7-2016

Clinical Associations of Immature Breathing in Preterm Infants. Part 1: Central Apnea

Karen Fairchild

Mary Mohr
William & Mary

Alix Paget-Brown

et al.

John B. Delos
William & Mary, jbdelos@wm.edu

Recommended Citation

Fairchild, Karen; Mohr, Mary; Paget-Brown, Alix; al., et; and Delos, John B., Clinical Associations of Immature Breathing in Preterm Infants. Part 1: Central Apnea (2016). https://doi.org/10.1038/pr.2016.43

HHS Public Access

Author manuscript

Pediatr Res. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

Pediatr Res. 2016 July ; 80(1): 21–27. doi:10.1038/pr.2016.43.

Clinical Associations of Immature Breathing in Preterm Infants. Part 1: Central Apnea

Karen Fairchild[1], **Mary Mohr**[3], **Alix Paget-Brown**[1], **Christa Tabacaru**[1], **Douglas Lake**[2], **John Delos**[3], **J. Randall Moorman**[2], and **John Kattwinkel**[1]

[1]Department of Pediatrics, The University of Virginia School of Medicine, Charlottesville, VA 22908

[2]Department of Medicine, The University of Virginia School of Medicine, Charlottesville, VA 22908

[3]Department of Physics, The College of William and Mary, Williamsburg, VA 23187

Abstract

Background—Apnea of prematurity (AOP) is nearly universal among very preterm infants, but neither the apnea burden nor its clinical associations have been systematically studied in a large consecutive cohort.

Methods—We analyzed continuous bedside monitor chest impedance and electrocardiographic waveforms and oxygen saturation data collected on all NICU patients <35 weeks gestation from 2009–2014 (n=1211; >50 infant-years of data). “ABDs”, defined as central apnea ≥10 sec associated with both bradycardia <100 bpm and oxygen desaturation <80%, were identified using a validated automated algorithm.

Results—Number and duration of apnea events decreased with increasing gestational age (GA) and post-menstrual age (PMA). ABDs were more frequent in infants <31 wks GA at birth but were not more frequent in those with severe ROP, BPD or severe IVH after accounting for GA. In the day before diagnosis of late-onset septicemia and necrotizing enterocolitis, ABD events were increased in some infants. Many infants continued to experience short ABD events in the week prior to discharge home.

Conclusions—Frequency of apnea events is a function of GA and PMA in infants born preterm, and increased apnea is associated with acute but not with chronic pathologic conditions.

Introduction

Apnea of prematurity (AOP) reflects immaturity of brainstem and peripheral chemoreceptors and occurs in essentially all infants born at <28 weeks’ gestation and many of those born between 28–34 weeks.(1–4) AOP is commonly defined as cessation of breathing for >20 seconds, or >10 seconds with associated bradycardia or oxygen

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

desaturation.(5) In our research we use the abbreviation ABD*n* for episodes of central apnea of at least *n* seconds duration, when accompanied by *both* bradycardia and desaturation.(9) Hypoxia associated with apnea could have detrimental effects on developing tissues and organs resulting in long-term or permanent impairment (6–10), and therapies such as respiratory support and caffeine are only partially successful in reducing the burden of AOP. (11,12)Management of refractory apnea, optimum levels and durations of various therapies, and determining readiness for discharge from the Neonatal Intensive Care Unit (NICU) continue to be major challenges, and accurate quantitation of apnea is required for both clinical care and outcomes research. (13)

Quantitation of apnea in NICU patients has historically involved one of two approaches: medical record documentation of events by bedside caregivers, or short pneumographic recordings of respiratory impedance or inductance signals, heart rate, and oxygen saturation. These approaches are limited, the former by inaccuracy of reporting(14–16) and the latter by requirements for extra attachments to infants and time and expertise required for signal interpretation. As a result, previous studies of AOP are limited by small numbers of infants studied over short periods of time. Our group recently developed a novel automated computer algorithm for quantifying central apnea of prematurity from waveform and vital sign data continuously collected from standard NICU bedside monitors.(17) This system was clinically validated and allows identification of central AOP events in large numbers of infants for the entire NICU stay.

Clinical variables affecting the severity of AOP and the timing of resolution as infants approach term-corrected age are not well defined. Prior studies have shown an inverse correlation between gestational age at birth and postmenstrual age at which apnea resolves. (18–20) Chronic or acute pathologic processes may also impact the occurrence, severity, and duration of AOP. For example, severe intraventricular hemorrhage (IVH) may be associated with central nervous system dysfunction that could manifest as central apnea(9,21,22), and bronchopulmonary dysplasia, with associated abnormal blood oxygen and carbon dioxide levels, may be associated with dysregulation of peripheral or central chemoreceptor sensitivity and increased apnea. Acute systemic inflammatory processes such as sepsis are known to lead to an abrupt increase in apnea over baseline in some infants.(23,24) It is also possible that hypoxemia association with AOP may contribute to pathology such as retinopathy of prematurity(7,10) or might contribute to neurodevelopmental impairment(6,10,25).

The goals of the current study were two-fold: to provide a comprehensive assessment of the burden of central apnea throughout the NICU stay of a large number of preterm infants, and to establish the association of AOP with chronic and acute pathologic processes.

Results

Demographics, clinical outcomes, and respiratory support

Of 1372 infants <35 weeks' gestation admitted to the UVa NICU during the study period, chest impedance waveform and vital sign data were available for analysis for 1268. Figure 1 shows the type of respiratory support for each infant relative to GA and PMA. Fifty-seven of

these infants were excluded from the ABD analysis because they had no chest impedance data off mechanical ventilation and prior to 40 weeks' PMA, either due to death or transfer from our unit. Demographics and clinical outcomes of the 1211 infants with ABDs analyzed are shown in Table 1. Median gestational age for the entire cohort was 32 weeks (25^{th}–75^{th}% 28–33 weeks). Birthweight distribution was 235 (19%) extremely low birth weight (<1000 grams) and 521 (43%) very low birth weight (<1500 grams).

Number of ABDs is inversely correlated with GA and PMA

ABD events were assessed when chest impedance, heart rate, and SpO_2 data were available and infants were not on mechanical ventilation including nasal intermittent positive pressure ventilation (NIPPV). Median number of days analyzed per infant was 15 (25^{th}–75^{th} percentile 7–34 days, > 50 infant-years of data).

Figure 2 shows an example of an algorithm-detected ABD10 event, with the major features described in the caption (2A), and a histogram showing the number of infants in each GA week with at least one ABD10 event during the NICU stay (2B). Percentage of infants with at least one algorithm-detected ABD based on GA group is as follows: 97% of infants <27 weeks, 92% of infants 27–30 weeks, 73% of infants 31–32 and 52% of infants 33–34 weeks.

Note that some infants with no detected ABDs may have been on prolonged mechanical ventilation or may have been transferred to our center at later PMAs for procedures.

Figure 3 includes two heat maps of the average daily number of ABD events for all 1211 infants based on GA and PMA, with ABD10 and ABD20 shown (3A, 3B). Note that ABD20 events (apnea at least 20 seconds with associated bradycardia <100 and desaturation <80% of any duration) are a subset of the ABD10 events. In these heat maps, warmer colors denote more apnea events each day, and are most evident in the lower left hand corners – lower GA and PMA. ABD10s persist to later PMAs compared to ABD20s – for example, the average number of ABD10s at 34 weeks PMA is 3 or more, while there is on average <1 ABD20 at 34 weeks PMA. The inset of Figure 3A shows that the number of ABD10s at 32–36 weeks PMA is about 3-fold greater for infants <31 weeks GA compared to those 31–34 weeks. Among the infants <31 weeks GA, however, there is no significant impact of GA on the number of ABD10 at these later PMAs.

Lack of association of number of ABDs with severe ROP, BPD, and severe IVH (Supplemental Figure S1, online)

Since ROP has been linked to aberrant oxygenation(7,26,27), and since apnea is a major cause of hypoxia(28,29) and rebound hyperoxia(30), we tested the hypothesis that the number of ABD events would be greater in infants who developed severe ROP requiring laser or bevacizumab therapy. After accounting for GA, we did not find a statistically significant difference in the mean number of ABD10s throughout the NICU stay in 47 infants with treated ROP compared to those without (Fig. S1A online). We also analyzed ABDs in infants with and without severe IVH (grade III-IV) and in those with BPD, since both of these conditions might be thought to lead to increased frequency of apnea. Considering all ABD10 events throughout the NICU stay, after accounting for GA there was no significant difference in number of apnea events in the 243 infants with BPD or the 51

infants with severe IVH (Fig S1B and S1C online) compared to infants without these morbidities. We further investigated whether, at later PMA when infants are maturing and nearing NICU discharge, infants with BPD or severe IVH have more central apnea spells with bradycardia and desaturation than those without. At 35 weeks' PMA, we found that GA is significantly associated with BPD and severe IVH (ROC AUCs 0.927 and 0.817, respectively, $p<0.0001$), but that after accounting for GA infants with BPD did not have more ABD10s at 35 weeks PMA compared to babies without BPD, (ROC AUC 0.927, change in AUC 0, $p=0.63$). For babies with severe IVH there was a trend toward more ABDs at 35 weeks PMA that was not statistically significant (ROC AUC 0.832, change in AUC 0.015, $p=0.085$).

Apnea increases before diagnosis of late-onset septicemia and NEC (Supplemental Figure S2 online)

Acute systemic inflammatory processes can be associated with apnea in preterm infants(23), and we therefore analyzed ABDs in these illnesses. We identified 28 cases of LOS and 21 cases of NEC in infants when they were not on mechanical ventilation and had chest impedance and vital sign data available for analysis >50% of the time in the 48 hour period prior to diagnosis. In seven cases of NEC (33%) and 12 cases of LOS (43%) infants had at least 2-fold increased ABD events in the 24h period prior compared to 24–48h prior to diagnosis. We also analyzed number of seconds of apnea associated with bradycardia and desaturation in the 24h period before diagnosis compared to 24–48h prior, and found similar results as shown in Figure S2 online.

ABD events in the week prior to discharge home from the NICU

We sought to determine whether infants continued to experience mild, self-resolved or not clinically recognized ABD events in the week prior to NICU discharge. Of the 1211 infants included in this analysis, 1048 were discharged home (the others either died or were transferred to another unit). Decisions about readiness for discharge were made by the clinical care team without knowledge of algorithm-detected ABDs. Caffeine was usually discontinued between 32–34 weeks' PMA, when the infant was off CPAP and no longer having significant clinically detected apnea events requiring stimulation. In our unit during the period of this study, there was a general policy of an 8-day "apnea countdown" with no events requiring intervention before discharge home.(18) Minor apnea events that are self-resolved or that occur during feeding generally do not delay discharge, and events that occur following immunizations or general anesthesia near the time of NICU discharge do not restart the apnea countdown. Cardiorespiratory monitors are routinely prescribed for infants going home on supplemental oxygen and are occasionally prescribed for other infants with clinical conditions or events at the discretion of the medical team.

PMA for the 1048 infants discharged home was 36.6 +/− 2.7 weeks. In the seven days prior to discharge, no ABD10s were detected by the automated algorithm in 508 infants (48%), whereas 146 infants (14%) had 10 or more events (Table 2). GA was significantly lower in infants with ABDs in the week before discharge, but PMA at discharge was similar for infants with and without discharge week ABDs. A home apnea monitor or pulse oximeter or both were prescribed at discharge for 168 infants (16%), including all infants discharged on

supplemental oxygen and 58 infants discharged on room air. Fourteen infants not on supplemental oxygen and with no ABDs detected by our algorithm in the week prior to discharge were sent home with a monitor, while 103 babies with more than 10 ABDs detected in the week prior to discharge were sent home without a monitor.

ALTE and SIDS

As shown in Table 2, fifteen infants were readmitted within 8 weeks of NICU discharge for apnea or apparent life-threatening event (ALTE), including 2% of infants with one or more discharge week ABDs and 0.8% of infants with no discharge week ABDs (p=0.17).

Reviewing matched birth/death records from the state of Virginia, we found one SIDS death in the study population. The infant was a 32 week GA twin discharged at 35 weeks PMA who died two weeks after NICU discharge with a forensic autopsy identifying cause of death as SIDS. As we previously reported, during her 3 weeks in the NICU, she had excessive periodic breathing – five-fold more than other 32 week infants – but no clinically recorded apnea and only one computer-detected ABD10 event, which did not occur in the week prior to discharge.(31)

Discussion

We provide a quantitative analysis of central apnea throughout the NICU stay of 1211 preterm infants that confirms some old concepts about AOP and challenges others. We found, as expected, that apnea accompanied by both bradycardia and oxygen desaturation is common in the NICU despite respiratory and pharmacologic treatments administered to nearly all very preterm infants. We confirmed that an acute increase in ABD events may occur in the day prior to diagnosis of an acute illness such as sepsis or NEC. On the other hand, chronic pathologic processes (ROP, BPD, IVH) were not significantly associated with the frequency of central apnea after controlling for gestational age. Finally, we found that longer apneas (ABD20s) resolve earlier than shorter ones, and ABD10 events are not uncommon in the week prior to NICU discharge of healthy preterm infants.

Limitations of the automated apnea detection system

Our apnea detection algorithm requires low or absent variance in the chest impedance signal to detect cessation of breathing efforts, and thus detects only central apnea. Preterm infants also have obstructive apnea, which may or may not be accompanied by some degree of motion of the chest wall and abdomen. The algorithm filters out gross motion artifact before identifying breathing signals in the impedance waveform, but it was not designed to identify obstructive apnea. Prior studies using measures of nasal airflow (thermistors or carbon dioxide detectors) and respiratory inductance plethysmography indicate that the majority of apnea events in preterm infants have both central and obstructive components. Our methodology will miss pure obstructive events but will capture pure central and most mixed central/obstructive events.

We employed a stringent definition of apnea, requiring both bradycardia and oxygen desaturation, in order to measure the most clinically significant events. Many other studies,

and the NICHD Consensus Statement(5), define AOP as cessation of breathing with bradycardia *or* desaturation and give slightly different thresholds for "BD". Also, the algorithm detects ABD events irrespective of whether they are noticed or are considered clinically important. We previously reported that medical record documentation does not accurately reflect occurrence of ABD events,(32) and speculate that many of the algorithm-detected events are self-resolved or are occurring during or following procedures, handling, or feeding and therefore not necessarily documented by bedside caregivers.

Finally, we are reporting only on the number of ABD events, thus we do not make any statements about depth or duration of bradycardia or oxygen desaturation.

Apnea prior to diagnosis of acute illness

An acute increase in apnea is generally thought to reflect acute stress or illness in preterm infants, and our study provides quantitative evidence of this. Apnea during septicemia or necrotizing enterocolitis is likely attributable at least in part to release of prostaglandins during a systemic inflammatory response (33–35). Many infants did not experience an increase in apnea during sepsis or NEC and we do not have enough cases to determine whether apnea is more likely to occur with specific organisms or reflects a higher severity of illness. Future work will focus on whether real-time analysis and display of abnormal respiratory or other vital sign patterns could provide early warning of potentially catastrophic illnesses, leading to earlier treatment and improved outcomes.

Lack of association of apnea frequency and chronic morbidities

After accounting for gestational age, we did not find a greater number of ABD events among infants with severe ROP. Large randomized clinical trials have demonstrated that targeting lower SpO_2 results in lower rates of ROP (27) but a smaller retrospective study suggested that intermittent hypoxia events are linked to more severe ROP.(7) It is likely that retinal vascular pathology is related to both hyperoxia and hypoxia and to the phase of development at which aberrant SpO_2 occurs. We did not analyze the timing, depth or duration of hypoxia during apneic events, nor did we assess hypoxia occurring without central apnea(36). Most of our infants with severe ROP were ≤25 weeks GA and were on prolonged mechanical ventilation, which precludes apnea but does not preclude dysoxia that might contribute to ROP.

The finding that infants with BPD did not have more central apnea was surprising, since chemoreceptor dysregulation might be expected in these infants(3). It is possible that infants with significant lung disease are on mechanical ventilation or other respiratory support and caffeine for prolonged periods of time when they are most susceptible, and thus apnea is masked. Infants with BPD may also be more prone to obstructive apnea(28,37,38) which we did not measure. Other studies reviewing apnea or bradycardia events documented in the medical record have reported more events in very preterm infants with BPD.(19,20)

We did not find a significant difference in number of ABDs in infants with severe IVH though there was a trend toward slightly more ABDs at later PMA. The number of infants with high-grade IVH in our cohort was small, and we did not separately analyze the even

smaller fraction of infants with post-hemorrhagic hydrocephalus who might have more apnea. Additionally, our methods did not allow us to assess whether infants with IVH had more obstructive apnea as has been reported by others.(21) Larger studies would be required to determine whether, as has been reported in a small study, pre-discharge apnea predicts adverse neurodevelopment at several years of age in preterm infants with severe IVH.(8)

Resolution of apnea

We found, consistent with other reports, (18–20,23) that infants born at gestations <31 weeks had apnea to later PMA than those born less preterm. This reaffirms that a specific PMA (e.g. 36 weeks) cannot be used as a "safe" benchmark for low apnea risk without also considering GA. In the spectrum from 23–31 weeks' GA, however, our data show that the number of ABD events by the time infants reached 35 weeks PMA was no longer a function of GA at birth. This is in contrast to findings of other studies(19,20) that relied on medical record documentation of events and therefore probably captured more events that required intervention and were considered clinically important. These studies also included bradycardia *or* apnea episodes and thus likely included obstructive apnea and vagal bradycardia which we did not measure.

Many infants in our cohort who were otherwise ready for discharge home continued to have short algorithm-detected ABDs. These events may have been self-resolved or occurred during feeding or stressors such as immunization, (39) Most infants were sent home without a monitor and very few were readmitted to our hospital within 2 months for apnea or ALTE, which is in keeping with other reports.(40) Our unit protocol of discharging infants after a week free of needing stimulation to resolve an apneic spell has not changed based on our studies to date, and further work in larger patient populations is needed to establish criteria for safe NICU discharge, since the cost of additional hospital days simply for an "apnea countdown" is substantial.(41)

Conclusion

Apnea events with associated bradycardia and oxygen desaturation occur frequently in hospitalized preterm neonates in spite of respiratory support and caffeine. Further research is needed to determine the long-term impact of these events and identify therapies to minimize apnea burden in the NICU.

Methods

Study Population and Data Collection

We stored and analyzed the bedside monitor waveforms and vital signs of all infants <35 weeks' gestation in the University of Virginia NICU from January 2009 through March 2014. The study was approved by the UVA Institutional Review Board as requiring no consent, since all data were analyzed retrospectively and could not influence patient care.

Demographic and clinical data, including dates on and off mechanical ventilation and other respiratory support, were obtained from the electronic medical record. Clinical decisions

were made by the care team without knowledge of computer algorithm-detected apneas. Caffeine was given based on our unit policy of initiating caffeine for all infants <32 weeks GA at birth, and discontinuing caffeine after 32 weeks postmenstrual age once the infant was off continuous positive airway pressure and having little or no clinically recognized apnea requiring stimulation. Decisions about dosing and duration of caffeine and readiness for discharge home were based on standard assessment of bedside monitor data, medical record documentation, and nursing reports of apnea events. Generally in our unit during the years of this study, an 8-day period free of apnea requiring stimulation was required prior to discharge.(18)

Clinical events and conditions were recorded in a relational clinical database. Severe intraventricular hemorrhage (IVH) grade III-IV was identified by serial head ultrasounds. Bronchopulmonary dysplasia (BPD) was defined as requirement for supplemental oxygen in our NICU at 36 weeks postmenstrual age. Infants who were transferred to an outside hospital on oxygen prior to 36 weeks' PMA and for whom the subsequent oxygen status was not known were not included in the BPD analysis. Late-onset septicemia (LOS) was defined as signs of sepsis >3 days from birth, positive blood culture, and antibiotic treatment for at least 5 days. Diagnosis of necrotizing enterocolitis required abdominal signs with abdominal radiograph showing pneumatosis, portal venous air, or pneumoperitoneum, or requirement for surgery. Cases of NEC with associated septicemia were classified as NEC alone. Severe retinopathy of prematurity (ROP) was defined as requiring laser photoablation or intravitreous bevacizumab therapy.

Data Analysis

Development and validation of the apnea detection system used in this study were previously reported(17). Bedside monitor data were collected using a central network server (BedMaster Ex, Excel Medical, Jupiter, FL), including chest impedance waveforms (60 Hz), electrocardiogram waveforms (3 leads at 240 Hz each), and every 2 second oxygen saturation from pulse oximetry signals (using 8 second SpO_2 averaging). A computer algorithm was developed to detect episodes of low variance in the chest impedance waveform signal after eliminating heart beat and motion artifact. Temporally associated declines in heart rate to less than 100 bpm and in oxygen saturation to less than 80% were identified. The algorithm identified ABD*n* events as central apnea of at least *n* seconds with both bradycardia and desaturation of any duration. For example, ABD10 denotes an episode of cessation of chest movement of 10 or more seconds with associated bradycardia <100 bpm of any duration and desaturation <80% of any duration. The algorithm underwent extensive development, testing, and validation(17).

Statistical Analysis

Continuous variables were analyzed by t-test or ANOVA and categorical variables by Fischer exact test. Receiver operator characteristics curves were constructed, and change in ROC area was analyzed to determine the impact of GA, severe IVH, and BPD on number of ABD events at 35 weeks PMA. Number of ABDs in the day prior to septicemia or NEC diagnosis was compared to the prior 1-day baseline for each infant by sign rank test.

Statistical significance was considered as two-tailed $p<0.05$, and analyses were conducted in MATLAB (MathWorks, Natick, MA)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support: NIH HD072071, HD064488

References

1. Katz-Salamon M. Delayed chemoreceptor responses in infants with apnoea. Arch Dis Child. 2004; 89:261–6. [PubMed: 14977706]
2. Darnall RA. The role of CO2 and central chemoreception in the control of breathing in the fetus and the neonate. Respir Physiol Neurobiol. 2010; 173:201–12. [PubMed: 20399912]
3. Gauda EB, McLemore GL, Tolosa J, Marston-Nelson J, Kwak D. Maturation of peripheral arterial chemoreceptors in relation to neonatal apnoea. Semin Neonatol. 2004; 9:181–94. [PubMed: 15050211]
4. Poets, CF. Principles and Practice of Pediatric Sleep Medicine. 2. Elsevier Inc; 2012. Apnea of Prematurity; p. 195-200.
5. Finer NN, Higgins R, Kattwinkel J, Martin RJ. Summary proceedings from the apnea-of-prematurity group. Pediatrics. 2006; 117:S47–51. [PubMed: 16777822]
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; 24:763–8. [PubMed: 15329741]
7. Di Fiore JM, Bloom JN, Orge F, et al. A Higher Incidence of Intermittent Hypoxemic Episodes Is Associated with Severe Retinopathy of Prematurity. J Pediatr. 2010; 157:69–73. [PubMed: 20304417]
8. Cheung PY, Barrington KJ, Finer NN, Robertson CMT. Early childhood neurodevelopment in very low birth weight infants with predischarge apnea. Pediatr Pulmonol. 1999; 27:14–20. [PubMed: 10023786]
9. Pillekamp F, Hermann C, Keller T, Von Gontard A, Kribs A, Roth B. Factors influencing apnea and bradycardia of prematurity - Implications for neurodevelopment. Neonatology. 2007; 91:155–61. [PubMed: 17377399]
10. Poets CF, Roberts RS, Schmidt B, et al. Association Between Intermittent Hypoxemia or Bradycardia and Late Death or Disability in Extremely Preterm Infants. JAMA. 2015; 314:595–603. [PubMed: 26262797]
11. Gizzi C, Montecchia F, Panetta V, et al. Is synchronised NIPPV more effective than NIPPV and NCPAP in treating apnoea of prematurity (AOP)? A randomised cross-over trial. Arch Dis Child Fetal Neonatal Ed. 2015; 100:F17–23. [PubMed: 25318667]
12. Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. N Engl J Med. 2006; 354:2112–21. [PubMed: 16707748]
13. Butler TJ, Firestone KS, Grow JL, Kantak AD. Standardizing documentation and the clinical approach to apnea of prematurity reduces length of stay, improves staff satisfaction, and decreases hospital cost. Jt Comm J Qual Patient Saf. 2014; 40:263–9. [PubMed: 25016674]
14. Vergales B, Paget-Brown A. Accurate Automated Apnea Analysis in Preterm Infants. Am J Perinatol. 2014; 31:157–62. [PubMed: 23592319]
15. Amin SB, Burnell E. Monitoring apnea of prematurity: validity of nursing documentation and bedside cardiorespiratory monitor. Am J Perinatol. 2013; 30:643–8. [PubMed: 23254381]

16. Brockmann PE, Wiechers C, Pantalitschka T, Diebold J, Vagedes J, Poets CF. Under-recognition of alarms in a neonatal intensive care unit. Arch Dis Child Fetal Neonatal Ed. 2013; 98:F524–7. [PubMed: 23716498]
17. Lee H, Rusin CG, Lake DE, et al. A new algorithm for detecting central apnea in neonates. Physiol Meas. 2011; 33:1–17. [PubMed: 22156193]
18. Darnall RA, Kattwinkel J, Nattie C, Robinson M. Margin of safety for discharge after apnea in preterm infants. Pediatrics. 1997; 100:795–801. [PubMed: 9346978]
19. Eichenwald EC, Aina A, Stark AR. Apnea frequently persists beyond term gestation in infants delivered at 24 to 28 weeks. Pediatrics. 1997; 100:354–9. [PubMed: 9282705]
20. Lorch, Sa; Srinivasan, L.; Escobar, GJ. Epidemiology of apnea and bradycardia resolution in premature infants. Pediatrics. 2011; 128:e366–73. [PubMed: 21746726]
21. Butcher-Puech MC, Henderson-Smart DJ, Holley D, Lacey JL, Edwards DA. Relation between apnoea duration and type and neurological status of preterm infants. Arch Dis Child. 1985; 60:953–8. [PubMed: 3904637]
22. Colavita RD, Ment LR. The electrocardiogram in preterm infants with intraventricular hemorrhage and apnea. J Clin Monit. 1986; 2:1–5. [PubMed: 3711942]
23. Hofstetter AO, Legnevall L, Herlenius E, Katz-Salamon M. Cardiorespiratory development in extremely preterm infants: Vulnerability to infection and persistence of events beyond term-equivalent age. Acta Paediatr Int J Paediatr. 2008; 97:285–92.
24. Balan KV, Kc P, Hoxha Z, Mayer CA, Wilson CG, Martin RJ. Vagal afferents modulate cytokine-mediated respiratory control at the neonatal medulla oblongata. Respir Physiol Neurobiol. 2011; 178:458–64. [PubMed: 21397055]
25. Hunt CE, Corwin MJ, Baird T, et al. Cardiorespiratory events detected by home memory monitoring and one-year neurodevelopmental outcome. J Pediatr. 2004; 145:465–71. [PubMed: 15480368]
26. Martin RJ, Wang K, Köroğlu Ö, Di Fiore J, Kc P. Intermittent Hypoxic Episodes in Preterm Infants: Do They Matter? Neonatology. 2011; 100:303–10. [PubMed: 21986336]
27. 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; 105:55–63. [PubMed: 24247112]
28. 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; 94:100–4. [PubMed: 18277057]
29. Martin RJ, Abu-Shaweesh JM, Baird TM. Pathophysiologic Mechanisms Underlying Apnea of Prematurity. Neoreviews. 2002; 3:59e–65.
30. van Zanten, Ha; Tan, RNGB.; Thio, M., et al. The risk for hyperoxaemia after apnoea, bradycardia and hypoxaemia in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2014
31. Mohr MA, Fairchild KD, Patel M, et al. Quantification of periodic breathing in premature infants. Physiol Meas. 2015; 36:1415–27. [PubMed: 26012526]
32. Vergales B, Paget-Brown AO, Lee H, et al. Accurate Automated Apnea Analysis in Preterm Infants. Am J Perinatol. 2014; 31:157–62. [PubMed: 23592319]
33. Herlenius E. An inflammatory pathway to apnea and autonomic dysregulation. Respir Physiol Neurobiol. 2011; 178:449–57. [PubMed: 21762793]
34. Hofstetter AO, Saha S, Siljehav V, Jakobsson P-J, Herlenius E. The induced prostaglandin E2 pathway is a key regulator of the respiratory response to infection and hypoxia in neonates. Proc Natl Acad Sci U S A. 2007; 104:9894–9. [PubMed: 17535900]
35. Siljehav V, Hofstetter AM, Leifsdottir K, Herlenius E. Prostaglandin E2 Mediates Cardiorespiratory Disturbances during Infection in Neonates. J Pediatr. 2015
36. Poets CF, Stebbens VA, Richard D, Southall DP. Prolonged episodes of hypoxemia in preterm infants undetectable by cardiorespiratory monitors. Pediatrics. 1995; 95:860–3. [PubMed: 7761210]
37. Gerhardt T, Bancalari E. Apnea of prematurity: II. Respiratory reflexes Pediatrics. 1984; 74:63–6. [PubMed: 6739219]

38. Fajardo C, Alvarez J, Wong A, Kwiatkowski K, Rigatto H. The incidence of obstructive apneas in preterm infants with and without bronchopulmonary dysplasia. Early Hum Dev. 1993; 32:197–206. [PubMed: 8486121]

39. DeMeo SD, Raman SR, Hornik CP, Wilson CC, Clark R, Smith PB. Adverse Events After Routine Immunization of Extremely Low-Birth-Weight Infants. JAMA Pediatr. 2015

40. Subhani M, Katz S, DeCristofaro JD. Prediction of postdischarge complications by predischarge event recordings in infants with apnea of prematurity. J Perinatol. 2000; 20:92–5. [PubMed: 10785883]

41. Zupancic JAF, Richardson DK, O'Brien BJ, Eichenwald EC, Weinstein MC. Cost-Effectiveness Analysis of Predischarge Monitoring for Apnea of Prematurity. Pediatrics. 2003; 111:146–52. [PubMed: 12509568]

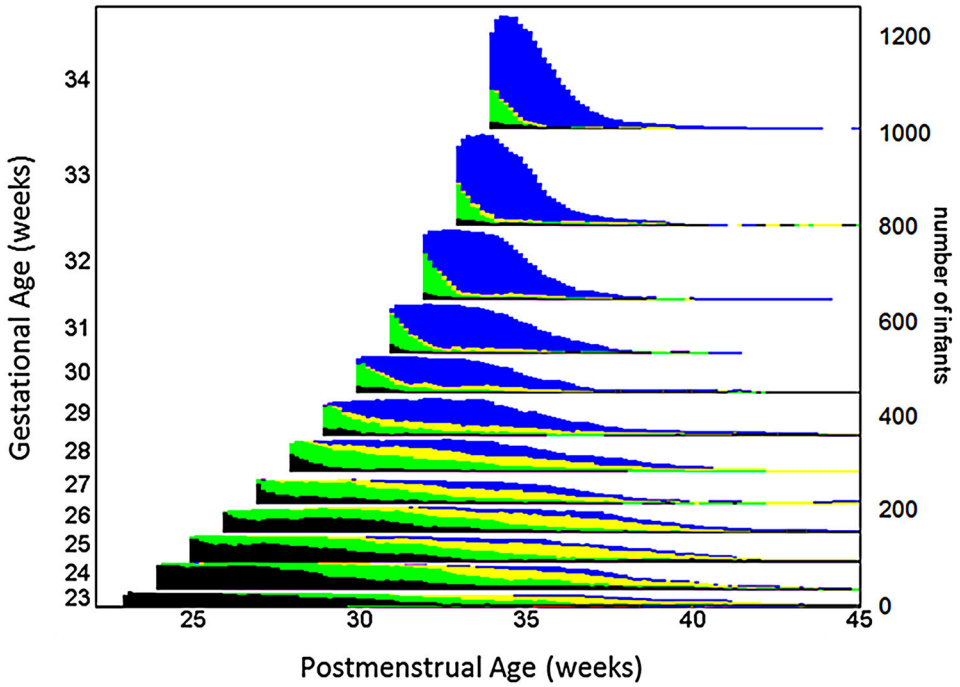

Figure 1. Respiratory support

Type of respiratory support over the course of the NICU stay is shown for all 1268 infants <35 weeks' GA with bedside monitor data available for analysis. Number of infants in each GA week group is shown on the right y axis, and the change in color represents mode of respiratory support with advancing postmenstrual age: ventilator (black), nasal continuous positive airway pressure (CPAP, green), nasal cannula (NC, yellow), and room air (blue).

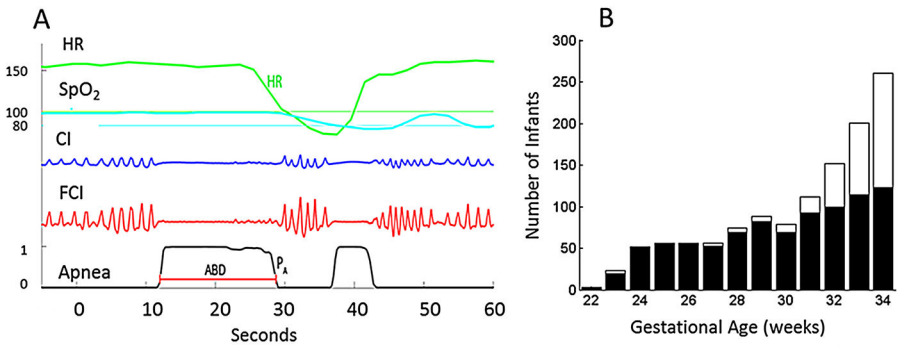

Figure 2. Apnea, bradycardia, desaturation example and incidence

Apnea at least 10 seconds with associated bradycardia <100 beats/minute and oxygen desaturation <80% were analyzed using a published algorithm(17) A) Graphic representation of 60 seconds of vital sign and waveform data showing a representative ABD event. From top to bottom: Heart rate (HR with 100 beats per minute threshold of bradycardia indicated by the thin green line), oxygen saturation (SpO_2 with 80% threshold of desaturation indicated by the thin blue line), chest impedance (CI), filtered chest impedance (FCI), and computer algorithm-detected probability of apnea (P_A). An “ABD10” event is shown, with apnea duration >10 seconds and associated bradycardia and oxygen desaturation. Another shorter breathing pause occurred without associated bradycardia, which did not meet our definition of an “ABD” event. B) ABDs were analyzed on all infants all times that bedside monitor data were available and the infant was not on mechanical ventilation. Number of infants of each gestational age with at least one algorithm-detected ABD10 event (black fill) and with no events detected (white) is shown.

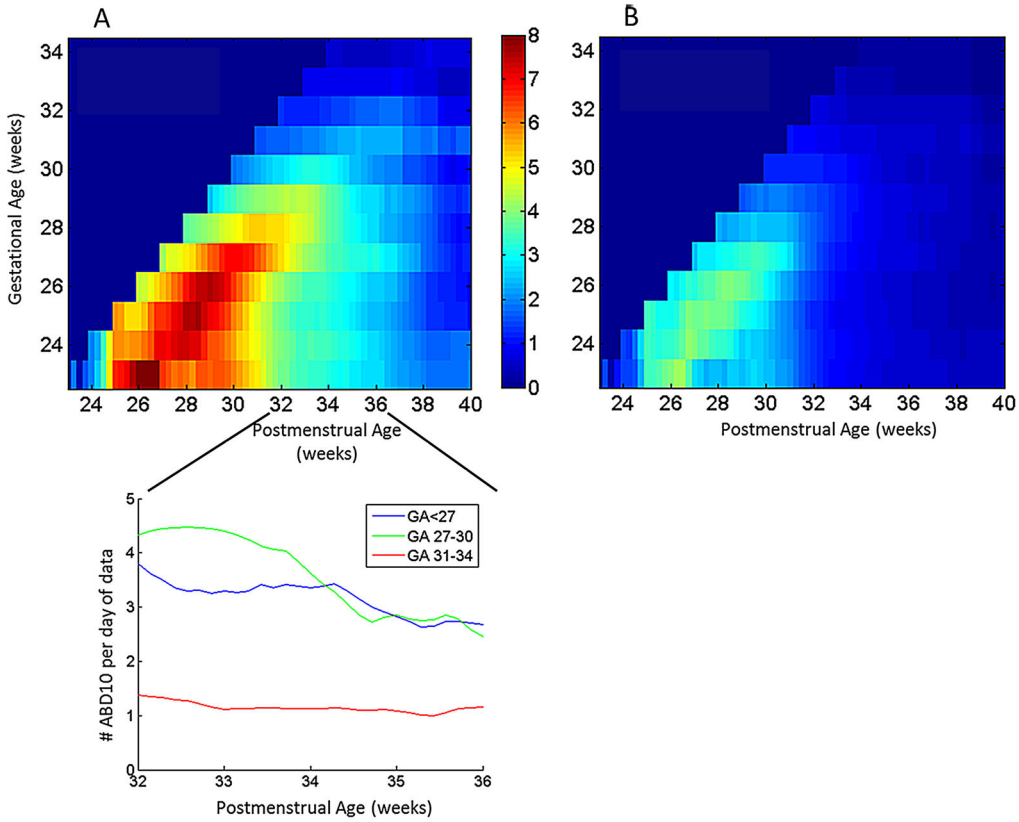

Figure 3. Mean number of ABD events per day based on gestational and postmenstrual age

For 1211 infants <35 weeks' GA, ABDs were analyzed during all times that data were available and infants were not on mechanical ventilation. A) Heat map of mean daily #ABD10s (apnea at least 10 seconds with associated bradycardia and desaturation) for each week of GA and PMA. Color scale goes from blue (zero) to red (eight) events per day. The line graph below showsmean daily #ABD10s for infants <27 weeks GA (blue), 27–30 weeks (green), and 31–34 weeks (red).

B) Mean daily #ABD20s (apnea at least 20 seconds with bradycardia and desaturation) for each week of GA and PMA.

Table 1

Characteristics and outcomes of 1211 infants with ABDs analyzed

	<27 wk (n= 190)	27–30 wk (n=297)	31–34 wks (n=724)
Gestational age weeks	25 (24–26)	29 (28–30)	33 (32–34)
Birth weight grams	750 (640–850)	1200 (1020–1440)	1950 (1670–2270)
Death before NICU discharge	7 (3.7%)	5 (1.7%)	7 (1.0%)
Severe IVH (Grade III–IV)	34 (16%)	10 (3.4%)	3 (0.4%)
Late-onset septicemia	62 (29%)	24 (8.1%)	9 (1.2%)
Necrotizing enterocolitis	16 (7%)	16 (5.4%)	9 (1.2%)
Bronchopulmonary dysplasia *	119/175 (68%)	72/283 (25%)	26/719 (3.6%)
Treated retinopathy of prematurity **	42 (22%)	4 (1.3%)	0
Discharged home	145 (68%)	244 (77%)	650 (88%)
Postmenstrual age at d/c home	39 (37–41)	36 (35–38)	35.5 (35–36)

Data presented as median (25th–75th%ile) or n (%)

* denominator is number for whom outcome at 36 weeks PMA is known

** Laser or bevacizumab

Table 2

ABD10s in the week before discharge home

	No ABDs (n=508)	1–10 ABDs (n=394)	>10 ABDs (n=146)	p = *
Gestational age weeks	33 (31–34)	31 (28–31)	30 (27–31)	<0.001
Discharge PMA weeks	36 (35–37)	36 (35–38)	36 (35–38)	0.45
No monitor ** at discharge	460 (91%)	319 (81%)	103 (71%)	<0.001
Oxygen and monitor at discharge	34 (6.7%)	51 (13%)	24 (16%)	<0.001
Monitor, no oxygen at discharge	14 (2.8%)	24 (6.1%)	19 (13%)	<0.001
Readmitted for apnea or ALTE †	4 (0.8%)	7 (1.8%)	4 (2.7%)	0.71

Median (25^{th}–75^{th}%) or n (%)

* ≥1 ABD versus no ABD

** Apnea monitor or pulse oximeter

† Admitted to UVa Hospital within 8 weeks of UVa NICU discharge