Pediatric RESEARCH

CLINICAL RESEARCH ARTICLE

Recovery from bradycardia and desaturation events at 32 weeks corrected age and NICU length of stay: an indicator of physiologic resilience?

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BACKGROUND: Preterm very low birth weight (VLBW) infants experience physiologic maturation and transitions off therapies from 32 to 35 weeks postmenstrual age (PMA), which may impact episodic bradycardia and oxygen desaturation. We sought to characterize bradycardias and desaturations from 32 to 35 weeks PMA and test whether events at 32 weeks PMA are associated with NICU length of stay.

METHODS: For 265 VLBW infants from 32 to 35 weeks PMA, we quantified the number and duration of bradycardias (HR <100 for ≥4 s) and desaturations (SpO_2 <80% for ≥10 s) and compared events around discontinuation of CPAP, caffeine, and supplemental oxygen. We modeled associations between clinical variables, bradycardias and desaturations at 32 weeks PMA, and discharge PMA.

RESULTS: Desaturations decreased from 60 to 41 per day at 32 and 35 weeks, respectively ($p < 0.01$). Duration of desaturations and number and duration of bradycardias decreased to a smaller extent ($p < 0.05$), and there was a non-significant trend toward increased desaturations after stopping CPAP and caffeine. Controlling for clinical variables, longer duration of bradycardias and desaturations at 32 weeks PMA was associated with later discharge PMA.

CONCLUSION: Delayed recovery from bradycardias and desaturations at 32 weeks PMA, perhaps reflecting less physiologic resilience, is associated with prolonged NICU stay for VLBW infants.

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INTRODUCTION

Episodes of bradycardia and oxygen desaturation, sometimes associated with apnea, are common among preterm very low birth weight (VLBW) infants in the Neonatal Intensive Care Unit (NICU).[1–3] Clinicians administer respiratory support and caffeine to infants early in the NICU course to reduce the frequency and severity of these events, and as infants' lung disease and control of breathing improve, therapies are weaned and discontinued.[4] In some infants, clinically significant bradycardias and desaturations persist as they approach term corrected age and are otherwise ready for discharge home,[5] and a more complete understanding of these events might lead to strategies to reduce NICU length of stay (LOS).

Bradycardias and desaturations attract clinical attention when they trigger bedside monitor alarms, and event quantitation typically relies on nursing documentation that underrepresents their frequency and severity.[6,7] Intermittent hypoxemia is associated with adverse outcomes,[8,9] and a more reliable method for quantitation of events is required to accurately describe their natural history and clinical associations as well as the impact of adding or withdrawing therapies. Our group previously developed an automated algorithm that analyzes NICU bedside monitor waveforms and vital signs for central apnea and periodic breathing.[1,10,11] More recently, we reported on bradycardia and desaturation events in the first 4 weeks following birth, irrespective of apnea, and their association with chronic respiratory morbidity and other adverse outcomes.[2] The natural extension of this work was to study these events closer to the end of the NICU stay.

Between 32 and 35 weeks postmenstrual age (PMA), most preterm VLBW infants experience physiologic maturation, which would be expected to reduce the frequency and severity of apnea spells. However, during this same period, many infants transition off continuous positive airway pressure (CPAP), caffeine, and supplemental oxygen, which might at least transiently increase obstructive or central apnea with associated decline in heart rate (HR) or oxygen saturation. We sought to quantitate the number and duration of bradycardia and desaturation events from 32 to 35 weeks PMA, including around the time of transition off therapies, and to test the hypothesis that more or longer events at 32 weeks PMA are associated with discharge at later PMA.

METHODS

Cohort

The study population was drawn from all VLBW infants 23–33 weeks' gestation admitted to the University of Virginia NICU between January 2009 and March 2014 who were discharged home and who did not have chromosomal syndromes or congenital anomalies that could impact oxygenation. We excluded infants with <7 days of bedside monitor vital sign data available in the first 4 weeks after birth in order to exclude those

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Table 1. Demographic and clinical variables by birth weight category

	<750 g	750–999 g	1000–1499 g	All <1500 g
Total	60 (23%)	84 (32%)	121 (46%)	265 (100%)
Demographics				
Female	32 (53%)	30 (36%)	68 (56%)	130 (49%)
Gestational age, weeks	24 (23, 25)	26 (25, 28)	29 (28, 31)	27 (25, 29)
Birth weight, g	650 (580, 720)	860 (810, 942)	1230 (1120, 1375)	961 (770, 1200)
Clinical variables				
Apgar 1 min	3 (1, 6)	5 (3, 7)	6 (4, 8)	6 (2, 7)
Apgar 5 min	7 (4, 8)	7 (6, 8)	8 (7, 8)	7 (6, 8)
Septicemia	13 (22%)	21 (25%)	11 (9%)	45 (17%)
Necrotizing enterocolitis	1 (2%)	10 (12%)	4 (3%)	15 (6%)
Respiratory Acuity Score at 32 weeks	1.18 (0.86, 1.68)	0.94 (0.67, 1.3)	0.31 (0, 0.84)	0.84 (0.22, 1.16)
Therapy transition times				
CPAP discontinuation PMA	34 (32, 36)	33 (31, 35)	31 (30, 32)	32 (31, 34)
Caffeine discontinuation PMA	35 (34, 37)	34 (33, 36)	32 (32, 33)	33 (32, 35)
Room air PMA	35 (33, 37)	34 (33, 36)	32 (31, 33)	33 (31, 35)
Discharge home				
Discharge PMA	39 (38, 40)	38 (36, 39)	36 (36, 37)	37 (36, 39)
Discharged ≥40 weeks PMA	22 (37%)	19 (23%)	6 (5%)	47 (18%)
Discharged with oxygen	35 (58%)	34 (40%)	14 (12%)	83 (31%)

Data shown as *n* (%) or median (25th, 75th percentile)
CPAP continuous positive airway pressure, *PMA* postmenstrual age

who were transferred to our unit at later ages for procedures. We also excluded infants with <48 h of cumulative monitor data available in the 32nd and 35th week PMA since those were the principal periods of interest for the analyses.

The University of Virginia NICU is a Level IV facility (Vermont Oxford Network Type C). This study was approved by the University of Virginia Institutional Review Board with waiver of consent. Algorithm analysis of bradycardia and desaturation events was performed after patients were discharged and not available to clinicians for decisions about patient care.

Clinical data collection

Study data included demographic and clinical features that were routinely extracted from the medical record into a relational clinical database (NeoData, Isoprime, Chicago, IL). Clinical variables potentially impacting NICU LOS based both on the literature[12] and on our prior work were recorded, including diagnosis of septicemia (positive blood culture and at least 5 days of antibiotics) and necrotizing enterocolitis (NEC Bell's stage 2–3) and days on ventilator. Ventilator support at 32 weeks PMA was incorporated into a Respiratory Acuity Score (RAS), which we previously published as being associated with bronchopulmonary dysplasia and other outcomes.[2] Briefly, mode of support at 32 0/7 weeks PMA is assigned a value, which is multiplied by the mean FiO_2 that day to arrive at the RAS. We also recorded, for each infant, the PMA at which CPAP, caffeine, and supplemental oxygen were discontinued. In the years of the study, CPAP was generally continued until a VLBW infant was >32 weeks PMA and on <40% supplemental oxygen. Caffeine was administered to all infants <32 weeks gestation at birth and discontinued when an infant was >32 weeks PMA, off CPAP, and not having significant apneic spells. Target SpO_2 range for VLBW infants on supplemental FiO_2 was 88–95%.

Bedside monitor data collection

HR from electrocardiogram and SpO_2 from pulse oximetry were collected from continuous bedside monitoring devices using BedMaster (Excel Medical, Jupiter, FL). HR and SpO_2 readings were sampled every 2 s (0.5 Hz). SpO_2 is monitored with Masimo technology, with an averaging time of 8 s.

Using the monitor data available for each infant between PMA 32 and 35 weeks (and excluding incontrovertible artifact of HR and SpO_2 values of zero), we employed an automated algorithm to identify bradycardia and desaturation events, as we have previously published.[2] Bradycardia was defined as HR <100 for ≥4 s and desaturation as SpO_2 <80% for ≥10 s. Events were joined if the value rose above then fell back below the threshold in <4 s for bradycardia and <10 s for desaturation events. We quantified the number and duration of events, normalized to amount of available data. For the figures and for modeling, median number and duration of events at 32 weeks PMA represents all days with data available from 32 0/7 to 32 6/7 and at 35 weeks PMA represents all days from 35 0/7 to 35 6/7.

Statistical analyses

Data are presented as median and interquartile range (IQR) unless otherwise noted. Number and duration of events across PMAs and after discontinuing therapies were compared with Wilcoxon rank-sum tests. Impact of event number and duration at 32 weeks PMA on discharge PMA was first analyzed with univariate linear regression modeling. We then performed multiple regression analysis to control for demographic and clinical variables shown in univariate analysis to impact NICU LOS. For both the univariate and adjusted methods, we tested the significance of event predictors using *T* tests of coefficients, and the variability explained by each model with adjusted R^2. Analyses were performed in R version 3.4.1 with statistical significance considered as $p < 0.05$.

RESULTS

Demographics

During the 5-year study period, 628 VLBW infants were admitted to the UVA NICU. Of these, 363 were excluded: 72 died or had

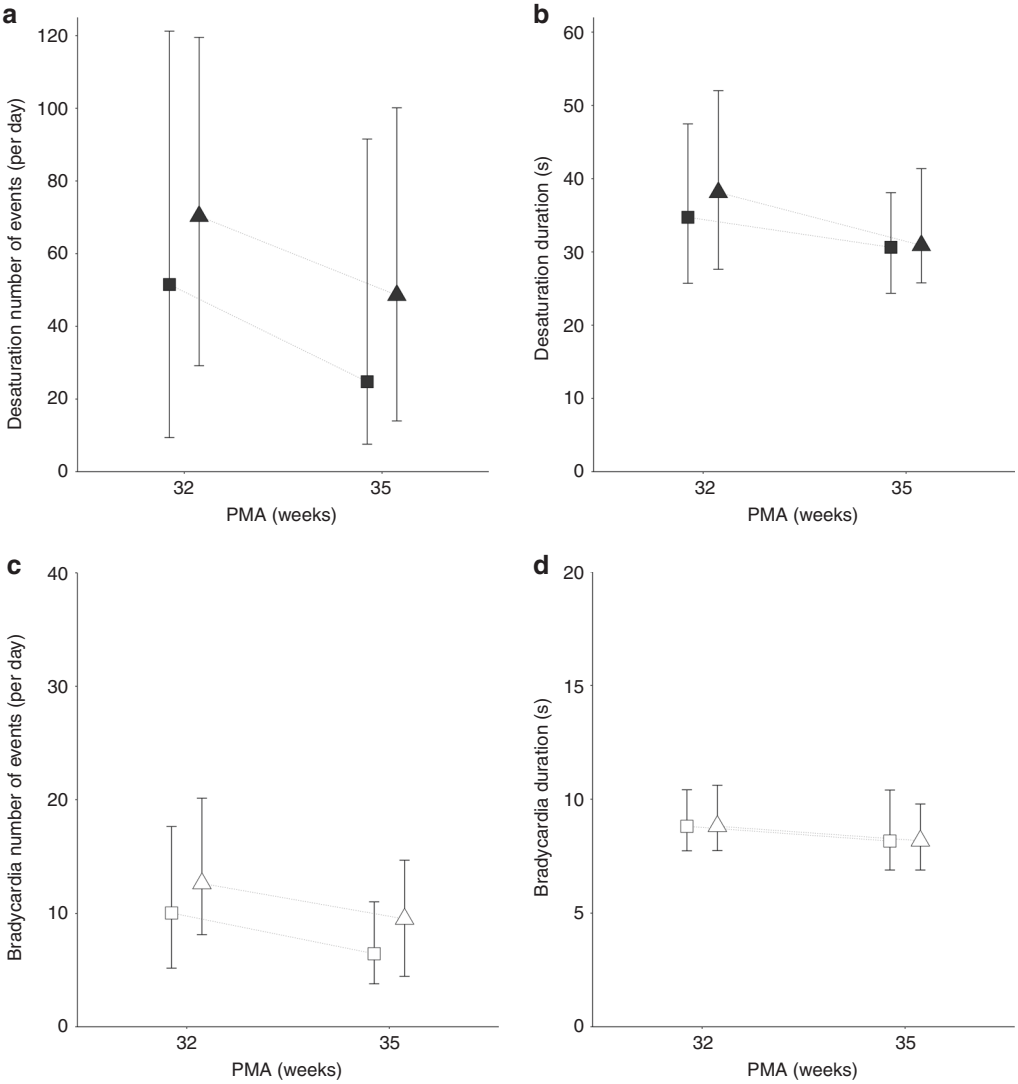

Fig. 1 Number and duration of bradycardia and desaturation events at 32 and 35 weeks postmenstrual age (PMA) by sex. Median daily number and duration of desaturations at 32 weeks PMA (32 0/7 to 32 6/7) and 35 weeks PMA (35 0/7 to 35 6/7) are shown as filled symbols (**a**, **b**); triangles for males, squares for females. Bradycardia number and duration at 32 and 35 weeks PMA are shown as open symbols (**c**, **d**). Error bars indicate interquartile range

major chromosomal or congenital anomalies that could impact oxygenation, 111 were transferred to an outside hospital or another unit, and 180 had insufficient bedside monitor data available. Reasons for insufficient monitor data included transfer to our unit at a late age or technical issues with the data collection system.

The study cohort included 265 VLBW infants with median gestational age (GA) 27 weeks. Table 1 shows demographic and clinical features for the entire cohort and for three birth weight subgroups. Median PMA at discharge home was 37 weeks and 83 infants (31%) were discharged on supplemental oxygen. Of the 47 infants (18%) discharged at or beyond 40 weeks PMA, 27 had discharge delayed owing to respiratory causes.

Frequency and duration of bradycardia and desaturation events from 32 to 35 weeks PMA

Percentage of time with HR and SpO_2 data available from 32 to 35 weeks PMA for the 265 infants was 87%, yielding >17 infant years of data with 81,947 bradycardia and 454,040 desaturation events analyzed. At the 32-week time point (from 32 0/7 to 32 6/7 weeks), all 265 infants had at least one bradycardia and one desaturation event per day (median), and 97% and 93% of infants had at least 10 bradycardias and desaturations, respectively. Figure 1 shows that desaturations were approximately six-fold more frequent and four-fold longer in duration compared to bradycardias. There was a decrease in the number of desaturations over time, from median 60 events per day at 32 weeks to 41 events per day at 35 weeks (from 35 0/7 to 35 6/7) ($p < 0.05$), with wide variability between infants. The decrease in number of bradycardias from 32 to 35 weeks was statistically significant but small (12 per day at 32 weeks and 8 per day at 35 weeks, $p < 0.05$). Male infants experienced more events than females: median 11 versus 9 bradycardias per day and 72 versus 41 desaturations per day ($p < 0.05$). Duration of events was slightly lower at 35 versus 32 weeks PMA (bradycardia 9 versus 8 s, $p < 0.05$, desaturation 36 versus 31 s, $p < 0.05$).

Impact of discontinuing CPAP, caffeine, and supplemental oxygen on the number of events

Supplemental Fig. S1 shows the relationship between the number and duration of bradycardia and desaturation events at 32 weeks PMA and the PMA at which CPAP, caffeine, and supplemental

oxygen were discontinued. There was an association between more desaturations and longer bradycardias and desaturations at 32 weeks PMA and later discontinuation of these therapies.

For infants who came off CPAP, caffeine, and supplemental oxygen between 32 and 35 weeks PMA ($n = 105$, 170, and 85, respectively), we analyzed the number of bradycardia and desaturation events before and after discontinuation. Figure 2 shows that bradycardia events did not change (median 8–10 events per day before and after). For desaturations, there was a non-significant, transient trend toward increased events in the week after discontinuing CPAP and caffeine but not after stopping supplemental oxygen. Desaturations peaked 9 days after coming off CPAP, with median 68 events per day (IQR 21, 132). This was slightly higher but not significantly different compared to the number of desaturations the day CPAP was discontinued (median 59, IQR 14, 97, $p = 0.34$). The small increase in desaturations 5 days following caffeine discontinuation was also not significantly different compared to the day of discontinuation ($p = 0.32$).

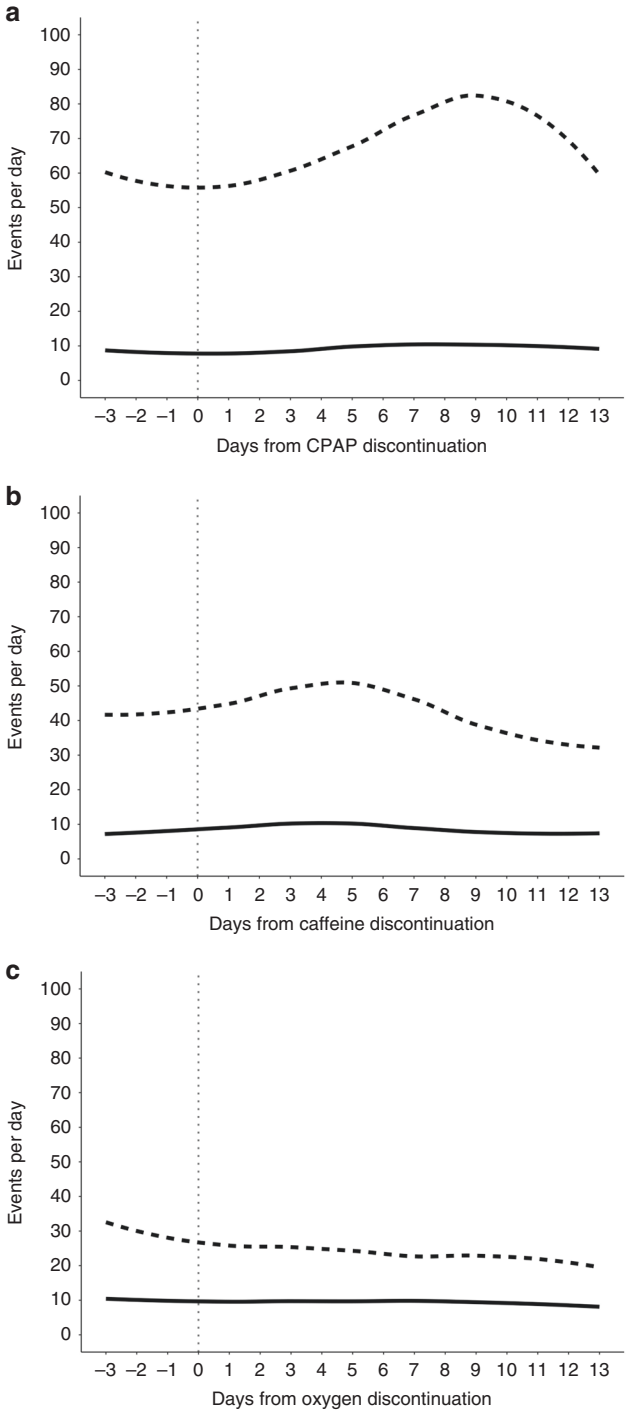

Fig. 2 Trends in bradycardia and desaturation events after continuous positive airway pressure (CPAP), caffeine, and supplemental oxygen discontinuation. Median number of bradycardias (solid lines) and desaturations (dashed lines) are shown from 3 days before until 13 days after discontinuation of CPAP (**a**), caffeine (**b**), and supplemental oxygen (**c**)

Association of bradycardia and desaturation events at 32 weeks PMA with LOS

Using linear regression modeling, we evaluated the association between discharge PMA, clinical variables, and bradycardia and desaturation characteristics at 32 weeks PMA. Table 2 shows results of univariate (top) and multivariate (bottom) analyses, including p values as well as beta coefficient indicating the direction and the R^2 value the strength of the association. In univariate analysis, the number and duration of desaturations and duration of bradycardias were associated with later discharge PMA, but the number of bradycardias was not ($p = 0.684$). Multiple clinical variables were associated with later discharge PMA in univariate analysis, but sex was not ($p = 0.109$). The clinical variable with the strongest association with late NICU discharge was Respiratory Acuity Score at 32 0/7 weeks PMA with R^2 of 0.336, compared to the next strongest variable of GA with R^2 of 0.189. A combined clinical model with GA, birth weight, sex, 1 and 5 min Apgar scores, 32 weeks Respiratory Acuity Score, and diagnosis of severe intraventricular hemorrhage, NEC, and septicemia had R^2 of 0.411. In multivariate analysis adjusting for all clinical variables, duration of bradycardia and desaturation events at 32 weeks PMA (but not number of events) contributed significantly to identifying infants with later discharge PMA ($p < 0.01$, R^2 0.428). This association of longer events at 32 weeks PMA (32 0/7 through 32 6/7) and longer NICU stay held true when analyses were repeated without the 47 infants discharged at ≥40 weeks PMA.

Figure 3 shows the association between average duration of bradycardia and desaturation events at 32 weeks PMA and discharge PMA. For every 1-s increase in mean bradycardia duration, NICU LOS increased by 1.3 days, and for every 1-s increase in mean desaturation duration, NICU LOS increased by 0.5 days.

DISCUSSION

In a large cohort of VLBW infants with continuous cardiorespiratory monitor data available from 32 to 35 weeks PMA, we quantified bradycardia and desaturation events and their impact on NICU LOS. The main finding is that events decreased slightly in both number and duration over this period and, after adjusting for demographic and clinical variables, duration (but not number) of bradycardia and desaturation events at 32 weeks PMA was associated with later PMA at discharge.

As VLBW infants approach term corrected age, occurrence of cardiorespiratory events is impacted by competing variables. On the one hand, the physiologic maturation taking place would be expected to decrease the number and severity of events. On the other hand, respiratory and apnea therapies are being withdrawn, which may lead to increased events. Overall, we found a modest decrease in the number of desaturations and a small decrease in the number of bradycardias from 32 to 35 weeks PMA, suggesting that maturation is occurring allowing infants to "outgrow" these spells. Duration of events decreased to an even smaller extent, suggesting that recovery time is slower to mature. After

Table 2. Univariate and multiple regression modeling showing association of clinical variables and bradycardia and desaturation characteristics at 32 weeks PMA with discharge PMA

	Beta value	*p* Value	R^2
BD characteristics (univariate)			
Number of bradycardias	NS	0.684	NS
Duration of bradycardias	0.187	<0.001	0.045
Number of desaturations	0.011	<0.001	0.09
Duration of desaturations	0.066	<0.001	0.254
Clinical variables (univariate)			
Sex (male)	NS	0.109	NS
Gestational age, weeks	−0.396	<0.001	0.189
Birth weight, g	−0.004	<0.001	0.179
Apgar 1 min	−0.272	<0.001	0.092
Apgar 5 min	−0.323	<0.001	0.073
Septicemia	1.339	<0.001	0.043
Necrotizing enterocolitis	1.949	0.002	0.034
Respiratory acuity score	1.482	<0.001	0.336
All clinical variables	NA	NA	0.411
BD characteristics (adjusted for all clinical)			
Number of bradycardias	NS	0.678	NS
Duration of bradycardias	0.12	0.003	0.428
Number of desaturations	NS	0.813	NS
Duration of desaturations	0.024	0.004	0.428

Beta value sign indicates the direction and R^2 the strength of the association
NS non significant, *PMA* postmenstrual age, *BD* bradycardia desaturation

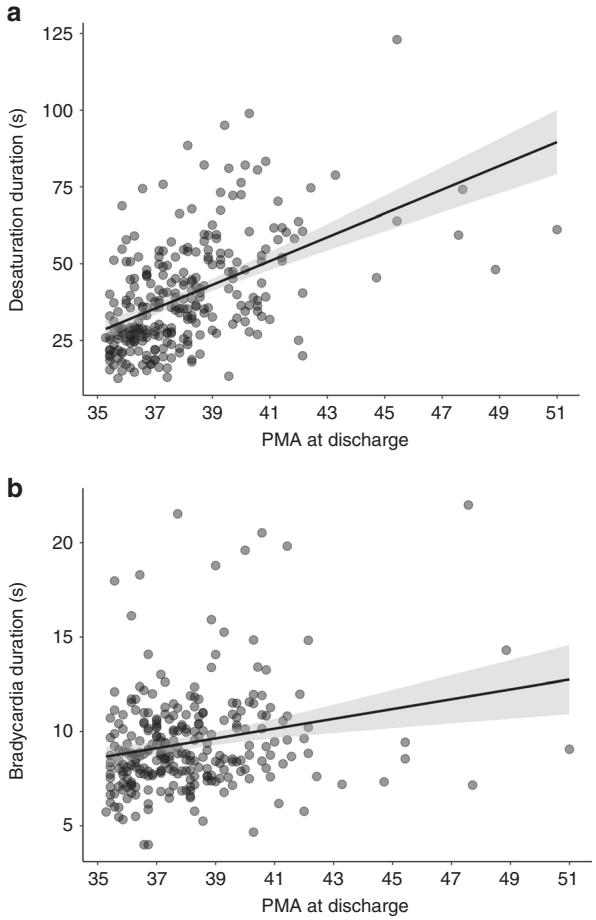

Fig. 3 Association between duration of bradycardia and desaturation events at 32 weeks and discharge postmenstrual age (PMA). Scatter plot, with one point for each of the 265 infants, demonstrating a positive linear relationship between PMA at discharge and average duration of desaturations (**a**) and bradycardias (**b**) at 32 weeks PMA. The solid line indicates the fitted linear model and gray shading indicates the 95% confidence interval around the trend

discontinuation of CPAP, caffeine, and supplemental oxygen, we did not find a significant change in events, in contrast to our prior report of a marginal, transient increase in central apnea with associated bradycardia and desaturation after stopping caffeine.[4] A limitation of the analyses is that we could not account for the many clinical variables that might impact HR deceleration and oxygen desaturation events with or without central or obstructive apnea during this PMA time frame. These include initiation of oral feeding, gastroesophageal reflux, administration of immunizations, performance of ophthalmologic examinations, thermal challenge during incubator weaning, physiologic nadir of anemia of prematurity,[13] and other clinical stressors. It is notable that some infants continued to experience a large number of events of SpO_2 <80% lasting at least 10 s even at 35 weeks PMA, highlighting the ongoing challenge of maintaining target oxygen saturations in preterm infants as they approach term corrected age.

Resilience, a term we use to refer to the ability to recover more quickly from cardiorespiratory events either spontaneously or with clinician intervention, may indicate a more stable physiologic state with advancing age. It is not surprising then that shorter duration of events at 32 weeks is associated with shorter LOS, since many preterm infants spend extra time in the NICU simply due to bradycardias and desaturations, especially when they are deep or prolonged or when they require caregiver intervention rather than self-resolving. Some of these events are due to immature control of breathing but they also may be impacted by chronic lung disease, which often prolongs NICU stay. We found that a high Respiratory Acuity Score at 32 weeks PMA, factoring in not only FiO_2 but also the level of ventilator support, was strongly associated with prolonged NICU stay, and duration of bradycardia and desaturation events increased the association. We speculate that prediction of prolonged NICU LOS through analysis of cardiorespiratory events at 32 weeks might identify a subset of infants who would benefit from longer duration of therapies such as caffeine, and this in turn might allow earlier discharge from the NICU.[14]

Our study is robust in that we analyzed >17 infant-years of HR and SpO_2 data on a large number of VLBW infants, but several limitations deserve consideration. The analyses did not address central apnea, which we have previously studied,[1,6,10] or obstructive apnea, which is difficult to quantify and contributes a great deal to episodes of bradycardia and desaturation. Also, in developing our algorithms we selected a relatively high threshold for bradycardia (<100 beats/min) and a low threshold for desaturation (<80%) compared to other studies.[3,15] Finally, we could not account for all the variables that might influence these events, nor did we carry the analyses through to discharge home. This area is ripe for further investigation since hypoxemia may impact multiple outcomes and since spells of bradycardia and desaturation are often the final factor delaying NICU discharge.

CONCLUSIONS

Longer duration of bradycardia and desaturation events at 32 weeks PMA, perhaps reflecting less physiologic resilience, is associated with prolonged NICU stay. Identification of infants with

long events at this maturational stage might allow advanced planning and interventions to facilitate earlier safe discharge home from the NICU.

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AUTHOR CONTRIBUTIONS

V.P.N. did the analyses and wrote the first draft. R.A.S. assisted with study design and data interpretation and edited the manuscript. D.E.L. and J.R.M. assisted with study design and statistical analysis. K.D.F. contributed to conceptualization, data analysis, and editing the manuscript. All authors approved the manuscript in its final form.

ADDITIONAL INFORMATION

The online version of this article (https://doi.org/10.1038/s41390-019-0488-3) contains supplementary material, which is available to authorized users.

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