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Behavioral Sleep States in Very Low Birth Weight Preterm Neonates: Relation to Neonatal Health and Vagal Maturation[1]

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Assessed the relation of behavioral codes of quiet versus active sleep state to neonatal health status in 62 very low birth weight preterm neonates. Sleep sessions (12 min) were coded for percentage time in active versus quiet sleep at 33, 34, and 35 weeks conceptional age. ECG was monitored during each sleep session to derive measures of heart rate, heart rate variability, and an index of cardiac vagal tone derived from respiratory sinus arrhythmia. Higher risk neonates spent more sleep session time in active sleep than healthier preterm neonates. Cardiac vagal tone showed a maturational change during the study weeks, whereas percentage of sampled sleep time in active sleep did not. Vagal maturation measured by age-related increases in the amplitude of respiratory sinus arrhythmia was associated with less active sleep overall, although weekly measures of respiratory sinus arrhythmia and sleep state were not related. Follow-up data on 30 of the neonates indicated that heart rate variability and cardiac vagal tone, but not sleep state measures, were related to better outcomes in mental processing, social skills, and motor skills, and to fewer behavior problems. Results are discussed in terms of the lack of coupling between behav-

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ioral and physiological components of preterm sleep states at this age as compared with that seen in full-term sleep states.

KEY WORDS: preterm; sleep state; vagal tone; respiratory sinus arrhythmia; outcome.

In full-term infants, the behavioral states of quiet and active sleep are associated with parallel physiological sleep state differences. Quiet sleep consists of periods of quiescence with regular respiration and heart rate, and synchronous EEG patterns. Active sleep consists of periods of movement with irregular respiration and heart rate, and desynchronous EEG patterns. Although it is possible to code behavioral states in preterm infants and fetuses, these behavioral states are not yet organized reflections of underlying physiological differences in state (Dreyfus-Brisac, 1970, 1974). Measures of heart rate, respiration, EEG, and motor activity remain undifferentiated with regard to sleep state during the preterm period. Temporary relations between different phenomena may be established and then disappear making it difficult to differentiate state (Dreyfus-Brisac, 1970; Parmelee, Wenner, Akiyama, Schultz, & Stern, 1967). The pattern of behavioral and physiological components defining typical active sleep begins to emerge at approximately 35 weeks conceptional age, and that of quiet sleep at approximately 37 weeks (Dreyfus-Brisac, 1970). Thus, active and quiet sleep states in the preterm, although easy to code behaviorally, do not reflect the same neurophysiological substrate as observed during sleep states in the full-term infant.

Given that preterm sleep states are not correlated with fully differentiated physiological states, what information, if any, is provided by behavioral coding of preterm sleep states? In full-term infants, states are useful for assessment and prediction of outcome precisely because they reflect the integration of "widespread integrative processes in the central nervous system" (Thoman & Whitney, 1990). If behavioral sleep states in preterms do not reflect neurobehavioral organization, then perhaps they are not useful in assessment and/or outcome prediction. The present study assessed the informativeness of distinguishing between active and quiet sleep in very low birth weight (VLBW) preterm infants from 33 to 35 weeks conceptional age with regard to clinical status and developmental outcome. In addition, given that a maturational shift in heart rate patterns from 33 to 35 weeks is related to developmental outcome (Doussard-Roosevelt, Porges, Scanlon, Alemi, & Scanlon, in press), comparisons of sleep state measures to cardiac measures (heart rate, heart rate variability, and respiratory sinus arrhythmia as an index of cardiac vagal tone) in the preterm period were made. Questions addressed regarding the pattern of active and quiet sleep included: (a) Is there a maturational shift in the pattern from 33 to 35 weeks? (b) Is the pattern

related to clinical status in the preterm period? (c) Is the pattern related to measures of heart rate, heart rate variability, or cardiac vagal tone? (d) Is the pattern predictive of developmental outcome?

Evidence suggests that active sleep is more primitive than quiet sleep and that decreasing amounts of active sleep reflect maturation (Roffwarg, Muzio, & Dement, 1966). Supporting the primitive nature of active sleep, animals born with relatively immature central nervous systems spend relatively more time in active sleep than do counterparts with more mature central nervous systems at birth (Jouvet-Mounier, Astic, & Lacote, 1970). Others have suggested that active sleep is more strongly related to brainstem mechanisms while quiet sleep reflects higher order central nervous system (CNS) structures (Berg & Berg, 1987; Parmeggiani, Morrison, Drucker-Colin, & McGinty, 1985). Consequently, as the infant's CNS matures, there is a developmental decrease in active sleep over the first several months of life. While 50% of sleep is active at term, the amount of active sleep decreases to adult-like levels over time. Preterm infants before 30 weeks gestational age spend 90% of sleep time in active sleep (Zaiwalla & Stern, 1993). Thus, the maturational effect begins during the preterm period. Given that typical active sleep develops by 35 weeks (Dreyfus-Brisac, 1970), and assuming that the developmental increase in heart rate patterns from 33 to 35 weeks reflects neurophysiological maturation, it is possible that a maturational shift in sleep states will be seen during this stage of the preterm period.

If a decrease in active sleep is found in the preterm period, then it would likely be related to CNS maturation and integrity, and in turn, provide information regarding clinical status. In the present study, we examined whether or not active sleep decreases (with a consequent increase in quiet sleep) across time. In addition, we examined whether or not decreasing active sleep is more typical of healthier rather than higher risk low birth weight preterm neonates.

Fully developed active and quiet sleep are defined based on a combination of behavioral and physiological variables. Definitions of active sleep include irregular heart rate and respiration as critical features. In contrast, quiet sleep components include regular heart rate and respiration patterns. In adults (e.g., Zemaityte, Varoneckas, & Sokolov, 1984) and infants (e.g., Haddad, Epstein, Epstein, Leistner, & Mellins, 1980; Harper, Frostig, & Taube, 1983; Schectman, Harper, & Kluge, 1989) active sleep is associated with increased heart rate, increased heart rate variability, and decreased amplitude of respiratory sinus arrhythmia (RSA) as compared with quiet sleep. While the behavioral coding of quiet and active sleep differs in adults versus infants (i.e., adults exhibiting atonia during active sleep and infants with small movements during active sleep), both groups exhibit distinguishable EEG patterns and heart rate patterns during the two states. Studying the maturation of state-related physiological variables

over time (Harper et al., 1983), and the coherence or correlation of maturational changes in variables defining sleep states (Dreyfus-Brisac, 1970: Schectman & Harper, 1992), provide evidence of the complexity of the relation between the physiological and the behavioral characteristics of active and quiet sleep. Cardiorespiratory factors in particular demonstrate an erratic developmental progression as control makes transitions from parasympathetic to sympathetic to forebrain mechanisms (Schectman & Harper, 1992; Scher et al., 1994). Given evidence of shifts in heart rate variability and the amplitude of RSA from 33 to 35 weeks, the present study addressed the question as to whether these changes are correlated with the pattern of active and quiet sleep over this time period.

Finally, if a decrease in active sleep is exhibited in the preterm period, and if the decrease is related to medical risk and to heart rate patterns, then it would likely serve as an index of CNS integrity and could serve as a predictor variable for developmental outcome. Beckwith and Parmalee (1986) used the amount of *trace alternant* pattern in EEG (quiet sleep) as an index of neurophysiological maturity and integrity in full-term infants. Infants with less quiet sleep at birth had lower scores on standardized tests at 4 months with lasting effects on intelligence continuing through 8 years of age. These findings suggest that in infancy the percentage of time spent in active versus quiet sleep is concomitant with maturity of higher nervous system structures, and that less active sleep is associated with better outcome.

Given that active sleep in the preterm infant prior to 35 weeks is markedly different from the fully developed active sleep of the full-term infant, preterm active sleep may or may not be related to nervous system maturation or to developmental outcome. Groome, Bentz, & Singh (1995) examined sleep states in fetuses (37–41 weeks) and reported that the amount of time in undefined states (in which the patterns of associations of heart rate, eye movements, and body movements are not consistent with any state definition) is correlated with the amount of time in active sleep and wakefulness, independent of time in quiet sleep. The authors suggest that the undefined state is a manifestation of a failure of CNS control mechanisms to achieve and maintain an active sleep or an awake state. Thus, less time in active sleep may reflect brainstem regulation problems. Therefore, developmental outcome may be related not only to decreasing active sleep in the newborn period but also to decreases in active sleep in the preterm period.

Each of the four questions outlined above was addressed in the present study. Behavioral measures of sleep state and measures of heart rate patterns were recorded in VLBW preterm neonates in weekly sessions at 33, 34, and 35 weeks conceptional age. Age-related changes in sleep states were assessed. Differences in the pattern of active and quiet sleep between those of higher medical risk versus lower medical risk were examined. The next question addressed concerned whether or not sleep states were related to heart rate measures.

In healthy infants active sleep is associated with greater heart rate, greater heart rate variability, and lower amplitude RSA (an index of cardiac vagal tone). Analyses examined whether maturational changes in the heart rate measures are correlated with changes in active sleep. Finally, analyses addressed the question of whether or not sleep state measures provide information regarding developmental outcome. Relative ability of vagal maturation (i.e., developmental shifts in the amplitude of RSA) and maturational changes in active sleep to predict developmental outcome at 3 years were assessed. Areas of outcome assessed included mental processing, achievement, social skills, behavior problems, and motor skills.

METHOD

Participants

Sixty-two VLBW (<1,500 grams) neonates were seen weekly in the hospital neonatal intensive care unit between 33 and 35 weeks of age. Demographic information, including the Hobel Risk Index (Hobel, Hivarinen, Okada, & Oh, 1973), were extracted from hospital records, and are included in Table I. The Hobel Risk Index assessed medical risk based on clinical variables (e.g., birth weight, intraventricular hemorrhage, respiratory problems) and was used to divide the sample into two groups based on medical risk. Medical information for the Lower Medical Risk group (n = 28) and the Higher Medical Risk group (n = 34) are presented in Table II. A subsample of 30 infants (13 lower risk, 20 higher

Table I. Demographic Information of Low Birth Weight Preterm Sample (N = 62)

Variables	n
Gender	
Male	29
Female	33
Race	
Caucasian	9
African American	48
Hispanic	2
Asian American	3
Birth weight	
Extremely low birth weight (<1,000 g)	33
Very low birth weight (<1,500 g)	29
Parental employment	
Unemployed	16
Employed	46

Table II. Health Status in Lower and Higher Medical Risk Groups[a]

	Lower medical risk (n = 28)		Higher medical risk (n = 34)	
Variable	*M*	Range	*M*	Range
Birth weight (grams)	1,040	650–1325	865	470–1,120
Gestational age at birth (weeks)	29	24–33	27	23–32
Discharge age (weeks)	37	36–39	40	36–50
Days on ventilation	6	0–38	24	0–70
Hobel Medical Risk Index	53	25–75	91	71–136

[a]All group comparisons significant, $p < .01$.

risk) was seen in a University testing suite at 3 years of age in a follow-up study. Maternal informed consent was obtained by the nurse for the neonatal study and by the experimenter for the follow-up study.

Apparatus

ECG data were collected via three Ag/AgCl electrodes connected to a Delta Biometrics Vagal Tone Monitor (Delta-Biometrics, Bethesda, MD). The Vagal Tone Monitor collects continuous ECG analog data and outputs a digitized file of interbeat intervals accurate to the nearest millisecond. These files were edited and analyzed using MXedit software (Delta-Biometrics, Bethesda, MD).

Design and Procedure

ECG data were recorded during each of three weekly (7 ± 2 days) sessions approximately 12 minutes in length. The ECG data were digitized off-line to quantify sequential times between heart beats (i.e., interbeat interval or heart period) to the nearest millisecond. Sessions occurred at least 1 hour following a feeding while the neonate slept. Behavioral state was recorded every 15 seconds during the 12-minute recording session using a six-state coding scheme based on eye movements and motor activity. The coding scheme included quiet sleep, active sleep, drowsy, quiet awake, active awake, and crying. Quiet sleep was defined as a period with eyes closed and no motor activity. Active sleep was defined as a period with eyes closed and small motor movements. Of the total epochs, 97% were classified using these two categories. The remaining 3% consisted of periods of drowsy sleep or crying. State coding was performed by the neonatologist who was trained to criterion. The number of 30-second epochs in each of the two sleep states (active sleep, quiet sleep) at each age was re-

corded. A score reflecting the mean number of epochs across the three recordings as well as a difference score from first to last recording, reflecting sleep state maturation, were computed for each state. These variables represent summary data derived from randomly sampled periods of sleep and are assumed to reflect the characteristics of the infant's entire sleep pattern.

Heart rate, heart rate variability, and cardiac vagal tone estimates were derived from the first 10 minutes of beat-to-beat heart rate data in each session. The index of cardiac vagal tone was calculated via the Porges (1985) method of quantifying respiratory sinus arrhythmia. Respiratory sinus arrhythmia is a naturally occurring arrhythmia characterized by rhythmic increases and decreases in heart rate at approximately the frequency of breathing. The amplitude of these oscillations provides an accurate index of the component of cardiac vagal tone originating in the nucleus ambiguus located in the medulla, traveling through the vagus (the tenth cranial nerve) and terminating on the sinoatrial node (the primary cardiac pacemaker).

The Porges method applies time series techniques to beat-to-beat interval data (i.e., interbeat intervals or heart periods) defined by the time between successive R-waves of the ECG measured to the nearest millisecond. The heart periods are resampled at 5 Hz. A 21-point moving polynomial filter is stepped through the time-sampled data to create a smoothed template of slow oscillations. The resulting trend is removed from the original time series yielding a residual series free of both linear and higher order trends. Finally, a band-pass filter extracts the variance within the respiration frequency band for this age group (0.30–1.30 Hz) and the natural logarithm of this variance quantifies respiratory sinus arrhythmia as an index of cardiac vagal tone. A vagal maturation score was calculated for each child based on the difference in the amplitude of respiratory sinus arrhythmia from 33 to 35 weeks conceptional age. Similarly, heart rate and heart rate variability measures within each testing session and difference scores from 33- to 35-week conceptional age for heart rate and heart rate variability were calculated. Although RSA and heart rate variability are each measures of the variability in the beat-to-beat heart rate, the latter is a global measure of all variance, and the former isolates the variance associated with the vagal contribution to heart rate (see Porges, 1983, 1995b) and thus, is treated as an index of cardiac vagal tone.

A subsample of 30 infants was seen in a University testing suite at 3 years of age in a follow-up study. The assessment at 3 years included administration of the Kaufman Assessment Battery for Children (Kaufman & Kaufman, 1983), including the Mental Processing Composite Scale and the Achievement Scale. The Revised Denver Prescreening Questionnaire for Motor Abilities (Frankenburg, 1986) was completed by an examiner and subscores for gross motor skills and fine motor skills were calculated. In addition, mothers provided demographic information and completed three standardized questionnaires concerning their

children's behavior. The Child Behavior Checklist/2–3 Years (Achenbach, 1988) consists of 100 items assessing six areas of behavior problems. The California Preschool Social Competency Scale (Levine, Elzey, & Lewis, 1969) provides maternal ratings on 30 items in the area of social achievement (e.g., sharing, following instructions, initiating interactions, accepting limits). The Parenting Stress Index (Abidin, 1983) contains 50 items in its child subscales which index maternal perception of child characteristics (e.g., mood, distractibility, demandingness, adaptability).

RESULTS

The first question, regarding differences in active and quiet sleep as a function of gestational age was examined with a repeated measures analysis of variance (ANOVA). In addition, the pattern of active versus quiet sleep was viewed based on percentage of session in each state. Developmental effects as well as the relation between active and quiet sleep measures were assessed. Second, the question regarding the relation of sleep state patterns to health status were examined with a Group (higher risk, lower risk) × Condition (active, quiet) analysis of variance with groups defined by Hobel medical risk scores. Comparisons of neonates with higher medical risk (Hobel index > 75, $n = 34$) and lower medical risk (Hobel index < 76, $n = 28$) are presented. Third, the question of the relation of sleep state variables to heart rate variables is addressed using within-age comparisons (e.g., 35-week heart rate variability to 35-week active sleep) as well as comparisons of summary variables representing mean values and the maturational change in each variable across gestational age. Fourth, the ability of sleep state and heart rate variables to predict 3-year outcome in this high-risk preterm sample is tested with correlational analyses.

Mean values for percentage of session time in active sleep and for the cardiac measures at 33, 34, and 35 weeks are presented in Table III. The percent-

Table III. Sleep State and Cardiac Measures at 33, 34, and 35 Weeks Conceptional Age

	33 weeks		34 weeks		35 weeks	
	M	*SD*	*M*	*SD*	*M*	*SD*
% time in active sleep	70	0.27	69	0.29	59	0.34
Heart rate (beats/min)	158	13.2	161	9.6	158	9.0
Heart rate variability	3.6	0.90	3.9	0.89	3.9	0.99
Cardiac vagal tone	0.73	0.64	0.95	0.70	1.07[a]	0.81

[a] $p < .01$.

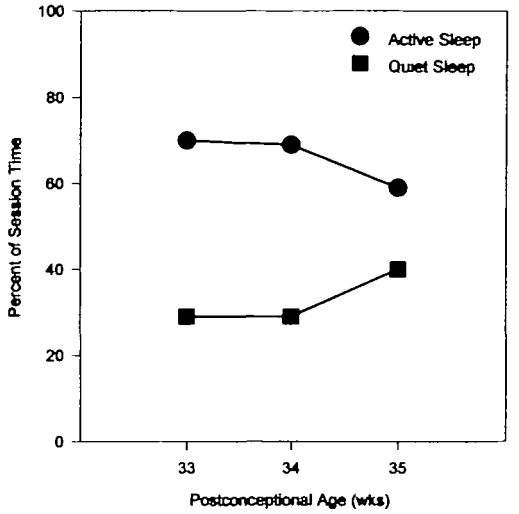

Fig. 1. Percentage of session time spent in active sleep and in quiet sleep as a function of age.

age of session time spent in active sleep and in quiet sleep as a function of age is plotted in Figure 1. This figure illustrates the inverse relation of the active and quiet sleep patterns in this sample. Very little time (3%) was spent in any state other than quiet or active sleep. Pearson correlations between active and quiet sleep at each age, $r(62) = -.976$ at 33 weeks, $r(62) = -.992$ at 34 weeks, and $r(62) = -.995$ at 35 weeks, confirm that statistics for one state are the inverse of statistics for the other. Therefore, once the pattern of active and quiet sleep is described, most analyses concentrate on amount of active sleep with the understanding that similar analyses on amount of quiet sleep would yield inverse but identical results.

Percentage of time spent in active versus quiet sleep during the test session at each age appears to show a developmental decrease in active sleep. Percentage of session time in active sleep from 33 to 35 weeks was: 70% at 33 weeks, 69% at 34 weeks, and 59% at 35 weeks. However, a repeated measures ANOVA with amount of time spent in active sleep as the within-subjects repeated measure yielded no significant developmental effect, $F(2, 122) = 2.58$, $p > .05$.

Neonates were divided into two groups based on Hobel medical risk scores. Neonates with risk scores less than 76 constituted Group 1 and those with risk scores of 76 or greater constituted Group 2. Table II provides health information on the two groups. Group 2 had significantly lighter birth weights, lower gestational age, spent more days on ventilation, and were discharged from the hospital at a later chronological age. The two groups were not different with respect to mean heart rate, mean heart rate variability, or mean cardiac vagal tone. Figure 2

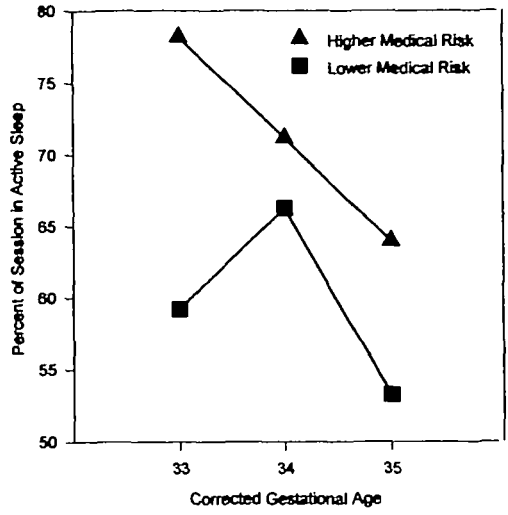

Fig. 2. Percentage of session time spent in active sleep as a function of age and medical risk group.

presents the percentage of session time each group spent in active sleep. Within this high-risk sample, the healthier neonates exhibited less active sleep and more quiet sleep than those in the higher risk group. On average, collapsing across age, healthier neonates spent 60% of their time in active sleep, 39% in quiet sleep, and 1% in other states. The higher risk group spent 71% of their time in active sleep, 27% in quiet sleep, and 2% in other states.

A repeated measures Group (higher risk, lower risk) × Age (33, 34, 35 weeks) ANOVA on mean time in active sleep, indicated a main effect for Group, $F(1, 60) = 6.41$, $p < .05$, with no effect of Age, and no Group × Age interaction. Healthier neonates spent less time in active sleep during the recording session than their higher risk counterparts, regardless of comparison age. Neither group demonstrated a significant developmental decrease in active sleep.

Even though the developmental decreases in active sleep were not significant, the relation of sleep state to heart rate measures is of interest. Correlations between sleep measures (mean epochs in quiet sleep, mean epochs in active sleep) and cardiac measures (heart rate, heart rate variability, cardiac vagal tone) averaged across the three test sessions are presented in Table IV. Heart rate variability is associated with sleep state at every age, with greater heart rate variability related to more session time spent in active sleep at each age. Heart rate and cardiac vagal tone were not associated with sleep state at any age. In this sample, heart rate did not show a maturational effect, whereas heart rate variability, $F(2, 122) = 2.89$, $p < .10$; and cardiac vagal tone, $F(2, 122) = 6.45$, p

Table IV. Correlations of Sleep State and Cardiac Measures at 33, 34, and 35 Weeks Postconceptional Age

	Active sleep	Quiet sleep
	33 weeks	
Heart rate	−.01	−.03
Heart rate variability	.29[a]	−.33[a]
Cardiac vagal tone	.23	−.22
	34 weeks	
Heart rate	.03	−.03
Heart rate variability	.32[a]	−.35[b]
Cardiac vagal tone	.01	−.03
	35 weeks	
Heart rate	.18	−.17
Heart rate variability	.43[b]	−.43[b]
Cardiac vagal tone	.24	−.24

[a] $p < .05$.
[b] $p < .01$.

$< .01$, did. Both vagal maturation (i.e., change in cardiac vagal tone from 33 to 35 weeks) and heart rate variability maturation (i.e., change in heart rate variability from 33 to 35 weeks) were related to the change in active sleep from 33 to 35 weeks, $r(61) = .34$, $p < .01$, and $r(61) = .50$, $p < .001$, respectively. Increases in heart rate variability and cardiac vagal tone were associated with an increase in active sleep. However, although greater vagal maturation was related to an increase in active sleep over time, those neonates exhibiting greater vagal maturation spent less time in active sleep averaged across sessions, $r(61) = -.25$, $p < .05$.

Finally, sleep state and heart rate measures were assessed as predictors of developmental outcome in a subset ($n = 30$) of the sample who participated in a follow-up study at 3 years of age. Analyses using the maturational changes as well as means across the three test sessions for heart rate, heart rate variability, cardiac vagal tone, and active sleep as predictors of 3-year outcome were conducted. The outcome variables represented broad areas of development: mental processing, achievement, social skills, behavior problems, and motor skills. Table V presents the areas of development and the instruments used in their measurement.

Mean active sleep and change in active sleep were not correlated with the outcome variables. Mean heart rate was correlated with social skills, $r = -.44$, $p < .05$, with lower heart rate associated with better social skills. Change in heart rate variability was correlated with behavior problems as measured by the Child Behavior Checklist, $r = .39$, $p < .05$. Vagal maturation was correlated with

Table V. Outcome Variables and the Measurement Instruments for the Follow-Up Study

Outcome variables	Measurement instruments
Mental processing	Kaufman Assessment Battery for Children: Mental processing composite score
Achievement	Kaufman Assessment Battery for Children: Achievement score
Social skills	California Preschool Social Competency Scale
Behavior problems	Child Behavior Checklist 2–3: Total score
	Parenting Stress Index: Child scale score
Motor skills	Revised Denver Prescreening Questionnaire for Motor Abilities
	Gross motor items
	Fine motor items

mental processing, $r = .38, p < .05$, and with gross motor skills, $r = .38, p < .05$. Mean heart rate variability was related to mental processing, $r = .44, p < .05$, social skills, $r = .43, p < .05$, fine motor skills, $r = .52, p < .01$, and child behavior problems as measured by the Parenting Stress Index (Abidin, 1983), $r = -.37, p < .05$. Greater heart rate variability was associated with better mental processing, social skills, and fine motor skills, and with fewer behavior problems measured with the Parenting Stress Index. Greater vagal maturation was associated with better mental processing and gross motor skills.

In summary, there was no developmental decrease in active sleep. Healthier preterm neonates spent less sleep session time in active sleep than their higher risk counterparts. Neonates exhibiting greater vagal maturation, operationally defined by an increase in the amplitude of RSA from 33 to 35 weeks, spent less sleep session time in active sleep, but showed an increase in active sleep over time. Neonates exhibiting an increase in heart rate variability over time, showed an increase in active sleep over time. Heart rate variability, but not cardiac vagal tone, was related to the amount of sleep session time in active sleep at each age.

DISCUSSION

Sleep states in full-term healthy infants are easily measured and provide information on the newborn's neurobehavioral status. Designers of newborn exams (e.g., Neonatal Behavioral Assessment Scale, Brazelton, 1973; Assessment of Preterm Infants' Behavior, Als, Lester, Tronick, & Brazelton, 1982) recognized the important achievement represented by state regulation in the newborn. Active and quiet sleep states, as observed behaviors, are easily measured in VLBW preterm infants as well. The purpose of this paper was to examine behaviorally coded sleep states in preterm infants and to assess the

information they might provide regarding clinical status and developmental outcome.

For the sample as a whole, the decrease in active sleep from 33 to 35 weeks conceptional age approached statistical significance ($p < .09$). In the repeated measures analysis of variance with medical risk group there was no group by age interaction. Neither group demonstrated a significant decrease in active sleep over time as assessed during our time-sampled weekly test sessions. However, the analysis did reveal a level difference between groups, collapsing across age. The healthier group spent less session time in active sleep than did the higher risk group.

The next issue addressed was whether or not mean time in active sleep was related to the physiological measures. Average time in active sleep was not related to mean heart rate variability or mean cardiac vagal tone, but measures of active sleep and heart rate variability were correlated at each age. Greater heart rate variability was associated with more time in active sleep. Vagal maturation was negatively correlated with time in active sleep overall, but positively correlated with the maturational change in active sleep. Finally, sleep state measures and physiological measures were correlated with outcome variables in a subset of infants who participated in a 3-year follow-up study. Sleep state measures were not correlated with outcome variables. Greater heart rate variability was correlated with better mental processing, fine motor and social skills, and fewer behavior problems. Increasing cardiac vagal tone over time was associated with better mental processing and gross motor skills.

The increase in respiratory sinus arrhythmia during this critical period (33–35 weeks conceptional age), referred to as vagal maturation, is assumed to reflect maturation of the neural circuits monitoring and regulating heart rate via the vagus nerve. Clairambault, Curzi-Dascalova, Kauffmann, Medigue, and Peirano (1991) also reported vagal tone maturation in the preterm period although they reported a steep increase at 37–38 weeks compared with our increase at 34–35 weeks. The 37- to 38-week period is difficult to assess in our database as discharge of most preterm infants occurs at 35–36 weeks in the United States. Assuming vagal maturation is a reflection of neural integrity, then one would expect to find a relation between both respiratory sinus arrhythmia maturation and respiratory sinus arrhythmia mean levels and measures of sleep state regulation. In the full-term infant, cardiac vagal tone is associated with the ability to regulate state in response to environmental and visceral demands (Porges, 1995a). With the knowledge that active sleep is associated with lower levels of cardiac vagal tone in full-term infants, we investigated sleep state and cardiac vagal tone in our preterm sample. Whereas heart rate variability was related to time spent in active versus quiet sleep state at each age, cardiac vagal tone was not. This effect may reflect the sensitivity of a global measure of heart rate

variability to the transitory influences of motor activity that characterize active sleep. In contrast, cardiac vagal tone, measured solely by quantifying the respiratory-related increases and decreases in heart rate, is less sensitive to transitory shifts in heart rate (e.g., motor-related heart rate changes).

Therefore, as supported by the literature, noting a lack of coherence in physiological and behavioral components of active and quiet sleep in preterm infants (e.g., Dreyfus-Brisac, 1970, 1974), the amount of session time spent in active sleep was not related to cardiac vagal tone when assessed at each age. Yet heart rate variability was related to time spent in active sleep at each age. In contrast to respiratory sinus arrhythmia, which was used as our index of cardiac vagal tone, heart rate variability is more strongly influenced by all mechanisms mediating changes in heart rate (e.g., vagal, sympathetic, myocardial reflexes). With the increased activity, which defines the active sleep state, motor-related heart rate changes contribute to heart rate variability. Thus, heart rate variability would be expected to increase during active sleep regardless of the integrity of the CNS or the maturity of mechanisms controlling sleep state.

According to Dreyfus-Brisac (1970, 1974) behavior patterns begin to appear at 32 weeks gestational age that resemble active and quiet sleep. These patterns begin to merge with component EEG, heart rate, and motor values at 35 weeks, and by 38 weeks the typical components of active sleep are present. However, unlike patterns in full-term healthy infants, the patterns in preterm infants are filled with discontinuities. The evolution of the organization of sleep states does not progress evenly because component phenomena independently appear and disappear. Temporary relations among phenomena may be established at one age and disappear at a later age (Dreyfus-Brisac, 1970).

Schectman and Harper (1992) suggested that changes in the relations among component phenomena may be due to changes in the mechanisms controlling each specific phenomenon. For example, couplings between heart rate measures and sleep states may change as the mechanisms controlling heart rate and respiration mature. The Polyvagal Theory (Porges, 1995b) provides additional support for this interpretation. The Polyvagal Theory proposes that maturation of neural control of the heart follows a phylogenetic sequence. This sequence begins with a primitive unmyelinated vagal system originating in the dorsal motor nucleus of the vagus, followed by the sympathetic nervous system, and lastly in mammals by a phylogenetically newer vagal system with myelinated fibers originating in the nucleus ambiguus. The latter receives direct input from limbic and other subcortical and cortical structures. It is the nucleus ambiguus vagal system that was monitored in this study via measurements of respiratory sinus arrhythmia. Because the nucleus ambiguus is involved in the regulation and coordination of sucking, swallowing, breathing, and vocalizing, monitoring the nucleus ambiguus vagal system may provide an important assessment window to the clinical status and developmental outcome of the high-risk infant (Porges, 1996).

In the current study, heart rate measures did not exhibit a coherent relation with behaviorally coded sleep state other than the fact that heart rate variability increased with the increased movement defining active sleep. Changes in vagal maturation observed from 33 to 35 weeks were related to less active sleep when collapsed across age but to an increase in active sleep over time. Heart rate variability, too, was associated with an increase in sleep over time. The results do not support the notion of sleep states reflecting underlying neurobehavioral organization. Rather, the behavior seen in the sleep states appears to influence the measures of heart rate and heart rate variability, while the relations to changes in cardiac vagal tone are less straightforward. The latter point suggests that with the preterm neonate, the determination of specific sleep state does not appear to have a robust influence on the monitoring of vagal tone via measures of the amplitude of respiratory sinus arrhythmia.

If preterm sleep states do not reflect an underlying neurobehavioral organization, it is less likely that they may be informative regarding clinical status and developmental outcome. However, the sleep states may be related to noncardiac measures of neurophysiological organization not tested in this design. Thus, it was possible they would relate to clinical status and outcome, independent of their relation to cardiac vagal tone, and would provide unique sources of prediction. Results indicate that sleep state measures are related to Hobel medical risk scores. Within our sample of high-risk VLBW neonates, those with fewer medical complications in the hospital spent less time in active sleep as sampled during test sessions. Thus, sleep state characteristics did provide discriminative information regarding medical status. As predictor variables for later outcome, the measures of active and quiet sleep and their relation to age in the period from 33 to 35 weeks did not provide a source of variance.

Future research is required to examine a larger window of development within the preterm period. We chose the span of 33 to 35 weeks for two reasons. First, the majority of preterm neonates are present in the neonatal intensive care nursery during this time, allowing us to construct a data set in which all subjects are represented at each age so that repeated measures analyses can be used to examine age-related changes. Using a larger window would exclude many neonates who were either born after 32 weeks or discharged at 35 weeks or earlier. Second, the period from 33 to 35 weeks had proven to be a period in which developmental changes occur in the vagal control of the heart, as evidenced by a maturational shift in the amplitude of respiratory sinus arrhythmia. This suggests a period of myelination and neural maturation with possible wide-range effects on outcome. The fact that sleep states at this age are not related to cardiac vagal tone or to outcome suggests that this window is not particularly informative in terms of sleep state. Thoman and colleagues (e.g., Davis & Thoman, 1987; Whitney & Thoman, 1994) have studied preterms after discharge (41–45 weeks postterm) and found their patterns of sleep–wake to show irregular development

compared with full-term sleep–wake development. Specifically, their preterm sample exhibited signs of more mature patterns in some areas and less mature patterns in others, leading to the description of preterm development of behavioral sleep–wake cycles as uneven. In their research (Whitney & Thoman, 1994), preterm sleep–wake characteristics did not predict follow-up information provided by mothers up to age 3. Future research should address whether or not preterm behavioral sleep states at any age within the preterm period provide information regarding developmental outcome.

To summarize the major findings, the study identifies that less active sleep for the high-risk preterm neonate during the period of 33 to 35 weeks gestational age is related to neonatal health (i.e., mean time in active sleep is lower for healthier neonates) and is not related to simultaneously monitored cardiac vagal tone or to developmental outcome. However, sleep state is related to simultaneously monitored heart rate variability. Unlike the vagal tone measure that is defined solely by respiratory-related changes in heart rate, overall heart rate variability is influenced by motor activity, a parameter that distinguishes between active and quiet sleep. In conclusion, sleep states in VLBW preterm infants at 33 to 35 weeks of age are not the same as sleep states of the healthy full-term infant. In particular, due to the lack of consistent correspondence between behavioral measures of state and physiological measures over time, behavioral coding of preterm sleep states offers little information regarding physiological maturity or neurobehavioral integrity. Consequently, based upon our data, we conclude that knowledge of sleep states during the 33- to 35-week period is not related to simultaneously collected measures of cardiac vagal tone and offers little predictive information of outcome in very low birth weight infants.

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