Cerebral Oxygenation in Preterm Infants

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KEY WORDS
preterm birth, sudden infant death syndrome, prone sleeping position, cerebral oxygenation, blood pressure

ABBREVIATIONS
ANOVA—analysis of variance
AS—active sleep
CA—corrected age
CBF—cerebral blood flow
GA—gestational age
Hb—hemoglobin
HR—heart rate
MAP—mean arterial pressure
QS—quiet sleep
SIDS—sudden infant death syndrome
Spo2—pulse oxygen saturation
TOI—tissue oxygenation index

Ms Fye participated in recruitment for the study, conducted the data collection, carried out the data analyses, wrote the first draft of the manuscript, and critically reviewed and revised the manuscript; Dr Yiallourou contributed to design of the study, participated in data collection, and reviewed and revised the manuscript; Dr Wong contributed to design of the study, obtained funding for the study, assisted in recruitment for the study, and reviewed and revised the manuscript; Ms Odoi participated in data collection and reviewed and revised the manuscript; Dr Walker contributed to design of the study, obtained funding for the study, and reviewed and revised the manuscript; Dr Horne conceptualized and designed the study, obtained funding for the study, supervised data collection and analysis, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.


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(Continued on last page)

WHAT’S KNOWN ON THIS SUBJECT: Prone sleeping is a major risk factor for sudden infant death syndrome (SIDS). Cerebral oxygenation and blood pressure are reduced in the prone sleeping position in healthy term infants. Preterm infants are at significantly increased risk of SIDS.

WHAT THIS STUDY ADDS: Preterm infants display reduced cerebral oxygenation compared with term infants, most prominently at 2 to 3 months corrected age in the prone position when blood pressure is concurrently reduced. This may contribute to the increased risk for SIDS among infants born preterm.

abstract

BACKGROUND AND OBJECTIVE: Prone sleeping is a major risk factor for sudden infant death syndrome (SIDS) and preterm infants are at significantly increased risk. In term infants, prone sleeping is associated with reduced mean arterial pressure (MAP) and cerebral tissue oxygenation index (TOI). However, little is known about the effects of sleeping position on TOI and MAP in preterm infants. We aimed to examine TOI and MAP in preterm infants after term-equivalent age, during the period of greatest SIDS risk.

METHODS: Thirty-five preterm and 17 term infants underwent daytime polysomnography, including measurement of TOI (NIRO-200 spectrophotometer, Hamamatsu Photonics KK, Japan) and MAP (Finapress Medical Systems, Amsterdam, Netherlands) at 2 to 4 weeks, 2 to 3 months, and 5 to 6 months postterm age. Infants slept prone and supine in active and quiet sleep. The effects of sleep state and position were determined by using 2-way repeated measures analysis of variance and of preterm birth by using 2-way analysis of variance.

RESULTS: In preterm infants, TOI was significantly lower when prone compared with supine in both sleep states at all ages (P < .05). Notably, TOI was significantly lower in preterm compared with term infants at 2 to 4 weeks, in both positions (P < .05), and at 2 to 3 months when prone (P < .001), in both sleep states. MAP was also lower in preterm infants in the prone position at 2 to 3 months (P < .01).

CONCLUSIONS: Cerebral oxygenation is reduced in the prone position in preterm infants and is lower compared with age-matched term infants, predominantly in the prone position when MAP is also reduced. This may contribute to their increased SIDS risk. Pediatrics 2014;134:435–445
Preterm birth is increasing in incidence and now accounts for over 10% of live births annually worldwide. Preterm infants are at significantly increased risk of sudden infant death syndrome (SIDS), with 29% of SIDS victims being born preterm. SIDS peaks in incidence at 2 to 4 months of age and is believed to involve an uncompensated cardiovascular event presumed to occur during sleep, in conjunction with failure of the life-saving arousal response. Preterm infants exhibit immature cardio-respiratory control, which persists past term-equivalent age, is related to gestational age (GA) at birth, and may contribute to their heightened risk for SIDS.

Prone sleeping is a major risk factor for SIDS, particularly among infants born preterm. Term infants sleeping prone have alterations in cardiovascular control and we have previously demonstrated that this is reflected in the cerebral circulation, expressed as reduced cerebral oxygenation and altered cerebrovascular control. It has been suggested that reduced cerebral oxygenation may contribute to impaired arousal, which is seen in the prone position in both term and preterm infants and is likely to be significant in the pathophysiology of SIDS.

Preterm infants display immature cerebrovascular control before term-equivalent age. The severity of which is related to their GA at birth. However, little is known about cerebral oxygenation in preterm infants during the period of greatest SIDS risk. We measured cerebral oxygenation and blood pressure during sleep in both the prone and supine positions in preterm infants across the first 6 months postterm. We hypothesized that cerebral oxygenation would be lower in infants born at earlier GA in the prone position, at 2 to 3 months postterm corrected age (CA) and in preterm compared with term infants and that perturbations in cerebral oxygenation would be associated with alterations in systemic cardiovascular parameters.

METHODS

Ethical approval was obtained from the Monash Health and Monash University human research ethics committees. Written parental consent was obtained, and no monetary incentive was provided for participation.

Subjects

Thirty-five preterm infants born at 26 to 36 weeks’ GA and 17 term infants born at 38 to 42 weeks’ GA were studied with daytime polysomnography (Table 1). All infants were appropriately grown for GA, born to nonsmoking mothers, had no family history of SIDS and routinely slept supine at home. In the preterm cohort, exclusion criteria included intraventricular hemorrhage (grade III or IV), and chronic lung disease requiring ongoing respiratory stimulant medication or oxygen therapy at term-equivalent age.

Of the preterm infants, 24 were studied on 3 occasions at 2 to 4 weeks, 2 to 3 months, and 5 to 6 months postterm CA, 7 were studied at only 2 to 4 weeks CA, and 4 were studied only at 2 to 3 months and 5 to 6 months CA. Term infants were all studied at 3 ages: 2 to 4 weeks, 2 to 3 months, and 5 to 6 months chronological age, and data from this study have previously been published.

Study Protocol

Daytime polysomnography was performed in a sleep laboratory with constant temperature (22–23°C), dim lighting, and quiet conditions. Infants slept both prone and supine, with the initial sleep position randomized. Sleep position was changed after a midday feed. Electrodes required for determining sleep state were applied during a morning feed; these included EEG, electrooculogram, submental electromyogram, electrocardiogram, and abdominal and thoracic

### Table 1 Neonatal History and Characteristics at the Time of Study of Preterm and Term Infants

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Preterm Infants (n = 35)</th>
<th>Term Infants (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA, wk</td>
<td>31.2 (0.4)***</td>
<td>40.1 (0.3)</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>1697 (52)***</td>
<td>3666 (105)</td>
</tr>
<tr>
<td>Boy/girl (% boy)</td>
<td>21/14 (60%)</td>
<td>9/8 (53%)</td>
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<tr>
<td>Appgar scores</td>
<td></td>
<td></td>
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<tr>
<td>1st min</td>
<td>6 (2–9)***</td>
<td>9 (7–9)</td>
</tr>
<tr>
<td>5th min</td>
<td>9 (5–9)**</td>
<td>9 (9–10)</td>
</tr>
<tr>
<td>Received respiratory stimulant during hospitalization, n (%)</td>
<td>20 (57%)**</td>
<td>0</td>
</tr>
<tr>
<td>Antenatal steroids, n (%)</td>
<td>25 (71%)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia of prematurity, n (%)</td>
<td>14 (40%)</td>
<td>0</td>
</tr>
</tbody>
</table>

2–4 weeks

| Age, wk                        | 3.2 (0.1)                | 3.4 (0.1)             |
| Weight, g                      | 3742 (103)               | 3956 (148)            |
| Length, cm                     | 51.9 (0.5)               | 53.3 (0.6)            |

2–3 months

| Age, wk                        | 10.6 (0.2)               | 10.6 (0.2)            |
| Weight, g                      | 5323.9 (185)             | 5214 (179)            |
| Length, cm                     | 56.9 (0.7)               | 57.8 (0.4)            |

5–6 months

| Age, wk                        | 22.7 (0.3)               | 22.3 (0.3)            |
| Weight, g                      | 7179 (209)               | 6884 (200)            |
| Length, cm                     | 83.7 (0.5)               | 64.3 (0.5)            |

Values are presented as mean (SEM) with the exception of Appgar scores, which are presented as median (range). ***P < .001 term versus preterm. **P < .01 term versus preterm.

* Nineteen preterm infants received caffeine before discharge, and 1 infant received theophylline and aminophylline; no infants were receiving respiratory stimulant medication at the time of study.

** CA for preterm infants; postnatal age for term infants.
respiratory belts (Resp-ez bands, EPM Systems, Midlothian, VA). Pulse oxygen saturation (SpO2; Masimo, Frenchs Forrest, NSW, Australia) and abdominal skin temperature (ADInstruments, Sydney, NSW, Australia) were also recorded.

Cerebral Oxygenation
Cerebral tissue oxygenation index (TOI %) was measured continuously by using near-infrared spectroscopy (NIR-200 spectrophotometer, Hamamatsu Photonics KK, Tokyo, Japan). Near-infrared spectroscopy enables calculation of cerebral TOI by using continuous-wave light emission and detection measured over the frontal region of the infant’s brain, with the detection probe placed 4 cm away from the emission probe. TOI was computed at 6 Hz by using a spatially resolved spectroscopy algorithm33 and represents mixed oxygen saturations of all cerebral vascular compartments.

Mean Arterial Pressure
Mean arterial pressure (MAP) was measured by using a photoplethysmographic cuff (Finapress Medical Systems, Amsterdam, Netherlands) placed around the infant’s wrist, using a technique previously validated by our group.34 Data were collected in 1- to 2-minute epochs with at least 2 minutes between inflations to prevent venous pooling in the hand.

All physiologic variables were recorded with a sampling rate of 512 Hz by using an E-series sleep system with Profusion software (Compumedics, Abbotsford, VIC, Australia).

Data Analysis
At the completion of each study, data were transferred to LabChart7 software (ADInstruments) for analysis. Sleep state was defined as either quiet sleep (QS) or active sleep (AS).35 Beat-to-beat values were calculated for cerebral TOI, MAP, heart rate (HR), SpO2, and temperature during each 1- to 2-minute epoch; data were averaged for each epoch and pooled for each sleep state and position within each infant. An average of 6 epochs was analyzed in each sleep state and position for each infant. Data containing movement artifact and epochs where MAP data lay >1.5 times the interquartile range outside the first and third quartiles were excluded from further analysis.36

Statistical Analysis
Statistical analysis was performed by using SigmaPlot 12.0 software (Systat Software Inc, San Jose, CA). Linear regression was used to determine the relationships between GA at birth and cerebral TOI and between GA at birth and MAP. The effects of sleep state and position were determined by using 2-way repeated measures analysis of variance (ANOVA) at each CA. The effect of increasing CA was determined by using 2-way repeated measures ANOVA with CA and sleep state as factors. The effect of preterm birth was determined by using 2-way ANOVA with birth and sleep state as factors. When a significant difference was indicated on ANOVA, the specific source of the difference was identified with Student-Newman-Keuls posthoc analysis. Results are presented as mean ± SEM with significance taken at P < .05.

RESULTS
Effects of GA at Birth in Preterm Infants
No significant correlation was found between cerebral TOI and GA at birth or between MAP and GA at birth at any age studied in either sleep state or position (data not shown).

Effects of Sleep Position in Preterm Infants
Cerebral TOI
In preterm infants, cerebral TOI was lower in the prone compared with the supine position in both sleep states at 2 to 4 weeks (P < .05), 2 to 3 months (P < .01), and 5 to 6 months CA (P < .01; Fig 1).

MAP and HR
MAP was not significantly affected by sleep position at any age, although a trend toward lower MAP was evident in the prone position at 2 to 3 months CA, in both sleep states. Overall, HR was higher in the prone compared with the supine position at both 2 to 4 weeks (P < .05) and 5 to 6 months CA (P < .01), reaching significance in QS (2 to 4 weeks CA P < .05; 5 to 6 months CA P < .01). In AS, HR tended to be higher in the prone position at 2 to 4 weeks (P = .085) and 5 to 6 months CA (P = .069). At 2 to 3 months CA, there was no effect of position on HR.

Temperature and SpO2
Temperature (Fig 1) was higher in the prone compared with the supine position in both sleep states at 2 to 4 weeks, 2 to 3 months, and 5 to 6 months CA (P < .001 for all). SpO2 (data not shown) was higher in the supine compared with the prone position in AS at 2 to 4 weeks CA and in QS at 5 to 6 months CA (P < .05); however, differences were within 1% and unlikely to be of clinical significance.

Effects of Sleep State in Preterm Infants
Cerebral TOI
TOI was higher in QS compared with AS in both the supine and prone positions (P < .01) at 2 to 4 weeks CA (Table 2). At 2 to 3 months CA, cerebral TOI was not affected by sleep state in either position. At 5 to 6 months CA, cerebral TOI was lower in QS compared with AS in both the supine and prone (P < .01) positions.

MAP and HR
MAP was higher in AS compared with QS at 2 to 4 weeks CA (P < .001) and 2 to 3 months CA (P < .05) in both sleep positions, and at 5 to 6 months CA (P < .05) in
the supine position. HR tended to be higher in AS compared with QS, reaching significance at 2 to 3 months CA in the supine position (P < .05) and at 5 to 6 months CA in both the supine (P < .001) and prone (P < .001) positions.

**Skin Temperature and SpO2**

Temperature and SpO2 were not affected by sleep state at any age in either position.

**Effects of Postterm CA in Preterm Infants**

**Cerebral TOI**

In the supine position in QS, TOI was higher at 2 to 4 weeks compared with 2 to 3 months CA (P < .05) and 5 to 6 months CA (P < .05), with no difference between 2 to 3 months and 5 to 6 months CA (Table 2). In the supine position in AS, TOI was lower at 2 to 3 months compared with 5 to 6 months CA (P < .05). In the prone position, in both QS and AS, TOI was higher at 2 to 4 weeks compared with 2 to 3 months CA (P < .05) and higher at 5 to 6 months compared with 2 to 3 months CA (P < .05). In AS in the supine position and in both sleep states in the prone position, there was no difference in TOI between 2 to 4 weeks and 5 to 6 months CA, so that an age-related nadir in TOI was evident at 2 to 3 months CA.

**MAP and HR**

Age-related differences in MAP were evident in QS in the supine position, where MAP was higher at 5 to 6 months CA compared with 2 to 4 weeks CA (P < .01), and in both QS and AS in the prone position where MAP was higher at 5 to 6 months CA compared with both 2 to 4 weeks (P < .001) and 2 to 3 months CA (P < .01). HR declined significantly in both sleep states and in both sleep positions with increasing postterm CA (P < .05 for all).

**Temperature and SpO2**

There was no effect of postterm CA on temperature. SpO2 was higher (~1%) at 2 to 4 weeks compared with 5 to 6
months CA in QS in the supine position (P < .05), a difference unlikely to be of clinical significance.

Effects of Preterm Birth

There were no differences between term and preterm infants for age, weight, and length at any of the 3 studies (Table 1).

Cerebral TOI and MAP

At 2 to 4 weeks CA, cerebral TOI was lower in preterm compared with term infants in both sleep states in the prone (P < .01 for both) and supine (P < .05 for both) sleep positions (Fig 2). At 2 to 3 months CA, there was no difference in cerebral TOI between term and preterm infants in the supine position. However, in the prone position cerebral TOI was lower in preterm compared with term infants in both QS and AS (P < .001 for both). At 5 to 6 months, there was no effect of preterm birth on TOI.

In the supine position at all 3 ages, and in the prone position at 5 to 6 months CA, there was no effect of preterm birth on MAP (Fig 2). In the prone position, there was an overall effect of preterm birth on MAP at 2 to 4 weeks CA, with MAP being lower in the preterm cohort (P < .05), although posthoc analysis did not identify whether the difference lay in AS or QS. At 2 to 3 months CA, MAP was lower in the preterm cohort in both QS (P < .01) and AS (P < .01).

**HR, Temperature, and Spo2**

In both sleep positions, there was no effect of preterm birth on HR at 2 to 4 weeks CA and 5 to 6 months CA, in either sleep state (Table 3). At 2 to 3 months CA, HR was lower in the preterm cohort in QS in the supine position (P < .05) and in both QS (P < .01) and AS (P < .01) in the prone position.

Temperature was higher in term compared with preterm infants (P < .05) in all sleep states and positions except AS in the supine position at 5 to 6 months. Spo2 was higher in preterm compared with term infants in both QS and AS in the prone and supine position at 2 to 4 weeks (P < .001 for all) and 5 to 6 months CA (P < .05 for all). At 2 to 3 months CA, there was no effect of preterm birth on Spo2.

**DISCUSSION**

To our knowledge, this is the first study to assess the effects of sleeping position on cerebral TOI in preterm infants during the period of greatest SIDS risk. We found cerebral TOI to be consistently lower in the prone compared with the supine position, with the maximal difference at 2 to 3 months CA. Furthermore, we found cerebral TOI to be lower in preterm compared with term-born infants at similar postterm ages, most prominently at 2 to 3 months in the prone position, coinciding with a reduction in MAP and HR.

**Effects of GA at Birth**

In contrast to our hypothesis, we found no association between GA at birth and cerebral TOI among this cohort of preterm infants born at 26 to 36 weeks’ GA. Any potential effect of GA may have been obscured by studying the infants at similar postconceptional ages, when brain maturation may have been similar regardless of GA at birth. Furthermore, our strict exclusion of infants with significant intracranial pathology ensured a low-risk cohort. Previous MRI studies assessing brain maturation in low-risk preterm infants have revealed only subtle effects of GA.37 Similarly, we found no association between GA at birth and MAP, probably because infants had reached normal weight by the time of study, a strong predictor of MAP.38 with no differences in weight between term and preterm infants.

**Effects of Sleep Position**

Cerebral TOI was consistently reduced in the prone compared with the supine position in preterm infants, a finding

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**TABLE 2** Effect of Sleep State and Increasing CA on Cerebral TOI, MAP, HR, Abdominal Skin Temperature, and Spo2

<table>
<thead>
<tr>
<th>CA</th>
<th>TOI, %</th>
<th>MAP, mm Hg</th>
<th>HR, beats per min</th>
<th>Abdominal Skin Temperature, °C</th>
<th>Spo2, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–4 weeks CA</td>
<td></td>
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<tr>
<td>Supine</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>QS</td>
<td>63.2 (0.4)**‡‡‡</td>
<td>63.1 (1.6)**‡</td>
<td>136.3 (0.6)###‡‡‡</td>
<td>35.7 (0.2)‡</td>
<td>98.8 (0.1)‡‡‡</td>
</tr>
<tr>
<td>AS</td>
<td>59.9 (0.5)‡</td>
<td>70.1 (1.6)‡</td>
<td>137.1 (0.6)###‡‡‡</td>
<td>35.8 (0.2)‡</td>
<td>98.6 (0.1)‡‡‡</td>
</tr>
<tr>
<td>Prone</td>
<td></td>
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</tr>
<tr>
<td>QS</td>
<td>58.0 (0.5)*#</td>
<td>61.8 (1.7)***‡‡‡</td>
<td>130.3 (0.6)###‡‡‡</td>
<td>36.7 (0.2)‡</td>
<td>99.0 (0.1)‡‡‡</td>
</tr>
<tr>
<td>AS</td>
<td>56.2 (0.4)#</td>
<td>70.3 (1.6)‡‡‡</td>
<td>139.2 (0.6)###‡‡‡</td>
<td>36.6 (0.2)‡</td>
<td>98.8 (0.1)‡‡‡</td>
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<tr>
<td>2–3 months CA</td>
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<tr>
<td>Supine</td>
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<td></td>
</tr>
<tr>
<td>QS</td>
<td>59.6 (0.5)**</td>
<td>67.6 (1.8)††</td>
<td>126.8 (0.5)†††‡</td>
<td>35.6 (0.1) †</td>
<td>98.1 (0.1) †††‡</td>
</tr>
<tr>
<td>AS</td>
<td>57.1 (0.5)†</td>
<td>73.1 (1.9)†</td>
<td>128.7 (0.5)†††‡</td>
<td>35.6 (0.1) †</td>
<td>98.2 (0.1) †††‡</td>
</tr>
<tr>
<td>Prone</td>
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</tr>
<tr>
<td>QS</td>
<td>50.9 (0.5)†</td>
<td>64.7 (1.9)***‡‡‡</td>
<td>128.5 (0.5)††</td>
<td>36.2 (0.1) †</td>
<td>98.3 (0.1) †††‡</td>
</tr>
<tr>
<td>AS</td>
<td>51.9 (0.6)†</td>
<td>70.4 (2.0)††</td>
<td>129.6 (0.5)††† †</td>
<td>36.3 (0.1) †</td>
<td>98.4 (0.1) †††‡</td>
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<tr>
<td>5–6 months CA</td>
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<td>Supine</td>
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</tr>
<tr>
<td>QS</td>
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<td>72.0 (2.5)**</td>
<td>117.2 (0.4)***</td>
<td>35.0 (0.1) †</td>
<td>97.7 (0.10) *</td>
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<tr>
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<td>76.3 (2.8)‡</td>
<td>121.2 (0.5) ††</td>
<td>35.0 (0.1) †</td>
<td>98.0 (0.1) ††</td>
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<tr>
<td>QS</td>
<td>55.3 (0.5)**</td>
<td>75.5 (2.8)‡</td>
<td>120.4 (0.4)***</td>
<td>35.1 (0.1) †</td>
<td>98.3 (0.1) ††</td>
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<tr>
<td>AS</td>
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<td>123.5 (0.5) ††</td>
<td>36.2 (0.1) †</td>
<td>98.5 (0.1) ††</td>
</tr>
</tbody>
</table>

Values are presented as mean (SEM). **P < .01; ***P < .001; †††P < .001 QS versus AS, †††P < .001; ††‡P < .01, †‡‡P < .001 2 to 4 weeks versus 2 to 5 months. †P < .05; ††P < .01; †‡‡P < .001 2 to 5 months versus 5 to 6 months. †§P < .05; †§§P < .01; †§§§P < .001 2 to 4 weeks versus 5 to 6 months.
similar to our previous study in term-born infants. Cerebral TOI reflects the ratio of oxygenated to deoxygenated hemoglobin (Hb) in the cerebral vasculature and is largely influenced by changes in the cerebral venous compartment because of its greater volume relative to the arterial compartment. Thus impaired cerebral venous drainage, resulting in venous congestion, may contribute to the reduction in cerebral TOI seen in the prone position. Additionally, impaired cerebral blood flow (CBF) may be an important contributor. Previous studies have revealed blood flow to be impaired through the internal jugular vein and the vertebral and basilar arteries of infants in the prone position with their heads turned to the side. Furthermore, in preterm infants these prone-related deficits in vertebral artery flow were found to be maximal at 1 month CA compared with the newborn period, suggesting position-dependent changes in CBF may be aggravated with advancing age.

We found the maximal effect of sleep position on cerebral TOI to occur at 2 to 3 months CA, with cerebral TOI averaging 51% in prone sleeping. Although the lower threshold for safe cerebral TOI in infancy remains unclear, in animal studies cerebral TOI falls below 40% during.

FIGURE 2
Effect of preterm birth on cerebral TOI (left) and MAP (right) at 2 to 4 weeks (upper), 2 to 3 months (middle), and 5 to 6 months postterm age (lower). Results are mean ± SEM. *P < .05; **P < .01; ***P < .001 term versus preterm.
imposed hypoxic-ischemic insults.44 With cerebral TOI values approaching this level in the prone position, preterm infants may be at risk for critically impaired cerebral TOI during hypoxic or hypotensive episodes occurring during sleep.

The effect of prone sleeping in preterm infants may be maximal at 2 to 3 months CA because of impaired cardiovascular control during this period. It is well established that prone sleeping is associated with an increase in temperature and peripheral vasodilation in infancy.20,45,46 This reduction in peripheral vascular resistance stimulates a baroreflex-mediated increase in HR to maintain MAP.19,45 This reflex response is consistent with our observations at 2 to 4 weeks and 5 to 6 months CA, where HR and temperature were increased in the prone position and MAP was maintained. In contrast, we found no increase in HR in the prone position at 2 to 3 months CA, despite the observed increase in temperature; this coincided with a tendency for MAP to be lower in the prone compared with the supine position. This suggests that baroreflex-mediated HR responses may be impaired during this period, resulting in a reduced ability to maintain MAP in the prone position, potentially reflecting reduced cardiac output. This is consistent with findings of reduced cardiac index, a measure of cardiac output relative to body surface area, in adults47,48 and children49 in the preterm compared with the supine position. Reduced cardiac output may explain the large decrease in cerebral oxygenation seen in the prone position at 2 to 3 months CA.

Although still present at 5 to 6 months CA, the effect of position on cerebral TOI lessens with age. This is likely due to maturation of cardiovascular control, anatomic maturation allowing improved blood flow through position-affected vessels and a reduced head-to-body ratio with growth of the infant.22

**Effects of Sleep State**

Consistent with our findings in term infants, cerebral TOI was also influenced by sleep state in the preterm cohort.22 At 2 to 4 weeks CA cerebral TOI was lower in AS compared with QS, at 2 to 3 months no effect of sleep state was observed and at 5 to 6 months CA cerebral TOI was higher in AS compared with QS. We suggest that this age-related progression is due to maturation of CBF-metabolism coupling during this period. AS is a state of increased brain activity, similar to wakefulness, and CBF normally increases from the level in QS to meet the heightened metabolic demands.50,51 In the mature brain, CBF usually overshoots the metabolic demands of AS resulting in an increase in oxygenated Hb relative to deoxygenated Hb and therefore increased cerebral TOI.52 At 2 to 4 weeks CA, the CBF-metabolism coupling response appears to be relatively immature with inadequate increases in CBF22 during AS resulting in increased oxygen extraction, increased deoxygenated Hb, and decreased cerebral TOI. The reversal of this observation at 5 to 6 months CA suggests that maturation of CBF-metabolism coupling is occurring during this period.

**Effects of Postterm CA**

Consistent with previous findings in term infants,22 increasing age had a considerable influence on cerebral TOI in preterm infants. TOI reached a nadir at 2 to 3 months CA, most consistently in AS. We speculate that immature CBF-metabolism coupling at 2 to 3 months CA in combination with continuing brain growth and accompanying increases in cerebral oxygen requirements result in a mismatch between cerebral metabolic demands and the capacity for cerebral oxygen delivery during this period. Furthermore, physiologic anemia peaks at ~10 weeks of age in term infants with the nadir in Hb being more severe and earlier in onset in preterm infants.53 Anemia is associated with reduced cerebral TOI because of increased oxygen extraction necessitated by a reduced oxygen carrying capacity.54 Although Hb was not measured in

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**TABLE 3 Effect of Preterm Birth on $SpO_2$, HR, and Temperature**

<table>
<thead>
<tr>
<th></th>
<th>Preterm</th>
<th>Term</th>
<th>Preterm</th>
<th>Term</th>
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<th>Term</th>
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<tr>
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<tr>
<td>Supine</td>
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<tr>
<td>QS</td>
<td>98.8 (0.2)**</td>
<td>97.3 (0.3)</td>
<td>135.8 (1.3)</td>
<td>137.8 (1.8)</td>
<td>35.7 (0.2)**</td>
<td>36.8 (0.2)</td>
</tr>
<tr>
<td>AS</td>
<td>98.6 (0.2)**</td>
<td>97.0 (0.4)</td>
<td>136.9 (1.4)</td>
<td>139.5 (1.9)</td>
<td>35.8 (0.2)**</td>
<td>36.8 (0.2)</td>
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<tr>
<td>QS</td>
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<td>96.9 (0.3)</td>
<td>139.2 (1.8)</td>
<td>141.2 (2.0)</td>
<td>36.7 (0.2)*</td>
<td>37.3 (0.2)</td>
</tr>
<tr>
<td>AS</td>
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<td>96.9 (0.3)</td>
<td>139.2 (1.8)</td>
<td>141.4 (2.0)</td>
<td>36.6 (0.1)*</td>
<td>37.2 (0.2)</td>
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<td>126.8 (1.9)*</td>
<td>133.2 (2.5)</td>
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<tr>
<td>AS</td>
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<td>97.8 (0.3)</td>
<td>129.3 (1.9)</td>
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<tr>
<td>QS</td>
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<td>98.2 (0.2)</td>
<td>128.5 (1.8)*</td>
<td>136.1 (2.3)</td>
<td>36.2 (0.1)**</td>
<td>37.2 (0.1)</td>
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<tr>
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<td>98.3 (0.2)</td>
<td>128.4 (1.8)**</td>
<td>137.4 (2.3)</td>
<td>36.3 (0.1)**</td>
<td>37.1 (0.1)</td>
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<tr>
<td>QS</td>
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<td>AS</td>
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<td>97.4 (0.3)</td>
<td>124.5 (2.0)</td>
<td>128.8 (2.1)</td>
<td>36.2 (0.1)**</td>
<td>37.0 (0.2)</td>
</tr>
</tbody>
</table>

Values are mean (SEM). *P < .05; **P < .01; ***P < .001 preterm versus term.
Effects of Preterm Birth

We found cerebral TOI to be lower in preterm compared with term infants until 2 to 3 months CA. To exclude differences in arterial SpO₂ as a cause for the difference in cerebral TOI, we assessed arterial SpO₂ and found higher SpO₂ in preterm infants at 2 to 4 weeks CA and no difference at 2 to 3 months CA. The differences in SpO₂ were within 2% and therefore unlikely to be either clinically significant or underlie the differences in cerebral TOI. Therefore, we can assume that the difference in cerebral TOI is due to increased oxygen extraction in the preterm infant brain, resulting in increased deoxygenated Hb and reduced cerebral TOI. A limited number of previous studies have assessed cerebral TOI in preterm and term infants with conflicting findings. However, these studies failed to match infants according to postconceptional or term-equivalent age, so age-related differences were likely to be obscured by the range of developmental stages.

Lower cerebral TOI in preterm infants compared with term infants may be due to inadequate cerebral oxygen delivery relative to consumption. Impaired oxygen carrying capacity because of anemia, which is likely to be more severe in preterm infants, as mentioned previously, may contribute to this mismatch. Furthermore, it is well established that prematurity and a period of neonatal intensive care can result in altered brain maturation as evidenced by MRI studies at term-equivalent age assessing cerebral volumes and cortical folding, and neural networks. Although few data exist on brain development in preterm infants after term-equivalent age, we suggest that the preterm infant brain undergoes significant ‘catch-up’ growth resulting in an increased cerebral metabolic rate for oxygen compared with term infants, a maturational difference that appears to resolve by 5 to 6 months CA.

Interestingly, the effect of preterm birth was greatest in the prone position at 2 to 3 months CA, with a cerebral TOI deficit of ∼10%. We attribute this to our finding of significantly reduced MAP and HR in preterm compared with term infants in the prone position during this period. We suggest preterm infants may have altered cardiovascular regulatory responses to prone sleeping at 2 to 3 months CA, as they appear not to increase HR to maintain MAP. Previous studies in the supine position have revealed alterations in the development of autonomic cardiovascular control in preterm compared with term infants during the first 6 months of life. Specifically, high frequency HR variability reflecting parasympathetic cardiac modulation has been found to be lower in preterm compared with term infants at term-equivalent age. At 2 to 3 months CA, altered peripheral vaso-motor tone is seen in preterm compared with term infants in the supine position. Moreover, preterm infants, assessed at term-equivalent age, displayed a diminished HR response to a cardiovascular stress compared with term infants. Our data provide evidence that impaired autonomic cardiovascular control seen in preterm infants in the supine position may be exacerbated in the prone sleep position at 2 to 3 months CA, manifesting as significant differences in MAP and HR between term and preterm infants.

Implications for SIDS

Our findings of reduced cerebral TOI in preterm infants, particularly in the prone position, in conjunction with reduced MAP in preterm compared with term infants in the prone position at 2 to 3 months CA, have significant implications for SIDS. We speculate that reduced cerebral TOI in the prone position may reflect impaired oxygen delivery to the brainstem and contribute to deficient autonomic activation and blunted arousal responses in the prone position. Furthermore, lower baseline cerebral TOI in preterm infants may represent an increased vulnerability for critically impaired cerebral TOI during a hypotensive or hypoxic event occurring during sleep. Our data suggest that deficits in cerebral oxygenation are exacerbated by immature systemic cardiovascular control as periods during which cerebral oxygenation was lowest were associated with concomitant reductions in MAP and HR.

It is important to note that epidemiologic studies have identified that the peak in SIDS deaths occurs at a slightly
earlier postterm CA (7–9 weeks CA depending on GA at birth) for preterm compared with term infants.8 In this study we chose to investigate term and preterm infants at similar postterm CAs to enable comparison at equivalent developmental ages. It may be that the cerebral oxygenation and cardiovascular differences we observed were in fact underestimated, as our infants were studied at a slightly older age than that of peak SIDS risk in preterm infants.

CONCLUSIONS

Cerebral oxygenation is depressed in the prone sleep position in preterm infants until at least 5 to 6 months CA. In addition, cerebral oxygenation is reduced in preterm compared with term infants until ~2 to 3 months CA, predominantly in the prone position. The greatest deficit in cerebral oxygenation between term and preterm infants was seen at 2 to 3 months CA in the prone position, when MAP and HR were concurrently reduced in preterm infants. We suggest preterm infants may be particularly vulnerable to critically impaired cerebral oxygenation in the prone position, particularly in the presence of cardiovascular instability, contributing to their heightened risk of SIDS.

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