HHS Public Access

Author manuscript

Pediatr Res. Author manuscript; available in PMC 2019 April 29.

Published in final edited form as:

Pediatr Res. 2019 June ; 85(7): 987–993. doi:10.1038/s41390-018-0223-5.

Oxygen desaturations in the early neonatal period predict development of bronchopulmonary dysplasia

Karen D Fairchild, **V Peter Nagraj**[1,2], **Brynne A Sullivan**[1], **J Randall Moorman**[3], and **Douglas E Lake**[3]

[1]Department of Pediatrics, University of Virginia, Charlottesville, VA

[2]School of Medicine Research Computing, University of Virginia, Charlottesville, VA

[3]Department of Medicine, University of Virginia, Charlottesville, VA

Abstract

Background: Bradycardia and oxygen desaturation episodes are common among preterm very low birthweight (VLBW) infants in the Neonatal Intensive Care Unit (NICU), and their association with adverse outcomes such as bronchopulmonary dysplasia (BPD) is unclear.

Methods: For 502 VLBW infants we quantified bradycardias (HR <100 for ≥ 4 seconds) and desaturations (SpO_2 <80% for ≥ 10 seconds), combined bradycardia and desaturation (BD) events, and percent time in events in the first 4 weeks after birth (32 infant-years of data). We tested logistic regression models of clinical risks (including a respiratory acuity score incorporating FiO_2 and level of respiratory support) to estimate the risks of BPD or death and secondary outcomes. We then tested the additive value of the bradycardia and desaturation metrics for outcomes prediction.

Results: BPD occurred in 187 infants (37%). The clinical risk model had ROC area for BPD of 0.874. Measures of desaturation, but not bradycardia, significantly added to the predictive model. Desaturation metrics also added to clinical risks for prediction of severe intraventricular hemorrhage, retinopathy of prematurity and prolonged length of stay in the NICU.

Conclusions: Oxygen desaturations in the first month of the NICU course are associated with risk of BPD and other morbidities in VLBW infants.

Background:

Very low birth weight (VLBW <1500 grams) preterm infants in the Neonatal Intensive Care Unit (NICU) commonly have episodes of bradycardia and oxygen desaturation, separately or together. These occur in spite of respiratory and pharmacologic support for lung disease and apnea, and in spite of clinicians' efforts to titrate supplemental oxygen to achieve target oxygen saturation levels, generally in the 88–95% SpO_2 range. A link between frequent or

Corresponding author: Karen Fairchild, Dept. of Pediatrics, P.O. Box 800386, University of Virginia, Charlottesville, VA 22908 kdf2n@virginia.edu office: (434)924-5428 fax: (434)924-2816.

Conflicts/disclosures related to this work: none

severe bradycardia and desaturation episodes in the neonatal period and development of bronchopulmonary dysplasia (BPD) and other common morbidities of preterm infants has not been well established.

Hypoxemia may cause cell and tissue damage if severe, prolonged, or frequent[1], and recovery from hypoxemia, in some cases with rebound hyperoxemia when excessive oxygen is administered, may stimulate release of oxygen radicals that contribute to inflammation and other injury cascades[2,3]. In preterm infants, intermittent hypoxemia events or targeting a lower versus higher SpO_2 have been associated with a number of adverse outcomes including retinopathy of prematurity[4,5] neurodevelopmental impairment[6,7], pulmonary hypertension[8] and death[9] Large gaps in knowledge remain about causality and about characteristics of desaturation episodes that lead to injury. Bradycardia episodes are also common in preterm infants, with or without temporally associated oxygen desaturation[7,10]. Heart rate deceleration may occur with central or obstructive apnea or may be related to vagal or baroreflex responses. While bedside monitor bradycardia alarms tend to attract more attention than low SpO_2 alarms, association of these drops in heart rate with adverse outcomes has not been established.

Apnea is a common cause of bradycardia and desaturation in preterm infants when they are not on mechanical ventilation. We previously developed an automated algorithm to quantify central apnea accompanied by both bradycardia and desaturation[11] which allowed us to describe combined apnea, bradycardia, desaturation (ABD) events and their association with various outcomes in preterm infants [12–14]. Many bradycardia and desaturation episodes occur in absence of central apnea, and in the current study our first aim was to describe these events irrespective of apnea, both on and off the ventilator. We then used statistical modeling to test the hypothesis that measures of oxygen desaturation with or without bradycardia add to clinical data to predict the primary outcome of BPD. Finally, we tested these models as predictors of other clinical outcomes that might be associated with aberrant oxygenation, including severe intraventricular hemorrhage (IVH), treated retinopathy of prematurity (ROP), and prolonged length of stay in the NICU.

Methods

Patient population and BPD diagnosis

VLBW infants 23–33 weeks' gestation admitted to the University of Virginia NICU January 2009 through March 2014 were included. This is a Level 4 NICU (Vermont Oxford Network Type C) and is a regional referral center for infants with complex medical and surgical conditions. The study was approved by the Institutional Review Board. We excluded infants who died within the first week after birth, infants with severe syndromes or congenital anomalies likely to impact oxygenation, and infants with <7 days of pulse oximetry data available for analysis. BPD was defined as need for supplemental oxygen or positive airway pressure at 36 weeks postmenstrual age (PMA), and severe BPD was defined as being on >30% supplemental oxygen at 36 weeks PMA. Efforts were made daily to wean respiratory support and supplemental oxygen to achieve target oxygen saturations but a formal oxygen reduction challenge was not routinely performed. Ten infants died after 7 days of age and

before 36 weeks PMA, all on ventilatory support and supplemental oxygen, and these infants were included in the BPD group.

Demographic data, ventilator days, and Respiratory Acuity Score

Demographic and clinical data were obtained from the electronic health record. Days on mechanical ventilation were counted if an infant spent any part of the day on mechanical ventilation. To assess the mode of respiratory support and supplemental oxygen at 7 and 28 days of age, we devised and calculated a Respiratory Acuity Score (RAS7 and RAS28). On day 7 and day 28, points were assigned for level of respiratory support and this value was multiplied by the mean FiO_2 on that day (or if the infant was on low flow nasal cannula, the effective FiO_2 calculated by the method of Finer et al.)[15]. Respiratory support values were assigned as follows: zero if an infant was on room air, 1 if on low flow nasal cannula (<1 liter per minute, LPM), 2 for 1–2 LPM high flow nasal cannula, 3 for high flow nasal cannula >2 LPM, 4 for continuous positive airway pressure (CPAP), 6 for conventional ventilator, and 8 for high frequency ventilator. RAS7 and RAS28 were associated with BPD in univariate and multivariate logistic regression (Table 2).

Monitor data collection and BD analyses

Bedside monitor pulse oximeter and waveform data were collected using a central network server (BedMaster, Excel Medical, Jupiter, FL). Heart rate (HR) values from the electrocardiogram were collected at 0.5 Hz (one value every 2 seconds). SpO_2 values were also collected at 0.5 Hz, using Masimo pulse oximeters with 8-second averaging. The target SpO_2 range for VLBW infants on supplemental oxygen throughout the period of study was 88–95%.

In our prior work on central apnea of prematurity, we used a bradycardia threshold of <100 beats/minute and a desaturation threshold of SpO_2<80%, with no minimum duration specified[11–14]. In order to focus on episodes more likely to be clinically important, we here defined a bradycardia event as lasting at least 4 seconds and a desaturation at least 10 seconds. Episodes were joined if the HR or SpO_2 rose above then dropped below the threshold within 4 seconds for bradycardia or 10 seconds for desaturation. Individual episodes were identified as well as combined BDs with bradycardia and desaturation starting within 30 seconds of each other.

In addition to quantifying the number and duration of episodes, we measured the percentage of the total time that was spent below the HR or SpO_2 threshold and the area under the threshold.

Statistics

Spearman correlation coefficients were used to assess correlation between GA, BW, and bradycardia and desaturation episodes. We used logistic regression to test hypotheses about how variables added predictive information, first assessing clinical risk factors individually in univariate analysis, with results expressed as area under the receiver operator characteristic curve (ROC area). Number of ventilator days (VD) were examined in three time frames in the neonatal period: first week, fourth week, and first four weeks. Respiratory

Acuity Score was assessed on day 7 (RAS7) and on day 28 (RAS28). A multivariate model with all clinical variables (GA, BW, VD, RAS) was then tested for each outcome. Next, this baseline model of clinical predictors was adjusted for each bradycardia and desaturation variable separately. Unlike stepwise regression, the final result of this method was not a fully adjusted model but rather a series of models individually adjusted for the physiologic features, allowing for side-by-side comparison of variables. The ROC area values for these adjusted models are reported in Table 2 if the coefficient for the given feature was significant in the logistic regression model ($p < 0.05$).

To further assess the relative importance of individual predictors, we used random forest variable importance analysis to predict BPD using clinical risks, respiratory support variables, and bradycardia/desaturation features (number, duration, percent time, and area under thresholds). The approach included 500 trees and used the Gini measure of mean difference impurity [16–18] to rank predictors, using the RandomForest R package implemented via the caret interface.

All analyses were performed using the R statistical computing language version 3.2.1.

Results:

Patient population and outcomes

In the five-year period of study, 502 of the 682 VLBW infants of 23 $^{0/7}$ to 33 $^{6/7}$weeks' gestation admitted to the University of Virginia NICU survived at least a week and met criteria for inclusion. Table 1 shows characteristics and outcomes of these infants as a group and based on birth weight categories. BPD or death beyond day 7 of age occurred in 187 of the 502 infants (37%) and 108 of these infants had severe BPD. Of the fifteen infants that died, 10 died before 36 weeks PMA (all on ventilatory support and supplemental oxygen and included in the BPD group) and 5 died after 36 weeks PMA (all with BPD). Rates of other clinical variables and outcomes are shown in Table 1.

Episodes of bradycardia, desaturation, and BD on and off mechanical ventilation

The total number of days of data available for analysis in the first 28 days after birth was 11,608 (4,616 days on and 6,992 days off mechanical ventilation).

Bradycardia and desaturation events were common: in total, there were 146,428 bradycardias ≥ 4 seconds and 550,985 desaturations ≥ 10 seconds. On average, infants spent more than 45 minutes per day in one, the other or both events in the first 28 days. Figure 1 shows the cumulative frequency on the y axis of all bradycardia and desaturation episodes of increasing duration in seconds shown on the x axis. The median duration of bradycardia was 8 seconds and desaturation 30 seconds. Event durations are continuously distributed, with no inflections at the cutoffs of 4 seconds for bradycardia and 10 seconds for desaturation that were used for subsequent analyses. These cutoffs were selected not based on distribution of event durations but rather based on the concept that very brief events are less likely to be clinically important.

The number of desaturations was inversely proportional to gestational age and birth weight (Spearman correlation coefficient for GA r= −0.63 and for BW r= −0.77 both p<0.01). The mean percent time in desaturations (<80% for ≥10 seconds) for all VLBW infants was 3.3% and was significantly higher in the lower birth weight infants as shown in Figure 2. For bradycardias, there was a statistically significant but much weaker correlation with GA but no correlation with BW (for GA r= −0.15 p<0.05 and for BW r= −0.07 p=0.1).

Figure 3 shows the natural course of desaturations and bradycardias from birth to day 28. Desaturations were more frequent while infants were on mechanical ventilation and increased over time both on and off the ventilator, peaking around 3 weeks of age. Bradycardias, in contrast, occurred with approximately equal frequency on an off the ventilator without a major increase over time.

Predictive Modeling

Table 2 shows the results of univariate and multivariate analysis of demographic, respiratory, and desaturation and bradycardia metrics in relation to BPD and other outcomes. As expected, GA and BW were highly correlated with BPD and treated ROP (ROC area range 0.829–0.877) and significantly but less strongly associated with severe IVH and prolonged length of stay (ROC area range 0.671–0.763).

The numbers of days on mechanical ventilation in the first week, fourth week, and first 4 weeks after birth were significantly associated with BPD in univariate analyses. We also developed a Respiratory Acuity Score (RAS), the product of FiO_2 and a number reflecting the level of respiratory support on two days. RAS at 7 and 28 days of age was significantly higher for infants with BPD compared to those without: mean RAS7 was 228 (137) versus 76 (94), and mean RAS28 was 237 (165) versus 47 (77). Both RAS measures were significantly associated with all outcomes in univariate analysis (ROC area range 0.718–0.897). In multivariate analysis, combining all clinical and respiratory support variables increased ROC area for each outcome (ROC area 0.902 for BPD and 0.776–0.901 for other outcomes)

Logistic regression analysis was used to predict BPD and other outcomes based on the combined clinical model (GA, BW, ventilator days, RAS) and bradycardia/desaturation metrics. Table 2 shows that the desaturation metrics were more likely to significantly add to outcomes prediction compared to the bradycardia or combined bradycardia-desaturation metrics (chi square and p values for the models are shown in Supplemental Table S1). Desaturation metrics later in the NICU course (fourth week and first 4 weeks) gave slightly better prediction of BPD and treated ROP, while earlier desaturation metrics (first week) were slightly more predictive of severe IVH and prolonged length of stay. Figure 4 shows ROC curves for prediction of BPD using GA alone, GA+RAS28, and GA+RAS28+%time in desaturation events <80% for ≥10 seconds. ROC areas are 0.829, 0.889, and 0.902, respectively. For prediction of severe BPD, ROC areas using the same 3 models are 0.842, 0.913, and 0.923.

As a complementary approach, we used random forest methods to assess the relative importance of the clinical and physiologic variables for predicting BPD. Supplemental

Figure S1 shows that clinical variables and desaturation variables were more important than bradycardia variables for BPD prediction.

DISCUSSION

We studied bradycardia, oxygen desaturation, and combined bradycardia-desaturation episodes in the first 4 weeks after birth in 502 VLBW infants. Our major finding is that oxygen desaturation events early in the NICU course, but not bradycardia events, are associated with development of BPD and other adverse outcomes.

Preterm infants in the NICU are notorious for having “ABDs”, episodes of central, obstructive, or mixed apnea with temporally associated decline in heart rate and/or SpO_2. Oxygen desaturation also occurs without apnea, including while on mechanical ventilation, and may be related to acute and chronic lung disease, intracardiac and intrapulmonary shunts, and inadequate gas exchange that may occur, for example, when an infant is agitated[19,20]. Heart rate deceleration may also occur in absence of apnea, for example with vagus nerve activation[21] or as a baroreflex response to blood pressure changes during a Valsalva maneuver[22]. In prior work, we found that 51% of bedside monitor alarms in the NICU were due to SpO_2 below 88%, whereas bradycardia alarms accounted for only 3% of total alarms[23]. In that analysis, VLBW infants spent 13% of the total time in the NICU with SpO_2 <88% whereas in the current analysis, which was limited to events of SpO_2 <80% lasting ≥10 seconds occurring in the first 4 weeks after birth, we found that infants spent, on average, 3.3% of the time in those episodes. We also found, as have others, that intermittent hypoxemia events increase in the first few weeks after birth[19], both on and off mechanical ventilation, whereas bradycardia events do not change significantly. This highlights that, while central apnea is a cause of both bradycardia and desaturation, they often occur separately due to other physiologic processes.

While it was previously thought that mild hypoxemia was safe and perhaps even desirable for preterm infants due to risks of oxygen toxicity, more recent evidence from some randomized trials suggests there is higher mortality with a lower SpO_2 target range of 85–89%[24,25]. Duration of desaturation episodes appears to play a role in pathologic consequences. In a post-hoc analysis of 1019 preterm infants enrolled in the Canadian Oxygen Trial, desaturations <80% lasting at least 60 seconds, but notbradycardia episodes, were correlated with adverse neurodevelopmental outcomes at 18 months corrected age, [7]. While it is impossible to prevent all hypoxemia episodes in critically ill preterm infants, improvement in SpO_2 targeting with strategies such as servo-controlled oxygen delivery[26] and more rigorous management of apnea[27] might improve long-term outcomes.

A major aim of this work was to use bedside monitor data early in the NICU course to assist in identifying VLBW infants at highest risk for BPD, which might eventually be useful for decisions about therapies, risk stratification in clinical trials, and benchmarking across NICUs. Low gestational age and birthweight are highly predictive; the vast majority of 23 week infants and very few 32 week infants develop BPD. We found that the number of days on mechanical ventilation early in the NICU stay and a Respiratory Acuity Score (RAS) incorporating level of ventilatory and oxygen support added significantly to GA and BW for

BPD prediction. This finding is similar to an analysis of more than 3000 VLBW infants in the National Institutes of Health Neonatal Network NICUs that led to development of an online BPD risk calculator [28]. In the current analysis we additionally found that measures of hypoxemia early in the NICU course add substantially to demographic and respiratory support variables for BPD prediction. In contrast, we found that bradycardia and combined bradycardia-desaturation events did not add predictive value. In our prior work we also found that events of bradycardia and desaturation associated with central apnea did not occur more frequently in infants with BPD compared to GA-matched infants without BPD[14].

Secondary outcomes of prolonged NICU stay, severe IVH, and treated ROP were predictable through analysis of oxygen desaturation, but not bradycardia, early in the NICU stay. For ROP, GA and BW alone were excellent predictors, and percent time and area under 80% SpO_2 in the first four weeks added significantly. Severe IVH and prolonged NICU stay were less predictable by GA and BW compared to the other outcomes, and in logistic regression adding various desaturation metrics from the first week after birth substantially increased the ROC area.

There are limitations to this study. We required a minimum duration of 4 seconds of bradycardia and 10 seconds of desaturation, which underestimates the true burden but focuses on events more likely to be clinically important[5,20]. Also, we utilized a standard SpO_2 averaging time of 8 seconds which smooths the data, underrepresenting the depth but exaggerating the duration of low SPO_2 events. In prior modeling work we estimated that 8 second averaging would miss 30% of episodes of $SpO_2 < 88\%$ that were picked up by 2 second averaging[23]. We also acknowledge that selecting lower thresholds or longer durations for cardiorespiratory events may result in better predictive models.

In conclusion, oxygen desaturations in the first weeks after birth add to demographic and clinical variables for predicting BPD and other adverse outcomes in VLBW infants. In most clinical practice settings, precise quantitation of hypoxemia events is not feasible. However, some newer pulse oximeters display a daily SpO_2 histogram that informs on how successful bedside caregivers have been in keeping SpO_2 in target range. These data might be useful for identifying infants requiring more rigorous therapies for lung disease or apnea, and more careful titration of supplemental oxygen.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support: NIH HD072071, HD064488

References

1. Martin RJ, Wang K, Köroğlu Ö, Di Fiore J, Kc P. Intermittent Hypoxic Episodes in Preterm Infants: Do They Matter? Neonatology. 2011 1;100(3):303–10. [PubMed: 21986336]

2. Dylag AM, Mayer CA, Raffay TM, Martin RJ, Jafri A, MacFarlane PM. Long-term effects of recurrent intermittent hypoxia and hyperoxia on respiratory system mechanics in neonatal mice. Pediatr Res. 2017 4 14;81(4):565–71. [PubMed: 27842056]

3. Darnall RA, Chen X, Nemani K V, Sirieix CM, Gimi B, Knoblach S, et al. Early post-natal exposure to intermittent hypoxia in rodents is pro-inflammatory, impairs white matter integrity and alters brain metabolism. Pediatr Res. 2017 4 7;

4. Saugstad OD, Aune D. Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation target studies. Neonatology. 2014 1;105(1):55–63. [PubMed: 24247112]

5. Di Fiore JM, Kaffashi F, Loparo K, Sattar A, Schluchter M, Foglyano R, et al. The relationship between patterns of intermittent hypoxia and retinopathy of prematurity in preterm infants. Pediatr Res. 2012 12;72(6):606–12. [PubMed: 23037873]

6. Janvier A, Khairy M, Kokkotis A, Cormier C, Messmer D, Barrington KJ. Apnea is associated with neurodevelopmental impairment in very low birth weight infants. J Perinatol. 2004 12;24(12):763–8. [PubMed: 15329741]

7. Poets CF, Roberts RS, Schmidt B, Whyte RK, Asztalos EV, Bader D, et al. Association Between Intermittent Hypoxemia or Bradycardia and Late Death or Disability in Extremely Preterm Infants. JAMA. 2015 8 11;314(6):595–603. [PubMed: 26262797]

8. Kanaan U, Srivatsa B, Huckaby J, Kelleman M. Association of unit-wide oxygen saturation target on incidence of pulmonary hypertension in very low birthweight premature infants. J Perinatol. 2018 2 19;38(2):148–53. [PubMed: 29048404]

9. Di Fiore JM, Martin RJ, Li H, Morris N, Carlo WA, Finer N, et al. Patterns of Oxygenation, Mortality, and Growth Status in the Surfactant Positive Pressure and Oxygen Trial Cohort. J Pediatr. 2017 7;186:49–56.e1. [PubMed: 28279433]

10. Schmid MB, Hopfner RJ, Lenhof S, Hummler HD, Fuchs H. Cerebral oxygenation during intermittent hypoxemia and bradycardia in preterm infants. Neonatology. 2015 1;107(2):137–46. [PubMed: 25531368]

11. Lee H, Rusin CG, Lake DE, Clark MT, Guin L, Smoot TJ, et al. A new algorithm for detecting central apnea in neonates. Physiol Meas. 2011 1;33(1):1–17. [PubMed: 22156193]

12. Mohr MA, Vergales BD, Lee H, Clark MT, Lake DE, Mennen AC, et al. Very long apnea events in preterm infants. J Appl Physiol. 2014 3 30;118(5):558–68. [PubMed: 25549762]

13. Vergales B, Paget-Brown AAO, Lee H, Guin LE, Smoot TJ, Rusin CG, et al. Accurate Automated Apnea Analysis in Preterm Infants. Am J Perinatol. 2014 2;31(2):157–62. [PubMed: 23592319]

14. Fairchild K, Mohr M, Paget-Brown A, Tabacaru C, Lake D, Delos J, et al. Clinical associations of immature breathing in preterm infants: part 1-central apnea. Pediatr Res. 2016 3 9;80(1):21–7. [PubMed: 26959485]

15. Finer NN, Bates R, Tomat P. Low flow oxygen delivery via nasal cannula to neonates. Pediatr Pulmonol. 1996 1;21(1):48–51. [PubMed: 8776266]

16. Botta V, Louppe G, Geurts P, Wehenkel L. Exploiting SNP correlations within random forest for genome-wide association studies. Chen L, editor. PLoS One. 2014 4 2;9(4):e93379. [PubMed: 24695491]

17. Lebedev A V, Westman E, Van Westen GJP, Kramberger MG, Lundervold A, Aarsland D, et al. Random Forest ensembles for detection and prediction of Alzheimer's disease with a good between-cohort robustness. NeuroImage Clin. 2014;6:115–25. [PubMed: 25379423]

18. Worachartcheewan A, Shoombuatong W, Pidetcha P, Nopnithipat W, Prachayasittikul V, Nantasenamat C. Predicting Metabolic Syndrome Using the Random Forest Method. ScientificWorldJournal. 2015;2015:581501. [PubMed: 26290899]

19. Martin RJ, DiFiore JM Di, Macfarlane PM, Wilson CG. Physiologic basis for intermittent hypoxic episodes in preterm infants. Adv Exp Med Biol. 2012;758:351–8. [PubMed: 23080182]

20. Esquer C, Claure N, D'Ugard C, Wada Y, Bancalari E. Mechanisms of hypoxemia episodes in spontaneously breathing preterm infants after mechanical ventilation. Neonatology. 2008 1;94(2): 100–4. [PubMed: 18277057]

21. Gamble YD, Lutin WP, Mathew OP. Non-sinus bradyarrhythmias in very low birth weight infants. J Perinatol. 2007 1 14;27(1):65–7. [PubMed: 17180134]

22. Abu-Osba YK, Brouillette RT, Wilson SL, Thach BT. Breathing pattern and transcutaneous oxygen tension during motor activity in preterm infants. Am Rev Respir Dis. 1982 4;125(4):382–7. [PubMed: 7073106]

23. McClure C, Jang SY, Fairchild K. Alarms, oxygen saturations, and SpO2 averaging time in the NICU. J Neonatal Perinatal Med. 2016 1;9(4):357–62. [PubMed: 27834782]

24. Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010 5 27;362(21):1959–69. [PubMed: 20472937]

25. Stenson BJ, Tarnow-Mordi WO, Darlow BA, Simes J, Juszczak E, Askie L, et al. Oxygen saturation and outcomes in preterm infants. N Engl J Med. 2013 5 30;368(22):2094–104. [PubMed: 23642047]

26. van Kaam AH, Hummler HD, Wilinska M, Swietlinski J, Lal MK, te Pas AB, et al. Automated versus Manual Oxygen Control with Different Saturation Targets and Modes of Respiratory Support in Preterm Infants. J Pediatr. 2015 9;167(3):545–50.e1–2. [PubMed: 26144575]

27. Dobson NR, Patel RM, Smith PB, Kuehn DR, Clark J, Vyas-Read S, et al. Trends in Caffeine Use and Association between Clinical Outcomes and Timing of Therapy in Very Low Birth Weight Infants. J Pediatr. 2014 5 22;164(5):992–998.e3. [PubMed: 24461786]

28. Laughon MM, Langer JC, Bose CL, Smith PB, Ambalavanan N, Kennedy KA, et al. Prediction of Bronchopulmonary Dysplasia by Postnatal Age in Extremely Premature Infants. Am J Respir Crit Care Med. 2011 6 15;183(12):1715–22. [PubMed: 21471086]

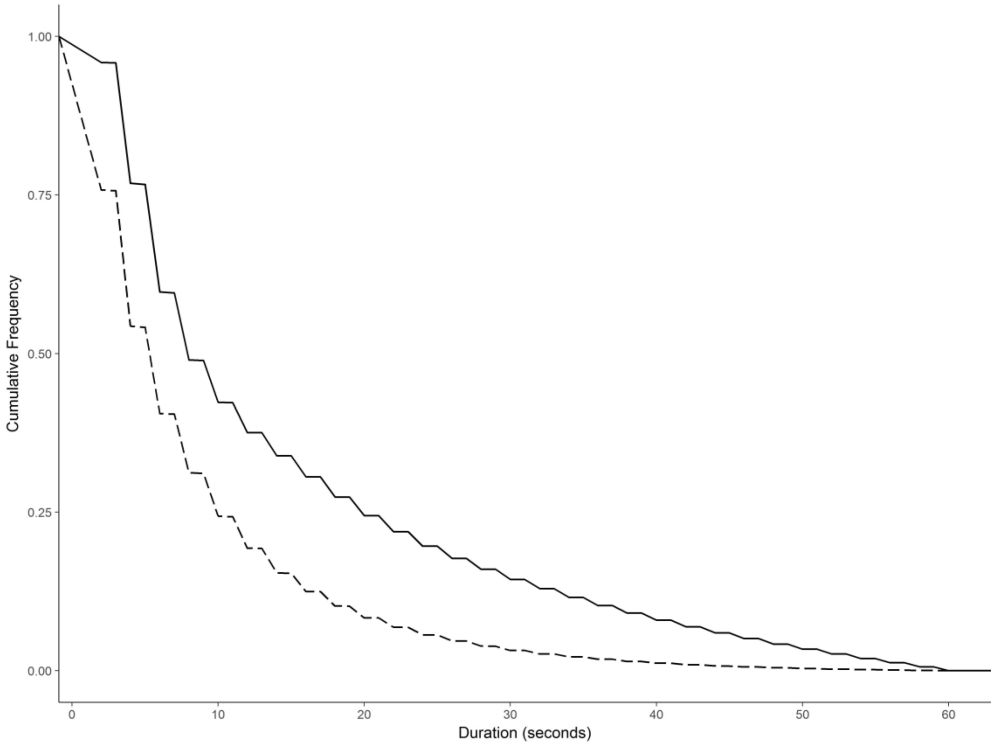

Figure 1: Duration of bradycardia and desaturation events.

Cumulative frequency of bradycardias (dashed line; heart rate <100 beats/minute) and desaturations (solid line, SpO_2 < 80%) are shown for 502 VLBW infants in the first 28 days from birth.

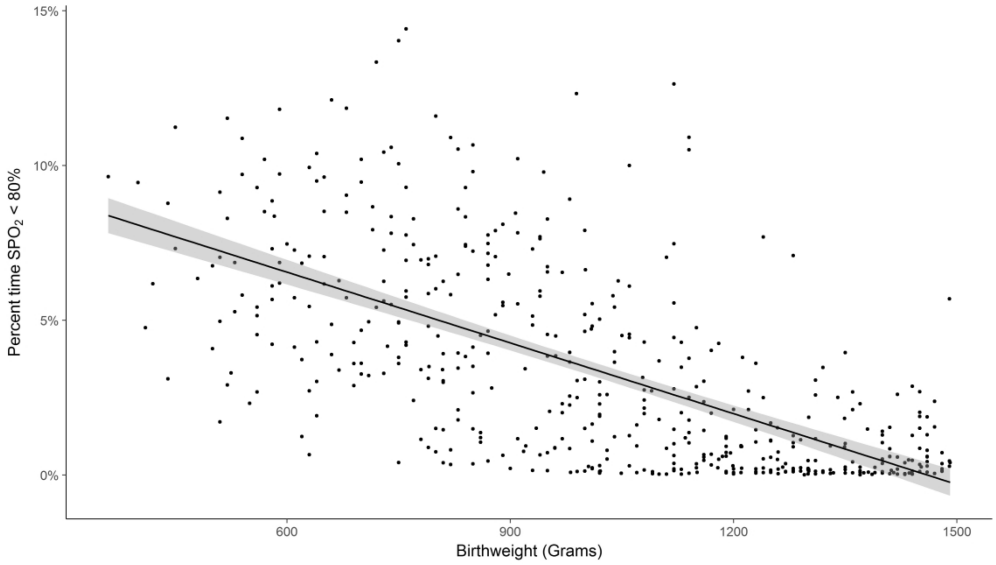

Figure 2: Percent of time in desaturation events, by birthweight.

Each of the 502 infants is represented as a dot based on birthweight, and the percent of time with SpO_2 <80% for ≥ 10 seconds in the first 28 days after birth is shown. A linear regression line is shown, with grey shading representing the 95% confidence interval.

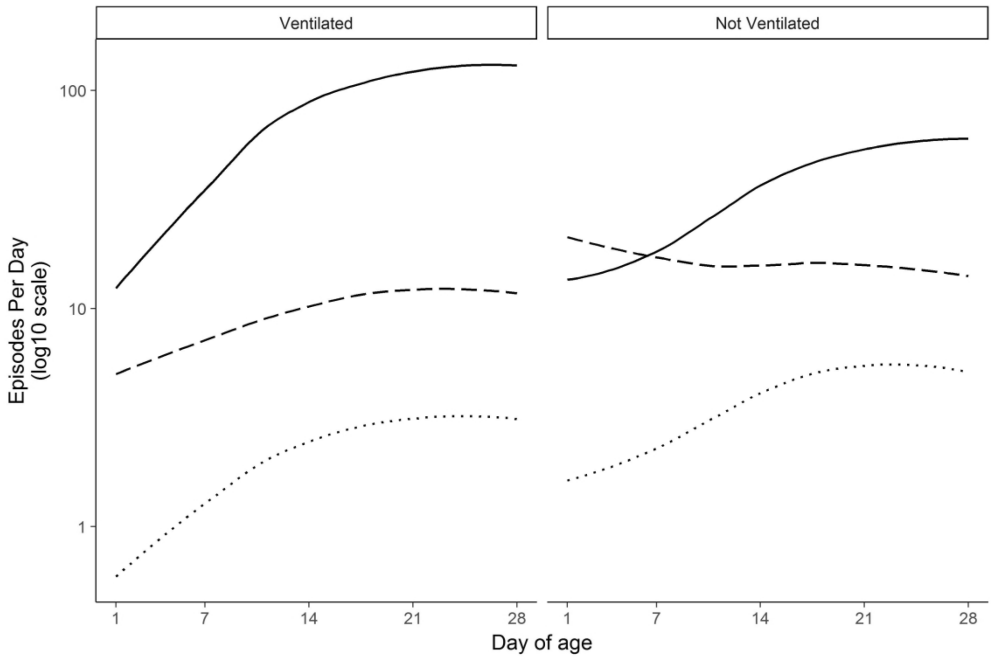

Figure 3: Trend over time of number of bradycardia and desaturation and combined BD events.
For infants on mechanical ventilation (left) and off (right), mean number of episodes of bradycardia (dashed line), desaturation (solid line) and combined BD (dotted line) are shown from day 1 to day 28 after birth.

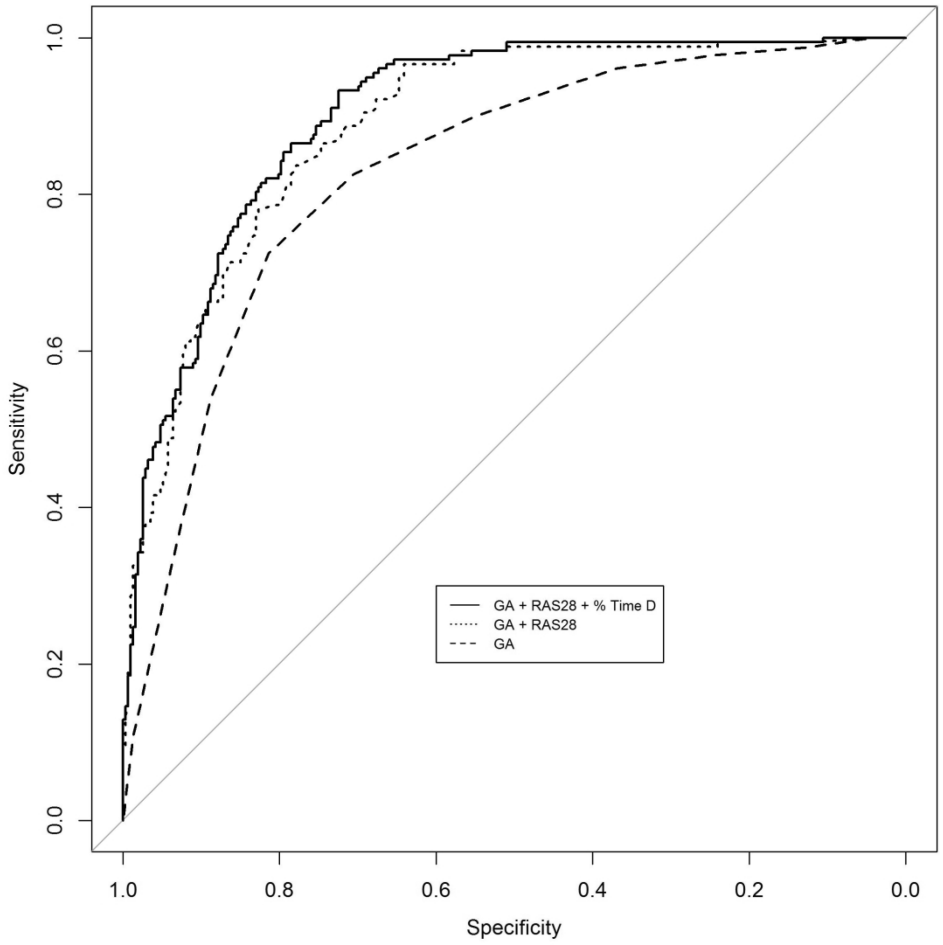

Figure 4: Receiver operator characteristics curves for BPD.

ROC curves are shown for prediction of BPD by gestational age alone (dashed line), for GA plus Respiratory Acuity Score at day 28 (dotted line), and for GA plus RAS28 plus percent of time in events of desaturation <80% for ≥ 10 seconds (solid line). ROC areas are 0.829, 0.889, and 0.902 respectively.

Table 1:

Demographic and Clinical Variables of 502 VLBW Infants

Birthweight Category	<750 grams	750–999 grams	1000–1499 grams	All <1500 grams
n (%)	96 (19)	134 (27)	272 (54)	502
GA weeks	24 (24–25)	25 (25–28)	29 (28–31)	28 (25–29)
BW grams	620 (548–683)	860 (805–934)	1240 (1120–1370)	1020 (800–1250)
SGA (<10%)	19 (20)	8 (6)	10 (4)	37 (7)
Female	53 (55)	54 (40)	150 (55)	257 (51)
Cesarean delivery	65 (68)	89 (66)	173 (64)	327 (65)
Inborn	76 (79)	110 (82)	229 (84)	415 (83)
Total ventilator days	28 (22–34)	8 (0–12)	0 (0–2)	3 (0–21)
Death	8 (8)	2 (1)	5 (2)	15 (3)
Day of age at death	78 (31–131)	33 (30–35)	29 (23–31)	34 (26–78)
BPD (O2 at 36w)	70 (73)	72 (54)	30 (11)	172 (34)
Length of Stay, days	104 (86–120)	82 (63–99)	46 (33–60)	62 (42–93)
Discharge >40w PMA	41 (43)	30 (22)	15 (6)	86 (17)
Severe IVH	10 (10)	18 (13)	10 (4)	38 (8)
Severe ROP	33 (34)	18 (13)	3 (1)	54 (11)

median (25–75th%) or n (%)

GA Gestational Age, BW Birth Weight, SGA Small for GA, BPD Bronchopulmonary Dysplasia, w weeks, IVH Intraventricular Hemorrhage, ROP Retinopathy of Prematurity, PMA Postmenstrual Age

Table 2:

ROC area for outcomes prediction based on clinical variables alone and clinical + bradycardia or desaturation metrics in the first week, fourth week, and first four weeks after birth. ROC areas are shown for each B and D metric added to all clinical variables for which the p value of the coefficient in the regression model was significant. Note that Respiratory Acuity Scores are calculated from level of support and FiO_2 on Day 7 and on Day 28. Model chi square and p values are shown in Supplemental Table 3.

	BPD			**Severe IVH**			**Treated ROP**			**Discharge > 40 Weeks PMA**		
GA	0.830			0.733			0.877			0.729		
BW	0.829			0.671			0.860			0.763		
Days of Age	**1–7**	**22–28**	**1–28**	**1–7**	**22–28**	**1–28**	**1–7**	**22–28**	**1–28**	**1–7**	**22–28**	**1–28**
Ventilated Days	0.792	0.787	0.874	0.737	0.683	0.772	0.768	0.814	0.867	0.725	0.776	0.835
RAS Day 7	0.792	na	0.869	0.786	na	0.767	0.870	na	0.850	0.796	na	0.798
RAS Day 28	na	0.897	0.894	na	0.739	0.718	na	0.853	0.868	na	0.832	0.833
All Clinical (all of the above)	**0.874**	**0.894**	**0.902**	**0.793**	**0.758**	**0.776**	**0.910**	**0.888**	**0.901**	**0.797**	**0.826**	**0.843**
B and D metrics added to all clinical												
D number	0.880	0.900	0.908	0.803	0.785	ns	ns	0.899	0.910	0.805	ns	ns
D area	ns	0.901	0.908	ns	ns	ns	ns	0.903	0.911	0.804	ns	ns
D % time	ns	0.905	0.911	0.811	ns	ns	ns	0.902	0.911	0.807	ns	ns
D mean duration	ns	0.905	0.908	0.805	ns	ns	ns	ns	ns	ns	ns	ns
B number	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
B area	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
B % time	ns	ns	ns	ns	ns	ns	ns	ns	ns	0.811	ns	ns
B mean duration	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
BD number	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

BPD Bronchopulmonary Dysplasia, IVH Intraventricular Hemorrhage, ROP Retinopathy of Prematurity, PMA Postmenstrual Age, GA Gestational Age, BW Birth Weight

RAS Respiratory Acuity Score, D Desaturation, B Bradycardia, BD Bradycardia-Desaturation, na not applicable, ns not significant