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**Jornal de Pediatria**




# Let's feed the preterm lung

**Alan H. Jobe***

The lung is generally viewed as a static structure once growth has occurred. Its size or ability to regenerate becomes interesting with disease or physiologic stresses. The general teaching is that the adult human lung septates beginning at about 32-36 weeks of gestation to form alveoli, and this process continues until the child is several years of age. Subsequent growth is in lung size, with a constant number of about 500 million alveoli until about 20 years of age. Alveolar number and lung elasticity then decrease progressively with age. Alveolar loss by destruction in emphysema appears to be an irreversible process. Yet, lung growth and alveolarization can occur even in the mature lung. Lung resection in young animals results in prompt growth and expansion of the gas surface area in the remaining lung. More directly relevant to the article on nutritional effects on the developing lung published by Mataloun et al.[1] in the Jornal are studies of the effects of starvation on adult lungs. Humans who were starved to death in the Warsaw Ghetto during World War II were noted to have emphysema at autopsy.[2] Young women with anorexia nervosa have emphysema as assessed by CT scans.[3] These observations indicate that changes in lung structure do occur in the adult lung and that nutritional status is a modulator of lung structure.

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A number of experimental observations demonstrate just how "dynamic" lung structural changes can be. Starvation of adult rats will alter the pressure-volume curves of the lungs and decrease surfactant amounts. Don Massaro and his group showed that calorie restriction of 33% of normal reduced alveolar number by 55% (alveolar loss or destruction) and alveolar surface area by 25%.[4] This loss of alveoli was accompanied by increased apoptosis and loss of DNA in alveolar walls. Caloric restriction resulted in increased granzyme and caspace gene expression within hours.[5] Perhaps most remarkable is that within 72 hours of refeeding, the rat lungs had normal alveolar numbers and surface areas, a clear demonstration that the adult lung can grow alveoli. Although malnutrition and lung structure have been the focus of most of the research, there are multiple other effects that could be clinically important. For example, Sakuma et al.[6] reported that starved rats had a 38% decrease in the rate of alveolar fluid clearance. The malnutrition interfered with amiloride-insensitive and dibutyryl-cGMP-sensitive fluid clearance pathways in the lung. This abnormality reverted to normal with refeeding.

For the pulmonary physician, emphysema means a destructive process associated with industrial exposures and smoking. Lungs with a similar appearance can result from a developmental delay resulting in an arrest of secondary septation. In multiple transgenic models in mice, inflammation during the period of alveolarization – from about 3 days to 3 weeks of age – will yield an emphysematous lung.[7] Inflammation interferes with lung development, but that interference may be an injury rather than a direct interference with development.

Other clinically relevant factors are known to interfere with alveolarization in the developing lung. Corticosteroids (an anti-inflammatory agent) and chorioamnionitis, mechanical ventilation, and oxygen (all pro-inflammatory) disrupt alveolarization.[7] These factors no doubt contribute to variable degrees to the development of bronchopulmonary dysplasia (BPD) in the saccular lung of the preterm human. Mataloun et al.[1] report that nutritional restriction and hyperoxic exposures each interfere with alveolarization of the preterm rabbit

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lung. These results are consistent with other reports using newborn rats or mice. They also show that the combination of hyperoxia and nutritional restriction further interfere with alveolarization. Their results further support the hypothesis that the lung abnormalities in BPD are caused by multiple adverse effects on lung development that compound each other.

Malnutrition comes in many forms: total caloric inadequacy, insufficient protein, and vitamin deficiency, for example. Before routine vitamin E supplementation, Ehrenkranz et al.[8] demonstrated that supplementation of preterm infants with vitamin E could decrease BPD. Subsequently, Tyson et al.[9] found that vitamin A supplementation decreased BPD, and a large experimental literature demonstrates that retinoids are mediators of alveolarization. Protein and caloric undernutrition also can interfere with alveolarization, as shown by Mataloun et al.[1] and previously by others.[10] There is no integrated body of clinical or experimental information that can tell us the relative importance of adequate nutrition vs. mechanical ventilation, oxygen, infection and other factors in the development of BPD. No doubt the balance of adverse factors is somewhat different for each case. However, with the information presently available, it seems prudent to feed the baby – enterally or parenterally – with a goal of feeding the lung. Perhaps the decrease in severe BPD in very low birth weight infants results from our greater emphasis on early and sustained nutritional support.

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# Music is medicine for the heart

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Music as medicine for the mind and body is an ancient concept. Apollo, the Greek god of mythology, was the giver of medicine *and* music. While there has been for centuries an appreciation of the benefits of music for those who are ill, it is only in recent years that this benefit has been more scientifically studied. Music has been shown to affect physical, emotional, cognitive and social needs of individuals of all ages.

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Music has been of beneficial effect on patients' experience of pain,[1] allaying preoperative anxiety in children,[2] acting on the autonomic nervous system by reducing heart rate, blood pressure and pain postoperatively,[3] and having a positive effect after acute myocardial infarction.[4] Music reduces anxiety and pain following open-heart surgery in adults.[5] In a study of pain following abdominal surgery, the introduction of both relaxation and music was effective in reducing the degree of pain.[6] Music's effect in blunting pain works through the gate-control theory of pain by acting as a competing stimulus that distracts the patient and directs the patient's attention away from the pain, thus modulating noxious stimuli. Imaging studies of the brain have shown activity in the auditory pathway, auditory cortex and limbic system in response to music. Music has been shown to lower