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Frequent hypoxemia found in infants with bronchopulmonary dysplasia after weaning home oxygen

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Abstract

Objective: Parental reports and brief clinical examinations are the primary information used to assist clinicians in weaning home supplemental oxygen in infants with bronchopulmonary dysplasia (BPD). Recorded nocturnal oximetry provides an objective assessment of hypoxemia; however, it is unknown if it identifies clinically undetected hypoxemia in the home setting. Our objective was to determine if nocturnal oximetry can identify unreported hypoxemia in infants with BPD who appear ready to wean from supplemental oxygen.

Study Design: We conducted a retrospective chart review of infants born <32 weeks gestation with BPD who were discharged to home receiving supplemental oxygen and completed recorded nocturnal oximetry in room air during an 18-month period. Abnormal oximetry was defined as >5 min with SpO_2 < 90% and/or an oxyhemoglobin desaturation index (ODI4) >5. Comparative analysis of patients with normal and abnormal overnight oximetry was performed using Fisher Exact and Wilcoxon signed-rank test.

Results: Thirty-five former premature infants completed nocturnal oximetry at 5.8 (3.4–8.3) months corrected age. Nocturnal oximetry was abnormal as defined in 67% of the cohort (n = 21). Five percent of patients were hypoxemic, 52% had frequent desaturation events, and 43% had both. No significant differences existed in neonatal characteristics between patients with normal and abnormal studies.

Conclusions: Nocturnal oximetry was abnormal in the majority of infants with BPD who were otherwise clinically ready to wean from oxygen support, suggesting that recorded home oximetry could be a feasible and useful tool to evaluate for otherwise clinically unapparent nocturnal hypoxemia in patients with BPD.

KEYWORDS

bronchopulmonary dysplasia, neonatal pulmonary medicine, oxygenation and therapy

Abbreviations: AHI, Apnea–Hypopnea Index; BPD, bronchopulmonary dysplasia; IQR, interquartile ratio; LPM, liters per minute; NICU, neonatal intensive care unit; ODI, oxyhemoglobin desaturation index; OSA, obstructive sleep apnea; PMA, postmenstrual age; PSG, polysomnography.

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1 | INTRODUCTION

Upon discharge from their initial neonatal intensive care hospitalization, former premature infants with bronchopulmonary dysplasia (BPD) remain at high risk for intermittent hypoxemia. Term infants in the first 3 days of life and preterm infants at term adjusted ages have been found to have increased episodes of oxyhemoglobin desaturation, particularly during nocturnal monitoring.[1] This is thought to be related to brief central apneas as a result of respiratory instability in early infancy that decrease over the first few months of life. Infants with BPD are at higher risk for more significant desaturations during apnea due to decreased pulmonary reserve. There is a myriad of clinical evidence that chronic hypoxemia can have poor clinical outcomes,[2–7] but there is little known regarding how the frequency, severity, or duration of desaturation events influence clinical outcomes of growth, development, or cardiac function in infants with BPD at term and post-term adjusted ages. We are only beginning to appreciate how even subtle alterations in oxygen levels can affect both short- and long-term outcomes.[8] Studies in extremely preterm infants have shown postnatal patterns of intermittent hypoxemia,[9,10] but there remains a paucity of normative data describing desaturation events in preterm neonates as they mature, and there is little known about the trajectory of intermittent and chronic hypoxemia in patients with BPD.

Infants with BPD may reach a phase in their medical treatment when all of their medical issues have stabilized except for their need for continuous oxygen supplementation. To facilitate discharge to home, home oxygen therapy can be prescribed. Approximately one quarter of infants born ≤28 weeks gestational age with a diagnosis of BPD require discharge to home with supplemental oxygen from the neonatal intensive care unit (NICU),[11] and about half of infants born <32 weeks gestational age with BPD at Level IV NICUs are discharged receiving supplemental oxygen.[12] Clinical practices for weaning home oxygen therapy in the outpatient setting vary greatly between centers, and the large majority of surveyed pulmonary providers report utilizing nocturnal oxygen saturations for weaning of oxygen therapy.[13]

One method of home saturation monitoring that offers the provider objective measurements is recorded nocturnal oximetry, which provides continuous, quantitative analysis of nocturnal oxygenation with a short averaging time. Recorded oximetry reports the total and percentage of time a patient spends in saturation ranges, heart rate range and mean, oxyhemoglobin desaturation events and duration, and an oxyhemoglobin desaturation index. Further, recorded nocturnal oximetry has been shown to highly correlate with the apnea/hypopnea index (AHI).[14,15] There is currently a paucity of literature describing recorded nocturnal oximetry at home in infants with BPD who clinically appear ready to wean from supplemental oxygen.[16,17] With the capability to detect subtle desaturation events that may not be readily apparent by clinical observation, we sought to gather more insight to high-risk patterns associated with both short- and long-term morbidity that may have been previously unrecognized. We performed a descriptive review of recorded nocturnal oximetry data collected in infants with BPD who were discharged home with supplemental oxygen to evaluate whether oximetry tests identified otherwise undetected hypoxemia in this population. Recorded nocturnal oximetry data were collected when patients appeared clinically ready to wean from oxygen support in the outpatient setting, based on clinical exam and parental reports.

2 | MATERIALS AND METHODS

We conducted a retrospective chart review of recorded nocturnal oximetry studies performed on infants seen in the NICU follow-up clinic who were born at less than 32 weeks gestational age with a diagnosis of moderate or severe BPD requiring supplemental oxygen at the time of NICU discharge between January 2018 and July 2019. BPD severity was defined utilizing the 2001 NIH consensus definition.[18] Subjects were identified by our Biomedical Informatics Department via Electronic Medical Record billing records. Exclusion criteria included presence of a tracheostomy, any significant congenital anomaly, or a genetic condition that significantly impacted respiratory or neurologic status. The primary outcome of interest was to assess the proportion of infants with detectable nocturnal hypoxemia, which was defined as SpO_2 < 90% for >5 min and/or an oxyhemoglobin desaturation index >5, and compare them to parental report and clinician assessment of readiness to discontinue home supplemental oxygen.

Locally, infants with BPD discharged on home supplemental oxygen were managed by neonatologists and pulmonologists through our Neonatal Follow Up Program. During this time period, a standardized outpatient oxygen weaning guideline was followed (Figure 1). This guideline entailed that infants were assessed monthly for baseline oxyhemoglobin saturations, growth parameters, a parental report of pulse oximeter alarms, and a 15–30-min trial in the office on decreased respiratory support. Oxygen flow was decreased by 50% each month that infants met weaning criteria. Weaning criteria included adequate growth defined as stable or increasing *Z* scores, oxyhemoglobin saturations >95% consistently at home per parental report, and toleration of oxygen wean trial during the visit. Once infants were stable on a 0.125 liters per minute (LPM) flow, a trial of room air was completed in the office. If infants tolerated the room air trial, they were sent home in room air during the day with continued nocturnal oxygen and pulse oximeter monitoring. After 1 month of nocturnal oxygen only, if infants had no hypoxemia per parental report with documented adequate weight gain, they were deemed clinically ready to wean from nocturnal supplemental oxygen. When an infant met these clinical criteria, a home-recorded nocturnal room air oximetry test was completed. If the infant had a normal oximetry study per criteria as previously described, nocturnal oxygen was discontinued. If the study was abnormal per criteria, nocturnal oxygen was continued for an additional 1–2 months, when testing was repeated. If oximetry abnormalities persisted through 12 months corrected age, or there

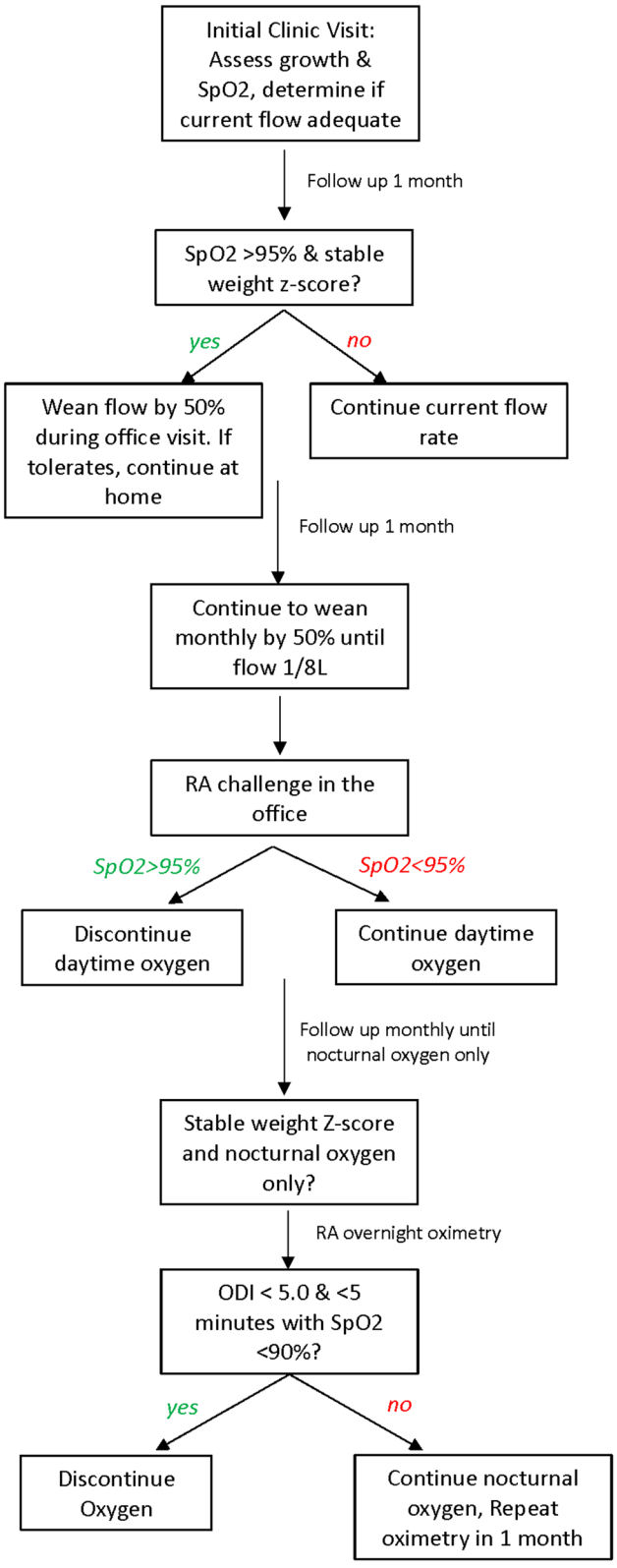

FIGURE 1 Flow diagram depicting oxygen weaning protocol utilized during the study period [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Demographics of infants with home oximetry

Gestational age at birth (weeks), median (IQR)	25.3 (24.4–27.2)
Birthweight (g), median (IQR)	740 (650–876)
Postmenstrual age at discharge (weeks), median (IQR)	41.6 (39.4–44.6)
Male, *n* (%)	17 (48.6)
Small for gestational age, *n* (%)	3 (8.6)
Antenatal steroids, *n* (%)	32 (91.4)
Any infant steroids for BPD, *n* (%)	21 (60)
Severe BPD, *n* (%)	28 (80)
Diagnosis of pulmonary hypertension, *n* (%)	11 (31.4)
Treatment of pulmonary hypertension at NICU discharge, *n* (%)	2 (5.7)
Surgical NEC, *n* (%)	1 (2.9)
Severe ROP, *n* (%)	4 (11.4)
Severe IVH (≥Gr III), *n* (%)	3 (8.6)
Periventricular leukomalacia, *n* (%)	2 (5.7)

Abbreviations: BPD, bronchopulmonary dysplasia; IQR, interquartile ratio; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; ROP, retinopathy of prematurity.

were clinical concerns for obstructive sleep apnea (OSA), the patient was referred to undergo polysomnography (PSG).

Nocturnal home oximetry tests were performed using a Masimo Radical-8 with a 2 s averaging time. A desaturation event was defined as a decrease in SpO_2 by ≥4% lasting ≥10 s. The desaturation event index (ODI4) was defined as the number of events lasting ≥10 s per sampled hour. Recorded oximetry data were reviewed for time spent with SpO_2 < 90%, ODI4, and length and frequency of oxyhemoglobin desaturation events. An automated analysis program, PROFOX pulse oximetry software (2011, Oximetry version Respironics RR2011.00-1001), was used to evaluate oximetry data. In addition, charts were reviewed for NICU course clinical parameters, including gestational age at birth, birth weight, postnatal comorbidities (Table 1), respiratory support at 36 weeks adjusted age, postmenstrual age (PMA) at time of hospital discharge, and oxygen flow rate at hospital discharge. Outpatient documentation was also reviewed for clinical characteristics at the time of the oximetry study completion, including growth data, oxygen flow rate, and corrected age at completion of home oximetry study.

Nocturnal hypoxemia in an oximetry study was defined as >5 min of oxyhemoglobin saturation (SpO_2) <90% as defined by the International Classification of Sleep Disorders,[19] and/or an ODI4 > 5. ODI has been found to be predictive of abnormalities on PSG and correlates with AHI[15]; therefore >5 was chosen as the cutoff value most consistent with a moderate degree of sleep-disordered

breathing based on available literature.[20] For any infant who remained on supplemental oxygen due to initial oximetry test results, follow-up studies were reviewed, but not included in the primary analysis.

Statistical differences between infants with and without hypoxemia were analyzed using Fisher Exact for categorical data and Wilcoxon signed-rank test for continuous data. Statistical significance was defined by a p value less than 0.05.

The institutional review board at Cincinnati Children's Hospital Medical Center approved this study. Informed consent was waived.

3 | RESULTS

During the 1.5-year study period, 37 infants completed overnight oximetry. Two patients met exclusion criteria due to airway surgeries. The 35 infants that met inclusion criteria were 49% male, born at a median (IQR) gestational age at birth of 25.3 (24.4–27.2) weeks, and median (IQR) birth weight of 740 (650–876) grams. Sixty percent of the cohort received treatment with postnatal systemic steroids for BPD, and 26% received multiple courses. Eighty percent of the cohort met the diagnostic criteria for severe BPD, and the remainder met the criteria for moderate BPD. Forty-three percent of the cohort required respiratory support of continuous positive airway pressure or greater at 36 weeks adjusted age, demonstrating the illness severity of this population. The median (IQR) PMA at discharge was 41.9 weeks (39.4–44.6). The majority of patients required 0.25 LPM NC at discharge (60%), but support at discharge ranged from 0.125 to 0.5 LPM. Additional demographic characteristics are demonstrated in Table 1.

Recorded nocturnal oximetry studies were performed at a median (IQR) of 5.8 (3.4–8.3) months corrected age. While an oxygen weaning guideline had been implemented with recommendations for timing of oximetry, oxygen flow varied between 0.125 and 0.5 LPM at the time the overnight oximetry test was ordered due to provider or parental preference to wean support. However, the oximetry study was always performed in room air, and the level of oxygen support immediately before the study was not predictive of hypoxemia. Oximetry was abnormal in 67% of the cohort ($n = 21$). Five percent of patients had $SpO_2 < 90\%$ for >5 min, 52% had an ODI4 > 5, and 43% met criteria for both parameters (Table 2). Thirty-two percent of patients that met the criteria for an abnormal desaturation index had values of 10 or greater. There were no statistically significant differences in NICU clinical course, neonatal morbidities, or corrected age at the time of the study between patients with normal and abnormal overnight oximetry studies (Table 3).

Twelve of 21 patients remained on supplemental oxygen after meeting the criteria for an abnormal recorded nocturnal oximetry study. Ten of 12 patients had repeat oximetry studies, 1 was weaned from supplemental oxygen at the next visit without a follow-up study, and 1 was referred directly to undergo PSG due to clinical symptoms of OSA. Of the 10 repeat studies, 4 normalized and 6 remained abnormal due to an ODI4 > 5 only. Three patients with persistently elevated ODI4 were continued on supplemental oxygen, and three were weaned from supplemental oxygen due to improvement in the ODI4 from the previous study. Two of the patients that remained on supplemental oxygen therapy were ultimately referred for PSG due to persistently abnormal ODI4 in follow-up studies. In the entire cohort, nine patients (26%) were weaned from nocturnal supplemental oxygen despite having abnormal oximetry studies as previously defined. This was related to provider preference based on the child's clinical progress, elevated ODI4 without meeting SpO_2 criteria on oximetry, and/or family nonadherence. One patient required discharge to home back on nocturnal supplemental oxygen after a respiratory-related hospital admission, compared to no patients who were continued on oxygen at the initial abnormal test.

The median (IQR) age patients weaned to room air was 6.9 months corrected age (5.3–9.7 months). A total of three patients in the cohort were referred for formal PSG related to their abnormalities on home oximetry and/or clinical symptoms. One was diagnosed with OSA and required adenoidectomy, the second patient was diagnosed with severe central apnea mixed with mild OSA of unclear etiology that was able to be treated with prolonged supplemental oxygen, and the third patient did not tolerate a PSG, but was able to wean from supplemental oxygen due to improvement in ODI seen on recorded home nocturnal oximetry.

4 | DISCUSSION

In this cohort of infants with BPD, recorded nocturnal oximetry detected hypoxemia and frequent desaturations in the majority of infants who were determined by parental report and clinical examination to be ready to wean from supplemental oxygen. All patients demonstrated appropriate growth, reassuring respiratory exams, and parental report of normal oxyhemoglobin saturations at home. Gestational age at birth, neonatal comorbidities, level of oxygen support, and corrected age at the time of oximetry were not able to reliably predict abnormalities identified on nocturnal oximetry. Recorded home nocturnal oximetry testing provided additional objective data to providers to aid in the decision to wean a patient from supplemental oxygen therapy, and also provided insight into intermittent desaturation events that would have been otherwise undetected. Our results describe that even at 6 months adjusted age, many ex-premature infants with severe BPD met our criteria for nocturnal hypoxemia as well as had heightened intermittent desaturation events. The high prevalence of nocturnal hypoxemia on recorded home oximetry suggests a potential benefit of objective monitoring of oxyhemoglobin saturation when weaning supplemental oxygen consistent with the published guideline from the American Thoracic Society.[4]

There is a known increase in sleep disordered breathing in premature infants with BPD, including OSA, central sleep apnea, hypoventilation, and nonapneic hypoxemia,[21] which could explain the increased frequency of desaturation events in this cohort. It has also

TABLE 2 Abnormal nocturnal oximetry results

Patient	Mean SpO_2	Highest SpO_2	Lowest SpO_2	Time $SpO_2 \geq 90\%$ (HR:MM:SS)	% time $SpO_2 \geq 90\%$	Time spent < 90% (HR:MM:SS)	Time SpO_2 80% −89% (HR:MM:SS)	Time SpO_2 70% −79% (HR:MM:SS)	Time SpO_2 60% −69% (HR:MM:SS)	Mean length desat events ≥ 10 s	Desat Index of Events ≥ 10 s (events per sampled hour)	Desat Index of Events ≥ 0 s (events per sampled hour)
4	96.3	100	69	23:44:28	97.7	0:33:32	0:31:40	0:01:44	0:00:08	38.7	10.8	16.5
5	96.1	100	76	10:42:54	99	0:06:44	0:06:34	0:00:10	0:00:00	31.5	8.2	9.5
7	94.8	100	77	7:58:32	98.7	0:06:02	0:06:02	0:00:00	0:00:00	60.6	12.6	22.7
8	93.6	99	82	12:36:26	97.1	0:22:34	0:22:34	0:00:00	0:00:00	57.1	7.4	8
9	96.1	100	74	8:13:40	99.1	0:04:16	0:03:52	0:00:24	0:00	39.3	8.4	11.2
10	97.5	100	53	11:37:46	98.5	0:10:40	0:04:30	0:04:28	0:01:26	50.3	7.6	9.4
13	97.4	100	75	7:44:04	99.6	0:01:48	0:01:38	0:00:10	0:00:00	55.8	7.6	8.6
14	96.6	100	80	11:00:48	99.6	0:02:56	0:02:56	0:00:00	0:00:00	37.8	5.3	6
15	96	100	82	10:20:29	98.9	0:07:04	—	—	—	—		40
16	98.7	100	61	8:14:58	99.2	0:04:38	0:03:08	0:00:36	0:00:04	26.8	9.3	11.5
17	97.5	100	75	12:53:14	99.9	0:00:52	0:00:44	0:00:08	0:00:00	44.2	4	5.6
18	96.3	100	77	7:40:44	99.6	0:01:54	0:01:46	0:00:08	0:00:00	41.2	7	10.5
20	94.4	100	75	9:04:00	98.1	0:10:38	0:10:28	0:00:10	0:00:00	43	27.6	51.4
23	97.8	100	80	8:33:40	99.4	0:02:58	0:02:58	0:00:00	0:00:00	27.2	10.8	22.9
24	95.9	100	61	9:41:40	99.4	0:03:30	—	—	—	—		41
26	97.3	100	73	17:10:04	99	0:10:02	0:08:28	0:01:34	0:00:00	41.5	3.6	4.1
28	96.8	100	51	8:34:06	98.7	0:06:36	0:04:40	0:01:32	0:00:20	48.7	6.3	8
29	96.1	100	74	10:29:54	99.2	0:04:48	0:03:32	0:01:16	0:00:00	52.1	8.6	13.4
31	97.7	100	81	9:37:34	99.8	0:01:26	0:01:26	0:00:00	0:00:00	34.6	6.7	16.2
33	97.5	100	65	10:02:42	95.7	0:27:10	0:20:40	0:06:26	0:00:04	35.9	7.6	8.8
34	97.2	100	79	9:26:34	99.9	0:00:48	0:00:36	0:00:12	0:00:00	38.4	5.8	8.4

TABLE 3 Comparison of patients with normal and abnormal home oximetry

	Normal (n = 14)	Abnormal (n = 21)	p value
General characteristics			
Gestational age at birth (weeks), median, IQR	24.9 (24.6–25.9)	25.6 (24.4–27.7)	0.46
Birthweight (g), median, IQR	720 (660–794)	840 (640–1065)	0.17
Small for gestational age, n (%)	3 (14)	0 (0)	0.056
Male, n (%)	6 (43)	11 (52)	0.733
Caucasian race, n (%)	9 (64)	15 (71)	0.721
Antenatal steroids, n (%)*	13 (93)	19 (90)	1.00
Postnatal steroids, n (%)	10 (71)	11 (52)	0.311
Postmenstrual at discharge (weeks), median, IQR	42.2 (41.3–48)	41.1 (39–42.7)	0.18
Corrected age at time of study (months), median, IQR	6.2 (3.9–9.5)	5.7 (3.0–7.4)	0.38
Oxygen support at time of study (L/min), mean	0.2	0.19	0.56
Neonatal morbidities			
Severe BPD, n (%)	12 (86)	16 (76)	0.676
Severe ROP, n (%)	1 (7)	3 (14)	0.635
Severe IVH (≥Gr III), n (%)	1 (7)	2 (10)	1.00
Periventricular leukomalacia, n (%)	0 (0)	2 (10)	0.506
Surgical NEC, n (%)	1 (7)	0 (0)	0.40
Diagnosis of pulmonary hypertension, n (%)	6 (43)	5 (24)	0.283
Treatment of pulmonary hypertension at NICU discharge, n (%)	2 (14)	0 (0)	0.153

Abbreviations: BPD, bronchopulmonary dysplasia; IQR, interquartile ratio; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; ROP, retinopathy of prematurity.

been reported that the severity of BPD could augment the severity of sleep disordered breathing, implying that those infants who are discharged on home supplemental oxygen therapy would be at the highest risk for clinically significant sleep disordered breathing.[22] During sleep, there is a reduction in airway muscle activity and ventilatory effort, and activation of chemoreceptors in the carotid body allows for an immediate rise in ventilation to compensate for hypoxemia. Children with a history of BPD have been described to have abnormal ventilatory responses to hypoxic and hypercarbic challenges and abnormal carotid body development secondary to chronic hypoxemia or hyperoxia.[23] These changes in respiratory control may increase the risk of sleep disordered breathing in this vulnerable population. Premature infants are also predisposed to upper airway obstruction due to decreased upper airway muscle tone and increased chest wall compliance. This is expected to resolve, but the risk of airway obstruction and/or OSA due to prematurity persists until adulthood.[24] There is a lack of normative data on intermittent hypoxemia in both healthy preterm and term infants. In a study of 52 former preterm infants who did not require supplemental oxygen at the time of discharge from the NICU, the mean ODI4 was 11.8 at term adjusted ages.[1] Wellington et al.[25] reported that in infants born <32 weeks at birth the ODI4 decreases with advancing PMA. This study documented a baseline ODI4 of 7.7 at discharge that improved to 5.2 by 1-month post discharge, and the mean SpO_2 remained in the normal range over this time period in the cohort. This suggests that oxyhemoglobin desaturation indices may be a more sensitive measure of change in respiratory stability over time. It is not known at what threshold the severity or frequency of these events at term adjusted ages and beyond influences clinical outcomes, and there are no documented studies of normative data at term and post-term for infants with BPD. Due to this evidence along with the previously reported correlation between ODI and AHI, an ODI4 of 5 or less at well past term adjusted age was felt to be a reasonable goal to discontinue supplemental oxygen support. We recognize that further research is needed to investigate the impact particular desaturation indices with and without evidence of hypoxemia have on future outcomes in post-term corrected infants with BPD requiring home oxygen.

Half of the children with abnormal oximetry were for abnormal ODI without evidence of hypoxemia. The American Academic of Sleep Medicine defines hypopnea in children as a 50% reduction in airflow associated with either arousal or ≥3% decrease in saturation

from pre-event baseline.[26] There are no published studies in the neonatal population on clinical implications of desaturations without hypoxemia, but there is evidence in the adolescent population that OSA without significant hypoxemia is associated with increased autonomic dysfunction.[27] It has also been found that pediatric patients with primary snoring without evidence of hypoxemia or OSA have increased neurobehavioral deficits.[28] It is unknown what the implications are in infants and the developing brain, and it is possible that these events lack clinical significance in this population. Due to the level of detail home oximetry provides that has not been available in the past, these results remain exploratory until more outcome data are able to be established with ODI.

Home oximetry is more convenient and less expensive than inpatient formal PSG, and requires minimal participation from families.[29,30] Most providers utilize nighttime oxyhemoglobin saturations from oximetry to wean oxygen.[13] There are recent studies describing utilizing recorded home oximetry in an oxygen weaning protocol in place of a PSG,[31] but there are no published reports describing the desaturation index despite the link to the apnea −hypopnea index on PSG.[15] A recent report described employing downloadable home oximetry information to assist with weaning oxygen therapy at home outside of in-person visits, but this system requires the software, staffing resources, and monitoring available, as well as frequent family participation.[32] We were able to provide the monitor in the clinic or delivery via home care services, and we did not experience any delays in participation with this method.

Our study is limited by its retrospective nature, small sample size, and enrollment from a single perinatal institute, although we did have patients enrolled from both Level 3 and Level 4 NICU sites. While unidentified hypoxemia may have future impacts on growth, pulmonary hypertension, and neurodevelopmental impairment, this study was not designed or powered to evaluate those long-term effects. We also recognize there is a lack of normative data on frequent oxyhemoglobin desaturation events in children with BPD at term and post-term adjusted ages in the matter of defining ODI4 thresholds for supplemental oxygen therapy.

In our cohort of children with BPD on home oxygen, over half of patients thought to be ready clinically to wean to room air at night were found to have unrecognized hypoxemia and/or elevated ODI4 during sleep. Recorded home oximetry could be a feasible and useful tool to evaluate for otherwise clinically unapparent nocturnal hypoxemia in patients with BPD. Larger studies are needed to further evaluate our study's findings with the addition of longitudinal follow-up of longer-term growth and developmental outcomes, as well as to validate the parameters chosen to define abnormal.

AUTHOR CONTRIBUTIONS

Melissa House: conceptualization; formal analysis; methodology; writing—original draft; writing—review and editing. **Sarah Klein**: formal analysis; investigation; methodology; writing—original draft; writing—review and editing. **Danielle Parham**: writing—review and editing. **Erik Hysinger**: conceptualization; methodology; writing—review and editing; supervision. **Jennifer Brady**: conceptualization; investigation; methodology; writing—review and editing; supervision.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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