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COMMENTARY

To Intubate or Not to Intubate at Birth, This Is *Still* the Question! Will Experimental Studies Give Us the Answer?

Commentary on the article by Polglase *et al.* on page 67

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Providing nasal CPAP (nCPAP) rather than intubating, has been identified as a potential better practice according to basic quality improvement criteria (1). In fact, over the last decade, many studies have suggested an association between the increased use of nCPAP and lower rates of intubation and/or lower rates of bronchopulmonary dysplasia (BPD) (2–5). However, due to the observational and/or retrospective character of these studies, it is difficult to know whether this association can be attributed to a changing delivery room practice, focused on early initiation of nCPAP, or some other factor(s).

To date, three randomized controlled trials, employing an appropriate study design, have tried to test the hypothesis that not intubating preterm babies with respiratory distress syndrome, at or soon after birth, would have a positive effect on outcome. A large scale multicenter trial conducted by the IFDAS (Infant Flow Driver and Surfactant) study group (6), with a four group design consisting of 1) early nCPAP with prophylactic surfactant, 2) early nCPAP ± rescue surfactant, 3) early intermittent positive pressure ventilation (IPPV) with prophylactic surfactant, and 4) early IPPV ± rescue surfactant treatment, failed to show any inter-group differences in the incidence of chronic lung disease. This study was never published after peer-review, which makes a careful and eventual nuanced interpretation of the results impossible. Why these authors never managed to publish this large clinical multicenter trial remains open, but one reason may be due to the inability of investigators to reproduce clinically the observed results from the controlled setting of a laboratory (7). A second study, a single center study by Kugelman *et al.* (8), could show decreased requirement for endotracheal ventilation with the early use of nCPAP in premature infants with RDS. This was associated with a decreased incidence of BPD. The third study, again a large sized multicenter study, the COIN (Continuous Positive Airway Pressure or Intubation at Birth) trial (9), failed to show that a "not to intubate" strategy in very preterm infants (25-to-28 wk' gestation at birth) would also reduce BPD. Even though the CPAP group in this study had an increased incidence of pneumothoraces, they had fewer days of ventilation, and fewer infants received oxygen at 28 d.

Despite a high secondary intubation rate, 20% - 50%, in VLBW infants, based on current clinical evidence, use of early nCPAP in the labor room might be recommended since it has been shown to be safe, and it reduces the need for mechanical ventilation (10). However, to recommend "not to intubate" and rely on nCPAP at birth with the ultimate goal of reducing the incidence of BPD, is not justified due to the low quality evidence (*i.e.*, "Level 3" evidence (11)) presented in the "positive" retrospective/observational reports (2–5). Moreover, the only two evidence level 1 studies (6,9) that would qualify for a "Grade A" recommendation (11), failed to show that not intubating in the labor room improved long-term pulmonary outcome.

In this issue of Pediatric Research a well known group of investigators presents another experimental study (12) designed to test the hypothesis that spontaneous breathing with CPAP, *versus* CMV, would protect the premature lung and minimize the inflammatory response to an endotoxin challenge. Surprisingly, comparable acute effects on lung and systemic inflammation of CPAP and CMV, led to the conclusion that CPAP given shortly after birth failed to attenuate lung injury. This study's results counter the results from previous studies (7,13) but support the two large sized randomized controlled clinical trials (6,9) where no reduction of chronic lung injury in preterm infants was observed. However, while being interested in the concept of translational research, several questions arise.

While chronic lung disease in preterm infants is multifactorial in origin inflammation remains the central theme in the pathophysiology of BPD (14,15). Polglase *et al.* (12) instilled *Escherichia coli* endotoxin (LPS) into lungs as a pro-inflammatory mediator, thereby recreating this theme. Previously, this same group demonstrated that mechanical ventila-

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tion of inflamed lungs caused systemic inflammation and worsened preexisting lung inflammation (16). When comparing the two studies (12,16), discrepancies consist of the chosen denominator. With the exception of the number of BALF inflammatory cells, concentrations of measured cytokine mRNA for IL-B, IL-6 and IL-8 are referenced to BALF fluid volume in one study and to bodyweight in the other study. However, the actual findings are valid in, that by using this animal model either mechanical ventilation with specific pressure settings (PEEP of 5 cmH2O), tidal volume monitoring to maintain tidal volumes (Vt) around 8 mL/kg, and targeting PaCO2 at 50 to 60 mm Hg, or CPAP set to a pressure level of 8 cmH2O shows no difference in lung and systemic inflammation over a short term. On the other hand this same group of investigators reported a third study in the same animal model without LPS instillation, thereby not stimulating an acute pro-inflammatory response (13). The results of this third study demonstrated that ventilation increased lung inflammation (neutrophil in alveolar washes and hydrogen peroxide in cells form alveolar washes) more than CPAP. However, despite a trend favoring the CPAP group, there was no difference in pro-inflammatory cytokine (*i.e.*, mRNA for IL-B, IL-6 and IL8) concentrations from lung tissue or cells from alveolar washes. Again the authors present the cytokine concentrations relative to the values in the control rather than in absolute numbers before initiation of breathing. Thus, inter-study comparisons are (12,13) difficult at best. An interpretation of these investigations (12,13) may support a potential protective role of CPAP *versus* mechanical ventilation in the absence of inflammation. In addition, differences in ventilation settings, CPAP and pC02 ranges between studies serve as a huge impediment to translation.

For successful translation of these preclinical studies into clinical practice an optimal study design for a "clinical trial" is required to answer the eternal question as to whether it is better to intubate, or not to intubate, the preterm infant with RDS at birth. These experimental studies (12,13,16), although well conducted, illustrate one major problem when trying to translate laboratory results to the bedside. The classical method of randomizing patients in a clinical study employs epidemiologic parameters such as gestational age, race, or gender to one or the other treatment group, with one specific treatment strategy per study arm. This strategy does not account for subtle, and perhaps, important differences between patients (*e.g.*, various levels of preexisting pro-inflammatory activity; differences in lung functional parameters as a reflection of the severity of disease; differences in surfactant pool, secretion and composition). These differences will render varying thresholds of susceptibility for lung injury in a given patient population. Therefore, as long as we do not know how to individually tailor respiratory support to a given infant, we will probably never answer the question as to whether we should intubate or not at birth. The observation that the two large sized randomized controlled clinical studies (6,9) demonstrated a shorter duration of mechanical ventilation does not change this premise, since there is no evidence that these beneficial short-term effects translate into lower rates of long-term morbidity such as BPD or neurologic sequelae (17).

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