IMPACT OF INTERMITTENT HYPOXIA ON GROWTH IN VERY- AND EXTREMELY-PRETERM INFANTS

A Master's Thesis Presented

By

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ABSTRACT

Background. Premature infants are at risk for many complications. Among these, growth failure and intermittent hypoxia (IH) can independently impact the outcomes of other comorbidities. Recent data suggest that IH may directly affect postnatal growth. Our study aims to evaluate the impact of IH on growth velocity in preterm infants.

Methods. This prospective cohort study utilized inpatient oximetry, nutrition, and growth data to evaluate the relationship between IH and growth velocity. Enrolled infants were dichotomized by high- versus low-exposure to IH. This relationship was explored in both unadjusted analyses and generalized linear models with repeated measures.

Results. The study population included 19 preterm infants, with average birth gestational age of 29 weeks, each contributing one or more measures of weekly data. Infants in the high-exposure cohort had lower birth weight, higher rates of bronchopulmonary dysplasia, and longer duration of respiratory support and caffeine treatment. The unadjusted analysis revealed a marginally significant trend towards higher IH rates during weeks of slower growth. The logistic regression with repeated measures analysis also supported increased odds of slower growth associated with higher IH rates, but this relationship was also only marginally significant.

Conclusion. Our study suggests a relationship between exposure to IH and slower growth velocity in preterm infants. The prospectively collected data allowed for accurate measures of IH, growth, and nutrition, but the small sample size likely contributed to the lack of significance of our results.

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None.

LIST OF ABBREVIATIONS

Abbreviation	**Full Description**
BPD	Bronchopulmonary dysplasia
CGA	Corrected gestational age
GA	Gestational age
IH	Intermittent hypoxia
IRB	Institutional Review Board
Kcal/kg/day	Caloric density of daily feeds per kilogram body weight
OR	Odds Ratio
RIO	Recorded inpatient oximetry
UMMS	University of Massachusetts Medical School

PREFACE

This thesis work is a sub-project of a larger ongoing trial that I have been conducting throughout the duration of my master's studies. My primary research project is a randomized control trial (RCT) entitled "Optimizing Oxygen Weaning in Preterm Infants: The Recorded Inpatient Oximetry (RIO) Trial". My research mentor, Dr. Lawrence Rhein, is the Principal Investigator (PI) for this study, and I am the lead co-investigator. This is currently a single-center pilot RCT being conducted at University of Massachusetts Medical School (UMMS) that is evaluating the best practice for management of supplemental oxygen administered via low-flow nasal cannula in preterm infants. Once the pilot arm of this study is complete, we intend to move this trial into a larger multi-site RCT.

As co-investigator in this trial, my responsibilities for this study have been extensive. Along with Dr. Rhein, I developed the research question and proposed methodology for conducting the RCT. I wrote and submitted the documentation for Institutional Review Board (IRB) approval, conducted onboarding for the physicians, nurse practitioners, physician assistants, nurses, and respiratory therapists, and have been overseeing and participating in the consenting and enrolling of eligible study participants.

As background for the RIO trial, I was also co-investigator and co-author for a retrospective descriptive study during my master's studies, along with the study PI Dr. Rhein, primary author Dr. Jaclyn Daigneault, research coordinator Heather White, and statistician Dr. Austin Lee. This study highlighted the baseline characteristics of the preterm infants cared for in the UMMS NICU as well as the current practices for

respiratory management of those preterm infants. The manuscript for this study has been submitted for publication and is awaiting review.

While enrollment for RIO has been ongoing, Dr. Rhein and I have created this small prospective cohort study as my thesis, utilizing the recorded inpatient oximetry data as well as growth and nutrition data from the medical record to evaluate the potential relationship between episodes of intermittent hypoxia experienced by a preterm infant and their subsequent growth velocity. Our research team, including Heather White, Lindsey Simoncini, and Ciara Murphy, have been integral in helping me to collect and organize our data, and the Department of Pediatrics statistician, Dr. Lee, has assisted me in creating the tables and figures presented in our results section. We are very proud of the work we have accomplished in the past two years, and we look forward to the continued scholarly work ahead of us in completing the RIO trial.

CHAPTER I. Background

Infants who are born premature are at risk for having multiple complications that can impact their long-term health and outcomes,[1] including growth failure. Infants born very or extremely preterm have the highest rates of growth failure, chronic lung disease of prematurity, retinopathy of prematurity, intraventricular hemorrhage, and neurodevelopmental impairments, as well as higher mortality rates, when compared with those born moderate-to-late preterm or term.[1] Postnatal growth failure, defined as weight-for-gestational-age below the tenth percentile on the Fenton preterm infant growth curve, is a major contributor to worse outcomes for many of these complications.[2,3,4,5] Optimizing nutrition and adequacy of growth, and minimizing growth failure, have been major foci of recent neonatal research.[6,7] Many researchers, however, are using growth velocity, measured by change in weight-for-gestational-age Z-score as an important

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marker of growth adequacy[8,9,10] instead of or in addition to the classic definition based on an absolute growth percentile cutoff.

Apnea of prematurity is another common problem presenting in preterm infants.[11] Even brief episodes of apnea can result in intermittent hypoxia (IH), which is defined as a drop in oxygen saturation, measured by pulse oximetry, below a threshold for a brief period of time.[11] The prevalence of IH increases with decreasing gestational age (GA) at birth and is higher in those born small for gestational age.[12,13] While apnea is the primary driving factor for IH, IH appears to be the more crucial exposure affecting long-term outcomes in premature infants.[14] Current evidence suggests that episodes of IH have a cumulative effect on morbidity, including detrimental effects on neurodevelopmental outcomes,[15,16] increased rates of retinopathy of prematurity,[17] and mortality[18]. There are

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many other potential effects of IH on the developing infant that have been proposed in animal models,[19,20,21] but not yet confirmed in human subjects.

In this prospective cohort study, we evaluated the impact of IH on growth velocity in very and extremely preterm infants. Animal models have suggested an inverse association between frequency of IH and growth,[20,21] but this possible association has not been examined in clinical studies. We hypothesized that, when measured on a weekly basis, an increased number of episodes of IH will result in slower growth velocity among preterm infants.

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CHAPTER II. Methods

Data Source

This study utilized data collected through an ongoing single center randomized controlled trial at the University of Massachusetts Medical School (UMMS) entitled "The Recorded Inpatient Oximetry (RIO) Trial". The RIO trial is approved by the Institutional Review Board (IRB) at the UMMS, and written informed consent was obtained for all enrolled infants. This trial includes infants born at less than or equal to 32 0/7 weeks GA with a requirement for noninvasive positive pressure ventilation prior to 32 0/7 weeks corrected gestational age (CGA), with English- or Spanish-speaking parents. Infants were excluded from the trial if they had a diagnosis with an alternate basis for persistent hypoxia other than premature lung disease, such as congenital heart disease or pulmonary hypertension, or for influencing prolonged need for supplemental oxygen beyond that expected from chronic lung disease of prematurity. In the RIO study, enrolled infants had a study monitor (Masimo RAD-97 pulse oximeter, Masimo Corporation, Irvine, California) with a 2-second averaging time placed in addition to the bedside clinical monitor to continuously record the infant's oxygen saturation. The monitor was set to the sleep lab mode; therefore, it did not display information or alarm at the bedside. The pulse oximeter was connected to a central monitoring station (Masimo Patient SafetyNET System) through WIFI to allow for continuous monitoring and data recording. Data were downloaded on a weekly basis from enrolled infants through the monitoring station. Weekly growth and nutrition data were obtained from the electronic medical record.

Study Population

Data from each infant satisfying the trial inclusion criteria were evaluated on a weekly basis for number of IH events (as defined below) and weight and nutrition information. Each weekly data packet was further evaluated for inclusion in the study using the following inclusion and exclusion criteria. A data packet was included if it represented a complete week of both oximetry recordings and full enteral feeds of a quantifiable volume and caloric density. A data packet was excluded if it violated the inclusion criteria either by interrupted oximetry recordings or interrupted enteral feeding; data packets representative of a week including breastfeeding as a significant contributor to nutritional intake were also excluded due to an inability to quantify the volume and caloric density of breastfeeds.

Demographic information including birth GA, birth weight, race, and gender was abstracted from the medical record. Clinical variables, including multiple gestation, presence of moderate to severe bronchopulmonary dysplasia (BPD), days on mechanical ventilation, non-invasive positive pressure ventilation, requirement for low-flow nasal cannula, and CGA on last day of caffeine treatment were also collected from the electronic medical record.

Primary exposure and outcomes

The primary exposure in this study was the frequency of IH episodes in a one-week timeframe, expressed as an event rate of average number of IH episodes per hour. Episodes of IH were primarily defined as an oxygen saturation less than 90% for a

duration of at least 10 seconds. Other definitions of hypoxia were explored based on equipoise in the existing literature, including IH episodes below 90% with a duration time of at least 20 seconds and total percentage of time spent with oxygen saturation below the threshold of 90%.

Exposure to IH for each infant was dichotomized into either high or low exposure based on our primary definition of the IH event rate. High exposure was defined as exposure to at least one week with an event rate greater than 4.5 IH events per hour; low exposure was defined as no exposure in any week with an event rate greater than 4.5 IH events per hour. Potential confounding variables included GA at birth, CGA at the start of each week, and average caloric density of nutritional intake as measured by kcal/kg/day for the week.

The primary outcome in this study was weekly growth velocity, reported as a change in Z-score from the beginning to end of a week. This outcome was dichotomized into faster growth velocity versus slower growth velocity. Faster growth velocity was defined as a Z-score change greater (more positive) than or equal to -0.06 and slower growth velocity defined as a Z-score change less (more negative) than -0.06.[10]

Statistical Analysis

Information for the high and low exposure groups was examined by means and standard deviations for continuous variables and by frequencies for categorical variables. Between group differences in these factors were compared using Student's t-test for continuous variables and Fischer exact test for categorical variables. IH event rate by

CGA was evaluated using an unadjusted generalized linear model with repeated measures to demonstrate the natural course of IH through postnatal life.

The relationship between IH event rate and the dichotomous outcome of faster versus slower growth velocity was evaluated. In an unadjusted exploratory analysis, for each of the potential definitions of hypoxia described above, the mean IH event rate or mean percentage of time spent below threshold was compared for the faster versus slower growth velocity groups. The relationship was further evaluated using logistic regression with repeated measures analysis to control for the potential correlation of multiple data points from the same infant. This analysis was performed both for concurrent week data – evaluating the impact of the IH event rate for a given week on the growth velocity during that same week – and subsequent week data – evaluating the impact of the IH event rate for a given week on the growth velocity during the following week to account for any lag in effect that might exist.

CHAPTER III. Results

Study Population

The study population consisted of 19 infants with average birth gestational age of 28.8 weeks (standard deviation 2.4). Each infant contributed between 1 and 9 data packets, with an average of 4.5 (standard deviation 2.7) packets.

In comparing infants in the high versus low exposure groups (Table 3.1), those in the high exposure group were of lower birth weight, experienced more days of non-invasive positive pressure ventilation and low-flow nasal cannula, later CGA at time of caffeine discontinuation, and a larger percentage with a diagnosis of moderate to severe BPD. The high exposure group also trended towards lower birth GA and more days on mechanical ventilation, with marginal statistical significance.

Study Population Characteristics			
Variable	Low Exposure Group (n=6)	High Exposure Group (n=13)	p-value
	Mean (SD)	Mean (SD)	
Gestational Age at Birth (weeks)	30.2 (1.4)	28.3 (2.7)	0.059
Birth Weight (g)	1613 (361)	1200 (398)	0.045
Mechanical ventilation exposure (days)	0 (0)	1.3 (2.4)	0.076
Non-invasive positive pressure ventilation exposure (days)	13.2 (10.1)	34.1 (20.7)	0.009
Low-flow nasal cannula exposure (days)	0 (0)	19.9 (17.4)	<0.001
CGA on last day of caffeine	33.4 (0.28)	34.4 (0.9)	0.003
Variable	N (%)	N (%)	p-value
Caucasian (%)	3 (50.0)	10 (76.9)	0.30
Male (%)	3 (50.0)	7 (53.9)	1
Multiple birth (%)	0 (0)	4 (30.8)	0.3
BPD (moderate to severe) (%)	0 (0)	8 (61.5)	0.02

Table 3.1. Study Population Characteristics. Demographic and clinical characteristics of the study population, comparing those infants with low exposure to IH (n=6) with those with high exposure to IH (n=13). The first section of the table includes continuous variables, reported as mean and standard deviation for each exposure group. The second section of the table includes categorical variables, reported as a total N and frequency (%) for each exposure group. The comparison between groups is reported as a p-value, with statistical significance considered for $p < 0.05$.

Intermittent Hypoxia by Gestational Age

To evaluate the natural course of IH over the course of postnatal life, the IH event rate was examined according to CGA (Figure 3.1) using generalized linear regression with repeated measures. The mean IH rate was at its peak in the earliest gestational ages that were examined in this study. The subsequent mean IH rates decreased with increasing CGA.

Intermittent Hypoxia and Growth Velocity

The relationship between IH and growth velocity was explored for various working definitions of hypoxia (Figure 3.2). For each definition of hypoxia evaluated, there was a nonsignificant trend towards slower growth velocity in weeks with higher event rates of IH or higher percentages of time spent below the oxygen saturation threshold of 90% as compared with those with lower event rates or lower percentages of time spent below threshold.

The relationship between growth velocity and IH was further evaluated using logistic regression with repeated measures analysis. This regression analysis was performed for both the concurrent model and the lag-effect model, adjusting for GA at birth, CGA at start of the week, and caloric density of feeds (Table 3.2). The odds ratio (OR) for the odds of slower growth velocity for each unit increase IH was greater than 1 for each definition of hypoxia used in the model. Similar to the unadjusted exploratory analysis, this multivariable adjusted analysis revealed a marginally significant trend towards a higher odds of slower growth velocity in weeks with a higher event rate of IH than in those weeks with a lower event rate.

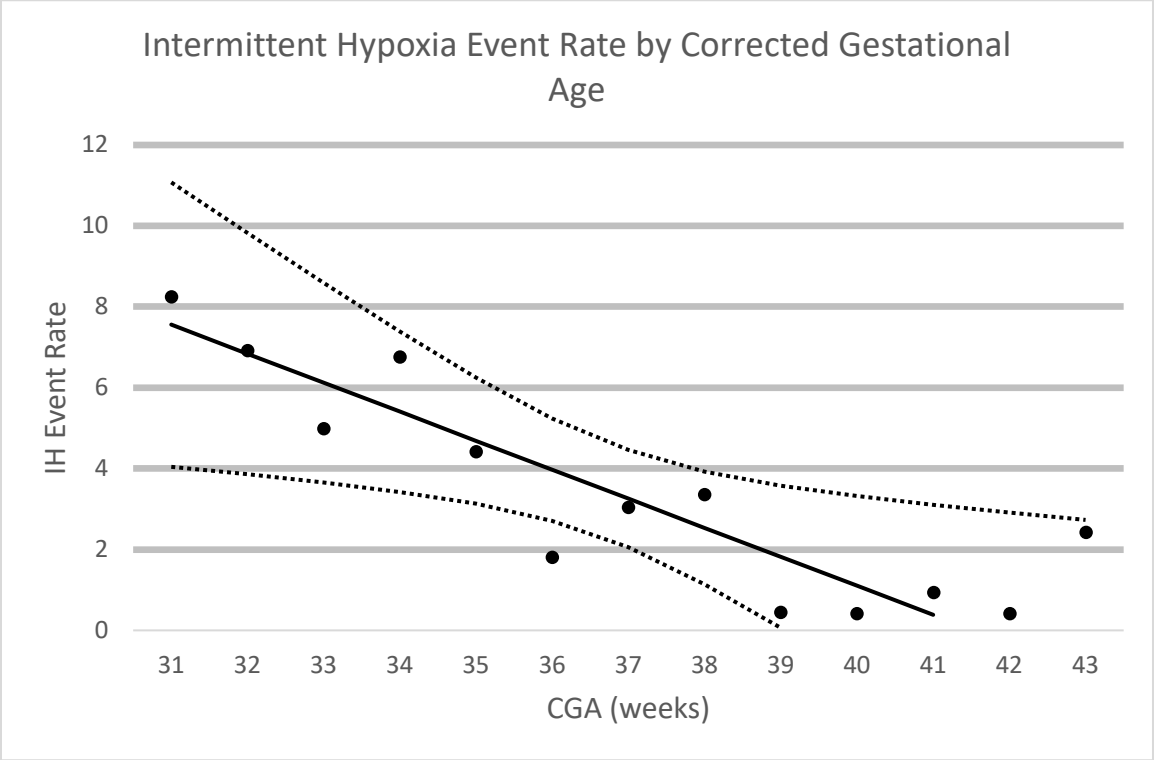

Figure 3.1. Intermittent Hypoxia Event Rate by Corrected Gestational Age. For each week of corrected gestational age, the observed average intermittent hypoxia event rate (# of IH episodes per hour) is denoted by the solid circles, predicted event rate from generalized linear model with repeated measures is displayed with the solid line, and the 95% confidence interval from the generalized linear model with repeated measures is displayed with dashed lines.

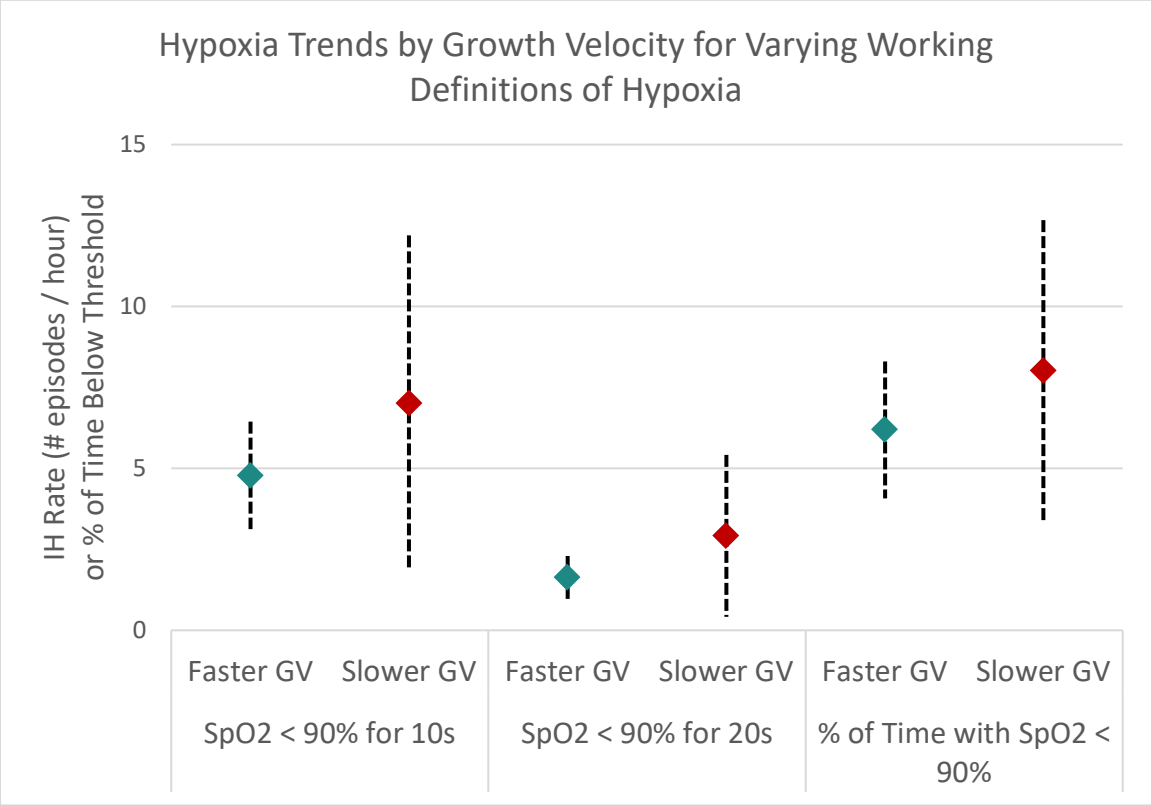

Figure 3.2. Hypoxia Trends by Growth Velocity for Varying Working Definitions of Hypoxia. The average event rate (number of IH episodes per hour) or average percentage of time spent hypoxic for each proposed definition of hypoxia (IH episodes with SpO2 <90% for at least 10 seconds, IH episodes with SpO2 <90% for at least 20 seconds, and percentage of time below 90%) for infants with faster growth velocity versus slower growth velocity. Faster growth velocity was defined as weekly Z-score change ≥ -0.06) and slower growth velocity was defined as Z-score change < -0.06. Results are reported as mean with 95% confidence intervals. The comparison of faster versus slower growth velocity for each definition of hypoxia all had $p > 0.05$.

Odds Ratios (ORs) for Odds of Slower Growth Velocity	
Working Definitions of Hypoxia Examined	Adjusted OR (95% CI)
Concurrent Model	
Event rate for SpO2 < 90% for at least 10s	1.04 (0.99, 1.08)
Event rate for SpO2 < 90% for at least 20s	1.08 (0.98, 1.18)
Percentage of time with SpO2 < 90%	1.02 (0.97, 1.08)
Lagged Model	
Event rate for SpO2 < 90% for at least 10s	1.01 (0.98, 1.04)
Event rate for SpO2 < 90% for at least 20s	1.03 (0.97, 1.08)
Percentage of time with SpO2 < 90%	1.01 (0.99, 1.04)

Table 3.2.Odds Ratios (ORs) for Odds of Slower Growth Velocity. Results of logistic regression with repeated measures analysis using various definitions of hypoxia as the primary exposure in the analysis. ORs for the odds of slower growth velocity for each unit increase in IH were obtained from the regression model, adjusted for GA at birth, CGA at start of week, and average caloric density of feeds for the week. This was evaluated for both the concurrent week model and lagged model.

CHAPTER IV. Discussion

The results of our study revealed a relationship between IH and slower growth velocity. While these results were only marginally significant, they were consistent across multiple definitions of hypoxia. This relationship was evaluated for effects of IH on growth velocity in the concurrent week as well as for the subsequent week. The results in the concurrent model were more significant than those in the lagged model, suggesting that intermittent hypoxia has a real-time effect on postnatal growth more than a delayed effect.

Natural History of Intermittent Hypoxia

The results of our study show that infants with higher exposure to IH were born at a lower GA and birth weight, presented with more significant respiratory disease, and required a longer duration of caffeine treatment than those with lower exposure to IH. The existing literature on IH has identified apnea of prematurity as a primary driver of IH[11, 15] and lower birth gestational age and birth weight as risk factors for development of apnea of prematurity and IH[12]. Our study population is reflective of this existing literature, supporting that those of lower gestational age and lower birth weight have a greater exposure to IH. Similarly, those in our study population with a higher exposure to IH also had longer durations of respiratory support and caffeine treatment, likely related to more significant apnea of prematurity leading to their increased exposure to IH.[22]

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The natural course of apnea of prematurity has been described to peak at 30-31 weeks gestational age[12]. The natural course of IH has thus far been explored by only postnatal age and suggests a peak in IH at 4-5 weeks postnatal age[17]. Our cohort had a peak in IH at 31 weeks CGA, but with persistently elevated rates as high as 34 weeks, which, given our cohort's average birth gestational age of 29 weeks, is consistent with existing IH incidence data. In accordance with the literature, the incidence of IH decreased, but was not always completely resolved at term and early post-term CGA.[23,24] Considering the above, our patient population can be considered reflective of the general preterm infant population.

Implications of Intermittent Hypoxia on Growth Velocity

The current literature on the impact of hypoxia on growth in preterm infants is minimal and primarily limited to animal-model studies. The STOP-ROP trial evaluated infant growth as a secondary outcome of the study, including absolute weight gain (in grams) over multiple time points of the study.[25] This trial did not find differences in weight gain between infants randomized to a higher or lower oxygen saturation target group. These results suggest that oxygen saturation targeting does not impact postnatal growth. However, even the low oxygen saturation group had a lower oxygen saturation

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target of 89%, and this comparison does not truly reflect the effects of hypoxia on growth.

There are a limited number of animal-model studies evaluating the impact of hypoxia on growth; the collective findings of these studies suggest that hypoxia in the neonatal period can have transient effects on neonatal growth, with eventual catch-up growth after the cessation of exposure to hypoxia, but can also contribute to failure to achieve lifelong catch-up growth in the evaluation of adult growth metrics.[19,20] However, the overall impact of hypoxia on neonatal growth remains unclear and requires further research.

Our study aimed to address this gap in the existing literature. We evaluated the effects of IH on growth velocity using concurrent respiratory and growth data to determine the impact of IH on growth in real time. We repeated the analysis for growth data in the week following the respiratory data to account for any potential lag effect. Since hypoxia can be defined in a variety of ways, including IH episodes of various duration or of total percentage of time spent below a target saturation, this relationship was evaluated for multiple definitions of hypoxia. In both the concurrent and lag-effect models, the exploratory analysis revealed a trend towards a higher event rate of IH in weeks of slower growth velocity. This trend was consistent across all definitions of hypoxia. Our findings in a relatively small population of very and extremely preterm infants suggest a trend towards slower growth velocity with increased number of IH episodes.

Study Strengths and Limitations

Our study had many unique features that contributed to its strengths. This was a prospective study with continuously recorded oximetry data that utilized a short averaging time, considered to be the gold standard for research, that provided granular respiratory data with regards to the identification of hypoxia, whether defined by IH episodes or percentage of time spent below the target threshold. Similarly, since these data were collected prospectively on inpatient infants, the growth and nutrition data were able to be collected in an accurate and complete manner. The daily nutritional intake in both volume and caloric density was available for all infants, allowing for the average daily caloric intake in kcal/kg/day to be used as a confounding variable in the analysis. These infants were also weighed daily, with absolute weight and Z-score recorded, such that weekly change in Z-score was able to be obtained for all included data packets.

The primary limitation of this study was the small sample size. Since the data were derived from a pre-existing randomized controlled trial, we were limited to the number of infants who completed enrollment in the trial, and the number of data packets each infant was able to contribute was limited by the inherent trial design. Early in the trial, infants' oximetry data was recorded only from approximately 31 weeks CGA until the infant was off of supplemental oxygen via low-flow nasal cannula or 34 weeks CGA if the infant never required low-flow nasal cannula; the study protocol was later addended to continue recording through discharge regardless of respiratory support needs. As such, early enrolled infants often only contributed 1-3 data packets, which limited the amount of data available.

Conclusions

The results of our prospective study examined the association between the occurrence of postnatal intermittent hypoxia and poor postnatal growth. Our results revealed a trend towards slower growth velocity in response to increased hypoxia. To address the study limitations and seek to answer the question about the impact of intermittent hypoxia on neonatal growth, future studies are needed. Beginning recording oximetry data from birth through discharge would significantly increase the availability of repeated measures for each enrolled infant; this combined with a larger sample size would allow for greater power to detect an even smaller effect size that we aimed for in this pilot study and assess its clinical importance.

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