

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ATS Press Room: 303-228-8473 (May 15-18)

Poster session time: 2:00-4:30 p.m. May 18
Location: Centennial Ballroom D (Third Level), Hyatt Regency Denver

PRESS CONFERENCE: **Monday, May 16, 2011, 11:30 a.m. MDT**

Inhaling Hydrogen May Help Reduce Lung Damage in Critically Ill Patients

ATS 2011, DENVER – Inhaling small amounts of hydrogen in addition to concentrated oxygen may help stem the damage to lung tissue that can occur when critically ill patients are given oxygen for long periods of time, according to a rat model study conducted by researchers in Pittsburgh. The study also found hydrogen initiates activation of heme-oxygenase (HO-1), an enzyme that protects lung cells.

The results will be presented at the ATS 2011 International Conference in Denver.

"We found that inhalation of hydrogen can reduce hyperoxic lung injury that occurs as the result of exposure to concentrated oxygen for prolonged periods, an important problem in critically ill, ventilated patients," said Tomohiro Kawamura, MD, research fellow at the University of Pittsburgh's Thomas E. Starzl Transplantation Institute. "Administering hydrogen treatment by providing gas for the patient to inhale is a new approach and may be feasible in clinical practice."

Highly concentrated oxygen is routinely administered to critically ill patients who cannot breathe efficiently, such as patients with severe heart or lung disease. Given over a prolonged period, oxygen toxicity can occur, causing severe lung injury which can lead to respiratory failure. In this study, the researchers hypothesized that the addition of hydrogen, which has potent

antioxidant and anti-inflammatory effects, might help mitigate the damage caused by prolonged exposure to concentrated oxygen.

To find out, the researchers assigned male rats assigned to four experimental groups: rats exposed to high concentrations of oxygen and either 2 percent nitrogen or 2 percent hydrogen, and rats given normal levels of oxygen and either 2 percent nitrogen or 2 percent hydrogen. Exposure periods for all groups were 60 hours. Lung function was evaluated by blood gas analysis of the arterial blood, and body weight, lung fluid volume, inflammatory cell count in lung fluids and HO-1 levels were measured.

Comparing oxygen exposure groups to controls, the researchers found exposure to 2 percent nitrogen with 98 percent oxygen for 60 hours markedly impaired lung function and caused inflammation and a build-up of fluid in the lung. In contrast, rats exposed to 2 percent hydrogen with 98 percent oxygen had less swelling and improved lung function, as well as significant reductions in inflammation compared to controls. In addition, levels of HO-1 were elevated in rats exposed to hydrogen.

“Hydrogen-induced hemeoxygenase-1 is a protein that protects the cells and has antioxidant and anti-inflammatory activities,” Dr. Kawamura noted. “HO-1 induction protects against harmful stimuli, including hyperoxia.

“HO-1 induction in the lung may be one of the mechanisms underlying the protective effects of hydrogen,” he added. “Our study is the first to show induction of HO-1 by hydrogen, and our results suggest that hydrogen functions by inducing protective proteins such as HO-1.”

Dr. Kawamura said he and his colleagues have conducted extensive research on the beneficial effects of hydrogen in lung injuries.

“In one recent mouse study, we showed that inhaled hydrogen could prevent acute lung injury induced by mechanical ventilation, and we also showed that inhaled hydrogen gas therapy for lung transplant donors and recipients reduced some transplant-associated injuries in a rat model study,” he said.

The results of this study indicate hydrogen inhalation therapy may have applications in other lung injuries, he added.

“Hydrogen has a therapeutic potential not only in treating acute lung injury, but also in treating chronic lung diseases such as chronic obstructive pulmonary disease (COPD), which is the fourth leading cause of death in the U.S.,” he said. “Hydrogen may help prevent progression of COPD, which could have a huge impact on treatment.

“Administering hydrogen treatment by providing gas for the patients to inhale is straightforward and may be feasible in clinical practice in the future,” Dr. Kawamura added.

Future research should focus on establishing efficacy and safety profiles of hydrogen inhalation therapy in animal models, prior to its possible use in a clinical setting, he said.

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"Inhalation Of Hydrogen Ameliorates Hyperoxic Lung Injury" (Session D97, Wednesday, May 18, 2:00-4:30 p.m., Centennial Ballroom D (Third Level), Hyatt Regency Denver; Abstract 16744)

** Please note that numbers in this release may differ slightly from those in the abstract. Many of these investigations are ongoing; the release represents the most up-to-date data available at press time.*

Abstract 16744

Inhalation Of Hydrogen Ameliorates Hyperoxic Lung Injury

Type: Scientific Abstract

Category: 13.01 - Oxidants/Antioxidants/Nitric Oxide/Carbon Monoxide (RCMB)

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Abstract Body

Introduction: Treatment of pulmonary and cardiovascular disease commonly requires high concentrations of oxygen. However, exposure to high concentrations of oxygen for prolonged periods causes hyperoxic lung injury, which can lead respiratory failure. Thus, successful abrogation of hyperoxic lung injury is critical and would have a huge impact on respiratory and critical care medicine. The potent antioxidant and anti-inflammatory effects of hydrogen underlie its potential as a therapeutic medical gas. Heme oxygenase (HO)-1, a heme-degrading enzyme, is highly induced by oxidative stress and protects against oxidative damage. In models of oxidative stress, HO-1 induction protects against harmful stimuli, including hyperoxia. The purpose of this research was to determine if hydrogen could reduce hyperoxic lung injury and investigate possible mechanisms underlying in the beneficial effects of hydrogen therapy, including induction of heme oxygenase (HO)-1.

Methods: Inbred male Lewis rats were assigned to four experimental groups: rats in hyperoxic conditions (98% oxygen) exposed to either 2% nitrogen or 2% hydrogen, and normoxia controls exposed to either 2% nitrogen or 2% hydrogen in air for 60 hours. The lung function was evaluated by blood gas analysis of the arterial blood. Body weight, pleural fluid volume, inflammatory cell count in the bronchoalveolar lavage fluid (BALF), histology, expression of mRNAs for inflammatory mediators, and expression of HO-1 were investigated.

Results: Exposure to 2% nitrogen with 98% oxygen for 60 hours markedly impaired the lung function, resulted in massive cellular infiltration and edema in the interstitial area, and was associated with upregulation of the mRNAs for TNF-α, ICAM-1 and IL-6. Hydrogen significantly improved PO2 levels (Figure 1A) and histologic lung injury scores (Table 1), and decreased pleural effusion and the number of the cells in the BALF (Figure 1B&C). Hydrogen significantly reduced of the upregulation of mRNAs for inflammatory mediators, indicating anti-inflammatory properties (Table 2). Interestingly, 2% hydrogen inhalation for 60 hours increased HO-1 mRNA and protein levels in the lungs (Figure 2).

Conclusion: Inhalation of hydrogen can ameliorate hyperoxic lung injury. Administering hydrogen treatment by providing gas for the patient to inhale is novel and may be feasible in clinical practice. Our results suggest that hydrogen modulates signal transduction and functions by inducing protective proteins such as HO-1.

Table 1. Histopathological analysis of the lungs

	Lung Injury Score				
Group	Alveolar congestion	Hemorrhage	Infiltration of neutrophils	Alveolar wall thickness	Total score
Normoxia (N_2)	0.67 ± 0.50	0	0.56 ± 0.53	0.56 ± 0.53	1.78 ± 0.97
Normoxia (H_2)	0.66 ± 0.50	0	0.22 ± 0.44	0.77 ± 0.44	1.67 ± 0.86
Hyperoxia (N_2)	2.78 ± 0.83	0	2.44 ± 0.73	1.44 ± 0.53	6.66 ± 1.41
Hyperoxia (H_2)	1.33 ± 0.70	0	2.11 ± 0.60	1.22 ± 0.67	4.67 ± 1.58*

Table 2 . Modulation of inflammatory mediator expression

	IL-6 mRNA	TNF-α mRNA	ICAM-1 mRNA
Normoxia (N_2)	0.3 ± 0.3	7.2 ± 3.5	16.1 ± 19.8
Normoxia (H_2)	0.4 ± 0.2	14.2 ± 21.0	32.6 ± 8.8
Hyperoxia (N_2)	125.3 ± 65.4	447.4 ± 136.9	146.5 ± 71.4
Hyperoxia (H_2)	57.6 ± 13.1*	133.1 ± 69.3*	88.1 ± 25.1*