Cerebral Oxygenation and Perfusion when Positioning Preterm Infants: Clinical Implications

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Objectives To evaluate cerebral tissue oxygenation (cTOI) and cerebral perfusion in preterm infants in supine vs prone positions.

Study design Sixty preterm infants, born before 32 weeks of gestation, were enrolled; 30 had bronchopulmonary dysplasia (BPD, defined as the need for respiratory support and/or supplemental oxygen at 36 weeks of postmenstrual age). Cerebral perfusion, cTOI, and polysomnography were measured in both the supine and prone position with the initial position being randomized. Infants with a major intraventricular hemorrhage or major congenital abnormality were excluded.

Results Cerebral perfusion was unaffected by position or BPD status. In the BPD group, the mean cTOI was higher in the prone position compared with the supine position by a difference of 3.27% ($P = .03$; 95% CI 6.28-0.25) with no difference seen in the no-BPD group. For the BPD group, the burden of cerebral hypoxemia (cumulative time spent with cTOI <55%) was significantly lower in the prone position (23%) compared with the supine position (29%) ($P < .001$). In those without BPD, position had no effect on cTOI.

Conclusions In preterm infants with BPD, the prone position improved cerebral oxygenation and reduced cerebral hypoxemia. These findings may have implications for positioning practices. Further research will establish the impact of position on short- and long-term developmental outcomes. *(J Pediatr 2021;235:75-82)*.

Premature infants born before 32 weeks of gestation are at a greater risk of death, cerebral palsy, vision, and/or hearing loss,[1,2] as well as bronchopulmonary dysplasia (BPD) defined as continued requirement of either supplemental oxygen and/or assisted ventilation at 36 weeks of postmenstrual age (PMA).[3] Neurodevelopmental deficits are high in infants with BPD.[4,5]

In Australia, preterm infants receive intensive care treatment in neonatal intensive care units (NICUs) and special care nurseries, which provide a step-down model of care for continuation of nonintensive treatment. In NICUs and special care nurseries, premature infants are routinely positioned prone to improve pulmonary function and oxygenation,[6,7] feed tolerance,[8-10] and energy expenditure[11] especially in infants receiving respiratory support in the form of mechanical ventilation and continuous positive airway pressure.[7] A recent study in preterm infants (at post-term corrected age) reported reduced cerebral oxygenation in the prone position as early as 2-4 weeks post-term, and raised concern that this may contribute to the risk of developing sudden infant death syndrome (SIDS).[12] It is well recognized that prematurity, prone position, and BPD are risk factors for SIDS.[13,14]

We could not find any studies comprehensively evaluating the effects of body position on cerebral and noncerebral oxygenation or cerebral perfusion in preterm infants before term corrected age. This raises an important question "does positioning preterm infants prone, reduce or affect their cerebral oxygenation?" We, therefore, investigated the effects of body position (supine vs prone) on cerebral and noncerebral oxygenation using near infrared spectroscopy (NIRS), and cerebral perfusion using pulsed Doppler in preterm infants with and without BPD. We hypothesized that cerebral oxygenation and perfusion may be lower in prone position. The findings of this study have implications for the wider community of neonatologists, general pediatricians, and nurses who manage preterm infants.

Methods

We conducted a single center, prospective, cross-over observational study at a tertiary NICU (Westmead Hospital, Sydney, Australia). This facility delivers health care to nearly a million residents, including specialist perinatal services to almost 6000 women annually. Approval

BPD	Bronchopulmonary dysplasia	NREM	Nonrapid eye movement
CO_2	Carbon dioxide	NS	Nonsignificant result
cTOI	Cerebral tissue oxygenation	PMA	Postmenstrual age
HR	Heart rate	PSG	Polysomnography
hTOI	Hepatic tissue oxygenation	REM	Rapid eye movement
MCA	Middle cerebral artery	SaO_2	Peripheral oxygen saturation
NICU	Neonatal intensive care unit	SIDS	Sudden infant death syndrome
NIRS	Near infrared spectroscopy		

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was obtained from the Human Research Ethics Committee (HREC/14/SCHN/373) prior to study commencement.

Clinically well preterm infants born before 32 weeks of gestation were studied at 36-37 weeks of PMA after written and informed parental consent. Exclusion criteria included significant intracranial pathology (intraventricular hemorrhage grade III or grade IV based on the Papile classification) as the cerebral oxygenation measurements are likely to be unreliable, major congenital cardiac disease, lethal chromosomal disorder, or lack of parental consent. The cohort was divided into 2 groups (BPD and no-BPD) based on presence or absence of BPD (defined as need for supplemental oxygen and/or assisted ventilation at 36 weeks of PMA).

All infants were studied during daytime hours at 36-37 weeks of PMA in both supine and prone positions. Infants remained in each position for 2-3 hours with a washout period of 20 minutes in between the 2 positions. In each position, we performed polysomnography (PSG), cerebral and noncerebral NIRS, and cerebral pulsed Doppler. For the duration of monitoring, infants were minimally handled, and positioned on a flat surface in a quiet dim lit room. For infants with BPD, respiratory support and fraction of inspired oxygen remained the same in both positions. We performed randomization using the variable block method for the initial body position by opening an opaque sealed envelope containing the randomization instructions on the day of monitoring. PSG was acquired using the Compumedics Grael device (Compumedics), including electroencephalogram, bilateral electro-oculogram, submental electromyography, electrocardiography, peripheral oxygen saturation using a pulse oximeter (Radical 7, Masimo Corporation), respiratory thoracoabdominal movements, nasal airflow, and transcutaneous carbon dioxide (CO_2).

Cerebral tissue oxygenation (cTOI) and hepatic tissue oxygenation (hTOI) were monitored continuously using a NIRO-200 spectrophotometer (Hamamatsu Photonic KK) by placing 1 probe on the frontotemporal region of the head and the second probe on the right upper quadrant of the abdomen over the hepatic region. The probes were secured using soft silicone tape. Each probe had an emitter and 2 detectors (1 shallow and 1 deep), with a 4-cm distance between detector and emitter. Probes were held in place using a moulded rubber case. We used a differential path-length factor of 3.85. NIRS monitoring was added to the PSG recording using an ex-link external DC input device. The burden of cerebral hypoxemia (cumulative time spent with cTOI <55% over the monitoring period) was calculated.

To minimize interobserver variability, 1 investigator recorded all cerebral pulsed Doppler flows in both positions. This investigator has experience, training, and certification in neonatal cranial ultrasound. We used an ultrasound machine (Vivid 7; GE Healthcare) and an 8-MHz curvilinear probe for measurements of the anterior cerebral artery and both middle cerebral arteries (MCAs). Pulsed Doppler was used for the anterior cerebral artery using the midline sagittal plane in the anterior fontanel, and for the MCAs using the temporal axial view. The angle of insonation for all measurements was less than 20°. Five sequential pulsed Doppler waveforms were averaged for these measurements. The sampling rate for all continuous physiological variables for PSG recording was 512 Hz. The sampling rate for NIRO-200 and Masimo radical 7 pulse oximeter was 2 seconds, and the averaging time for pulse oximeter was 8 seconds.

Sleep state interpretation was performed according to the current American Academy of Sleep Medicine manual,[15] with stages scored as either stage R for rapid eye movement (REM), stage N for nonrapid eye movement (NREM), stage T for transitional, or stage W for wake. Data containing artefacts were excluded. The monitoring data was entered into a spreadsheet (Excel, Microsoft) and then imported into statistical software for analysis.

Sample size was based on a paired means test analysis of the 2 positions with the assumption of a 10% difference in mean cTOI. This indicated that a sample size of 30 infants in each group would be sufficient to detect a difference with a power of at least 80% and an alpha of 0.05. Data analysis was undertaken with statistical software (STATA, v SE14). Descriptive statistics were used to summarize the study cohort. Data normality was confirmed by the Shapiro-Wilks test. We used ANOVA to determine differences in TOI and pulse Doppler flow between sleep state and position between the 2 groups. Within group differences were tested using the paired *t* test. Differences between means are presented as means and SD or SE of the mean. For all infants, linear regression was used to determine relationships between gestational age at birth, maternal antenatal steroids administration, and cTOI. Data presented for between groups and within group analysis are not adjusted. We considered $P < .05$ to be statistically significant.

Results

Demographics and baseline clinical characteristics of the cohort are shown in **Table I**. The BPD group had an earlier mean gestational age (by 1 week), and a higher proportion of infants who received a complete course of antenatal steroids, postnatal steroids, received caffeine on the day of monitoring, and developed retinopathy of prematurity. Regression analysis showed no significant relationship between cTOI and the following: gestational age at birth (BPD group: $R^2 = 0.001$, $P = .679$; no-BPD group: $R^2 = 0.004$, $P = .314$), and maternal antenatal steroid administration status (BPD group: $R^2 = 0.01$, $P = .141$; no-BPD group: $R^2 = 0.01$, $P = .562$), hence, unadjusted cTOI results are reported. In the BPD group, 14 infants were receiving nasal continuous positive airway pressure (pressure range 5-8 cm H_2O) with fraction of inspired oxygen between 0.21 to 0.38 and 16 infants were receiving supplemental low flow oxygen (flow range 0.02-0.08 L/minute). No infant developed apnea, had a patent ductus arteriosus or received blood transfusion during the monitoring period. No changes were made to the continuous positive airway pressure or fraction of inspired oxygen or supplemental oxygen flow during the monitoring period.

Overall, 53% of infants (n = 32) were studied in supine position first.

We observed all sleep states in all infants in both body positions. The no-BPD group had a higher proportion of NREM sleep and a lower proportion of awake time in the prone compared with the supine position (NREM: 31% vs 20%, nonsignificant result [NS]; awake 19% vs 28%, NS) with changes of lower magnitude in the BPD group (NREM: 22% vs 15%, NS; awake 27% vs 32%, NS) (**Figure 1**; available at www.jpeds.com).

The relationship between position, overall (includes sleep states and settled awake state) unadjusted mean cTOI and hTOI, and sleep states is shown in **Table II**. In the BPD group, the overall mean cTOI was higher in the prone position (65.39%) compared with the supine position (62.12%) by 3.27% ($P = .03$; 95% CI 6.28-0.25). In the no-BPD group, we found no difference in mean cTOI between the 2 positions. Differences between the 2 groups were not significant and there were no interactions on post-hoc analysis for effects of group, position, or sleep state on cTOI.

For each group, we explored the burden of cerebral hypoxemia (cumulative time spent with cTOI <55%) in supine and prone position (**Figure 2**). For the BPD group, the burden of cerebral hypoxemia was significantly lower in the prone position (23%) compared with the supine position (29%) ($P < .001$). For the no-BPD group, the difference in burden of cerebral hypoxemia was negligible (26% in each position). Sleep state reduced the burden of cerebral hypoxemia in the BPD group in all sleep stages (NREM: supine 25% vs prone 11%; REM: supine 30% vs prone 24%; transitional: supine 18% vs prone 10%; $P < .001$, **Figure 3**), but no effect was observed in the no-BPD group (NREM: supine 19% vs prone 22%; REM: supine 26% vs prone 27%; transitional: supine 23% vs prone 24%).

No differences were seen in hTOI within groups according to sleep stage or body position (**Table II**). Between group comparison showed that hTOI was higher in the supine position in the no-BPD group (mean difference 7.34, $P < .001$, 95% CI 2.91-11.77). There were no other significant interactions between group, position, sleep state, and hTOI.

The relationship between position, heart rate (HR), peripheral oxygen saturation (SaO_2), and transcutaneous CO_2 levels for the 2 groups is shown in **Table II**. Overall, in the BPD group, HR and SaO_2 were higher in the prone position (HR: mean difference = 5, $P < .001$; 95% CI 2.07-6.98, SaO_2: mean difference = 1, $P = .03$; 95% CI 0.06-1.35). HR was also higher in REM sleep in the prone position (mean difference = 5, $P = .01$; 95% CI 1.09-9.44). In the no-BPD group, there were no differences across sleep states for SaO_2, HR, or transcutaneous CO_2 levels.

Between group comparisons showed significant differences between HR and groups, position, and sleep states with interactions between groups and HR, position and HR, sleep states (NREM vs REM) and HR as well as groups × position and HR ($P < .001$). The combined model of group × position × sleep state showed no interactions. The BPD group had higher CO_2 levels compared with the no-BPD group (mean difference = 6.17, $P < .001$; 95% CI 4.76-7.58), but no differences were found between CO_2 levels by position or sleep state. On post hoc analysis CO_2 levels were higher in the BPD group compared with the no-BPD group (mean difference = 6.55, $P < .001$; 95% CI 3.71-9.40) in both supine and prone positions (mean difference = 5.79, $P < .001$ and 95% CI 2.95-8.63). There was no interaction between CO_2 levels and SaO_2 for the combined model of group, position, and sleep state.

Cerebral pulsed Doppler had higher peak systolic velocity in the left MCA by 7.7 cm/seconds in the no-BPD group

Table I. Characteristics of the study cohort (n = 60)

Clinical characteristics	BPD group (n = 30)	No-BPD group (n = 30)	*P* value
Gestational age at birth, in wk, mean (SD)	26 (1.7)	27 (1.7)	.003*
Birth weight g, mean (SD)	887 (260)	1009 (282)	NS
Corrected gestational age, in wk, mean (SD)	36.5 (0.5)	36.5 (0.5)	NS
Current weight, g, mean (SD)	2272 (492)	2250 (391)	NS
Complete antenatal steroids, n (%)	22 (73%)	13 (43%)	.04*
Received antenatal magnesium sulphate, n (%)	25 (83%)	17 (57%)	.02*
Spontaneous onset of labor, n (%)	16 (53%)	18 (60%)	NS
Birth by lower segment cesarean delivery, n (%)	19 (63%)	18 (60%)	NS
1-min Apgar score, mean (SD)	5 (2)	5 (2)	NS
5-min Apgar score, mean (SD)	7 (2)	7 (1)	NS
Received surfactant, n (%)	28 (93%)	25 (83%)	NS
Received postnatal steroids, n (%)	14 (47%)	1 (3%)	<.001*
Treated for presumed or proven late onset sepsis, n (%)	5 (17%)	3 (10%)	NS
Developed IVH (grade 1 or 2) on cranial ultrasound, n (%)	5 (17%)	4 (13%)	NS
Developed ≥ stage II retinopathy of prematurity, n (%)	13 (43%)	6 (20%)	.05*
Closest hemoglobin, g/L, mean (SD)	107 (12) (n = 29)†	106 (18) (n = 28)†	NS
Medications received on the day of monitoring, n (%)			
• Postnatal steroids	2 (7%)	1 (3%)	NS
• Caffeine	14 (47%)	4 (13%)	.005*
• Diuretics	2 (7%)	1 (3%)	NS

IVH, intraventricular hemorrhage.
NS = ($P > .05$).
*$P < .05$.
†Unable to record hemoglobin.

Table II. The relationship between position, NIRS measurements, physiological parameters, and sleep states in the BPD and the no-BPD group

	BPD group								No-BPD group							
	Supine position				Prone position				Supine position				Prone position			
Variables	REM	NREM	Transitional	All stages	REM	NREM	Transitional	All stages	REM	NREM	Transitional	All stages	REM	NREM	Transitional	All stages
cTOI, %	61.77 (1.86)	62.90 (2.06)	63.44 (1.93)	62.12* (0.96)	65.49 (2.31)	65.37 (2.36)	66.62 (2.28)	65.39* (1.15)	64.66 (2.33)	63.87 (1.98)	64.15 (2.34)	63.79 (1.08)	62.84 (2.02)	62.75 (1.98)	62.54 (2.08)	62.26 (0.99)
hTOI, %	53.54 (1.46)	53.77 (1.43)	52.30 (1.49)	52.90 (0.77)	54.82 (2.54)	54.99 (2.77)	53.35 (2.66)	54.41 (1.32)	60.48 (2.96)	60.82 (2.14)	60.65 (2.74)	60.18 (1.27)	60.56 (1.97)	58.89 (1.90)	59.24 (1.88)	58.87 (0.97)
SaO_2, %	95 (0.47)	96 (0.54)	96 (0.51)	95* (0.25)	96 (0.41)	97 (0.5)	96 (0.43)	96* (0.22)	98 (0.27)	97 (0.32)	98 (0.3)	97 (0.17)	97 (0.25)	97 (0.25)	97 (0.24)	97 (0.16)
cFTOE	0.35 (0.02)	0.34 (0.02)	0.33 (0.02)	0.34 (0.01)	0.32 (0.02)	0.32 (0.02)	0.31 (0.02)	0.32 (0.01)	0.34 (0.02)	0.34 (0.02)	0.34 (0.02)	0.34 (0.01)	0.35 (0.02)	0.35 (0.02)	0.35 (0.02)	0.35 (0.01)
hFTOE	0.43 (0.01)	0.44 (0.01)	0.45 (0.01)	0.44 (0.01)	0.42 (0.02)	0.43 (0.02)	0.44 (0.02)	0.43 (0.01)	0.38 (0.03)	0.37 (0.02)	0.37 (0.02)	0.38 (0.01)	0.38 (0.02)	0.39 (0.01)	0.39 (0.01)	0.39 (0.01)
TcM CO_2, mm Hg	46.90 (1.52)	48.24 (1.58)	47.83 (1.56)	47.20 (0.79)	46.81 (1.47)	47.05 (1.72)	47.50 (1.69)	46.61 (0.82)	41.36 (1.35)	41.06 (1.18)	39.94 (1.56)	40.45 (0.67)	40.47 (1.17)	40.62 (1.18)	41.18 (1.16)	40.61 (0.58)
HR, bpm	158* (2)	153 (2.09)	155 (2.12)	158† (1)	163* (2)	158 (2.12)	160 (2.05)	163† (1)	159 (2.04)	164 (1.82)	162 (1.93)	165 (1.05)	161 (1.84)	165 (1.55)	164 (1.73)	166 (0.95)

cFTOE, cerebral fractional tissue oxygen extraction [(SaO_2-cTOI)/SaO_2]; *hFTOE*, hepatic fractional oxygen extraction [(SaO_2-hTOI)/SaO_2]; *TcM CO_2*, transcutaneous CO_2 monitoring.
Results are unadjusted.
Values are presented as mean (SEM).
All stages include REM, NREM, and transitional sleep states and settled awake state.
*$P < .05$ for within group comparison.
†$P < .05$ for between groups comparison.

($P = .010$, 95% CI -13.48 to −1.96). No other differences were found between anterior cerebral artery and MCA velocities or resistive index between the 2 groups (**Table III**; available at www.jpeds.com).

Discussion

We observed that prone position was associated with higher cerebral oxygenation and lower burden of cerebral hypoxemia in all sleep states in the BPD group. Position did not produce any difference in the no-BPD group. Body position did not make any difference in cerebral arterial resistive index or hepatic oxygenation in either group. We confirmed previous studies,[16,17] showing a higher proportion of NREM sleep and a lower proportion of awake time in the prone position for both groups.

Prior studies suggest that the prone sleep position is associated with reduced blood pressure, reduced cerebral oxygenation, and impaired autonomic cardiovascular control in infants born at term and that these effects are amplified by preterm birth.[12,18] The results of those studies imply that placing preterm infants in a prone position is potentially harmful and has major implications for clinical practice.[19] Possible explanations for the differences in results are age of the infants when the monitoring occurred (a minimum age of 2-4 weeks post-term), variation in clinical and demographic characteristics of the study cohort, and place of monitoring (sleep laboratory vs NICU).

The prone sleep position and premature birth are both major risk factors for SIDS. Prospective observational studies in 20 preterm infants previously showed significantly higher peripheral oxygen saturation and lung function in the prone position at 36 weeks of PMA,[20,21] but in those studies sleep state, cerebral oxygenation, and cerebral perfusion were not measured. Moreover, none of these studies specifically examined the effects in preterm infants with BPD. Wong et al demonstrated a reduction in cerebral oxygenation in healthy term infants in the prone position during early infancy.[18] These concerning results coincide with the peak age for SIDS and suggest a potential contributing factor. In 2 further prospective studies, the group first found that cTOI was reduced in well preterm infants compared with well term infants in the prone position during early infancy, but infants with BPD were excluded.[12] In the second study, preterm infants born between 24 and 34 weeks of gestation were monitored weekly until term age or discharge or transfer from NICU. In infants born before 29 weeks of gestation, cerebral fractional tissue extraction had increased in the prone position at 1 week of age, suggesting a reduction in cerebral perfusion.[22] In contrast, Demirel et al found no effect of position on cerebral or mesenteric oxygenation in stable preterm infants without BPD.[23] This discrepancy could be attributed to differences in the ages of the cohort, in their maturity, and establishment of cerebral autoregulation as well as a relatively small sample size. None of these studies measured cerebral perfusion using ultrasound.

Cerebral autoregulation is a complicated physiological process that maintains a relatively constant circulation with variability in perfusion pressure. Vascular resistance directly affects cerebral perfusion. Key factors influencing vascular resistance include partial pressure of blood oxygen and CO_2, width of the blood vessel, and blood viscosity.[24] We previously reported that in the absence of a simple and reliable bedside device to measure cerebral perfusion, cerebral NIRS, and pulsed Doppler are surrogates to estimating cerebral perfusion.[25] NIRS is a safe, noninvasive technology measuring tissue oxygenation.[26] The reference range of 55%-85% for cerebral oxygenation represents mean cTOI (±1 SD) from an observational study of preterm infants born before 32 weeks of gestation and monitored in the first 72 hours of life.[27] Studies suggest that cTOI in preterm infants initially increases in the first week of life then gradually decreases over the course of their inpatient stay.[28,29] Based on existing literature, and taking into account interdevice differences, we considered the cerebral hypoxia threshold (cTOI 55%) is applicable to ex-preterm infants at 36-37 weeks of PMA. Regional oxygenation and fractional tissue oxygen extraction reflect a state of balance in oxygen demand-supply. Reduced cerebral perfusion from low blood flow, hypocarbia, anemia, hypoxia, or increased tissue metabolism causes cerebral hypoxemia, which contributes to brain injury in preterm infants.[30] Previous studies in preterm infants have reported no significant differences in cerebral oxygenation and cerebral perfusion between supine and prone position.[31,32]

In our study, the BPD group demonstrated higher cerebral oxygenation, a lower burden of cerebral hypoxemia, and higher HR in the prone position. Neonatal cardiac output is more dependent on HR than stroke volume. This intriguing finding may be explained by improved delivery of oxygen to cerebral circulation (increased HR) without changes in oxygen saturation, hemoglobin, CO_2, or cerebral blood flow velocities.

Our study provides new and reassuring information that position does not affect cerebral blood flow velocities in hospitalized preterm infants at 36-37 weeks of PMA. We found limited literature on position related changes to cerebral perfusion using ultrasound. Pulsed Doppler does not provide direct quantification or global measurement of cerebral perfusion, it only provides surrogate measurements for cerebral perfusion (peak systolic and end diastolic velocity, and resistive index: measure of end organ resistance to perfusion) in the artery used for measurement. Eichler et al also found no effects of body position on cerebral perfusion in the internal carotid arteries in premature infants who were well at the time of study.[31] The significance of the isolated difference in left MCA peak systolic velocity seen between our 2 groups in the supine position remains unknown. Clinically well ex-preterm infants at 36-37 weeks of PMA may have cerebral autoregulation well established or their body position does not affect cerebral perfusion as measured by pulsed Doppler.

Despite the nonsignificant differences in sleep states because of small participant numbers, we observed more awakening in the supine position in both groups. Our results add insight into the evidence from Goto et al, who reported similar findings in well preterm infants without BPD at 36 weeks of PMA.[16] This behavior may be protective against

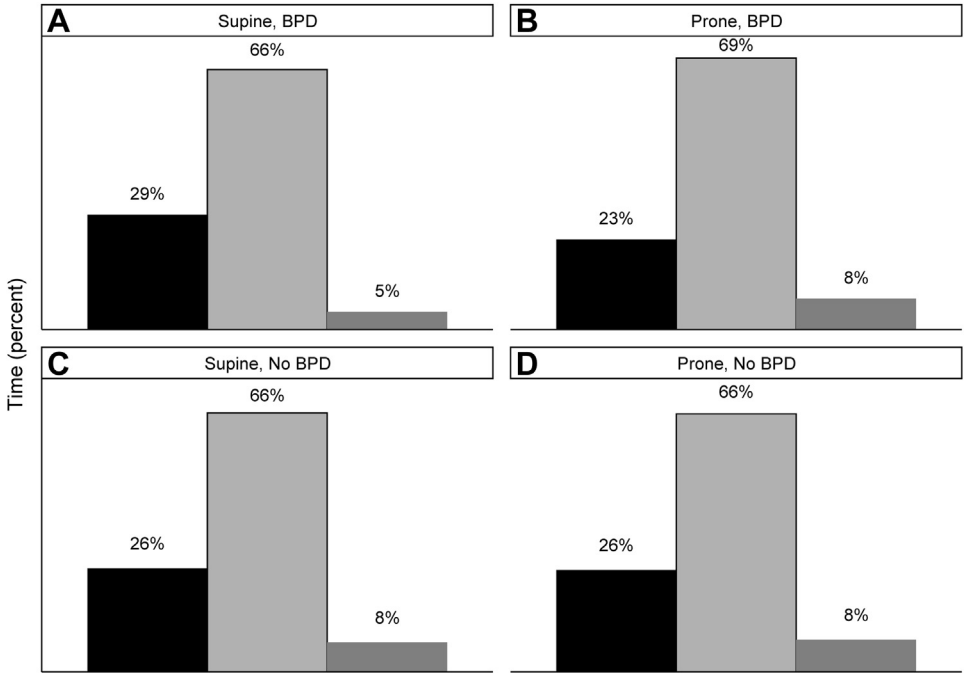

Figure 2. Relationship between cerebral oxygenation and body position for the 2 groups. **A**, Supine, BPD; **B,** Prone, BPD; **C,** Supine, No BPD; **D,** Prone, No BPD.

potentially harmful or life-threating event in preterm infants with or without BPD. We also observed a higher proportion of NREM sleep in prone position. In childhood, NREM sleep has been reported to have a positive relationship with brain maturation.[33] A study in 50 term infants with suspected seizures showed an association between presence of lower quiet sleep and poor neurodevelopment at 18 months of age.[34] In preterm infants, the influence of REM sleep deprivation on developmental outcomes is well established,[35] the significance of NREM sleep on developmental outcome remains unknown and needs further research.

These results may have important implications for clinicians that treat premature infants in NICUs and special care nurseries, allowing them to better understand the physiological changes attributable to body position. Although these results are reassuring, it is important to address developmentally supportive care when positioning preterm infants prone. In infants without BPD, the findings of our study align with recommendations from The American Academy of Pediatrics on positioning infants supine, at least from 32 weeks of PMA.[36] Clinicians should consider developing "a position transition program" to plan individualized care for every preterm infant based on their clinical stability and BPD status. In addition, this will provide early education to parents on safe sleeping practices.

A key strength of our study is its comprehensive evaluation of 2 high-risk groups for SIDS by performing NIRS, PSG, and

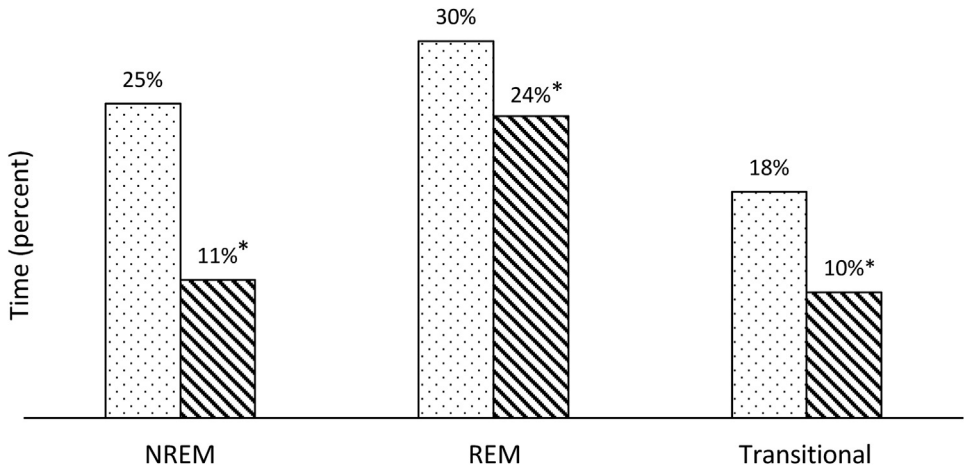

Figure 3. Burden of time spent with cerebral hypoxemia in the BPD group. *Significant difference $P < .05$.

cranial pulsed Doppler. Our study advances our understanding of the physiological changes because of position, and links improvement in respiratory function in the prone position (as demonstrated in previous studies) with a reduction in cerebral hypoxemia.

A limitation of our study is the potential for selection and measurement bias. We minimized its impact by randomizing the initial body position and blinding the statistician to the position for analysis. Another limitation is that pulsed Doppler only provides point measurements and is operator dependent. Using an investigator skilled in performing pulsed Doppler in newborns addressed this concern. Finally, our results must be interpreted with caution because they may not be applicable to younger gestational age infants, or infants in our excluded categories, including unwell or extremely preterm infants. Also, long-term developmental outcomes for this cohort are not reported.

In conclusion, our study demonstrates improved cerebral oxygenation in the prone position for preterm infants with BPD. These findings may have significant implications for clinicians and policy-makers for the development of optimal positioning practices for preterm infants. The present study lays groundwork for further research to establish the impact of position on short- and long-term developmental outcomes. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Neonatal Hypoglycemia: Progress and Predicaments

Beard A, Cornblath M, Gentz J, Kellum M, Persson B, Zetterström R, Haworth JC. Neonatal hypoglycemia: a discussion. J Pediatr 1971;79:314-24.

Pediatricians have long recognized the significance of neonatal hypoglycemia and the importance of timely treatment. However, the field continues to debate the standards of neonatal hypoglycemia detection, diagnosis, and management. In the report by Beard et al, Dr Behrman reported the survey of experts in neonatal hypoglycemia on the major controversies surrounding diagnosis and treatment. Despite significant research, many of those same questions remain unanswered today.

Knowledge continues to evolve regarding the normal physiologic changes in glucose during the first few days of life. Current definitions of normal neonatal glucose values vary from ≥35 to ≥50 mg/dL. The recent Glucose in Well Babies (GLOW) study[1] provided insight into blood glucose dynamics in healthy infants born at term; most infants maintain plasma blood glucose >47 mg/dL after the first 2 hours of life. Although universal agreement on hypoglycemia cutoffs and treatment thresholds remains elusive, modern guidelines are greater than the values recommended by Beard et al. In the original discussion, the experts generally agreed to intervene only when glucose levels fell <30 mg/dL and occasionally <20 mg/dl. The shift in hypoglycemia definition likely represents increased awareness of potential neurologic sequelae even in asymptomatic hypoglycemia.

Pharmacologic treatment for neonatal hypoglycemia also has changed, particularly for hyperinsulinemic hypoglycemia. Although largely avoided in the past, diazoxide is now considered among first-line therapies for infants with hyperinsulinism.[2] Only one of the sampled experts in 1971 would consider glucagon therapy (and then only in the acute setting). However, intravenous glucagon infusion is now frequently used for refractory hypoglycemia. Continuous glucagon infusions are also being investigated as a long-term treatment option for diazoxide unresponsive hyperinsulinism.[2] The discussions by Beard et al continued the important medical tradition of open exchange of ideas that remains a fundamental part of approaching newborn care.

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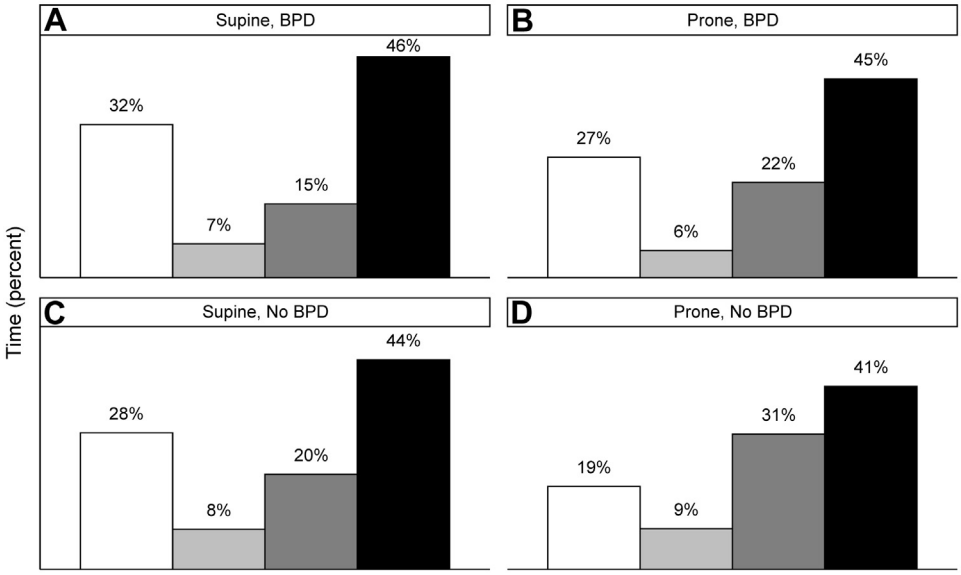

Figure 1. Relationship between body position, and sleep state between the 2 groups. **A,** Supine, BPD; **B,** Prone, BPD; **C,** Supine, No BPD; **D,** Prone, No BPD.

Table III. Relationship between position and pulsed Doppler flows between the 2 groups

	BPD group					No-BPD group				
			Within group comparison					Within group comparison		
	Supine position	Prone position	Difference in mean	*P* Value	95% CI	Supine position	Prone position	Difference in mean	*P* Value	95% CI
Anterior cerebral artery										
Peak systolic velocity	55.16 (1.65)	56.70 (2.04)	1.54	.408	−2.22 to 5.31	54 (1.78)	55.57 (1.98)	1.57	.432	−2.45 to 5.58
End diastolic velocity	11.32 (0.99)	13.03 (1.23)	1.71	.185	−0.87 to 4.30	10.35 (0.90)	10.20 (0.85)	−0.15	.878	−2.23 to 1.92
Resistive index	0.79 (0.01)	0.77 (0.01)	−0.02	.271	−0.05 to 0.01	0.80 (0.01)	0.81 (0.01)	0.01	.403	−0.02 to 0.05
Right MCA										
Peak systolic velocity	66.40 (2.20)	65.26 (2.99)	−1.14	.651	−6.20 to 3.94	63.35 (2.65)	65.18 (2.65)	1.83	.535	−4.13 to 7.78
End diastolic velocity	13.50 (1.36)	14.90 (1.41)	1.40	.364	−1.71 to 4.52	12.36 0.92)	12.41 (0.84)	0.05	.969	−2.39 to 2.48
Resistive index	0.79 (0.01)	0.76 (0.01)	−0.03	.148	−0.06 to 0.01	0.80 (0.01)	0.80 (0.01)	0	.766	−0.02 to 0.03
Left MCA										
Peak systolic velocity	66.44 (1.25)	64.85 (2.45)	−1.59	.484	−6.16 to 2.98	71.18 (2.37)	63.46 (2.93)	−7.72	.010*	−13.48 to −1.96
End systolic velocity	13.39 (1.24)	14.50 (1.20)	1.11	.432	−1.74 to 3.97	12.97 (1.07)	11.77 (0.92)	−1.20	.193	−3.05 to 0.64
Resistive index	0.79 (0.01)	0.77 (0.01)	−0.02	.130	−0.05 to 0.01	0.82 (0.01)	0.81 (0.01)	−0.01	.459	−0.03 to 0.01

Values are presented as mean (SEM), velocities are presented as cm/s.
Resistive index [(peak systolic velocity-end diastolic velocity)/peak systolic velocity].
*$P < .05$ for within group analysis.