Effects of Prone Sleeping on Cerebral Oxygenation in Preterm Infants

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Objective To determine the effect of prone sleeping on cerebral oxygenation in preterm infants in the neonatal intensive care unit.

Study design Preterm infants, divided into extremely preterm (gestational age 24-28 weeks; n = 23) and very preterm (gestational age 29-34 weeks; n = 33) groups, were studied weekly until discharge in prone and supine positions during active and quiet sleep. Cerebral tissue oxygenation index (TOI) and arterial oxygen saturation (SaO_2) were recorded. Cerebral fractional tissue extraction (CFOE) was calculated as CFOE = (SaO_2 - TOI)/SaO_2.

Results In extremely preterm infants, CFOE increased modestly in the prone position in both sleep states at age 1 week, in no change in TOI despite higher SaO_2. In contrast, the very preterm infants did not have position-related differences in CFOE until the fifth week of life. In the very preterm infants, TOI decreased and CFOE increased with active sleep compared with quiet sleep and with increasing postnatal age.

Conclusion At 1 week of age, prone sleeping increased CFOE in extremely preterm infants, suggesting reduced cerebral blood flow. Our findings reveal important physiological insights in clinically stable preterm infants. Further studies are needed to verify our findings in unstable preterm infants regarding the potential risk of cerebral injury in the prone sleeping position in early postnatal life. *(J Pediatr 2019;204:103-10).*

Advances in neonatal care have resulted in increased survival rates of preterm infants born at earlier gestational ages (GA).[1] However, the likelihood of brain injury and neurodevelopmental disability is concerning.[2] Although the etiology of preterm brain injury is complex, impairments in cardiovascular and cerebrovascular function leading to cerebral hypoxia-ischemia have been implicated.[3] During the early postnatal period, preterm infants undergo rapid brain growth and maturation, and the role of sleep in brain development is emphasized.[4] However, instabilities in cardiovascular and cerebrovascular function are most marked during sleep.[5] It is common practice for preterm infants in a neonatal intensive care unit (NICU) or special care unit (SCU) to be in the prone position for >50% of the time, with the understanding that the prone sleeping position improves respiratory function and oxygenation.[6] However, prone sleeping increases the risk of the sudden infant death syndrome (SIDS), and the association between the prone sleeping position and SIDS is 4-fold stronger in preterm infants compared with term-born infants.[7] In term-born infants, prone sleeping is associated with reduced cerebral oxygenation,[8] lower blood pressure,[9] and impaired autonomic cardiovascular control,[10] which are most marked at age 2-3 months when the risk of SIDS is greatest. These adverse effects are amplified by preterm birth.[11,12] To date, the effect of sleeping position on cerebral oxygenation and cardiovascular variables has not been examined longitudinally in preterm infants in the NICU.

Sleep state also has a significant effect on both cardiovascular and respiratory functions. Preterm infants spend the majority of their time in active sleep, a state in which cardiorespiratory control is most unstable.[13] The previously reported respiratory and SaO_2 improvements in the prone position may be confounded by the sleep state, because infants have more quiet sleep in the prone position, a state of reduced respiratory instability.[14] In addition, the high level of brain activity during active sleep results in greater cerebral oxygen consumption compared with quiet sleep during the newborn period.[15]

In this study, we aimed to examine the effect of sleeping position on cerebral oxygenation, cerebral oxygen extraction, and cardiovascular measures in preterm infants born at a range of GAs, studied longitudinally while in the NICU and SCU, taking into account the effect of sleep state. We hypothesized that the prone sleeping position would be associated with lower cerebral oxygenation compared with the supine position, and that the reduction in cerebral oxygenation would be most

CBF	Cerebral blood flow	MABP	Mean arterial blood pressure
CFOE	Cerebral fractional oxygen extraction	NICU	Neonatal intensive care unit
FiO_2	Fraction of inspired oxygen	SaO_2	Arterial oxygen saturation
GA	Gestational age	SCU	Special care unit
HR	Heart rate	SIDS	Sudden infant death syndrome
IVH	Intraventricular hemorrhage	TOI	Tissue oxygenation index

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prominent in preterm infants born at earlier GAs and at younger postnatal ages.

Methods

Ethical approval was obtained from the Monash Health and Monash University Human Research Ethics Committees. The project was carried out in accordance with the 2007 National Statement on Ethical Conduct in Human Research produced by the National Health and Medical Research Council of Australia. Written and informed parental consent was obtained, and no monetary incentive was provided for participation.

Preterm infants were studied while receiving care in the NICU or SCU at Monash Newborn, Melbourne, Australia. Exclusion criteria included intrauterine growth restriction, indwelling umbilical catheters, major congenital abnormalities, or major brain pathologies, such as grade 3-4 intraventricular hemorrhage (IVH) and periventricular leukomalacia. All aspects of the clinical management were at the attending physician's discretion. Infants were studied longitudinally on a weekly basis, with the first study performed at 1 week of life. Studies were continued until term age or until transfer or discharge from the NICU or SCU.

Each preterm infant underwent a daytime sleep study of 2-4 hours duration. Infants were studied with the prone/supine or supine/prone sequence according to the nursing schedule. In the supine position, the head was maintained in the midline, and in the prone position, the head was rotated homolaterally to the near-infrared spectroscopy probe placed on the temporoparietal region (see below). During the study, care procedures were minimized. Preductal arterial oxygen saturation (SaO_2) was measured using an oximeter probe (Masimo, Irvine, California) placed on the right upper limb. SaO_2 was maintained at 90%-95% with ventilatory and oxygen adjustments according to clinical protocol. Heart rate (HR) was recorded from electrocardiogram leads (Covidien, Dublin, Ireland).

Cerebral oxygenation, expressed as cerebral tissue oxygenation index (TOI; %), was continuously measured by near-infrared spectroscopy (NIRO 200NX; Hamamatsu Photonics, Hamamatsu, Japan). Two aligned photodetectors were housed inside the detection probe and fixed at 4 cm from the emission probe. The probes were placed over the temporoparietal region.

Mean arterial blood pressure (MABP) was measured using a small photoplethysmographic cuff (Finometer; Finapres Medical Systems, Enschede, The Netherlands) placed around the infant's wrist, as has been previously validated during sleep in preterm infants.[4] MABP data were collected in 1- to 2-minute epochs, with at least 4 minutes between inflations to prevent venous pooling in the hand. All physiological measures (electrocardiography, SaO_2, MABP, and TOI) were recorded simultaneously on a Powerlab system (AD Instruments, Sydney, Australia) at sampling rate of 400 Hz.

Infant sleep state was scored in 30-second epochs at the bedside using established behavioral criteria.[16] Quiet sleep was characterized by absence of eye movements, regular respiratory and HR patterns, and absence of body movements. Active sleep was characterized by the presence of eye movements, irregular respiration and HR patterns, and frequent gross and small body movements. When the criteria for neither quiet sleep nor active sleep were met, sleep was classified as indeterminate sleep, but these epochs were excluded from the analyses.

Data were analyzed using LabChart software (AD Instruments). Beat-to-beat values were calculated for TOI, SaO_2, and HR in 1- to 2-minute epochs when MABP was recorded.[11] By simultaneously monitoring TOI and SaO_2, cerebral fractional oxygen extraction (CFOE) can be calculated as CFOE = (SaO_2 - TOI)/ SaO_2.[17] In preterm infants with respiratory illness and fluctuating SaO_2 that affects the TOI values, CFOE is a useful indicator of the balance between cerebral blood flow (CBF) and cerebral oxygen consumption.[17] Data were averaged for each 1-2 min epoch and pooled for each sleep state and position within each postnatal week. An average of 4 (3-5) epochs were analyzed in each sleep state and position at each study.

Statistical Analyses

Statistical analysis was performed using SPSS version 24 (IBM, Armonk, New York). For demographic variables, the Fisher exact test or χ^2 test was used. Linear regression was used to assess the effect of GA at birth as a continuous variable in all infants on TOI, SaO_2, CFOE, HR, and MABP in each position and state at each postnatal week.

Two-way repeated-measures ANOVA with Student-Newman-Keuls post hoc testing was used to assess the effects of sleep position and sleep state on TOI, SaO_2, CFOE, HR, and MABP in each GA group (extremely preterm and very preterm) and at each postnatal week. The effect of postnatal age was determined using a linear mixed model with Bonferroni post hoc testing in each GA group and sleep state, with postnatal age and sleep position as fixed effects and subject as the random effect. Results are presented as mean ± SEM with significance taken at $P < .05$.

Results

We studied 56 preterm infants (28 females and 28 males) born at 24-34 weeks of GA. Regression analysis identified that during the first 3 weeks of life, TOI, SaO_2, and MABP were positively correlated with GA at birth in both sleep positions and both sleep states (**Tables I** and **II**; available at www.jpeds.com). During the first 2 weeks of life, CFOE was negatively correlated with GA at birth in the prone position in both sleep states. Because these initial analyses showed significant effects of GA on the physiological variables of interest, infants were subdivided into the 2 groups defined by GA for all subsequent analyses: $24^{0/7}$ to $28^{6/7}$ weeks GA (extremely preterm; n = 23) and $29^{0/7}$ to $34^{6/7}$ weeks GA (very preterm; n = 33). Extremely preterm infants had an average of 7 studies (range, 1-12), and the very preterm cohort had an average of 3 studies (range, 1-8) per infant.

Demographic characteristics for the group as a whole and in the 2 GA groups are presented in **Table III**. By design, GA at birth and birth weight were significantly lower in the extremely preterm group. The extremely preterm infant group had more intubations during resuscitation at birth and

Table III. Demographic characteristics of all infants and cohort split by GA into extremely preterm (<29 weeks) and very preterm (≥29 weeks) groups

Clinical features	All infants (n = 56)	Extremely preterm (n = 23)	Very preterm (n = 33)
Female sex, n (%)	28 (50%)	10 (44%)	18 (55%)
Twin, n (%)†	16 (28%)	6 (26.1%)	10 (30.3%)
GA at birth, wk, median (range)	29 (24-34)	27 (24-28)*	30 (29-34)
Birth weight, g, mean (range)	1307 (715-2133)	1040 (715-1719)*	1492 (1031-2133)
1-min Apgar score, median (range)	7 (3-9)	6 (4-8)	8 (3-9)
5-min Apgar score, median (range)	8 (3-10)	8 (3-9)	9 (6-10)
Resuscitation at birth-intubation, n (%)	7 (12)	5 (22)*	2 (6)
Received antenatal steroids, n (%)	46 (82)	21 (91)	25 (76)
Respiratory distress syndrome, n (%)	51 (91)	23 (100)	28 (85)
Apnea of prematurity requiring caffeine treatment, n (%)	47 (84)	23 (100)*	27 (82)
Bronchopulmonary dysplasia, n (%)	10 (18)	7 (30)	3 (9)
Early-onset sepsis, n (%)	2 (3)	1 (4)	1 (3)
Treated for presumed or proven late-onset sepsis after week 1, n (%)	52 (93)	22 (96)	30 (91)
Necrotizing enterocolitis, n (%)	4 (7)	2 (9)	2 (6)
IVH (grade 1 or 2) on cranial ultrasound, n (%)	4 (7)	2 (9)	2 (6)
Infants on respiratory support at study 1, n (%)	30 (54)	18 (78)*	12 (36)
FiO_2 of 22%-40% at study 1, n (%)	3 (5)	3 (13)	0
Infants on respiratory support at study 6, n/N (%)‡	12/20 (60)	10/15 (66)	2/5 (40)
Fractional inspired oxygen of 22-40% at study 6, n/N (%)‡	1/20 (5)	1/15 (7)	0/5
Hemodynamically significant patent ductus arteriosus requiring treatment, n (%)	3 (5)	2 (9)	1 (3)

*$P < .05$ extremely preterm vs very preterm.
†Only 1 infant was recruited from twin pregnancies.
‡Reduction in number of infants at later studies due to discharge from the NICU.

required more mechanical respiratory support than the very preterm group. All extremely preterm infants had apnea of prematurity. During the study period, all infants were clinically stable, and none received inotropic medications. At postnatal week 1, 18 of 23 extremely preterm infants required mechanical respiratory support; 5 were intubated and on intermittent positive-pressure ventilation (1 in fraction of inspired oxygen [FiO_2] of 25%-34% and 4 in air), 11 were on continuous positive airway pressure (CPAP) (2 in FiO_2 of 21%-32 %, 9 in air), and 2 were on high flow in air. In comparison, 12 of 33 very preterm infants required respiratory support (10 on CPAP in air and 2 on high flow in air; $P < .05$) at postnatal week 1. By week 6 of life, 10 of 15 of extremely preterm infants required respiratory support (1 on CPAP at an FiO_2 of 33%-36%, 5 on CPAP in air, 4 on high flow in air), whereas only 2 of 5 of very preterm infants required high flow in air. Two extremely preterm infants and 1 very preterm infant had a hemodynamically significant patent ductus arteriosus requiring indomethacin treatment.

In extremely preterm infants, there was no effect of sleeping position on TOI at any of the ages studied, except at week 3, when TOI was significantly higher in the prone position compared withthe supine position ($P = .05$; **Table IV**). SaO_2 was higher in the prone position compared with the supine position at postnatal weeks 1, 2, and 3 (main effect, $P < .05$ for all). CFOE was significantly higher, although differences were small, in the prone compared with the supine position at postnatal week 1 (main effect, $P < .001$), but not at any of the other ages studied. HR was higher in the prone position during active sleep at week 2 (state × position, $P < .05$) and higher in the prone position at week 6 (main effect, $P < .05$). There was no effect of sleeping position on MABP at any of the ages studied.

Examining the effect of sleep state in extremely preterm infants, TOI was significantly lower during active sleep compared with quiet sleep at postnatal weeks 1, 2, 3, and 6 (main effect, $P < .05$ for all; **Table IV**). SaO_2 was significantly lower during active sleep compared with quiet sleep at postnatal weeks 1, 2, 4, 5, and 6 (main effect, $P < .05$ for all). There was no effect of sleep state on CFOE at any of the ages studied. For HR, there was a significant interaction (state × position, $P < .05$) at week 2; however, post hoc analysis could not identify where these differences lay. HR was higher during active sleep compared with quiet sleep at week 5 (main effect, $P < .05$). There were no effects of sleep state on MABP at any age studied.

In very preterm infants, for TOI and CFOE, there was a significant interaction (state × position, $P < .05$ for both) at postnatal week 1, however post hoc analysis could not identify where these differences lay (**Table V**). TOI was higher and CFOE lower in the prone position only at postnatal week 5 (main effect, $P < .05$ for both). SaO_2 was higher in the prone position during active sleep at week 2 (state × position, $P < .05$), but not at any of the other ages studied. HR was significantly higher in the prone position at weeks 1 and 2 (main effect, $P < .05$ for both), but not at any of the other ages. There was no effect of sleeping position on MABP at any of the ages studied.

In very preterm infants, TOI was lower during active sleep compared with quiet sleep in the supine position at postnatal week 1 (state × position, $P < .05$) and lower during active sleep compared with quiet sleep at weeks 2 and 3 (main effect, $P < .001$ for both; **Table V**). SaO_2 was also significantly lower during active sleep compared with quiet sleep at postnatal weeks 1 and 3 (main effect, $P < .001$ for all), and SaO_2 was lower during active sleep compared with quiet sleep in the supine position at week 2 (state × position, $P < .05$). CFOE was higher during active sleep in the supine position at postnatal week 1

Table IV. Effects of sleep position and sleep state on cerebral TOI, SaO_2, CFOE, HR, and MABP over the first 6 weeks of life in extremely preterm infants

Week	Supine position, mean ± SEM		Prone position, mean ± SEM		Position *P* value	State *P* value	Position × state *P* value
	AS	QS	AS	QS			
Week 1 (n = 21)							
TOI, %	66.6 ± 1.3	68.3 ± 1.3	65.8 ± 1.2	66.2 ± 1.2	NS	**.04**	NS
SaO_2, %	93.5 ± 0.9	95.5 ± 0.5	95.7 ± 0.5	96.2 ± 0.5	**.02**	**.02**	NS
CFOE	0.29 ± 0.01	0.29 ± 0.01	0.31 ± 0.01	0.31 ± 0.01	**<.001**	NS	NS
HR, bpm	156 ± 2	156 ± 2	158 ± 3	157 ± 3	NS	NS	NS
MABP, mmHg	49.5 ± 1.9	48.2 ± 1.8	49.6 ± 2.7	49.6 ± 2.5	NS	NS	NS
Week 2 (n = 20)							
TOI, %	62.8 ± 1.8	63.8 ± 1.9	63.9 ± 1.7	64.4 ± 1.7	NS	**.01**	NS
SaO_2, %	93.9 ± 0.8	94.7 ± 0.7	95.2 ± 0.6	96.1 ± 0.4	**.02**	**.05**	NS
CFOE	0.33 ± 0.02	0.33 ± 0.02	0.33 ± 0.02	0.33 ± 0.02	NS	NS	NS
HR, bpm	155 ± 2	157 ± 2	158 ± 2	157 ± 2	**.04**	NS	**.03**
MABP, mmHg	46.8 ± 1.7	48.5 ± 2.2	50.1 ± 2.3	50.2 ± 2.7	NS	NS	NS
Week 3 (n = 20)							
TOI, %	63.9 ± 1.4	64.6 ± 1.5	64.9 ± 1.3	66.0 ± 1.4	**.05**	**.01**	NS
SaO_2, %	94.1 ± 0.6	94.5 ± 0.9	95.5 ± 0.5	96.1 ± 0.5	**.001**	NS	NS
CFOE	0.32 ± 0.01	0.32 ± 0.01	0.32 ± 0.01	0.31 ± 0.01	NS	NS	NS
HR, bpm	160 ± 3	160 ± 2	162 ± 2	161 ± 2	NS	NS	NS
MABP, mmHg	51.3 ± 2.1	51.3 ± 2.0	52.7 ± 1.8	54.1 ± 2.1	NS	NS	NS
Week 4 (n = 17)							
TOI, %	64.5 ± 1.1	65.4 ± 1.3	64.7 ± 1.3	65.1 ± 1.5	NS	NS	NS
SaO_2, %	95.9 ± 0.8	96.5 ± 0.8	96.0 ± 0.8	97.2 ± 0.7	NS	**.03**	NS
CFOE	0.33 ± 0.01	0.32 ± 0.01	0.33 ± 0.01	0.33 ± 0.01	NS	NS	NS
HR, bpm	156 ± 2	155 ± 3	158 ± 2	157 ± 2	NS	NS	NS
MABP, mmHg	48.9 ± 1.7	49.4 ± 2.0	51.8 ± 2.4	51.0 ± 2.1	NS	NS	NS
Week 5 (n = 17)							
TOI, %	64.5 ± 1.6	64.0 ± 1.5	64.0 ± 1.3	64.7 ± 1.3	NS	NS	NS
SaO_2, %	95.0 ± 1.0	95.5 ± 0.9	94.3 ± 1.1	95.5 ± 0.9	NS	**.01**	NS
CFOE	0.32 ± 0.02	0.33 ± 0.02	0.32 ± 0.02	0.32 ± 0.02	NS	NS	NS
HR, bpm	159 ± 2	157 ± 2	161 ± 2	158 ± 2	NS	**0.03**	NS
MABP, mmHg	52.6 ± 2.1	50.4 ± 1.8	54.8 ± 1.9	53.7 ± 2.3	NS	NS	NS
Week 6 (n = 15)							
TOI, %	63.5 ± 1.4	65.1 ± 1.4	64.3 ± 1.8	64.9 ± 2.0	NS	**<.001**	NS
SaO_2, %	95.7 ± 1.0	96.5 ± 1.1	96.2 ± 0.8	97.1 ± 0.7	NS	**.03**	NS
CFOE	0.34 ± 0.02	0.32 ± 0.02	0.33 ± 0.02	0.33 ± 0.02	NS	NS	NS
HR, bpm	161 ± 3	159 ± 2	163 ± 3	162 ± 2	**.01**	NS	NS
MABP, mmHg	55.7 ± 2.5	55.7 ± 2.7	58.0 ± 2.8	58.1 ± 3.0	NS	NS	NS

NS, not significant.
Signficant *P* values are in bold type.

(state × position, $P < .05$) and higher during active sleep at weeks 2 and 3 (main effect, $P < .05$ for both). There were no effects of sleep state on HR or MABP at any of the ages studied.

The effects of postnatal age are presented in the **Figure**. For extremely preterm infants, our mixed-model analyses found no overall significant effects of postnatal age or sleep on TOI or CFOE in either sleep state (**Figure**, A and C). There was an overall effect of postnatal age, but not of sleep position, on SaO_2 ($P = .02$) and HR ($P = .04$) during quiet sleep as both measures increased with age. However, post hoc analysis did not identify when the differences occurred. In both sleep states, there was an overall effect of postnatal age on MABP (overall $P < .01$ for both active sleep and quiet sleep). Post hoc analysis showed a higher MABP at week 6 compared with week 1 ($P = .03$, active sleep and quiet sleep) and week 2 ($P = .007$, active sleep).

In contrast to our findings in extremely preterm infants, there was an overall effect of postnatal age, but not sleep position, on TOI in very preterm infants, with TOI decreasing at later postnatal ages in both sleep states ($P = .04$, active sleep; $P = .02$, quiet sleep) (**Figure**, B). Post hoc analysis identified TOI was higher in at week 1 compared with week 6 during quiet sleep ($P = .05$). In both sleep states, there was an overall effect of postnatal age, but not of sleep position, on CFOE, which increased with postnatal age ($P < .001$ for both active sleep and quiet sleep) (**Figure**, D). Post hoc analysis identified lower CFOE at week 1 compared with week 6 ($P = .02$, quiet sleep).

For the very preterm infants, in both sleep states, there was an overall effect of postnatal age, but not of sleep position, on SaO_2 ($P = .03$, active sleep and quiet sleep), HR ($P < .001$, active sleep and quiet sleep), and MABP ($P = .004$, active sleep; $P = .001$, quiet sleep), with values increasing with postnatal age (data not shown). Post hoc analysis identified lower HR at weeks 1 and 2 compared with at weeks 3, 4, and 5 in both sleep states ($P < .05$ for all). In addition, HR during active sleep was lower

Table V. Effects of sleep position and sleep state on cerebral TOI, SaO_2, CFOE, HR, and MABP over the first 6 weeks of life in very preterm infants

Week	Supine position, mean ± SEM		Prone position, mean ± SEM		Position *P* value	State *P* value	Position × state *P* value
	Active sleep	Quiet sleep	Active sleep	Quiet sleep			
Week 1 (n = 34)							
TOI, %	68.6 ± 1.0	70.3 ± 1.1	69.2 ± 1.1	69.5 ± 1.1	NS	**.01**	**.02**
SaO_2, %	96.4 ± 0.5	97.1 ± 0.4	96.9 ± 0.3	97.4 ± 0.3	NS	**<.001**	NS
CFOE	0.29 ± 0.01	0.28 ± 0.01	0.29 ± 0.01	0.29 ± 0.01	NS	**.04**	**.02**
HR, bpm	152 ± 2	152 ± 2	156 ± 2	155 ± 2	**.001**	NS	NS
MABP, mmHg	54.1 ± 1.6	51.6 ± 1.5	55.5 ± 2.6	53.7 ± 1.9	NS	**.03**	NS
Week 2 (n = 30)							
TOI, %	66.5 ± 1.1	67.6 ± 1.2	67.8 ± 1.0	69.0 ± 0.9	NS	**<.001**	NS
SaO_2, %	96.6 ± 0.4	97.6 ± 0.3	97.3 ± 0.3	97.7 ± 0.3	NS	**<.001**	**.03**
CFOE	0.31 ± 0.01	0.31 ± 0.01	0.30 ± 0.01	0.29 ± 0.01	NS	**.03**	NS
HR, bpm	153 ± 2	153 ± 2	155 ± 1	155 ± 2	**.03**	NS	NS
MABP, mmHg	51.6 ± 1.6	50.1 ± 1.5	54.8 ± 1.8	52.7 ± 2.1	NS	NS	NS
Week 3 (n = 20)							
TOI, %	68.7 ± 1.3	69.8 ± 1.3	68.3 ± 1.3	69.6 ± 1.2	NS	**.001**	NS
SaO_2, %	96.9 ± 0.5	97.6 ± 0.4	97.4 ± 0.4	97.9 ± 0.4	NS	**<.001**	NS
CFOE	0.29 ± 0.01	0.28 ± 0.01	0.30 ± 0.01	0.29 ± 0.01	NS	**.03**	NS
HR, bpm	160 ± 2	160 ± 2	161 ± 2	161 ± 2	NS	NS	NS
MABP, mmHg	53.7 ± 2.3	53.4 ± 2.4	54.3 ± 2.4	54.3 ± 2.4	NS	NS	NS
Week 4 (n = 15)							
TOI, %	65.9 ± 1.4	66.5 ± 1.4	66.3 ± 2.0	67.7 ± 1.6	NS	NS	NS
SaO_2, %	97.5 ± 0.5	98.1 ± 0.4	97.7 ± 0.4	98.0 ± 0.4	NS	**.04**	NS
CFOE	0.32 ± 0.02	0.32 ± 0.02	0.32 ± 0.02	0.31 ± 0.02	NS	NS	NS
HR, bpm	162 ± 2	160 ± 2	164 ± 2	163 ± 2	NS	NS	NS
MABP, mmHg	56.2 ± 1.7	55.4 ± 2.5	58.8 ± 2.3	54.3 ± 1.4	NS	NS	NS
Week 5 (n = 10)							
TOI, %	65.8 ± 1.5	66.1 ± 2.0	69.1 ± 1.6	69.6 ± 1.8	**.03**	NS	NS
SaO_2, %	97.7 ± 0.7	98.3 ± 0.4	98.2 ± 0.4	98.4 ± 0.3	NS	NS	NS
CFOE	0.33 ± 0.02	0.33 ± 0.02	0.30 ± 0.02	0.29 ± 0.02	**.04**	NS	NS
HR, bpm	163 ± 3	161 ± 2	165 ± 1	165 ± 2	NS	NS	NS
MABP, mmHg	60.5 ± 1.9	58.5 ± 2.7	60.8 ± 2.8	63.1 ± 4.3	NS	NS	NS
Week 6 (n = 5)							
TOI, %	62.6 ± 2.1	63.3 ± 2.0	63.8 ± 1.9	63.7 ± 1.7	NS	NS	NS
SaO_2, %	97.1 ± 1.2	98.5 ± 0.8	97.8 ± 1.0	98.2 ± 0.8	NS	NS	NS
CFOE	0.35 ± 0.02	0.36 ± 0.02	0.35 ± 0.02	0.35 ± 0.02	NS	NS	NS
HR, bpm	152 ± 6	151 ± 4	152 ± 5	155 ± 6	NS	NS	NS
MABP, mmHg	55.7 ± 2.5	55.7 ± 2.7	58.0 ± 2.8	58.1 ± 3.0	NS	NS	NS

Signficant *P* values are in bold type.

at week 6 compared with at weeks 4 and 5 ($P < .05$ for both). MABP was lower at week 2 compared with week 5 during quiet sleep ($P = .01$) and week 6 ($P = .03$).

Discussion

We rigorously assessed the effects of sleeping position on cerebral and cardiovascular measures in preterm infants born at a range of GAs longitudinally during their time in the NICU or SCN, taking into account the effect of sleep state. We found increased CFOE in the prone position at 1 week of life in the extremely preterm infants, with no change in the TOI despite higher SaO_2 in the prone position. In contrast, we did not find position-related differences in CFOE until the fifth week of life in the very preterm infants. In addition, CFOE was higher in infants born at lower GA during the first 2 weeks of life, but this difference reached statistical significance in only the prone position (**Table I** and **Table II**). CFOE represents the amount of oxygen consumed as fraction of oxygen delivery. Assuming that oxygen consumption remains constant, an increase in CFOE is likely due to reduced cerebral oxygen delivery. Contributing factors to low cerebral oxygen delivery include low SaO_2, low CBF, and anemia. As CFOE accounts for changes in SaO_2 levels and the hemoglobin concentration is the same during a single study, the reduction in cerebral oxygen delivery is indicative of a reduction in CBF during prone sleeping. CBF is already extremely low in the preterm brain, especially in the white matter,[3] and also during the early postnatal weeks.[18] CFOE in the first 3 days of life is also higher in infants of lower GAs.[19] We also found that both TOI and SaO_2 positively correlate with GA in the first 3 weeks of life, indicating lower cerebral oxygen delivery in the most preterm infants.

Although preterm infants in the NICU are often placed in the prone position to promote respiratory status, there is no evidence that prone positioning improves long-term outcomes.[6] Furthermore, prone sleeping is associated with reduced cerebral oxygenation in term-born infants during the first 6 months,[8] with these effects more prominent in ex-preterm infants at the same post-term-corrected age.[11] In contrast to our hypothesis, sleep position had only minimal effects on cerebral TOI, with values averaging 1%-2% lower in the prone

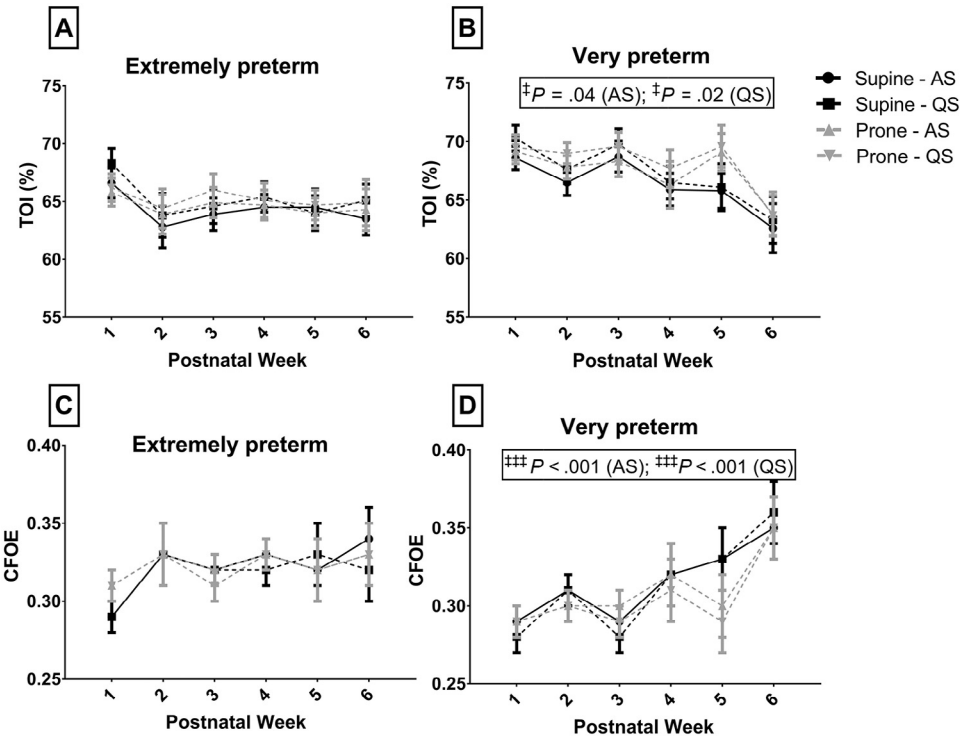

Figure. Effect of postnatal age on cerebral TOI and CFOE in extremely preterm infants (**A** and **B**) and very preterm infants (**C** and **D**). Results are mean ± SEM. ‡$P < .05$ overall effect of postnatal age; ‡‡‡$P < .001$ overall effect of postnatal age. *AS*, active sleep; *QS*, quiet sleep.

position, compared with 3%-5% in term infants and 4%-10% in preterm infants after term-corrected age.[11] The findings may be related to the significantly higher SaO_2 in the prone position in preterm infants with respiratory disease and contributing to a higher cerebral TOI, especially in the extremely preterm infants in the first 3 weeks of life.

We found increased CFOE in the prone position at week 1 of life in extremely preterm infants, likely due to reduced CBF in this position. In line with our results, others have found reduced cerebral oxygenation and CBF in the prone position compared with the supine position in preterm infants,[20] despite an increase in oxygen tension. In the less mature infants (GAs <26 weeks), cerebral blood volume decreased after head rotation from the midline position, possibly because of both vein and artery compression due to more compliant neck structures and increased head:body ratio in the smaller infants.[21] In addition, lower cardiac output has been reported in preterm infants in the prone position,[22] which could lead to reduced CBF. However, similar to previous studies,[20,22] we did not find any significant positional differences in MABP. Blood pressure may have been maintained due to a baroreflex-mediated increase in HR during prone sleeping,[23] given that we found higher HR in the prone position particularly in the very preterm group, similar to observations in preterm infants at post-term-equivalent age.[11]

The first week of life is a high-risk period for IVH in the extremely preterm infants, with a greater risk at lower GA.[24] Low CBF can increase the risk for severe IVH in preterm infants.[25] During the first 3-4 days after birth, CFOE was higher in infants who developed IVH compared with those who did not.[26] The higher CFOE in infants with IVH was also associated with lower left ventricular output and stroke volume,[26] which may have contributed to lower CBF and the development of IVH. Taking into account that TOI values are approximately 10% lower than regional O_2 saturation values used in other studies due to device differences,[26,27] our CFOE values were comparable with those reported in infants without IVH,[26] consistent with our cohort of clinically stable infants, as evidenced by their low ventilatory/oxygen requirements and low incidence of IVH.

Reassuringly, the TOI and CFOE levels that we found were within physiological ranges[19,26] and not in the high-risk ranges for neuropathy as reported in other studies,[11,28,29] suggesting that prone sleeping is safe in clinically stable preterm infants. However, it remains unknown whether our findings of higher CFOE in the prone position in the first week of life in extremely preterm infants can be extended to infants who are clinically unstable with high CFOE and at high risk of IVH,[26] thereby raising concerns about prone sleeping during this vulnerable period. Notably, the negative correlation between CFOE and GA in the prone position during the first 2 weeks of life supports the idea that the younger infants are at increased risk of cerebral hypoxia when in the prone position. Preterm infants, especially those with significant respiratory disease, are

routinely slept prone to promote respiratory status.[6] Our findings provide important physiological insight into CBF when placing extremely preterm infants prone during the first week of life. We speculate that avoiding the prone sleeping position may provide a simple, nonpharmacologic technique to optimize brain oxygenation in clinically unstable preterm infants, which may improve neurodevelopmental outcome. To date, no study has investigated the associations among sleep position, preterm brain injury, and neurodevelopmental outcome in preterm infants. Our results may provide the scientific basis for a future randomized control trial of sleep position with the potential to change clinical practice.

Earlier studies of the effects of sleep position in preterm infants did not take into account the effects of sleep state.[20,21] Consistent with our previous findings in preterm infants after term equivalent age,[11] TOI and SaO_2 were lower in active sleep in both preterm groups in the first 3 weeks of life. However, no sleep state differences in CFOE were found in the extremely preterm group, in contrast to the very preterm group which had increased CFOE in active sleep. This is likely due to an increase in oxygen extraction to sustain cerebral oxygen consumption during the increased metabolic demand of active sleep in the very preterm infants. This idea is supported by the finding that CBF does not increase during active sleep in preterm infants to meet the higher metabolic demand compared with quiet sleep, as it does in wakefulness.[30] Importantly, this response in CFOE was observed only in the very preterm infants. We suggest that the absence of change in CFOE with sleep state in the extremely preterm infants may be due to differences in brain activation in active sleep with maturation. In preterm infants of 24-30 weeks GA, rudimentary sleep-wake cycles, based on alternating periods of eye movements and no eye movements, electroencephalography characteristics, and cortical activity can be identified.[31] From 30 to 31 weeks onward, rapid eye movements and more specific EEG patterns for quiet sleep and active sleep are integrated with increasing concordance over postnatal age.[31]

Few previous studies have assessed the effect of prone sleeping position in preterm infants in the NICU,[20,21] and it is difficult to compare these cross-sectional studies, which included infants with a wide range of GA and postnatal age, with the infants in our study who were studied longitudinally. We found a significant effect of postnatal age on TOI and CFOE in the very preterm infants but not in the extremely preterm infants. A previous study found no association between TOI or CFOE and postnatal age in preterm infants with GA ranging from 23 to 31 weeks and postnatal age ranging from 1 to 31 days,[32] but consecutive measurements were not made in the same subjects. Our finding of decreased TOI and increased CFOE with postnatal age in infants born at older GA may represent a normal adaptation to extrauterine life and brain maturation. Such age-related changes were not found in our extremely preterm group, however. This may be related in part to the infants of lower GA already having a lower TOI and higher CFOE in the first 2 weeks of life, and as such, the postnatal decrease in TOI or increase in CFOE in the first few weeks of postnatal life appears to be dampened. Cerebral oxygen consumption increases in relation to postmenstrual age[18] and may outpace the increment in CBF, leading to lower cerebral oxygenation and higher CFOE with age.[33] This coincides with the substantial increases in brain activity complexity and metabolic demand when the preterm infants approached term age,[34] as what occurs by week 6 of life in very preterm infants.

Our study has several limitations. We excluded infants with moderate/severe IVH, and the infants studied were all clinically stable, as evidenced by oxygen requirement of <40%, a low incidence of IVH, and no infants receiving inotropic support. Although the reduced heterogeneity of our study population aided data interpretation, further studies are needed to verify the findings in sicker infants with hemodynamic and respiratory instability and moderate to severe IVH. In addition, we studied infants with the head maintained in midline in the supine position and head rotated in the prone position. We did not assess the effects of lateral deviation of the head in the supine position and thus cannot rule out the possibility of increased CFOE with changes in head rotation alone rather than with the prone positioning.

In conclusion, this study provides new physiological information about cerebral and cardiovascular measures in clinically stable preterm infants in the first weeks of life with respect to sleeping position, sleep state, GA at birth, and postnatal age. In extremely preterm infants, prone sleeping was associated with increased CFOE in the first week of life, suggestive of reduced CBF. Further studies in a larger population of infants, particularly those requiring high ventilatory and cardiovascular support, are needed to determine whether prone positioning increases the risk of cerebral injury in early postnatal life. ■

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Table I. Linear regression analysis of GA at birth with cerebral TOI, SaO_2, and CFOE in each sleep position (supine and prone) and sleep state (active and quiet sleep) over the first 6 weeks of life (categorized based on time from birth)

	TOI, r^2				SaO_2, r^2				CFOE, r^2			
Week	**S-AS**	**S-QS**	**P-AS**	**P-QS**	**S-AS**	**S-QS**	**P-AS**	**P-QS**	**S-AS**	**S-QS**	**P-AS**	**P-QS**
Week 1 (n = 56)	**0.10‡**	**0.10***	**0.13‡**	**0.13‡**	**0.18‡**	**0.09***	**0.09***	**0.09***	–0.03	–0.05	**–0.09***	**–0.09***
Week 2 (n = 50)	**0.14‡**	**0.11***	**0.11***	**0.17‡**	**0.14‡**	**0.14‡**	**0.08***	**0.09***	–0.07	–0.05	–0.07	**–0.13‡**
Week 3 (n = 39)	**0.14***	**0.15***	**0.11***	**0.11***	**0.18‡**	**0.20‡**	**0.15†**	**0.16†**	–0.07	–0.04	–0.07	–0.06
Week 4 (n = 30)	0.02	0.01	0.03	0.08	0.01	0.07	0.09	0.03	–0.01	–0.01	–0.01	–0.06
Week 5 (n = 27)	0.00	<0.01	**0.16***	0.12	**0.19***	**0.23‡**	**0.29‡**	**0.28‡**	–0.03	<–0.01	<–0.01	–0.02
Week 6 (n = 20)	0.01	0.01	<0.01	<0.01	0.10	0.17	**0.22***	0.10	–0.04	–0.06	–0.03	–0.02

AS, active sleep; *P*, prone; *QS*, quiet sleep; *S*, supine.
The bold type indicated the statistically significant results.
*$P < .05$.
†$P < .01$.
‡$P < .001$.

Table II. Linear regression analysis of GA at birth with HR and MABP in each sleep position (supine and prone) and sleep state (active and quiet sleep) over the first 6 weeks of life (categorized based on time from birth)

	HR, r^2				MABP, r^2			
Week	**S-AS**	**S-QS**	**P-AS**	**P-QS**	**S-AS**	**S-QS**	**P-AS**	**P-QS**
Week 1 (n = 56)	**–0.08***	**–0.10***	**–0.09***	–0.07	0.05	0.04	0.05	0.03
Week 2 (n = 50)	–0.01	–0.07	–0.07	–0.05	**0.13†**	0.02	0.07	0.01
Week 3 (n = 39)	–0.01	–0.09	–0.06	–0.05	**0.14***	**0.10***	0.07	0.01
Week 4 (n = 30)	**–0.14***	–0.11	**–0.16***	**–0.22‡**	**0.14***	**0.13***	0.06	0.05
Week 5 (n = 27)	–0.09	–0.04	–0.12	–0.13	**0.20***	0.01	0.07	0.09
Week 6 (n = 20)	–0.05	–0.05	–0.10	–0.10	**0.27***	**0.25***	0.05	0.13

The bold type indicated the statistically significant results.
*$P < .05$.
†$P < .01$.
‡$P < .001$.