Longitudinal Assessment of Hemoglobin Oxygen Saturation in Preterm and Term Infants in the First Six Months of Life

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Objective To report longitudinal home recordings of hemoglobin O_2 saturation by pulse oximetry (Spo_2) during unperturbed sleep in preterm and term infants.

Study design We recorded continuous pulse oximetry during the first 3 minutes of each hour of monitor use (nonevent epochs) for 103 preterm infants born at <1750 g and ≤34 weeks postmenstrual age (PMA), and 99 healthy term infants.

Results Median baseline Spo_2 was approximately 98% for both the preterm and term groups. Episodes of intermittent hypoxemia occurred in 74% of preterm and 62% of term infants. Among infants with intermittent hypoxemia, the number of seconds/hour of monitoring <90% Spo_2 was initially significantly greater in the preterm than the term group and declined with age at a similar rate in both groups. The 75th to 95th percentiles for seconds/hour of Spo_2 <90% in preterm infants were highest at 36 weeks PMA and progressively decreased until 44 weeks PMA, after which time they did not differ from term infants.

Conclusions Clinically inapparent intermittent hypoxemia occurs in epochs unperturbed by and temporally unrelated to apnea or bradycardia events, especially in preterm infants at 36 to 44 weeks PMA. *(J Pediatr 2011;159:377-83)*.

The memory monitor developed for the Collaborative Home Infant Monitoring Evaluation (CHIME) study was designed to automatically store all physiological data during the first 3 minutes of each hour.[1,2] These 3-minute nonevent epochs provided an opportunity to longitudinally record hemoglobin O_2 saturation (Hbo_2 SAT) by pulse oximetry (Spo_2) during nocturnal intervals unperturbed by apnea or bradycardia alarms that triggered an event recording. On the basis of these CHIME 3-minute nonevent recordings, we previously reported that healthy term infants at 2 to 25 weeks of age generally had baseline Spo_2 levels >95% but frequently had acute intermittent hypoxemia events (Spo_2 <90%), particularly during the earliest postnatal weeks.[3] There are no prior analyses of longitudinal Spo_2 during infancy that compare infants born preterm and at term. We hypothesized that preterm infants would have more episodes of intermittent hypoxemia. Our objective was to determine the frequency with which preterm infants have intermittent hypoxemia during unperturbed nocturnal epochs of apparent sleep recorded at home and to compare Spo_2 in infants born preterm with infants born at term.

Methods

Detailed methods for the CHIME study and for the recording and analysis of Spo_2 have previously been reported.[2,3] Written informed consent was obtained for each infant, and the study was approved by the institutional review board at each of the five clinical sites.

The CHIME study included preterm infants born at <1750 g and <35 weeks postmenstrual age (PMA) and healthy term infants. Because of the data processing costs associated with scoring physiological data for this analysis, a priori sample size considerations led to a targeted sample size of 100 healthy term and 100 preterm infants, giving 80% power to detect a medium effect size (difference in means divided by the standard deviation) of 0.40, or of detecting an OR of ≤ 2.4 for outcome events with a prevalence between 0.20 and 0.80. To ensure an

CHIME	Collaborative Home Infant Monitoring Evaluation
GEE	Generalized Estimation Equation
NICU	Neonatal intensive care unit
PMA	Postmenstrual age
Spo_2	Hemoglobin O_2 saturation by pulse oximetry
Hbo_2 SAT	Hemoglobin O_2 saturation

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adequate amount of monitoring data for analysis in each infant, only infants who were monitored for ≥50 hours over ≥3 months were included. Among the 472 preterm infants enrolled in the CHIME study, 207 met the monitor use criterion. Of these 207 infants, 176 did not have any episodes of apnea or bradycardia noted in the bedside nursing notes in the last 5 days before discharge (symptom-free preterm infants), and 31 did have at least one such episode noted during the 5 days before discharge (symptomatic preterm infants). To permit a comparison of symptom-free and symptomatic preterm infants and to achieve the target of approximately 100 total preterm infants, all 31 symptomatic preterm infants were included, and 73 of the 176 symptom-free preterm infants were randomly selected for inclusion. Data were weighted for analysis to account for this overrepresentation of symptomatic preterm infants in our sample. Our previously published study of term infants included the first 67 infants who met this minimum monitor use criterion. On completion of the CHIME study, there were 48 additional term infants with sufficient monitor use for inclusion, of whom 36 were randomly selected to be analyzed, with a goal of including approximately 100 infants in the term cohort. After excluding one term and one preterm infant for technical reasons or acute respiratory illness requiring hospitalization, the final number of infants included in this report is 103 preterm infants (30 symptomatic, 73 symptom-free) and 99 healthy term infants (Figure 1; available at www.jpeds.com).

Physiological Recordings

The CHIME monitor included an electrocardiographic monitor and cardiotachometer, an Ohmeda Minx pulse oximeter (Ohmeda Corp, Liberty Center, New Jersey), and an accelerometer-position sensor.[1,2] The Ohmeda oximeter measured fractional Spo_2, and the percent error of measurement is <3%. The oximeter used a 3-second moving average of Spo_2 that updated once per second. Standard reusable pulse oximeter probes (Ohmeda SoftProbe) were placed on a foot; the probes were routinely repositioned every 4 to 8 hours and replaced approximately monthly. The position sensor was taped on the diaper over the lumbar region to provide a continuous recording of infant position.

Each family was asked to monitor their infant at home during anticipated sleep from enrollment until 6 months PMA. Because most monitor use occurred between 10:00 p.m. and 7:00 a.m., we restricted this analysis to these 9 hours. For all preterm and term infants, the range of PMA for which home recordings were analyzed was limited to 36 to 59 and 43 to 65 weeks, respectively, because of insufficient data before and after these limits.

One innovative aspect of the CHIME monitor was that it was programmed to automatically record waveforms for all physiological variables during the first 3 minutes of each hour, separate and unrelated to the event-based recordings triggered by reaching the preset apnea or bradycardia threshold.[2]

Scoring

Tools for data analysis. The same individual (D.R.) at the Data Coordinating and Analysis Center rescored the 3-minute nonevent epochs from the previously reported healthy term infants and scored all of the epochs from the preterm and the additional term infants included in this report.[3] Scoring was performed on a computer with a 21-inch video display with a software tool developed and validated for this project.[3,4] The software tool was programmed to display only the 3-minute epochs. A protocol was similar to the previous report that described in detail the criteria for assessment of waveforms (Figure 2).[3] The physiological montage displayed during scoring included Spo_2 and the pulse signal from the oximeter, three respiratory channels (abdominal and thoracic inductance, sum), electrocardiography and heart rate, and sleep position. The software tool was used to display and assess each waveform in a consistent manner. For a pulse oximetry signal to be visually assessed as reliable and therefore used in scoring Spo_2, the pulse wave signal had to be free of artifact and the derived heart rate had to be consistent with heart rate from the corresponding electrocardiography-derived heart rate. Data were reported as the proportion of 3-minute epochs that met a specified criterion or as the total number of seconds during which specific criteria were met to account for multiple occurrences during a single epoch, for example, three episodes of intermittent hypoxemia within a single 3-minute epoch.

Assessment of Baseline Spo_2. Baseline Hbo_2 SAT was the longest interval ≥10 seconds in duration that met the following conditions: regular respiratory rate and amplitude, good pulse oximeter waveform, no movement artifact, and ≥15 seconds after any movement, sigh, or respiratory pause ≥5 seconds. The scoring software tool determined the baseline Spo_2 by calculating the mean of the 1 sample/sec saturation values during this segment.

Assessment of Acute Intermittent Hypoxemia. An acute decrease in Spo2 was defined as a decrease in absolute Hbo2 SAT of at least 10% from a stable preceding baseline interval (ie, from 93% to 83%) that was sustained below 90% for ≥5 seconds. For each intermittent hypoxemia event, four variables were recorded: duration of Spo2 <90% and <80%, lowest Spo2 reached, and the longest respiratory pause associated with the intermittent hypoxemia event.

For each 3-minute nonevent epoch, the total duration of each respiratory pause ≥5 seconds was measured and recorded (Figure 2). The sum channel was used to identify and measure the duration of each pause, hence including obstructed breaths as well as central pauses.[1] The duration of periodic breathing within each epoch was measured. Periodic breathing was defined as a sequence of at ≥3 episodes of apnea >3 seconds in duration and separated by ≥20 seconds of normal respiration. In many instances, the beginning or end of the periodic breathing episode did not

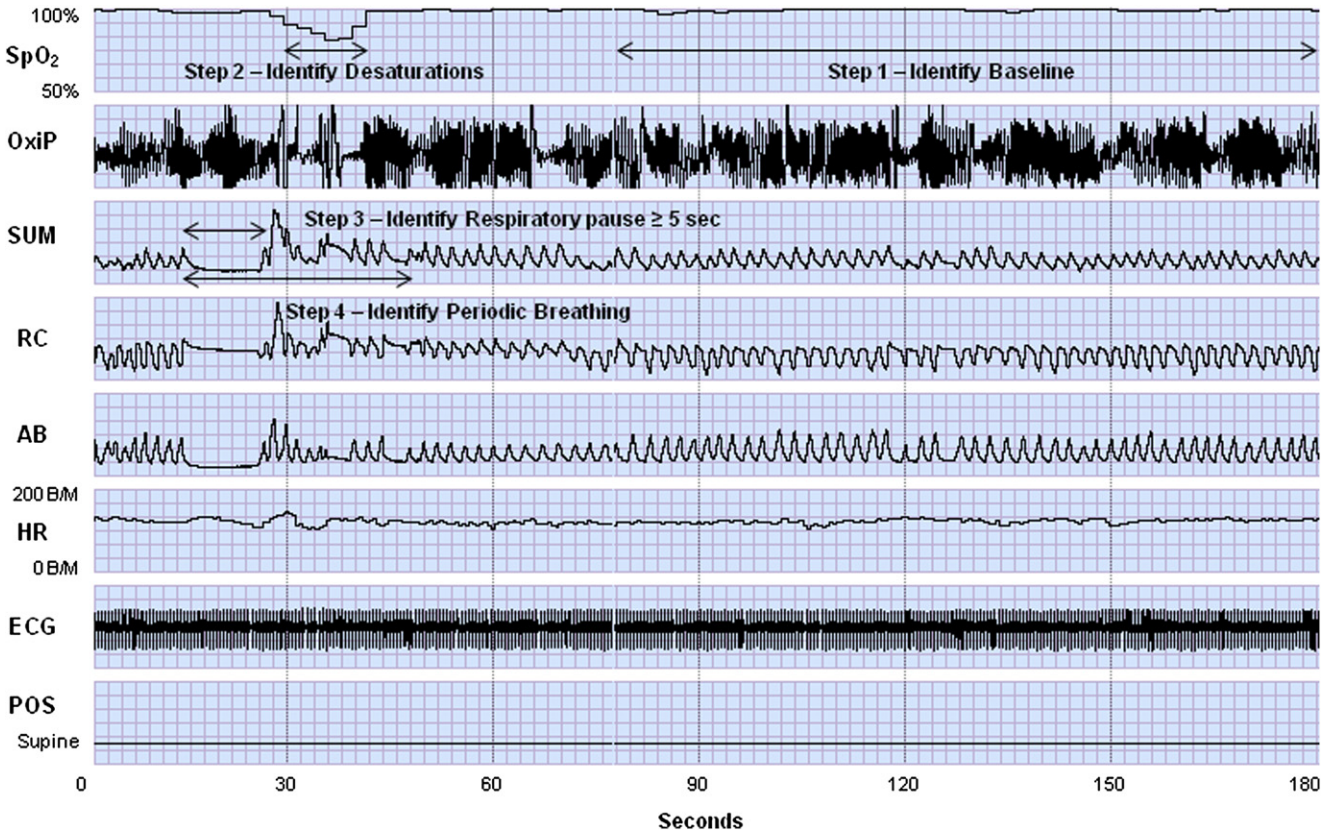

Figure 2. Assessment of 3-minute nonevent epoch. This epoch is from a healthy term infant at 63 weeks PMA. *Step 1*: Determine baseline Spo_2; the two cursor lines mark the beginning and end of the segment meeting criteria for baseline Spo_2. *Step 2*: Identify acute decreases in Spo_2: there is one acute decrease in this epoch. Each decrease is then scored for duration <90% and <80%, lowest Spo_2, and the longest respiratory pause associated with a decrease. *Step 3*: Identify all respiratory pauses >4 seconds; there is one respiratory pause >4 seconds in this epoch. The total number of pauses >4 seconds is counted and their duration recorded with the scoring tool. *Step 4*: Identify periodic breathing and the duration of each episode. There is only one apparent episode in this epoch. *Step 5*: Identify sleep position for baseline Spo_2 and acute decreases in Spo_2.

occur within the epoch. For each second during the 3-minute epoch, the software tool sampled and stored the infant's position as prone, side, or supine.

Statistical Analysis

Analyses were weighted to account for the overrepresentation of symptomatic preterm infants in our sample. Maternal and infant characteristics of the term and preterm cohorts were compared through the independent sample test for continuous measures and the χ^2 test for categorical measures. We then performed longitudinal multivariate analysis to assess group differences in baseline Spo_2 and occurrence of acute decreases over the follow-up time. For these analyses, per-epoch data for each infant were summarized to one observation per infant per week. To account for within-infant correlation resulting from having multiple weeks of data per infant, we used Generalized Estimation Equation (GEE) methodology using PROC GENMOD in SAS (SAS Institute, Inc, Cary, North Carolina) with an autoregressive 1 correlation structure.[5] Baseline Spo_2 was log-transformed for analysis to account for a non-Gaussian distribution and GEE logistic regression was used for the dichotomous acute decrease outcome. Per-epoch analyses involving differences between preterm and term infants for sleep position or periodic breathing were conducted through GEE logistic regression models controlling for within-infant correlation resulting from having multiple epochs from each infant. Type 1 error was set to 0.05 for all hypothesis testing.

Results

The maternal and infant characteristics of the preterm and term infants included in this report are summarized in the Table. To assess the extent that infants included in the analyses differed from those not included, we also compared the included infants with (1) those excluded because of insufficient monitor use and (2) those meeting the monitor use criterion but not selected for inclusion. Consistent with previously published data, infants included in this study had mothers who were older, better educated, more likely to be of white race, more likely to be to be married, and less likely to smoke.[2,3] Infants who met the

Table. Demographic characteristics of preterm and term infants

Group characteristics	Preterm infants* (n = 103)	Healthy term infants (n = 99)	*P* value
Infants			
Birth weight, g (SD)	1232 (312)	3329 (306)	<.001
% Male	44.7	49.5	.491
GA weeks at birth (SD)	29.4 (2.3)	39.4(1.0)	<.001
Age days at monitor start (SD)	50.1 (20.3)	16.1 (10.1)	<.001
Mothers			
Age, y (SD)	29.4 (6.3)	32.2 (5.3)	.001
Education, y (SD)	12.5 (3.5)	15.8 (2.7)	<.001
Race			<.001
% White	40.2	67.7	
% Hispanic	24.5	7.1	
% Black	16.7	2.0	
% Asian	10.8	10.1	
% Other	7.8	13.1	
% Married	68.6	91.9	<.001
% Pregnancy cigarette use	20.8	9.1	.021
% Pregnancy alcohol use	14.9	23.2	.131
Parity			.908
% One	37.3	34.3	
% Two	31.4	33.3	
% Three and more	31.3	32.4	

Maternal and infant characteristics for the enrolled cohorts of 103 preterm* and 99 healthy term infants. Total percentages may not equal 100% because of rounding. The differences between groups are as expected for a comparison of infants born preterm and term.
*<1750 g and ≤34 weeks postmenstrual weeks at birth.

monitor use criterion but were not selected for inclusion in this study did not differ significantly from those who were included in the analyses. As expected, compared with the mothers of term infants, mothers of preterm infants were significantly younger, had less education, and were more likely to be nonwhite, unmarried, and a smoker.

The total of 3-minute epochs assessed in the preterm and term groups was 75 286 and 68 920, respectively. After exclusions for movement artifact and no Spo_2 signal, 44 252 (59%), and 53 149 (77%) of epochs, respectively, remained for analysis. The median (extremes) number of hours assessed per infant was 17.9 (0.3; 66.2) and 26.4 (7.6; 55.8) in the preterm and term groups, respectively. The median (extremes) hours assessed per week for all infants combined was 102 (38; 121) and 126 (75; 152) in the preterm and term groups, respectively. Sleep position data were available in 44% and 61% of the preterm and term groups, respectively; the other infants had an indeterminate position or may not have had the sensor in place. Among those with sleep position recorded, 57% and 65% were supine ($P = .043$), and 28% and 25%, respectively, were prone ($P = .941$). Among all assessed epochs, only 0.06% and 0.08% in the preterm and term cohorts, respectively, included an event meeting the recording threshold for apnea (16 seconds).

Baseline Spo_2

Identification of a segment >10 seconds in duration meeting the criteria for measurement of baseline Spo_2 was possible in 97% of epochs in the preterm and 98% of epochs in the term cohorts. For each infant, we calculated the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentile for their baseline Spo_2 measurements for each study week; average percentiles of baseline Spo_2 by cohort and week are presented in Figure 3. Because the symptomatic and asymptomatic preterm subgroups did not differ in respect to baseline Spo_2, we combined the two subgroups for comparison of the aggregate PT cohort with the term cohort.

For both preterm (weeks 36 to 59) and term infants (weeks 43 to 65), there was a significant quadratic trend in median Spo_2 over time, reflecting an initial increase and then gradual decrease in median Spo_2 ($P < .001$ for quadratic trend in each group). At 50 to 59 weeks PMA (common observation time), both the preterm and term cohorts showed a similar decreasing linear trend in median Spo_2 (test for difference in slopes over time $P = .478$, test for significant common slope $P < .001$). Median Spo_2 is 0.8% lower, on average, for preterm compared with term infants ($P < .001$, controlling for time).

Intermittent Hypoxemia

Among all 3-minute epochs assessed, 1.4% and 0.7% ($P < .001$, aOR = 2.31 [1.49, 3.57] controlling for infant) in the preterm and term cohorts, respectively, had ≥1 episode of intermittent hypoxemia to <90%. Among all infants in the preterm and term cohorts, 79% and 65% ($P = .064$) of infants, respectively, had ≥1 intermittent hypoxemia episode. The median number of episodes of intermittent hypoxemia was four in the preterm and five in the term group, but the range was wide, 1-98 and 1-65, respectively.

The symptomatic and symptom-free preterm infants with any intermittent hypoxemia did not differ in their baseline comparisons or the frequency and severity of intermittent hypoxemia, and we therefore combined them for comparison with the term cohort. The percent of infants with ≥1 intermittent hypoxemia episode, by week, for the preterm and term cohorts is shown in Figure 4, A. For both the preterm and term cohorts, the percent of infants showed an initial drop over time (from week 36 to week 44 for preterm, $P < .001$; from week 43 to 50 for term, $P < .001$). For preterm infants, there was no significant decrease in the percent with intermittent hypoxemia episodes after this initial drop ($P = .275$), and for term infants there was a slower but significant decline through week 65 ($P < .001$). Between weeks 50 and 59 (common observation time and after the initial drop in intermittent hypoxemia episodes), there was no significant difference between the term and preterm cohorts on the risk of having intermittent hypoxemia, controlling for week ($P = .777$). Examining the time spent with Spo_2 <90% per week, those infants with ≥1 intermittent hypoxemia episodes showed a significant drop in time spent with Spo_2 < 90% for both preterm (from weeks 36 to 45, $P < .001$) and term infants (from weeks 43-50, $P < .001$) (Figure 4, B). After this initial drop, there was no significant change in the time spent with Spo_2 < 90% for either the preterm ($P = .732$) or term ($P = .332$) groups. Between weeks 50 and 59 (common observation time, and after the initial drop in time with Spo_2 < 90%) there was no significant difference in time with Spo_2 < 90% between the preterm and term cohorts ($P = .363$).

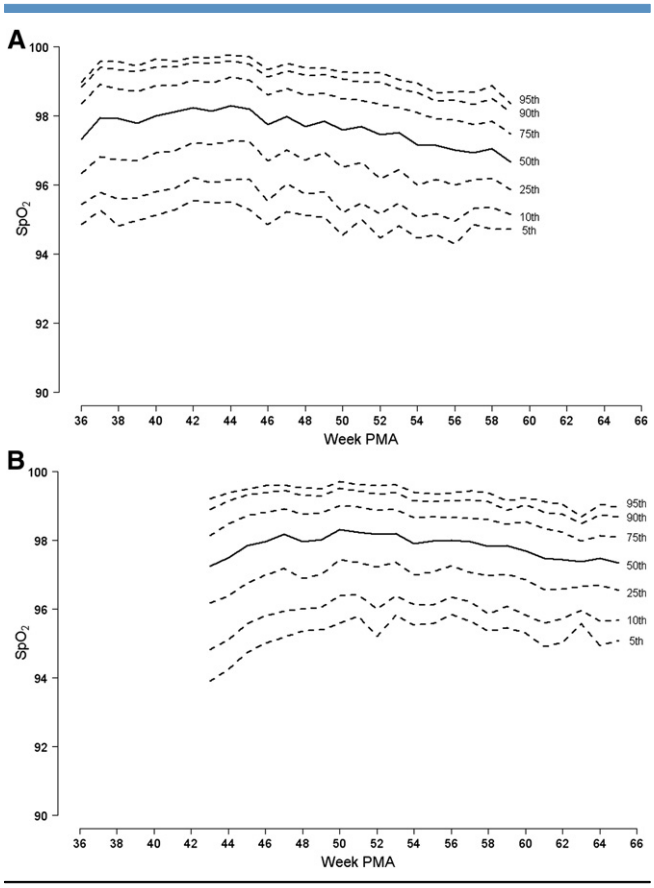

Figure 3. Baseline SpO_2 percentiles. **A,** Preterm cohort of 103 infants at 36 to 59 weeks PMA. **B,** Term cohort of 99 infants at 43 to 65 weeks PMA.

In preterm infants, 1.4% of both prone and supine epochs had intermittent hypoxemia (aOR = 1.13 [0.60, 2.12]). In term infants, for epochs in the prone versus supine positions, 0.5% versus 0.9% had intermittent hypoxemia (aOR=0.73 [0.45, 1.18], adjusting for infant and PMA).

In the preterm and term cohorts, 60% and 57%, respectively, of epochs with intermittent hypoxemia (aOR = 0.98 [0.64 , 1.52] adjusting for infant), included periodic breathing. Among all 3-minute epochs, 16% and 11% in the preterm and term cohorts, respectively, involved periodic breathing (aOR = 0.98 [0.64, 1.50] adjusting for infant and PMA). For preterm infants, the percent of epochs with periodic breathing was 12% versus 13% in the prone versus supine positions (aOR = 0.90 [0.77, 1.04] adjusting for infant and PMA). For term infants, the percent of epochs that included periodic breathing was 8.7% versus 10.9% for epochs in the prone versus supine positions (aOR = 0.99, [0.86, 1.15] adjusting for infant and PMA).

Comparing symptomatic (n = 30) and symptom-free (n = 73) preterm infants, fewer symptomatic infants had any intermittent hypoxemia (60% vs 79%, P = .041). However, there was no significant difference in the percent of symptomatic versus symptom-free patients with any intermittent hypoxemia episodes per week (aOR = 1.16 [0.62 , 2.13] controlling for infant and week) or in the seconds/hour with $Spo_2 < 90$. The time with $Spo_2 < 90$ was 5.4 sec/h lower for symptomatic vs symptom-free infants (P = .302) controlling for week.

Discussion

These data provide insight into expected Spo_2 values over time in apparently healthy preterm and term infants during the first 6 months of life studied in the home with noninvasive monitoring. Baseline values were similar for preterm and term infants, with median values of around 98%, although there were changes in median baseline values over time. Acute decreases in Spo_2 (intermittent hypoxia) were common in both preterm and term infants and strongly related to PMA. In preterm infants, the risk of intermittent hypoxemia and the number of seconds per hour below 90% during intermittent hypoxemia became similar to that of term infants by about 43 weeks PMA. These data are consistent with our previous report that the risk of an extreme cardiorespiratory event in preterm infants became similar to that of term infants at about 43 weeks PMA.[2] We had previously reported in term infants that acute decreases were more frequent in the supine position compared with the prone position, but that this observation was not significant when age was taken into account.[3] In this report, which included a larger sample of term infants, differences between prone and supine rates of acute decreases were not as large as in the prior study and were not statistically significant. In the preterm infants we did not observe significant differences in these acute decreases related to sleep position.

Several prior reports among preterm infants have documented that symptoms of immature breathing do not necessarily resolve before otherwise being ready for neonatal intensive care unit (NICU) discharge.[6-9] For example, 68% of preterm infants deemed clinically ready for discharge had recordings showing intermittent hypoxemia to ≤80% for ≥4 seconds associated with respiratory pauses, and recurrent apnea and bradycardia frequently persisted beyond 40 weeks gestation in preterm infants born at 24 to 28 weeks gestation.[6,7] Our finding of persisting intermittent hypoxemia in the early weeks after NICU discharge is consistent with these reports of delayed maturation.

The CHIME study was not powered to assess the extent of potential risk for sudden unexpected death associated with apnea or bradycardia events triggering a home monitor alarm and especially with the less common but more severe events meeting the threshold limits for an extreme event.[2] A subsequent CHIME analysis demonstrated that both preterm and term infants having five or more apnea or bradycardia events (often with associated intermittent hypoxemia) meeting threshold criteria for a monitor alarm, which includes both conventional and extreme CHIME events, had lower adjusted mean mental developmental indexes at 1 year of age than matched infants with no events or with just one to four events.[10] Although it is also possible that both the events and adverse neurodevelopmental outcome had a common underlying cause, a causal relationship is consistent with

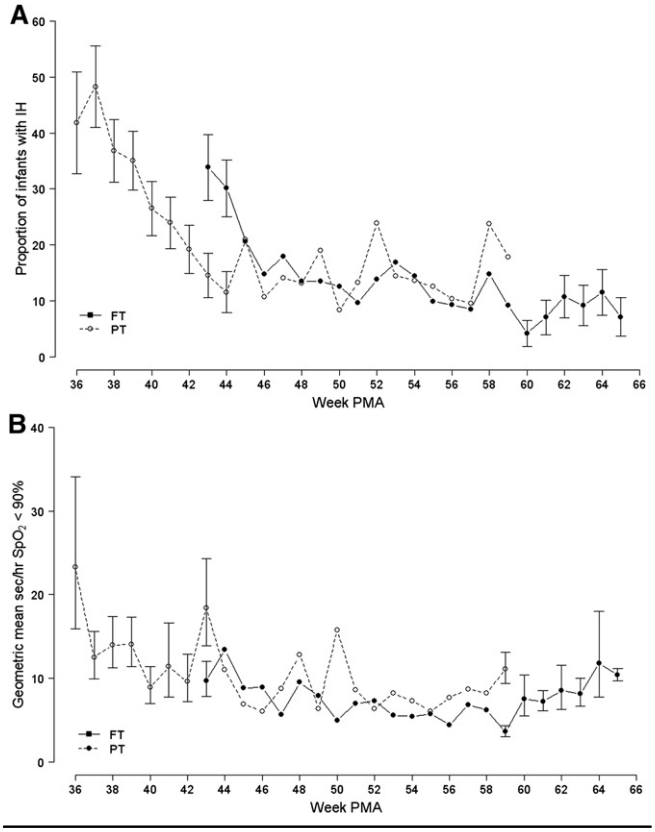

Figure 4. Frequency of intermittent hypoxia (Spo_2 <90%) in preterm and term cohorts. **A,** Percent of infants in preterm and term cohorts with ≥1 episode of intermittent hypoxemia. **B,** Number of seconds with Spo_2 <90% during intermittent hypoxemia, expressed per hour of recording time for each week PMA. **A,** SD bars, and **B,** SE bars have been included where the bars for the groups do not overlap. *IH*, intermittent hypoxia.

the cognitive and neurodevelopmental deficits in sleep-disordered breathing and associated intermittent hypoxemia in children and adults and in young children with a history of apnea of prematurity.[11-21]

Sleep-disordered breathing and associated intermittent hypoxemia have also been associated with poorer executive function and memory skills and lower general intelligence in 5-year-old children.[15] Especially in children born preterm, sleep-disordered breathing and intermittent hypoxemia in children had a negative impact on achievement and cognition, with deficits in selective measures of academic abilities, language comprehension, and planning and organizational skills at 9.5 ± 0.8 years.[16] These neurocognitive impairments suggest a causal association between intermittent hypoxemia and reduced memory, attention, and intelligence, as well as hyperactive behaviors and mood disturbances.[12,15,18] It is not possible, however, to determine the extent to which the neurocognitive and behavioral morbidities were causally related to intermittent hypoxemia, to associated sleep fragmentation, or to both.

Key strengths of this study include the extensive CHIME data base with maternal and infant characteristics and demographic and physiological data for a large number of preterm and term infants.[2] There are no comparable studies of longitudinal home physiological recordings during the first 6 months of age, especially that include pulse oximeter recordings. The innovative features of the CHIME monitor included the automatic recording of the first 3 minutes of each hour of home monitoring.[1-3] Analysis of these nonevent epochs allowed for the first time a comprehensive longitudinal assessment of Spo_2 at home unperturbed by monitor alarms and unrelated to prolonged apnea or bradycardia. We thus had an unprecedented window of opportunity to observe baseline Hbo_2 SAT and intermittent hypoxia during apparent sleep. It is a strength of this study that we had this first opportunity to review almost 100 000 total epochs and more than 100 hours of data comprised of these 3-minute epochs during each week of home recording.

The limitations of this study include the following: (1) an insufficient number of subjects to permit detailed subgroup comparisons between the symptom-free and symptomatic preterm infants; (2) although all 3-minute epochs included in our analyses were artifact-free nocturnal recordings and, hence, likely during sleep, there was no sleep state staging during these home recordings; (3) movement artifact or uninterpretable Spo_2 signal in 41% and 23% of epochs in preterm and term infants, respectively; and (4) absence of sleep position data in 56% and 39% of epochs in preterm and term infants, respectively.

Our results indicate that clinically inapparent intermittent hypoxemia was occurring in early infancy in both preterm and term infants and especially in preterm before 43 to 44 weeks PMA. Events sufficient to trigger a monitor alarm did not occur de novo but rather were often preceded by respiratory pauses, periodic breathing, and intermittent hypoxemia.[22] It is unclear to what extent the intermittent hypoxemia occurring during non-event epochs has clinical significance only as a potential precursor to events sufficient to trigger a monitor alarm or whether the intermittent hypoxemia occurring in these clinically silent epochs may be contributing to the neurodevelopmental impairments observed in other studies.[10] Future studies in preterm infants will need to better quantify the frequency and severity of intermittent hypoxemia before and after NICU discharge, the relative contribution of each to adverse neurodevelopmental outcome, and the extent to which these adverse outcomes can be ameliorated by intervention.[23] ■

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Appendix

The participants in the CHIME Study Group include the following:

Clinical Sites

Department of Pediatrics, Case Western Reserve University School of Medicine, Cleveland, Ohio

MetroHealth Medical Center: Terry M. Baird* (currently at Rainbow Babies and Children's Hospital)

Rainbow Babies and Children's Hospital: Richard J. Martin, Lee J. Brooks (currently at The Children's Hospital of Philadelphia), Roberta O'Bell‡

Department of Pediatrics, University of Toledo College of Medicine, Toledo, Ohio: Carl E. Hunt* (currently at Uniformed Services University of the Health Sciences, Bethesda, Maryland) David R. Hufford, Mary Ann Oess‡

Department of Pediatrics, Division of Respiratory Medicine, Rush Medical College of Rush University, Chicago, Illinois: Rush Children's Hospital at Rush University Medical Center: Debra E. Weese-Mayer* (currently at Children's Memorial Hospital and Northwestern University Feinberg School of Medicine, Chicago, Illinois) Jean M. Silvestri, Sheilah M. Smok-Pearsall‡

Department of Pediatrics, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, Hawaii: Kapiolani Medical Center for Women and Children: David H. Crowell,* Larry E. Tinsley (currently at Pediatrix Medical Group, Los Angeles, California), Linda E. Kapuniai‡

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Children's Hospital of Los Angeles: Thomas G. Keens, Sally L. Davidson Ward, Daisy B. Bolduc, Technical Coordinator.

Clinical Trials Operations Center

Department of Obstetrics and Gynecology, Case Western University School of Medicine and MetroHealth Medical Center, Cleveland, Ohio: Michael R. Neuman* (currently at Michigan Technological University, Houghton, Michigan), Rebecca S. Mendenhall‡

Data Coordinating and Analysis Center

Departments of Pediatrics and Epidemiology and Biostatistics, Boston University Schools of Medicine and Public Health, Boston, Massachusetts: Michael J. Corwin,* Theodore Colton, Sharon M. Bak,‡ Mark Peucker, Technical Coordinator, Howard Golub, Physiological Data Biostatistician, Susan C. Schafer, Clinical Trials Coordinator, Jean Cantey-Kiser.

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Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut: George Lister (currently at Southwestern Medical School, Dallas, Texas) National Institutes of Health (NIH): Pregnancy and Perinatology Branch, Center for Research for Mothers and Children, National Institute of Child Health and Human Development (NICHD), NIH, Bethesda, Maryland: Marian Willinger.

*Principal investigator

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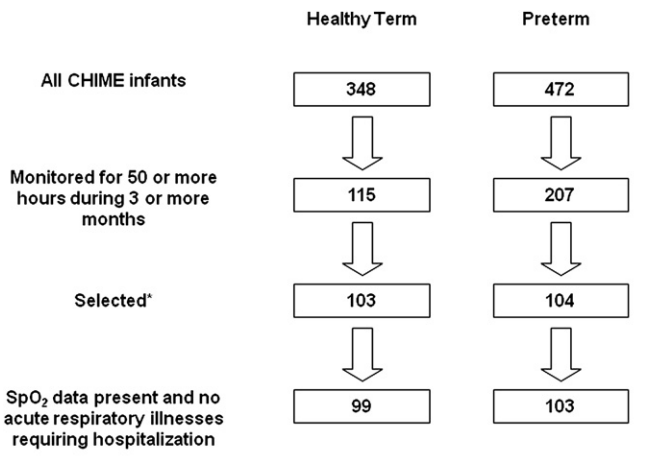

Figure 1. Summary of the selection process for reaching the final number of infants enrolled in the preterm and term infant groups. The healthy term cohort includes 67 infants previously reported.[3] Preterm: <1750 g and ≤34 weeks PMA in weeks, at birth.