The Longitudinal Effects of Persistent Apnea on Cerebral Oxygenation in Infants Born Preterm

Rosemary S. C. Horne, PhD[1], Annie C. H. Fung[2], Scott NcNeil[1], Karinna L. Fyfe, MBBS, PhD[1], Alexsandria Odoi, BNS (Hons)[1], and Flora Y. Wong, MBBS, PhD[1,3]

Objective To assess the incidence and impact of persistent apnea on heart rate (HR), oxygen saturation (SpO_2), and brain tissue oxygenation index (TOI) over the first 6 months after term equivalent age in ex-preterm infants.

Study design Twenty-four preterm infants born between 27 and 36 weeks of gestational age were studied with daytime polysomnography at 2-4 weeks, 2-3 months, and 5-6 months post-term corrected age. Apneas lasting ≥3 seconds were included and maximal percentage changes (nadir) in HR, SpO_2, and tissue oxygenation index (TOI, NIRO-200 Hamamatsu) from baseline were analyzed.

Results A total of 253 apneas were recorded at 2-4 weeks, 203 at 2-3 months, and 148 at 5-6 months. There was no effect of gestational age at birth, sleep state, or sleep position on apnea duration, nadir HR, SpO_2, or TOI. At 2-4 weeks, the nadirs in HR (–11.1 ± 1.2 bpm) and TOI (–4.4 ± 1.0%) were significantly less than at 2-3 months (HR: –13.5 ± 1.2 bpm, $P < .05$; TOI: –7.5 ± 1.1 %, $P < .05$) and at 5-6 months (HR: –13.2 ± 1.3 bpm, $P < .01$; TOI: –9.3 ± 1.2%, $P < .01$).

Conclusions In ex-preterm infants, apneas were frequent and associated with decreases in heart rate and cerebral oxygenation, which were more marked at 2-3 months and 5-6 months than at 2-4 weeks. Although events were short, they may contribute to the adverse neurocognitive outcomes that are common in ex-preterm children. *(J Pediatr 2017;182:79-84).*

Worldwide, 8%-10% of all infants are born preterm (<37 weeks of gestation). With improvements in neonatal intensive care techniques, the number of preterm infants surviving at younger gestational ages has increased dramatically. However, a substantial proportion of surviving infants born before 28 weeks of gestation will grow up with significant neurodevelopmental impairment.[1] There is an urgent need to understand the mechanisms involved so that these outcomes can be improved.

Development of respiratory control begins early in gestation. Fetal breathing movements are one of the earliest motor behaviors, and essential for normal antenatal lung growth and development.[2] Even in infants born at term, respiratory control is immature and requires weeks to months to become as stable as in adults. In preterm infants, the control of the respiratory system is even less mature, and this immaturity is frequently manifest as apnea of prematurity,[3] one of the most common diagnoses in the neonatal intensive care unit.[4]

Apnea of prematurity is defined as the cessation of breathing for >20 seconds or pauses of shorter duration if there is associated bradycardia (<100 bpm), cyanosis, or marked pallor.[4,5] Apnea of prematurity is inversely related to gestational age and occurs in more than 85% of infants born <34 weeks of gestation and in almost all infants born <28 weeks.[6] As brief pauses in breathing are often associated with bradycardia or hypoxemia, most apneas are shorter than 20 seconds.[4] Apnea of prematurity is normally resolved by term equivalent age, when the reported incidence does not exceed that in term infants.[7]

Studies have shown that excessive or persistent apnea of prematurity during infancy is associated with poorer long-term neurodevelopmental outcomes,[8,9] which have been suggested to be a result of hypoxic cerebral injury.[10] Furthermore, low regional cerebral oxygenation levels in preterm infants in the neonatal unit have been associated with poorer neurodevelopmental outcomes at 18 months.[11] Studies examining the effects of apnea on cerebral oxygenation in preterm infants before they are discharged home have shown that even short apneas are associated with falls in cerebral oxygenation measured using near infrared spectrophotometry (NIRS).[12-22] We have previously published the effects of periodic breathing on cerebral oxygenation.[23] To date, no studies have assessed the incidence and cerebral effects of persistent single apneic events after term equivalent age in infants born preterm.

CA	Corrected age
HR	Heart rate
NIRS	Near infrared spectrophotometry
SpO_2	Oxygen saturation
TOI	Tissue oxygenation index

From the [1]The Ritchie Center, Hudson Institute of Medical Research and Department of Pediatrics, Monash University, Melbourne, Australia; [2]Department of Pediatrics, Chinese University of Hong Kong, Hong Kong, China; and [3]Monash Newborn, Monash Health, Melbourne, Australia

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We aimed to assess the incidence and impact of persistent apnea during sleep on heart rate (HR), oxygen saturation (SpO_2), and brain tissue oxygenation index (TOI) over the first 6 months after term equivalent age.

Methods

The Monash Medical Center and Monash University Human Research Ethics Committees granted ethical approval for this project, and parents provided written informed consent.

In a larger study of polysomnography, 35 healthy preterm infants were recruited from Monash Newborn, Monash Medical Center and the Special Care Nursery at Jessie Macpherson Private Hospital, Melbourne, Australia.[24] For the current study, as we were investigating the longitudinal effects of persistent apnea, only data from the 24 infants who completed all 3 studies at 2-4 weeks corrected age (CA), 2-3 months CA, and 5-6 months CA were analyzed. Data on the effects of periodic breathing on cerebral oxygenation in this group of infants has previously been published.[23]

Infants were studied using daytime polysomnography at the Melbourne Children's Sleep Center, Monash Medical Center. All electrodes and measuring devices for polysomnography were attached during the infant's morning feed, and infants were then allowed to sleep naturally in a pram in a darkened room at constant temperature. Infants slept in both the prone and supine positions, with the initial starting position randomized. Sleep state was assessed as quiet or active sleep using electroencephalogram, behavioral, HR, and breathing pattern criteria.[25]

Polysomnographic recordings included continuous monitoring of electroencephalogram (C4/A1; O2/A1), electrooculogram, submental electromyogram, electrocardiogram, thoracic and abdominal breathing movements (Resp-ez Piezoelectric sensor; EPM Systems, Midlothian, Virginia), airflow from the nose and mouth (Breathsensor, Thermal Airflow Sensor; Mortora Instruments Australia, Sydney, New South Wales, Australia), and arterial SpO_2 with a 2 seconds averaging time (Masimo Radical Oximeter; Masimo Corporation, Irvine, California). In addition, we also measured cerebral oxygenation (NIRO-200 spectrophotometer, Hamamatsu Photonics KK, Tokyo, Japan) with optodes positioned 4 cm apart on the frontal region as previously described.[26] NIRS depends on the relative transparency of biological tissue to light in the near-infrared region of the spectrum. NIRS enables the noninvasive measurement of cerebral TOI. All physiological data were recorded at a sampling frequency of 512 Hz using an E-Series Sleep Recording system with ProFusion PSG 2 software (Compumedics Limited, Abbortsford, Victoria, Australia). At the completion of the study, data were exported via European Data Format to analysis software (Chart 7.0; ADInstruments, Sydney, Australia).

Apneic events were defined as those lasting ≥3 seconds.[27] Apneas occurring in episodes of periodic breathing, defined as 3 or more sequential apneas lasting ≥3 seconds interrupted by breathing lasting ≤20 seconds, were excluded. The frequency of apnea was determined for each infant as the total number of events recorded and also as an apnea index calculated as the number of apneas per hour spent in each sleep state and position. HR, SpO_2, and TOI values were extracted beat-to-beat from LabChart and a maximal (nadir) percentage change from baseline for each event were calculated for events that were movement artifact free to allow for differences between individual infants. To allow for the time lag in recording SpO_2 and TOI, nadirs were calculated during the event and up to 15 seconds after event termination.

Statistical Analyses

Data were first tested for normality (Shapiro-Wilk test) and equal variance. The effects of the sleep state and sleep position on apnea frequency, duration, apnea index, together with the cardiovascular effects (nadir percentage change in HR, SpO_2) and cerebral oxygenation (TOI) were tested at each age with 2-way ANOVA followed by a post-hoc test of Student-Newman-Keuls if required. The effects of postnatal age were tested with Kruskal-Wallis 1-way ANOVA on Ranks with Dunn method post-hoc testing if required. The relationship between duration of apneic events and gestational age and nadir % change in HR, SpO_2, and TOI were tested with Pearson correlation analysis. Results are expressed as mean ± SEM; and a P value of <.05 was considered statistically significant.

Results

Infants (13 male/11 female) were born between 27.3 and 36.2 weeks of gestational age (mean 31.2 ± 0.5 weeks, mean ± SEM) with birth weights of between 925 and 3060 g (mean 1698 ± 112 g). All infants were born with appropriate birth weight for gestational age. Apgar scores ranged from 2 to 9 (median 6) at 1 minute and 4 to 10 (median 9) at 5 minutes. Thirteen of 24 had been administered caffeine for apnea of prematurity during their hospital stay, and none were on caffeine at the time of the studies. None of the infants had been diagnosed with significant intraventricular hemorrhage (grades III or IV), and none were on supplemental oxygen at the time of the studies. Infants were studied at 2-4 weeks corrected age (CA) (mean 43 ± 0.1 weeks postconceptional age), 2-3 months (mean 51 ± 0.2 weeks postconceptional age), and 5-6 months (mean 63 ± 0.3 weeks postconceptional age). Mean total sleep time at 2-4 weeks was 3.5 ± 0.1 hour; at 2-3 months 2.9 ± 0.1 hour; and at 5-6 months 2.3 ± 2.6 hour.

All infants exhibited apneas at each age studied. A total of 253 apneas were recorded at 2-4 weeks, 203 at 2-3 months, and 148 at 5-6 months. Infants had 2-27 apneas at 2-4 weeks, 1-27 at 2-4 months, and 1-16 at 5-6 months with an average of 3 per hour at all 3 study times. Apnea duration ranged from 3.0 to 15.7 seconds at 2-4 weeks, from 3.1 to 7.3 seconds at 2-3 months, and from 3.0 to 8.1 seconds at 5-6 months. There were no effects of gestational age at birth on total apnea number, apnea index, or apnea duration at any study. The effects of sleep state and sleep position on apnea number, apnea index, and apnea duration are presented in **Table I**. At 2-4 weeks, apneas were more frequent in quiet sleep supine compared with quiet sleep prone ($P < .05$), and active sleep supine compared with