Published in final edited form as:

Free Radic Biol Med. 2008 September 1; 45(5): 570–571. doi:10.1016/j.freeradbiomed.2008.05.016.

Highlight Commentary on “Influence of lung oxidant and antioxidant status on alveolarization: role of light-exposed total parenteral nutrition”

Lou Ann S. Brown^{*} and **Theresa W. Gauthier**

Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Emory University, 2015 Uppergate Dr. Atlanta, GA 30322

Abstract

Bronchopulmonary dysplasia (BPD) is a frequent complication of premature newborns, particularly very low birth-weight babies (< 1500 g). Undoubtedly multiple mechanisms contribute to the adverse outcomes associated with BPD but oxidative stress is one causative factor. In this issue of *Free Radical Biology & Medicine*, Lavoie et al describe the increased peroxide generation when the multivitamin solution used for nutritional support, total parenteral nutrition (TPN), is exposed to ambient light. Since the premature newborn has limited antioxidant capacity, this increased oxidative burden from the TPN becomes increasingly significant. Infusion of this light-exposed solution in a newborn guinea pig decreased lung tissue vitamin C but vitamin E. When the multivitamin and lipid solutions were mixed and then exposed to light, alveolarization of the developing lung was decreased. This study by Lavoie et al highlights simple measures that may potentially decrease the oxidant burden delivered to this vulnerable population and improve alveolarization.

Keywords

bronchopulmonary dysplasia; BPD; oxidative stress; nutritional support; redox potential

Bronchopulmonary dysplasia (**BPD**) is a frequent complication of premature newborns born at less than 28 weeks of gestation. Neonatal morbidity and mortality for very low birth-weight babies has increased over the past decade despite technological and therapeutic advances [1;2]. BPD is associated with a variety of adverse outcomes including persistent pulmonary dysfunction, extended hospitalization, retinopathy of prematurity and adverse neurodevelopmental outcomes. While the origins of this disorder are multi-factorial, these diverse pathologies are linked by oxidative stress, a major causative factor [3]. Although necessary to sustain life, oxygen therapy directly exposes the lung to high concentrations of inspired oxygen, increasing the burden of toxic reactive oxygen species. Respiratory bursts by inflammatory cells and normal mitochondrial respiration also contribute to the oxidative stress. In healthy tissues, free radical scavengers and antioxidant systems interrupt the cycle of oxidant-induced tissue injury. However, the antioxidant capacity is limited in the

Corresponding author: Lou Ann S. Brown, PhD, Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Emory University, 2015 Uppergate Dr. Atlanta, GA 30322, Voice: 404-727-5739, Fax: 404-727-9834, Email: lbrow03@emory.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

premature newborn making the increased oxidative burden and risk for tissue injury increasingly significant [3]. Given the limited antioxidant capacity of the premature newborn, strategies to limit the oxidative burden become critical for this vulnerable population.

The paper by **Lavoie et al** examines the contribution of peroxides introduced by nutritional support to the oxidant burden and the subsequent impact on the developing lung. To maintain fluid and electrolyte status, very-low-birthweight newborns (<1500 g) are commonly given intra-venous nutritional support, termed total parenteral nutrition (TPN), which contains an appropriate supply of parenteral lipids, amino acids and multivitamin solutions. However, TPN can also contain peroxides that contaminate lipid emulsions, amino acid solutions or multivitamin solutions. Animal [4;5] and clinical [6–8] studies have demonstrated that generation of free radicals, peroxides and lipid peroxides are increased by the administration of TPN. Previous studies by this research group demonstrated that photosensitive components of TPN such as 5'-phosphate flavin mononucleotide, polysorbates and electron donors such as vitamin C can induce reactions with amino acids, polyunsaturated fatty acids, and even vitamin C and generate peroxides as well as alter the quality of the provided nutrients [9–11]. In the TPN specifically designed for premature newborns, the peroxide concentration could be as high as 300 micromol/L in ambient light [12]. Given the decreased adaptive capacity of the very low birth-weight newborn, this delivery of reactive species could contribute to oxidative stress and tissue injury in the newborn, particularly in subjects receiving supplemental oxygen therapy.

In North America, multivitamin solutions are added to the amino acid/dextrose solution whereas the European Society of Pediatric Gastroenterology, Hepatology and Nutrition recommend mixing the multivitamin solution with the lipid emulsion of the TPN. In the current paper by **Lavoie et al**, the investigators used a newborn guinea pig model to examine whether varying the protocol for mixing TPN components or protection from light increased the oxidative burden or impacted lung development. Exposure of the TPN admixture to ambient light increased the peroxide concentrations in the TPN solution approximately two-fold. This exposure of the TPN solution to light decreased the lung tissue concentration of vitamin C. However, there were no changes in lung tissue concentrations of vitamin E or 8-isoprostane suggesting that increased delivery of peroxides did not induce lipid peroxidation in lung tissue of the newborn guinea pig pup. This protection of vitamin E but not vitamin C may be related to the use of a light protective acetate ester of vitamin E but not vitamin C.

While light exposure increased peroxides in the TPN, lung concentrations of reduced and oxidized glutathione were not statistically different between groups. However, the redox potential of the glutathione thiol pair was more reduced when the group receiving light-exposed TPN was compared to those receiving light-protected TPN. This suggested that infusion of the light-exposed TPN resulted in an oxidant stress that up-regulated glutathione in the lung tissue and maintained the redox balance of this critical thiol pair. Although there were no statistical changes in the vitamin E concentration of the lung tissue, the vitamin E concentrations did influence the glutathione redox potential. In contrast, vitamin C did not influence the redox potential. Changes in the glutathione redox balance for the lung were not reflected in the blood suggesting that blood was not an appropriate sampling site to monitor oxidant stress in the lung.

The unique aspect that distinguishes BPD from other lung injuries is that the injury is superimposed on a lung that typically is in the saccular stage of development.

While pulmonary fibrosis is currently not as prominent a feature of BPD in very low birth-weight babies as it had been described in previous decades, persistent pulmonary dysfunction is characterized by a chronic pro-inflammatory state coupled with impaired alveolarization and vascular growth [1]. In BPD, the persistent structural changes in the lung alter lung mechanics and gas exchange. Undoubtedly multiple mechanisms contribute to this pulmonary dysfunction but oxidative stress and resulting tissue injury is one contributing factor.

Lavoie et al demonstrated that light exposure and the protocol for adding the multivitamin solution to the TPN had a cumulative effect on the alveolarization index of the newborn lungs as early as two days into the TPN delivery. In other words, mixing the multivitamins with the amino acids with subsequent light exposure of the TPN admixture resulted in decreased alveolarization of the developing lung. In this model, changes in alveolarization and the redox potential of the glutathione pair were two independent events. However, this study only examined alveolarization and redox potential after two and four days of TPN infusion. In clinical studies, altered glutathione homeostasis in the tracheal aspirate [14] or bronchoalveolar lavage [15] of the premature newborn was linked to an increased risk of BPD. Additional studies are needed to determine whether chronic exposure to oxygen therapy results in an oxidized glutathione redox potential within the micro-environment of the alveolar space and affects alveolarization. However, the work of **Lavoie et al** demonstrates in a guinea pig model that simple interventions such as the procedures used for mixing the TPN or protecting the admixture from ambient light decreases the delivery of oxidant radicals to the newborn. Given the causative role of oxidative stress in the development of BPD, identification of strategies that decrease the oxidant burden is an important goal for this population with compromised adaptive capacity for oxidative stressors. More importantly, these measures may improve alveolarization in the developing lung, a key to decreasing persistent pulmonary dysfunction in the very low birth-weight newborn.

References

1. Bhandari V, Gruen JR. The genetics of bronchopulmonary dysplasia. *Semin Perinatol* 2006;30:185–191. [PubMed: 16860158]
2. Tin W, Wiswell TE. Adjunctive therapies in chronic lung disease: examining the evidence. *Semin Fetal Neonatal Med* 2008;13:44–52. [PubMed: 17983879]
3. Welty SE. Is there a role for antioxidant therapy in bronchopulmonary dysplasia? *J Nutr* 2001;131:947S–950S. [PubMed: 11238792]
4. Chessex P, Friel J, Harrison A, Rouleau T, Lavoie JC. The mode of delivery of parenteral multivitamins influences nutrient handling in an animal model of total parenteral nutrition. *Clin Nutr* 2005;24:281–287. [PubMed: 15784490]
5. Lavoie JC, Chessex P. Development of glutathione synthesis and gamma-glutamyltranspeptidase activities in tissues from newborn infants. *Free Radic Biol Med* 1998;24:994–1001. [PubMed: 9607610]
6. Weinberger B, Watorek K, Strauss R, Witz G, Hiatt M, Hegyi T. Association of lipid peroxidation with hepatocellular injury in preterm infants. *Crit Care* 2002;6:521–525. [PubMed: 12493074]
7. Chessex P, Harrison A, Khashu M, Lavoie JC. In preterm neonates, is the risk of developing bronchopulmonary dysplasia influenced by the failure to protect total parenteral nutrition from exposure to ambient light? *J Pediatr* 2007;151:213–214. [PubMed: 17643781]
8. Khashu M, Harrison A, Lalari V, Gow A, Lavoie JC, Chessex P. Photoprotection of parenteral nutrition enhances advancement of minimal enteral nutrition in preterm infants. *Semin Perinatol* 2006;30:139–145. [PubMed: 16813972]

9. Lavoie JC, Belanger S, Spalinger M, Chessex P. Admixture of a multivitamin preparation to parenteral nutrition: the major contributor to in vitro generation of peroxides. *Pediatrics* 1997;99:E6. [PubMed: 9099771]
10. Laborie S, Lavoie JC, Chessex P. Paradoxical role of ascorbic acid and riboflavin in solutions of total parenteral nutrition: implication in photoinduced peroxide generation. *Pediatr Res* 1998;43:601–606. [PubMed: 9585005]
11. Laborie S, Lavoie JC, Pineault M, Chessex P. Protecting solutions of parenteral nutrition from peroxidation. *JPEN J Parenter Enteral Nutr* 1999;23:104–108. [PubMed: 10082001]
12. Laborie S, Lavoie JC, Pineault M, Chessex P. Contribution of multivitamins, air, and light in the generation of peroxides in adult and neonatal parenteral nutrition solutions. *Ann Pharmacother* 2000;34:440–445. [PubMed: 10772427]
13. Jobe AH, Ikegami M. Mechanisms initiating lung injury in the preterm. *Early Hum Dev* 1998;53:81–94. [PubMed: 10193929]
14. Boda D, Nemeth I, Pinter S. Surface tension, glutathione content and redox ratio of the tracheal aspirate fluid of premature infants with IRDS. *Biol Neonate* 1998;74:281–288. [PubMed: 9701650]
15. Collard KJ, Godeck S, Holley JE, Quinn MW. Pulmonary antioxidant concentrations and oxidative damage in ventilated premature babies. *Arch Dis Child Fetal Neonatal Ed* 2004;89:F412–F416. [PubMed: 15321959]