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Making Babies Breathe Better—Hopeful Signals?

Commentary on articles by Minocchieri et al. on page 141, and Sood et al. on page 159

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The issue of delivery and effectiveness of nongaseous medications *via* the airway into the lungs of babies is an area of significant clinical interest. The advantages are quite obvious: if a medication can be efficiently delivered to reach the distal areas of the lung and have an effective response to ameliorate or prevent lung disease, with minimal systemic adverse effects, it would be ideal (1). While effective medications have been developed for aerosol delivery targeted for a variety of pulmonary disorders (steroids for asthma, gentamicin for cystic fibrosis), a majority of them have only proven efficacious in adults or older children. Understanding the unique circumstances of the neonate deserves independent *in vitro* modeling and *in vivo* assessments and not mathematical extrapolation of data derived from adults and/or older children (2).

The efficacy of an aerosolized medication is dependent upon the targeted delivery of an adequate dose to the sites in the lung for maximum effectiveness. Factors influencing this include aerosol particle size, the neonate's respiratory status, the underlying pulmonary disease, the aerosol delivery system and its method of use (2). With *in vitro* studies using jet nebulizers, improvements have been made that have translated to increased aerosol delivery *in vivo*. These include decreased particle size, low inspiratory flow, high tidal volumes, nonhumidified ventilator circuits, and administration times of up to 40 min (3). While these improve aerosol delivery, the use of high tidal volumes and cold and dry gases is of significant clinical concern in such circumstances. It is hoped that there will be further advancements in nebulizer therapy (4). While increasing aerosol efficiency is able to deliver 15–22% of a medication in adults (2,5,6), in low birth weight infants, it is consistently $<2\%$ (2,7). A suggested improvement for jet nebulizer efficiency has been attempted in an *in vitro* study applicable to ventilated neonates, but requires comprehensive evaluation before attempting clinical implementation (8). Currently, the majority of neonatal intensive care units prefer to use a metered dose inhaler to deliver albuterol aerosol (9) given its superiority over a nebulizer (10–13).

Besides the issue of method of delivery, a major hindrance has been in the evaluation of how much of a medication actually reaches specific areas of the lungs in a neonate. The study by Sood *et al.* (14) is an attempt to correct this deficiency. While use of aerosolized Gadopentetate dimeglumine has been well described to evaluate pulmonary drug delivery in animal models and human adults using magnetic resonance imaging (MRI) (see references in Sood *et al.*) (9–18), this is the first study to do so in a neonatal ventilated *in vivo* animal model. After jet nebulization, the investigators noted a significant increase in signal intensity in the lungs within 10 min. So, while they were able to show that deposition of the aerosol occurred in various parts of the lungs within 10 min, actual quantification was not accomplished. It is important to keep in mind the other issues/limitations expressed by the investigators in the article about aerosol particle size, oxygen use (has paramagnetic properties and acts a "contrast" agent during MRI), manual ventilation, length of tubing and location of the nebulizer in the circuit and the fact that these animals were heavily sedated. In addition, these were "healthy" term neonates and the gas delivered was neither heated nor humidified. Physiologically, there is a strong rationale to deliver inspiratory gases that is at or close to core body temperature and is well humidified to endotracheally intubated and mechanically ventilated infants (15). Further research will be needed to assess the usefulness of the technique described by Sood *et al.* in developmentally appropriate models with lung injury (16), a clinically more relevant system. Notwithstanding, this study proves the feasibility of doing an *in vivo* evaluation of aerosol delivery during endotracheally intubated mechanical ventilation in a neonate.

Use of a novel endotracheal tube design that has lower resistance and dead space volume compared with a conventional endotracheal tube may be useful in facilitating earlier extubation (17). However, given the resurgence of noninvasive ventilation techniques, as exemplified by nasal continuous positive pressure (18) and synchronized nasal intermittent positive pressure ventilation (19–22), in the management of the premature neonate with respiratory distress, aerosolized delivery of effective medications without the need for an endotracheal tube would be a major advance.

The development of a premature upper airway modeling system as reported by Minocchieri *et al.* (23) is an important step in that direction. The investigators used MRI imaging to create a 3-D replica of the upper airway of a 32-wk gestational age premature neonate. This was validated using computed tomography scan images on the airway model. A cast was made and used for *in vitro* testing for aerosol delivery *via* a facemask. The investigators used aerosolized budenoside to test the usefulness of the model and found (expectedly) that lung dose delivered decreased with increasing flow rates. This system should prove useful in the testing of a variety of medica-

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tions potentially useful for pulmonary delivery. In preterm newborns, these include surfactant (24), perfluorocarbon (25), steroids (26), diuretics (27), nitrite (28), prostacyclin (29), prostaglandin E1 (30), and antibiotics, targeting a variety of disorders such as respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary hypertension and pneumonia.

Delivering surfactant in an infant with respiratory distress syndrome cannot be overemphasized as surfactant is not only essential for alveolar expansion, but also has a role in the maintenance of the patency of distal small airways. Exogenous surfactant (delivered as an aerosol or as an instilled suspension) has the ability to reduce airway collapse in surfactant-deficient lungs (31). Needless to say, avoidance of the need for endotracheal tubes by having an optimized delivery of an effective aerosolized surfactant preparation (24,32,33) would be first on my wish list!

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