Predicting Pulmonary Outcomes in Extremely Preterm Infants from Recordings of Cardiorespiratory Data: A Question of Chicken and Egg

Prediction of outcomes in preterm infants may involve events in the very near future and at high resolution (e.g., predicting when the next apnea will occur in an individual infant) or events in the medium term (e.g., the duration of a baby's hospital stay or his/her need for mechanical ventilation). Prediction may also involve longer term outcomes (e.g., death by 3 months of age or the development of cerebral palsy). These longer term outcomes were the subject of published studies using data from the SUPPORT (Surfactant Positive Pressure and Oxygen Trial) and COT (Canadian Oxygen Trial) studies, respectively. Di Fiore and colleagues, using the SUPPORT data, showed that lower oxygen saturation as measured by pulse oximetry (Sp_{O_2}) and more events with intermittent hypoxemia (IH) to <80% Sp_{O_2} in the first 3 postnatal days were associated with lower 3-month survival, particularly in infants born small for gestational age (GA) (1). Also, Poets and colleagues, using data from COT, reported that a large proportion of time spent with IH (Sp_{O_2} < 80% for ⩾1 min) was an independent risk factor for motor impairment (adjusted odds ratio, 5.20; 95% confidence interval, 2.48–10.92) and death after 36 weeks postmenstrual age (PMA) or disability (adjusted odds ratio, 3.4; 95% confidence interval, 1.95–5.93) (2). However, whether these associations would allow the prediction of these outcomes in individual patients was not addressed in these studies.

In this issue of the *Journal*, Ambalavanan and colleagues (pp. 79–97) report on an investigation of whether such associations could be used to predict adverse outcomes (3). They hypothesized that in infants born at <29 weeks' GA, cardiorespiratory monitoring data collected between extubation and 8–12 weeks of age would predict an unfavorable respiratory outcome at 40 weeks' PMA. For this, they evaluated routine neonatal ICU cardiorespiratory monitoring data in 717 infants (median GA at birth, 26.4 wk). At 40 weeks' PMA, about half of the infants had favorable outcomes, whereas the other half had unfavorable outcomes. An unfavorable outcome was defined as either death or remaining an inpatient and/or receiving respiratory medications, oxygen, or other support. They found that their recorded data predicted an unfavorable outcome, at both 32 and 40 weeks' PMA, with the proportion of time spent with Sp_{O_2} < 90% being the most predictive variable. IH was predictive of severe bronchopulmonary dysplasia (BPD) and death, or the need for mechanical ventilation, with an area under the receiver operating characteristic curve of 0.84–0.85 on Postnatal Days 7 and 14 and of 0.86–0.88 on Day 28 or at 32 weeks' PMA. However, clinical variables such as lower GA at birth, use of mechanical ventilation or sedation, being small for GA, and needing a high $F_{I_{O_2}}$ had even higher model accuracy than the physiologic parameters mentioned above (3).

These data confirm previous studies showing associations between IH (rather than apnea or bradycardia) and clinical outcomes such as BPD or BPD with pulmonary hypertension (4, 5). Those previous studies, however, did not investigate the precision of these physiologic parameters in predicting the above clinical outcomes. The finding that the clinical variables had even higher model accuracy than the physiologic parameters is consistent with earlier data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development neonatal network (6). It is also interesting to note that data on Sp_{O_2} were more predictive than those on apnea or bradycardia, confirming an earlier secondary analysis of data from COT (2).

What would an ability to predict the above outcomes on the basis of physiologic parameters obtained at 32 weeks' PMA mean in terms of clinical utility? Regarding BPD prevention, any therapy started beyond 32 weeks' PMA would be unlikely to change a given infant's risk of developing BPD, as the damage that ultimately leads to this outcome will already have occurred. There would also be minimal impact over the current counseling given to parents of babies born at <29 weeks' GA. However, the value of the data reported by Ambalavanan and colleagues (3) more likely lies in the fact that they may improve our understanding of the pathophysiology of the cardiorespiratory events the authors identified as predictors of adverse outcomes. It may be that these events might disturb cellular homeostasis to such an extent, and occur often enough, to result in an impaired ventilatory function.

Alternatively, could the fact that cardiorespiratory events were characteristic of infants subsequently developing impaired respiratory outcomes mean that they already had impaired lung function very early on in their course, such that they had to exert increased work of breathing, leading to diaphragmatic fatigue with subsequent apnea (7) (and IH) rather than reflecting a primary respiratory control disorder? This kind of chicken-and-egg question will be nearly impossible to answer with the currently available data. A clinical trial would be needed to study whether a reduction in time spent with IH, perhaps through the use of closed-loop oxygen controllers, will reduce BPD. Fortunately, such a trial is currently underway (8).

It is somewhat surprising that even events that resulted in <90% Sp_{O_2} were associated with an impaired respiratory outcome. The authors provide no information on the target range applied at the participating centers, but given that the American Academy of Pediatrics recommends a target range of 85–95% (9), values between 80% and 90% Sp_{O_2} are within or very close to this range. Again, this raises the chicken-and-egg question.

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For clinicians, the statistical analyses applied by the authors may seem overly complex and at times are difficult to follow. Also, as acknowledged by the authors, any assessment of the maturation of cardiorespiratory control was hampered by the fact that a large proportion of infants with poor respiratory outcomes were still mechanically ventilated, precluding any analysis of apnea and periodic breathing. Nonetheless, the basic message is rather clear and clinically meaningful: even cardiorespiratory events leading to mild decreases in Sp_{O_2} are associated with an increased risk of BPD or longer term need for respiratory support. We now need to find out whether this knowledge can be used to help us prevent these outcomes. ■

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