Neonatal Intermittent Hypoxemia Events are Associated with Diagnosis of Bronchopulmonary Dysplasia at 36 Weeks Postmenstrual Age

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Abstract

Background: Bronchopulmonary dysplasia (BPD) is a chronic lung disease and major pulmonary complication after premature birth. We have previously shown that increased intermittent hypoxemia (IH) events have been correlated to adverse outcomes and mortality in extremely premature infants. We hypothesize that early IH patterns are associated with the development of BPD.

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Methods: IH frequency, duration, and nadirs were assessed using oxygen saturation (SpO$_2$) waveforms in a retrospective cohort of 137 extremely premature newborns (<28 weeks gestation). Daily levels of inspired oxygen and mean airway pressure exposures were also recorded.

Results: Diagnosis of BPD at 36 weeks postmenstrual age was associated with increased daily IH, longer IH duration, and a higher IH nadir. Significant differences were detected through day 7 to day 26 of life. Infants who developed BPD had lower mean SpO$_2$ despite their expose to increased inspired oxygen and increased mean airway pressure.

Conclusions: BPD was associated with more frequent, longer, and less severe IH events in addition to increased oxygen and pressure exposure within the first 26 days of life. Early IH patterns may contribute to the development of BPD or aid in identification of neonates at high-risk.

Introduction

Bronchopulmonary dysplasia (BPD) is one of the most common serious pulmonary morbidities of prematurity. Approximately 10–15,000 US infants develop BPD annually, at a cost estimated to exceed $2.5 billion (1, 2). Infants with BPD have longer initial hospitalizations (3) and frequent childhood readmissions (4), increased risk for neurodevelopmental impairments (5), and potentially life-long deficits in pulmonary function (1, 6). BPD has a negative impact on the quality of life among both patients and caregivers (5, 7). Approximately 40% of extremely low gestational age newborns (ELGAN) cared for at tertiary academic centers will be diagnosed with BPD, defined as an oxygen requirement at 36 weeks postmenstrual age (PMA), with increased incidence amongst the most premature infants (8). Despite advances in neonatal care, the incidence of BPD among ELGAN survivors remains largely unchanged (8, 9).

The pathogenesis of BPD is an ongoing process of injury and recovery occurring in a developmentally immature lung beginning shortly after birth (10). Following an initial period of respiratory stability, many ELGANs experience pulmonary deterioration during the second week of life associated with a progressive increase in intermittent hypoxemia (IH) events (11) and greater inspired oxygen and positive pressure needs (12). Oxygen and positive pressure exposures during the early days and weeks of postnatal life are linked with the development of BPD (13, 14), but the temporal contribution of IH is unclear.

During the first four weeks of a premature infant's life, IH increases from approximately forty to over one-hundred events per day due to immature breathing patterns (15), inefficient gas exchange (16), and/or diminished oxygen stores (17). Thus IH has received increased attention in the pathogenesis of neonatal morbidity and mortality (18–21). IH events themselves have the potential to create a proinflammatory cascade (22) and oxidative stress (23, 24) which have both been implicated in the causation pathway of BPD (1, 10). Therefore, the aim of this study was to investigate the association of IH patterns with development of BPD at 36 weeks PMA.

Patients and Methods

Study Design and Population:

A retrospective cohort study of preterm infants (24 0/7 weeks – 27 6/7 weeks gestation) from 2005–2009 at the tertiary level 4 NICU at Rainbow Babies & Children's Hospital in Cleveland, Ohio were reviewed for hospitalization data. In a sample of convenience that expanded upon a previously published cohort (18), infants in whom daily respiratory support and continuous oxygen saturation monitoring were documented during the first 4 weeks of life and who survived to 36 weeks postmenstrual age (PMA) were included. Infants with congenital malformations were excluded. As this study included previously acquired data, Rainbow Babies & Children's Hospital Institutional Review Board approved a waiver of consent.

Data Collection:

Intermittent hypoxemia (IH) events were archived using high-resolution pulse oximetry data continuously recorded from postnatal day of life 1 to 28. Oxygen saturation (SpO_2) data were acquired continuously with a 2 second averaging and a 0.5 Hz sampling rate (Masimo Radical; Irving, CA). As we have previously described (18), IH was identified using customized software (Matlab, Natick, MA) and defined as a SpO_2 of 80% for 10 seconds and 180 seconds duration. For each infant, the number of IH events was calculated for each day of life. Additionally, SpO_2 nadir of events, IH durations, and IH frequency characteristics were analyzed. During the monitoring periods there were infrequent times when signal loss occurred due to infants not being monitored, corrupt files, and noise or motion artifact. Periods with 0% SpO_2 or 0 bpm for heart rate were considered artifact and removed from the data stream with the remaining data analyzed in 24 hour or 1 hour sliding windows. Large areas of missing data, i.e. 24 hours, were treated as missing cells in the statistical analysis.

Hospital charts were reviewed for birth history and daily values of weight, treatment with caffeine, presence and level of respiratory support including mechanical ventilation, CPAP, nasal cannula, and supplemental oxygen were documented. Unit policy was to dose maintenance caffeine citrate at 5–10 mg/kg/day based on clinical effect, serum caffeine levels were not routinely monitored. Supplemental oxygen was recorded as the fraction of inspired oxygen (FiO_2) at the end of defined 6 hour periods (0:00, 6:00, 12:00 and 18:00) and the maximum level for that day, and daily cumulative exposures were calculated as previously described (25) and reported as an area-under-the-curve exposure by day (13, 25). Mean airway pressure (MAP) was recorded as the highest documented exposure of each day. In patients who were supported by a nasal cannula, effective FiO_2 was estimated using the formula described in the STOP-ROP trial (26) and generation of mean airway pressure by nasal cannula flow was calculated by the formula published by Wilkinson *et al* (27).

In this study, bronchopulmonary dysplasia was diagnosed by the National Institutes of Health (NIH) physiologic definition as described by Walsh *et al* (28). Briefly, infants were assessed at 36 weeks PMA, those on positive pressure or receiving 30% oxygen were given the diagnosis of BPD, infants on <30% oxygen nasal cannula or oxygen hood underwent a

step-wise reduction in supplemental oxygen down to room air and were continuously monitored for 60 minutes - infants with $SpO_2 < 88\%$ were diagnosed with BPD, those who remained ≥ 88% were labeled as "no BPD." Severe intraventricular hemorrhage (IVH) was made by radiologic diagnosis of a Grade 3 or 4 IVH by head ultrasound during hospitalization. Sepsis was designated by culture positive bacteremia or fungemia.

Data Analysis:

Statistical analysis was performed on daily averages of IH frequency, duration, nadir of events, etc. computed for each subject. A two-sided t-test or Mann-Whitney U-test was used for patient characteristic comparisons between "BPD" and "no BPD" groups after testing for normalcy. In this study, BPD was defined using the NIH physiologic definition at 36 weeks PMA, but previous definitions of BPD have also used 28 days of life (2). Therefore, comparisons of time-course trajectories were restricted to before 28 days of life. Summary statistics are presented as means ± standard deviation (SD) or median (25% - 75% quartiles) and n (percent) for continuous and categorical variables, respectively. Longitudinal profiles of oxygen saturation waveform measures were modeled and compared between two groups of infants (BPD vs no BPD) using linear mixed models with cubic splines (18). Modeling the curvilinear trajectory of each outcome with knots at 7, 14, 21, and 26 days adequately represented the infants' profiles with lower AIC (Akaike Information Criterion) values. Models included covariates of gestational age, birth weight, race, sex, multiple gestations, and their interactions with terms involving day (18). The linear mixed effects models included random intercepts and slopes, and were modeled using unstructured variance covariance matrices that resulted in distinct estimates of all variance and covariance parameters. Correlations among the repeated measures obtained from an infant were modeled by a first-order autoregressive structure. For better model fitting, a logarithmic or square root transformation was applied when the original data were skewed. The maximum likelihood estimation approach was used in estimating all parameters of the model. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and longitudinal graphs were created using R software version 3.5.1 (R Foundation, Vienna, Austria).

Results

The study population included 137 infants, of whom 47 (34%) were diagnosed with the NIH physiologic definition of BPD at 36 weeks PMA. Population characteristics of this cohort showed that infants with BPD were of a lower average gestational age and a lower average birth weight (Table 1). There were no significant differences observed between infant groups for sex, race, severe IVH, or sepsis. As expected, infants with BPD had longer median days of exposure to supplemental oxygen (71 (66–75) vs 32 (17–53) days, p<0.0001) and positive pressure (71 (64–75) vs 45 (32–61) days, p<0.0001) at 36 weeks PMA. One-hundred thirty-six of the 137 study infants received caffeine therapy; day of life initiated and duration of treatment did not significantly differ between groups.

After adjusting for day of life, gestational age, birth weight, race, sex, and multiple gestations, the mean SpO_2 of BPD infants was significantly lower at the predefined curvilinear knots at 7 (p=0.003), 14 (p=0.008), 21 (p=0.0004), and 26 days of life (p=0.002)

(Figure 1a). Intermittent hypoxemia frequency increased dramatically between the first and third weeks of life in this cohort of ELGANs with a significantly higher occurrence of IH in the BPD group at curvilinear knots at 21 (p=0.01) and 26 days of life (p=0.007) (Figure 1b). Infants diagnosed with BPD also had higher IH events, with differences detected at curvilinear knots at days 14 (p=0.001), 21 (p=0.0005), and 26 days of life (p=0.0002) (Figure 1c). Interestingly, the BPD group had higher IH nadirs on average, with divergence in IH nadirs at curvilinear knots at 7 (p=0.001) and 14 days of life (p=0.0004) (Figure 1d). IH events occurring 1–20 minutes apart diverged between groups at curvilinear knots at days 21 (p=0.0003) and 26 (p=0.0007) (Figure 2b) with a trend towards a higher incidence of IH <1 min apart at day 26 (p=0.052) (Figure 2a). There were relatively few events occurring >20 min apart with no significant differences observed between infant groups (Figure 2c).

Among the BPD group, levels of inspired oxygen (Figure 3a) and mean airway pressure (MAP) from both invasive and non-invasive positive pressure respiratory support (Figure 3b) were significantly higher at the predefined curvilinear knots at 7, 14, 21, and 26 days of life (all p<0.0001).

Discussion

Our findings demonstrate an association between temporal patterns of IH and BPD in extremely preterm infants. Within the first 26 days of life, we observed increased IH event frequency and durations, and elevated IH nadirs among ELGANs diagnosed with BPD at 36 weeks PMA. BPD was also associated with early exposure to increased supplemental oxygen and mean airway pressure. Level and duration of respiratory therapy have been well described in the injury pathways of BPD and significant differences between exposure groups are observed relatively early (13, 14). This study has shown that temporal patterns of IH may play a role as an additional early marker for future diagnosis of BPD.

The first four weeks of life are characterized by a rapid and profound increase in postnatal destabilization (29). Previous data have shown a 3-fold increased incidence of BPD in newborns with low or decreasing supplemental oxygen and ventilator requirements in the first week of life that deteriorate with increased FiO_2 and respiratory support in the second postnatal week (12). IH events among our study cohort also indicate a pattern of pulmonary deterioration in the second week, with infants that went on to develop BPD displaying marked increases in daily IH events into the third week of life. The trajectory of IH during this time period may provide additional insight on the likelihood of the diagnosis of BPD at 36 weeks PMA.

Previous studies have shown an association between IH and morbidity in neonates. For example, IH frequency and time spent in hypoxemia are increased in premature infants that develop severe retinopathy of prematurity (11), neurodevelopmental disabilities including risk for cerebral palsy (19, 20), and death (20, 21). While IH commonly occurs in infants already diagnosed with BPD (30), a paucity of clinical data exists regarding the association of these early neonatal IH events and BPD risk. Newborn hyperoxic animal models have shown that superimposed IH may potentiate a more severe BPD phenotype (31–34).

The specific patterns of daily IH events have also been investigated in neonatal morbidity and mortality (18, 20, 21). Specifically, IH events occurring between 1 and 20 minutes apart or those of a duration greater than 1 minute have been linked to retinopathy of prematurity requiring laser surgery and late death or disability (18, 20). This pattern of increased IH events occurring 1–20 minutes apart and of a longer average duration was also relevant in our BPD outcome, as detected at postnatal day 21 and day 14, respectively. An animal model of induced IH describes a burst of superoxide during hyperoxic recovery that peaks at 5 minutes and returns to baseline over 20 minutes that may indicate a critical window of IH induced oxidative stress (24). There was a trend towards an increase in IH <1 min apart at day of life 26 that was not previously seen in infants with severe ROP (18). Further investigations of detrimental IH patterns in experimental BPD, as well as, observational studies in high-risk infants are needed.

While the BPD cohort had increased use and levels of supplemental oxygen and positive pressure during the first month of life, they continued to have more frequent and longer duration IH events with a lower mean SpO_2. We have previously reported in infants with severe ROP the nadir of IH events to be higher (18). Again, we observe this pattern of more frequent, longer duration, yet higher IH nadirs in infants who were diagnosed with BPD. We speculate that infants with frequent and greater duration IH due to immature breathing patterns may be clinically perceived to require elevated levels of supplemental oxygen which may successfully increase IH nadirs but also potentially contributes to the development of BPD. We were unable to account for transient increases in supplemental FiO_2 at the bedside in response to an acute or sustained IH event, but speculate that a lower oxygen reserve and a tendency to desaturate (35) may be indicative of infants with more severe lung disease who proceed on to develop BPD. As such, it is important to note that our study is unable to identify a sequence of causation. We cannot conclude what came first - early parenchymal lung disease and worse lung function predisposing infants to increased IH events and diagnosis of BPD or frequent IH events in the setting of immature lung and respiratory control leading to lung injury and diagnosis of BPD. Translational animal models would indicate that neonatal IH alone is unlikely to cause parenchymal and mechanical BPD lung changes (31, 32), but IH in the setting of supplemental oxygen creates an equal or more severe BPD phenotype (31–34). Taken together, IH likely has a role in both prolonging neonatal exposures to oxygen and positive pressure in a still developing lung while also contributing to additional lung injury.

Duration and initiation of caffeine therapy was comparable between infant groups with all but one infant treated with caffeine. Caffeine is among the most effective therapies for the prevention of BPD (36). Caffeine has been shown to significantly decrease the frequency of IH events compared to placebo (37) most likely through stabilization of an immature respiratory drive and prevention of apnea (15). Our data collection did not include chest impedance to correlate apnea with IH events, but it is speculated that caffeine reduces the duration of exposure to noxious supplemental oxygen and positive pressure thereby decreasing an infant's risk for developing BPD, particularly when started relatively early in premature infants requiring respiratory support (38). Diminished IH events may in-part also explain the role of prophylactic caffeine in BPD prevention.

This study is a retrospective secondary analysis of an ELGAN cohort of convenience (18) to investigate associations of IH and the physiologic diagnosis of BPD at 36 weeks PMA from a single-center, which may limit its generalizability to other centers. Variation in practice and definitions of BPD among institutions may also limit our findings, however the NIH consensus definition for BPD attempts to control for variance of indications for supplemental oxygen and correlates with important early childhood morbidity (4). As supplemental oxygen at 28 days of life is a requirement for the NIH diagnosis of BPD (1), a final knot at 26 days of life was chosen for the curvilinear trajectory models. Also, we only examined IH 80% during the first 4 postnatal weeks of life; using another threshold or longer duration may have yielded different results. As there is no standard definition for neonatal IH, future studies could focus on multiple thresholds for distinguishing "mild", "moderate", or "severe" hypoxemia. This study used a 2 second averaging time to minimize SpO_2 signal distortion. Anecdotally, many NICUs use a longer averaging time of 8 seconds which has been shown to have minimal effect on the detection of IH events >10 seconds as defined in this study (39). Current oximeters report time spent within defined saturation thresholds. However, future oximeter software upgrades, as well as, central archiving of cardiorespiratory monitoring waveforms could include more detailed analysis of IH patterns as described in this study.

In conclusion, this study demonstrates that premature infants diagnosed with BPD at 36 weeks PMA had increased frequency, duration, and less severe neonatal intermittent hypoxemia episodes during the first 26 days of postnatal life. Neonates who go on to develop BPD have lower baseline SpO_2 despite increased levels of supplemental oxygen and mean airway pressure support. The future implementation of oximeter or central server reporting of detailed oximetry patterns may assist in early identification of infants at risk for BPD.

Acknowledgements

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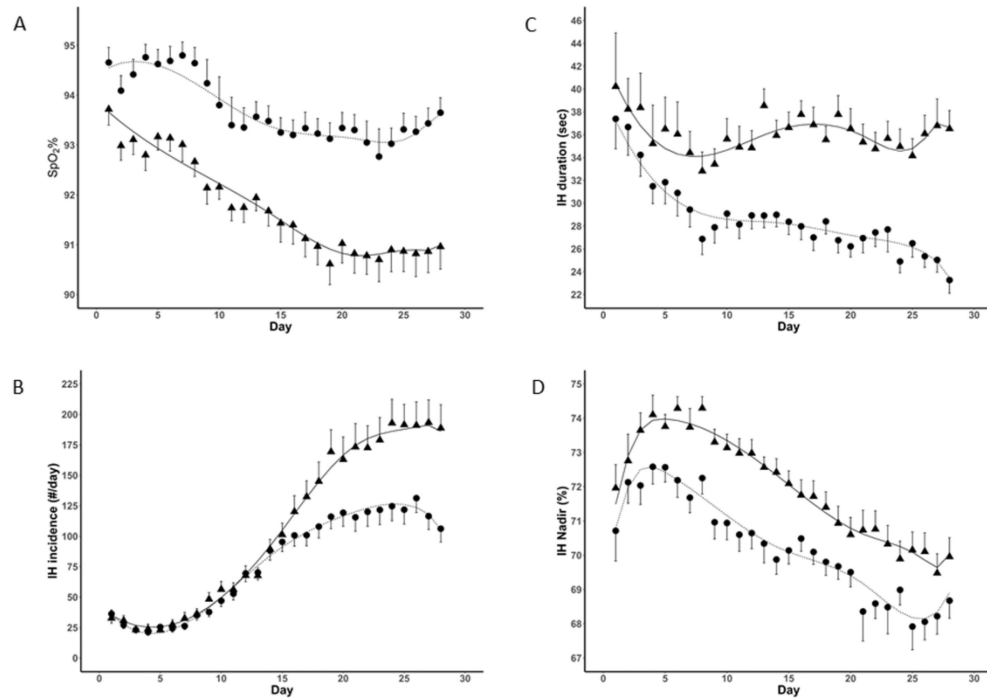
Figure 1: Patterns of Hypoxemia during the First Four Weeks of Life.
Longitudinal daily means (±SEM) of bronchopulmonary dysplasia (BPD) group (triangles) vs No BPD group (circles). Lines indicate covariate adjusted modeling. Mean oxygen saturations (SpO_2) A) was significantly lower in the BPD group at days 7, 14, 21, and 26 (p < 0.001). Frequency of intermittent hypoxemia (IH) events B) was significantly increased in the BPD group at days 21 and 26 (p   0.01). Mean duration of IH events C) was significantly increased in the BPD group at days 14, 21, and 26 (p   0.001). SpO_2 nadir of IH events D) was higher at days 7 and 14 (p   0.001).
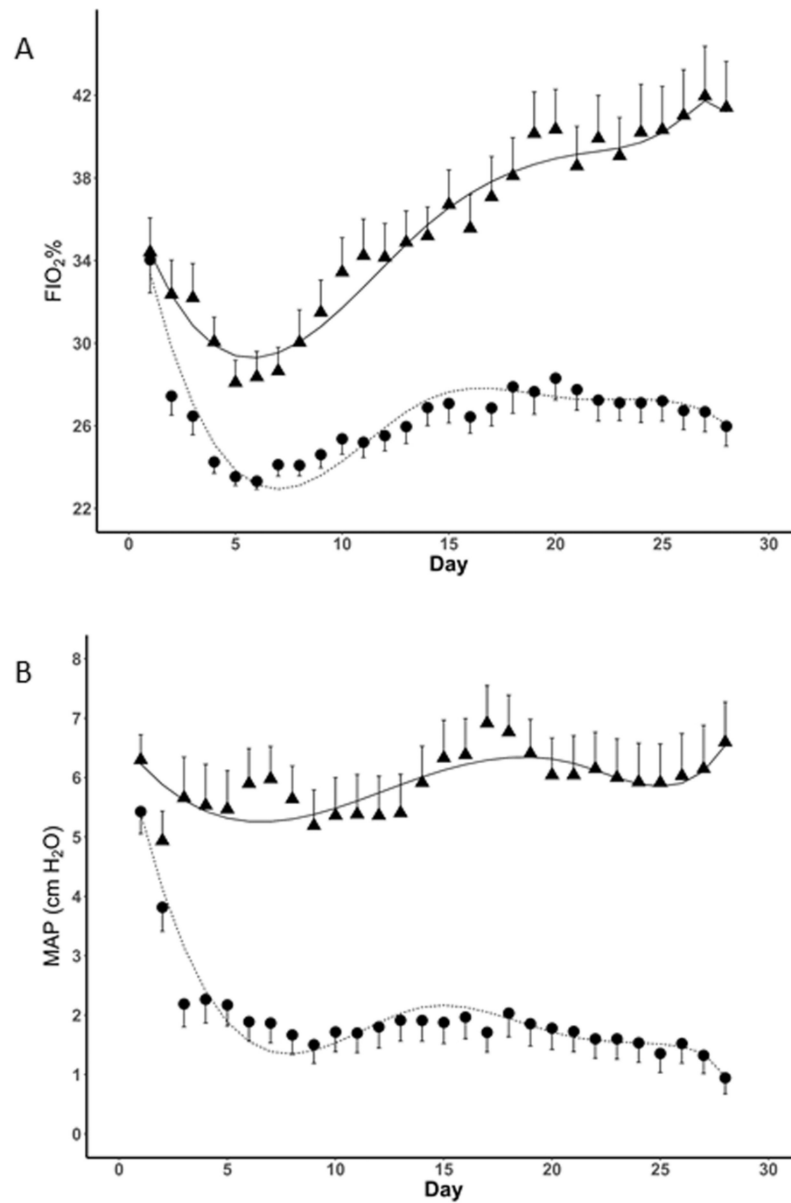
Figure 2: Stratification of Events by Time Interval during the First Four Weeks of Life.
Longitudinal daily means (±SEM) of bronchopulmonary dysplasia (BPD) group (triangles) vs No BPD group (circles). Lines indicate covariate adjusted modeling. Intermittent hypoxemia (IH) events with a time interval between events of <1 minute apart A), 1–20 minutes apart B), and >20 minutes part C). IH events occurring between 1–20 minutes apart were significantly increased in the BPD group at days 21 and 26 (p < 0.001). Events <1 minute apart or >20 minutes apart did not significantly differ between groups.
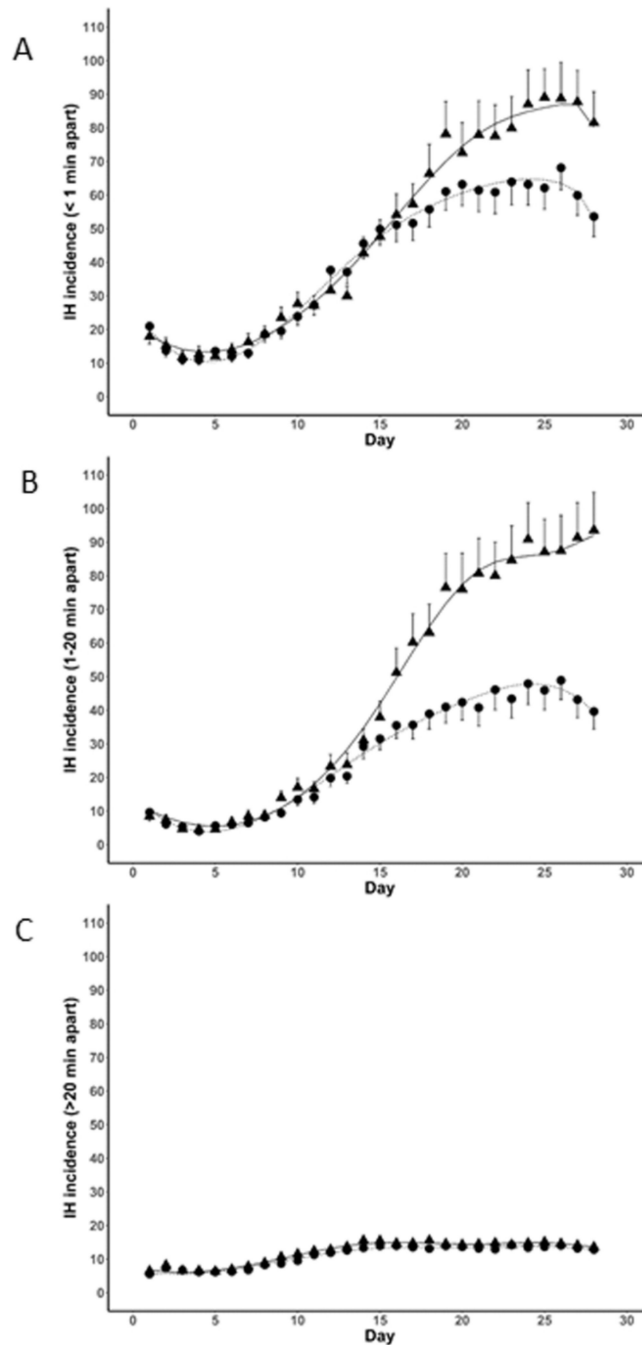
Figure 3: Inspired Oxygen and Mean Airway Pressure during the First Four Weeks of Life.
Longitudinal daily means (±SEM) of bronchopulmonary dysplasia (BPD) group (triangles) vs No BPD group (circles). Lines indicate covariate adjusted modeling. Mean fraction of inspired oxygen (FiO$_2$) A) was significantly higher in the BPD group at days 7, 14, 21, and 26 (p < 0.0001). Mean airway pressure (MAP) B) was significantly higher in the BPD group at days 7, 14, 21, and 26 (p < 0.0001).

Table 1:

Patient Characteristics

	No BPD (n=90)	BPD (n=47)	p-value
Gestational Age (weeks) *	26.6 (25.5–27.3)	25.7 (25.0–26.6)	0.002
Birth Weight (grams) *	878 (741–1010)	760 (620–870)	<0.001
Male Sex, n (%)	41 (45.5%)	29 (61.2%)	0.073
Race (Black), n (%)	52 (57.8%)	27 (57.4%)	0.97
Caffeine Therapy Duration (days) **	49.3 ±16.8	54.0 ±17.7	0.13
Caffeine Therapy Initiation (days of age) *	2 (1–2)	2 (1–4)	0.17
Severe Intraventricular Hemorrhage, n (%)	6 (6.7%)	5 (10.6%)	0.42
Sepsis, n (%)	22 (24.4%)	11 (23.4%)	0.89

*
median (25–75%iles)

**
mean (±SD)