

Cardiorespiratory Behavior during Sleep in Full-Term and Preterm Neonates at Comparable Postconceptional Term Ages¹

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ABSTRACT

Cardiorespiratory behavior during sleep has been investigated by comparing visually analyzed minutes of EEG sleep with the digitized values of these two physiologic variables for each corresponding minute. Continuous 3-h nighttime sleep studies on 37 full-term and preterm neonates at comparable postconceptional term ages were acquired under controlled conditions, using a 24-channel computerized monitoring system and an automated event-marker program. Five thousand, two hundred ninety-four minutes were assigned an EEG state by traditional criteria. Eighteen preterm infants were compared with 19 full-term infants with respect to six cardiac and six respiratory measures: two nonspectral calculations (*i.e.* average per minute and variance of the means) and four spectral calculations of the cardiorespiratory signal (*i.e.* bandwidth, spectral edge, mean frequency, and ratio of harmonics). The relative capabilities of these measures to predict a sleep state change were investigated using discriminant analysis. A stepwise selection algorithm in discriminant analysis was used to identify the order of significance for the remaining variables. Eight cardiorespiratory measures were then submitted to multivariate analysis of variance to assess sleep state or preterm–full-term differences: mean frequency, bandwidth, average per minute, and ratio of harmonics for cardiac signals; and spectral edge, mean

frequency, logarithm of variance, and ratio of harmonics for respiratory signals. Differences among the sleep states and between neonatal groups were highly significant ($p < 0.0001$). Interaction between sleep state and neonatal group was also significant ($p < 0.034$). Two variables differentiated preterm from full-term respiratory behavior: ratio ($p \leq 0.001$) and mean frequency ($p \leq 0.02$). Three variables demonstrated differences between preterm and full-term cardiac behavior: average heart rate per minute ($p \leq 0.001$), ratio ($p \leq 0.05$), and bandwidth ($p \leq 0.08$). Notably, the lowest values for most spectral measures were noted during tracé alternant quiet sleep compared with the three other segments of the ultradian sleep cycle. Our findings demonstrate sleep state–specific differences in cardiorespiratory behavior in neonates regardless of prematurity. Differences between preterm and full-term infants reflect altered functional development of the brain because of adaptation to prematurity, an extrauterine experience, or both and may contribute to a model of physiologic vulnerability of certain infants for sudden infant death syndrome. (*Pediatr Res* 36: 738–744, 1994)

Abbreviations

SIDS, sudden infant death syndrome

EEG sleep organization, in general, is comparable for all newborns at postconceptional term ages regardless of prematurity at birth (1, 2). However, differences also

have been described between full-term and preterm infants in cardiorespiratory behavior, rapid eye movements, spectral content, and state organization (3–11).

We have reported differences between full-term and preterm infants at matched postconceptional term ages with respect to sleep architecture, continuity, phasic, spectral, and rectal temperature measures (9–11). The two aims of our present study were to investigate cardiorespiratory behavior in neonates during sleep and compare these physiologic measures between full-term and preterm groups of healthy infants who were subsequently normal on neurodevelopmental assessments.

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METHODS

Patient population. Nineteen full-term and 18 preterm at postconceptional term age infants were studied (Table 1). Preterm infants had an average gestational age at birth of 28.98 wk but comparable postconceptional term ages and body weights at the time of the EEG sleep recordings.

Healthy preterm neonates of ≤ 32 wk gestational age were prospectively selected from an inborn population at a large obstetrical hospital. Selection criteria were strict, excluding infants with major illnesses. No infants required ventilatory care or suffered intracranial hemorrhage, sepsis, or other major organ system disorders. Monthly EEG sleep studies were obtained on the preterm group until postconceptional term ages.

The last EEG sleep records of the preterm group were compared with EEG studies for a group of full-term neonates at comparable postconceptional term ages. Records for each full-term infant were obtained between 2 and 3 d of age.

All 37 subjects were examined by at least 18 mo of life and were judged to be healthy and appropriate for neurodevelopmental milestones. Thirty-one subjects were available for the following psychometric evaluations: Bayley Motor and Mental Performance Scales, Carey Temperament Scales, and Vineland Social Maturity Scales. The remaining six were healthy and age appropriate by parental or physician report.

EEG sleep recording sessions. Paper and computer recordings of EEG sleep studies were collected and analyzed using the protocol listed in Figure 1. A 24-channel study was recorded for each infant on a computer workstation (Apollo computers, Hewlett-Packard, Inc., Palo Alto, CA). The initial 3 h of a 12-h nighttime study were simultaneously recorded on paper using a Nihon-Kohden model 4221 machine (Irvine, CA) from which a visually scored EEG sleep state was assigned for each minute of the recording. Architectural, phasic, and continuity measures were scored for each minute of sleep. The ultradian neonatal sleep cycle consists of a sequence of state segments that begin and end in active sleep, with two quiet sleep segments occurring between these active sleep segments: mixed frequency active sleep \rightarrow high-voltage slow quiet sleep \rightarrow tracé alternant quiet sleep \rightarrow low-voltage irregular active sleep (1, 2). Minutes of wakefulness and indeterminate sleep were also noted (Fig. 2). Behavioral observations regarding sleep behavior, artifacts, and environmental conditions were also recorded

Table 1. Demographics of neonatal population

Full-term group	
8 Males/11 females	
Gestational age: 40.6 ± 1.2 (37–42) wk	
Weight: 3551 ± 458 (2700–4670) g	
Preterm at term group	
9 Males/9 females	
Gestational age: 28.98 ± 1.4 (26–31) wk	
Postconceptional ages: 40.7 ± 1.7 (37–43) wk	
Weight: 3579 ± 451 (2400–4082) g	

Data Collection and Analysis Protocol

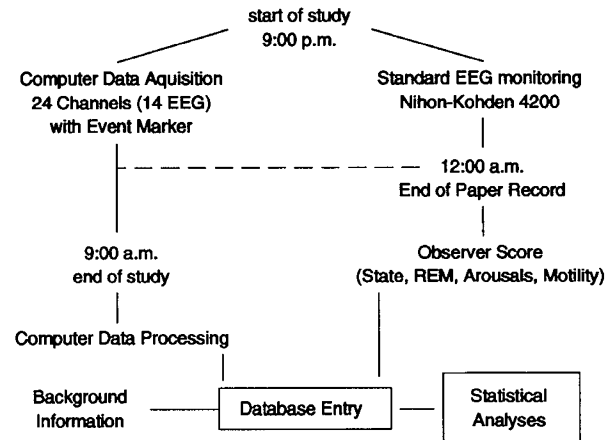


Figure 1. Data collection and analysis protocol. Analyses for this project were obtained from the first 3 h of the 12-h recording. REM, rapid eye movements.

on the computer using an event-marker program developed in our laboratory (12). Demographic, clinical, technical, and EEG sleep data were recorded on handwritten data sheets and then entered into a relational database (Borland-Interbase, Inc., Scotts Valley, CA).

Data were acquired with a sampling rate of 64 Hz. Values for each signal (*i.e.* heart and respiratory calculations, EEG energies) were computed and averaged for every minute. These averages were subsequently entered into our relational database. Minutes during feedings and diaper changes were eliminated. Cardiorespiratory signals were filtered using a five-point median filter. Artificially induced high and low values were also eliminated. For this particular study, only cardiorespiratory measures were compared between the two study groups based on the visually scored minute of sleep. Continuous measurements of heart rate were collected with a standard ECG electrode on the chest. Respiratory excursions were recorded from the thorax using inductive plethysmography.

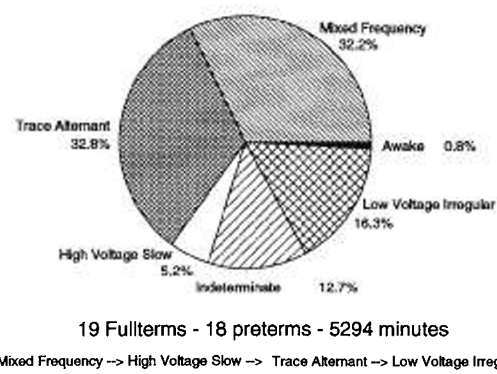


Figure 2. Sleep state distribution in our study group. Note the predominance of active sleep (*i.e.* mixed frequency and low-voltage irregular sleep segments). Quiet sleep segments comprise tracé alternant and high-voltage slow segments. Indeterminate or transitional sleep and waking portions are also listed.

Data analyses. Computer programs were written to analyze the cardiorespiratory signals. Cardiorespiratory measures can be subdivided into nonspectral and spectral values; two nonspectral measures were average rate and variance of the means. Spectral cardiorespiratory measures consisted of four calculations of the spectral content of the cardiac and respiratory signals: bandwidth, spectral edge, mean frequency, and ratio of harmonic energies. Each of these six measures was averaged over 1 min and identified with the visually identified EEG sleep for that minute.

Bandwidth calculates the spectral content as measured by the distance between the point at which the spectrum is first greater than 50% of the maximum of the spectral value and the point at which the spectrum is last less than 50% of the maximum spectral value. Spectral edge calculates the frequency below which 90% of the total spectral value is represented. Mean frequency is defined as the center of gravity of the spectrum, and the ratio of harmonics measures the degree of difference between an idealized signal with a sinusoidal pattern and the physiologic signal with which it is compared. Each of these four spectral measures represents either the predominant frequencies contained in the cardiorespiratory signal (*i.e.* bandwidth, spectral edge, mean frequency) or the regularity of the signal over time (*i.e.* ratio of harmonics).

Statistical analyses. All analyses were performed using the SAS statistical package (Cary, NC), and the SPSS statistical package (Chicago, IL). Six calculations were applied separately to the raw cardiac signal and six calculations to the respiratory signal. The relative capability of these values to predict sleep-state change was then investigated by stepwise discriminant analysis. The natural logarithmic transformation was used on one variable, the variance of the respiration rate, to achieve a normal distribution. Correlations between pairs of variables did not exceed 0.7. A hierarchical ordering of measures was obtained by the use of a stepwise selection algorithm in discriminant analysis. As a result, the remaining cardiorespiratory measures were submitted to a multivariate analysis of variance using a doubly multivariate repeated measures design.

RESULTS

Tables 2 and 3 list the mean, SD, and range values for cardiac and respiratory variables. Eight highly significant cardiorespiratory measures were chosen by stepwise discriminant analysis. These included four measures for cardiac signals—mean frequency, bandwidth, ratio of harmonics, and average per minute—and four measures for respiratory signals—spectral edge, mean frequency, variance, and ratio of harmonics.

As a result of multivariate analysis of variance using all data, the difference among the sleep states and the difference between neonatal groups were highly significant ($p < 0.0001$). Interaction between sleep state and neonatal group was also significant ($p < 0.034$).

Two cardiac and one respiratory measure differentiated active from quiet sleep states in all infants, as well as differentiated preterm from full-term cardiorespiratory behavior during these states. Figures 3–7 graphically illustrate the differences between sleep states and between preterm and full-term groups for these selected cardiorespiratory measures (Tables 4–6).

Figure 3 illustrates state-specific changes in average heart rates during active and quiet sleep for all neonates, with lower rates during *tracé alternant*. Higher average heart rates were noted for preterm infants for all four segments of the neonatal EEG sleep cycle compared with full-term infants. This was the only nonspectral measure that demonstrated differences among states ($p < 0.01$, Table 4) as well as between neonatal groups ($p < 0.001$, Table 5).

Figure 4 illustrates mean values of the heart rate ratio of harmonics. Differences were noted between active and quiet sleep for all neonates. Lower heart rate ratios were noted for preterm compared with full-term infants during quiet sleep only (Table 5).

Using heart rate bandwidth, differences were noted between active and quiet sleep in all neonates (Fig. 5). A difference between groups was noted during low-voltage irregular sleep state, with higher values for the preterm group (Table 5).

Figure 6 demonstrates differences between active and quiet sleep-state segments for all neonates determined by using respiratory rate ratio of harmonics. The preterm differed from the full-term group, with lower values for the preterm group more prominently noted during both active sleep segments and *tracé alternant* quiet sleep (Table 5).

Finally, in Figure 7, no sleep state differences in the mean respiratory frequency were noted (Table 4). Differences were noted between full-term and premature infants only during active sleep (Table 5).

Two spectral measures of cardiac behavior, ECG bandwidth and heart rate ratio, demonstrated a significant interaction between sleep state and neonatal group. These persisted when we used only active *versus* quiet sleep rather than all four states. No respiratory measures demonstrated interaction (Table 6).

DISCUSSION

We have reported differences in cardiorespiratory behavior between active and quiet sleep in all neonates, as well as between preterm and full-term infant groups at comparable postconceptional term ages. Lower cardiorespiratory values for most measures were noted in the preterm group during *tracé alternant* quiet sleep than during the other three segments of the sleep cycle.

We previously reported differences between preterm and full-term infants at matched postconceptional term ages with respect to sleep architecture, continuity, phasic, spectral, and temperature measures (9–11). The sleep cycle of the preterm infant at a postconceptional term age

Table 2. Cardiac variables: means, SD, and ranges*

Variable, sleep state, and neonatal group	Mean	SD	Range	Variable, sleep state, and neonatal group	Mean	SD	Range
Average rate				Bandwidth			
M				M			
Full	127.49	7.63	110.54–136.70	Full	20.03	2.11	15.98–24.70
Pre	148.67	5.65	137.88–156.85	Pre	21.11	1.09	19.03–23.23
LVI				LVI			
Full	128.70	12.79	91.38–152.25	Full	20.18	2.03	15.62–23.91
Pre	148.96	7.00	137.23–160.51	Pre	21.67	1.48	19.78–26.00
HVS				HVS			
Full	123.62	8.59	110.73–142.34	Full	19.62	1.91	15.65–22.69
Pre	147.63	6.57	138.12–158.15	Pre	20.60	1.32	18.04–22.76
TA				TA			
Full	122.73	9.76	112.50–149.69	Full	20.04	1.79	15.56–22.87
Pre	145.97	7.15	131.81–159.27	Pre	20.25	1.30	17.56–23.00
Variance				Ratio of harmonics			
M				M			
Full	3 562.09	2 804.27	1 077.4–11 263.9	Full	0.98	0.02	0.93–1.00
Pre	9 907.05	13 016.08	1 037.0–43 891.0	Pre	0.97	0.02	0.92–1.00
LVI				LVI			
Full	3 551.28	2 535.88	1 039.7–11 077.9	Full	0.98	0.01	0.94–1.00
Pre	8 476.42	11 826.47	1 043.5–41 953.0	Pre	0.97	0.02	0.92–1.00
HVS				HVS			
Full	3 168.31	2 126.33	939.4–9 286.0	Full	0.98	0.02	0.93–1.00
Pre	8 080.15	11 318.02	898.1–39 730.5	Pre	0.96	0.002	0.91–1.00
TA				TA			
Full	2 672.62	1 434.16	849.4–5 642.8	Full	0.97	0.02	0.94–1.00
Pre	7 704.45	10 400.35	929.8–37 606.6	Pre	0.95	0.03	0.89–1.00
Mean frequency				Spectral edge			
M				M			
Full	15.10	3.93	9.43–20.26	Full	26.43	3.14	19.59–29.7
Pre	15.22	3.23	9.27–20.44	Pre	27.23	1.85	23.60–29.8
LVI				LVI			
Full	14.90	3.98	9.26–20.35	Full	26.44	3.03	19.18–29.72
Pre	15.09	3.28	9.66–20.47	Pre	27.30	1.87	23.90–29.91
HVS				HVS			
Full	15.60	3.96	8.75–20.15	Full	26.67	3.19	19.38–29.55
Pre	15.50	3.02	8.96–20.55	Pre	27.51	1.69	23.74–30.04
TA				TA			
Full	15.80	3.35	9.64–20.11	Full	27.12	2.54	19.58–29.65
Pre	16.38	2.94	11.81–21.61	Pre	27.68	1.60	24.82–30.31

* Full, full-term; Pre, preterm; M, mixed-frequency active sleep; LVI, low-voltage irregular active sleep; HVS, high-voltage slow quiet sleep; TA, tracé alternant quiet sleep.

is one third longer than for the full-term infant, with a greater percentage of quiet sleep. Preterm neonates have fewer movements, fewer and shorter arousals, higher mean rectal temperatures, and lower spectral EEG energies during specific sleep-state segments than full-term infants. As supported by our present findings, differences in cardiorespiratory behavior also exist between full-term and preterm groups at postconceptional term ages. Differences in these features of sleep organization in preterm neonates may reflect the influences of prematurity, extrauterine experience, or both on brain maturation.

Sleep-state differences in cardiac control have been described for full-term newborns and infants during the first 6 mo of life (13). However, studies of cardiorespiratory behavior in preterm infants are less numerous. In 1988, Aärimala *et al.* (14) studied only mean heart rate during quiet sleep. Katona *et al.* (15) evaluated cardiac behavior for all sleep cycles but only concerning heart rate variability; these authors reported that preterm in-

fants displayed higher heart rates than term infants until 7 mo of age. Curzi-Dascalova *et al.* (16) reported state-dependent differences in neonates as young as 31 wk postconceptional age with respect to cardiorespiratory behavior. They also noted that preterm neonates at postconceptional term ages had higher heart rates and lower heart rate variability than full-term neonates; active sleep could be distinguished from quiet sleep by shorter R-R intervals in both high- and low-frequency ranges of heart rate variability. Differences were noted most dramatically between younger and older preterm infants, rather than between near-term and full-term infants. Based on analyses of interbeat intervals, these authors also suggested a steep increase in vagal tone at 37–38 wk postconceptional age with stability afterward and a more regular increase in sympathetic tone from 31 to 41 wk (17).

Automated spectral techniques mathematically differentiate parasympathetic and sympathetic contributions

Table 3. Respiration variables: means, SD, and ranges*

Variable, sleep state, and neonatal group	Mean	SD	Range	Variable, sleep state, and neonatal group	Mean	SD	Range
Average rate				Spectral edge			
M				M			
Full	47.38	5.72	33.56–59.11	Full	1.41	0.24	1.05–2.12
Pre	38.75	6.34		Pre	1.21	0.16	0.90–1.49
LVI				LVI			
Full	46.32	7.22	32.70–62.12	Full	1.43	0.24	1.16–2.26
Pre	39.09	7.27	22.29–55.59	Pre	1.23	0.15	0.91–1.56
HVS				HV			
Full	48.61	8.61	35.71–68.85	Full	1.38	0.57	0.97–3.28
Pre	41.76	8.17	26.85–57.46	Pre	1.26	0.51	0.62–2.99
TA				TA			
Full	45.67	8.73	31.91–67.22	Full	1.12	0.30	0.81–1.93
Pre	41.07	8.58	29.19–61.45	Pre	1.14	0.47	0.69–2.56
Mean frequency				Variance			
M				M			
Full	0.86	0.14	0.62–1.14	Full	288 864.2	325 239.7	51 319.1–1 451 398
Pre	0.74	0.09	0.57–0.90	Pre	336 720.5	260 515.4	30 202.7–1 136 194
LVI				LVI			
Full	0.86	0.13	0.67–1.19	Full	298 623	288 908.8	56 780.0–1 292 870
Pre	0.74	0.10	0.52–0.99	Pre	321 447.7	316 344.2	30 535.1–1 102 278
HVS				HV			
Full	0.86	0.16	0.64–1.16	Full	250 788.6	306 251.2	23 090.3–1 049 193
Pre	0.79	0.15	0.41–1.05	Pre	188 123.9	162 313.9	29 080.7–690 359
TA				TA			
Full	0.84	0.17	0.61–1.23	Full	179 022.5	241 510.5	20 419.6–1 030 356
Pre	0.79	0.14	0.60–1.07	Pre	156 990.1	160 133.8	25 230.7–560 335
Bandwidth				Ratio			
M				M			
Full	1.70	0.63	1.17–3.49	Full	0.86	0.02	0.81–0.89
Pre	1.60	0.52	1.01–2.76	Pre	0.81	0.03	0.77–0.87
LVI				LVI			
Full	1.66	0.60	1.10–3.32	Full	0.86	0.03	0.80–0.89
Pre	1.56	0.47	0.95–2.83	Pre	0.82	0.04	0.77–0.89
HVS				HV			
Full	1.68	0.96	0.95–4.59	Full	0.78	0.06	0.65–0.86
Pre	1.80	1.34	0.87–6.70	Pre	0.74	0.08	0.53–0.85
TA				TA			
Full	1.68	0.92	1.69–4.56	Full	0.66	0.07	0.58–0.83
Pre	1.71	1.11	0.61–5.03	Pre	0.59	0.07	0.48–0.73

* Full, full-term; Pre, preterm; M, mixed-frequency active sleep; LIV, low-voltage irregular active sleep; TA, tracé alternant quiet sleep.

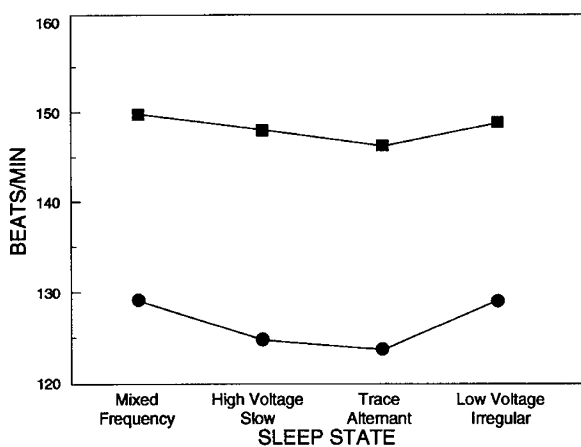


Figure 3. Average heart rate values for study infants comparing preterm and full-term subjects. Higher average heart rates were noted for preterm infants during all stages of sleep.

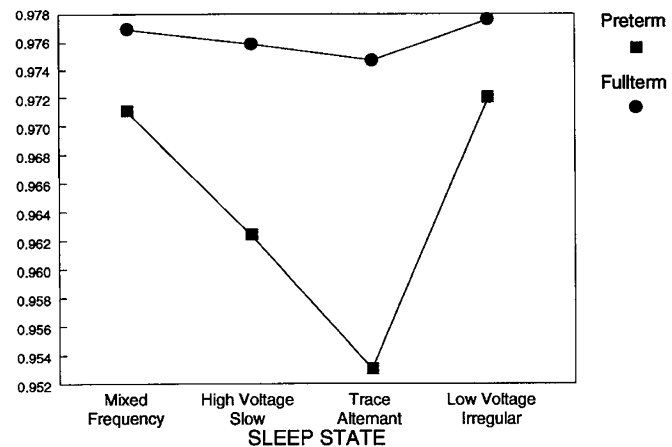


Figure 4. Ratio of harmonics spectral calculation for heart rate are plotted for all subjects, with a lower ratio for the preterm infant most notable during tracé alternant quiet sleep.

to cardiac variability (18–20). Automated analyses of digitally acquired cardiorespiratory signals can also help differentiate respiratory and heart rate control by the CNS. Marked effects of breathing patterns on heart rate

and heart rate variability have been described in healthy full-term newborns (21, 22). Studies of cardiac interbeat variability not only increase one's understanding of the ontogeny of physiologic responsivity of the autonomic

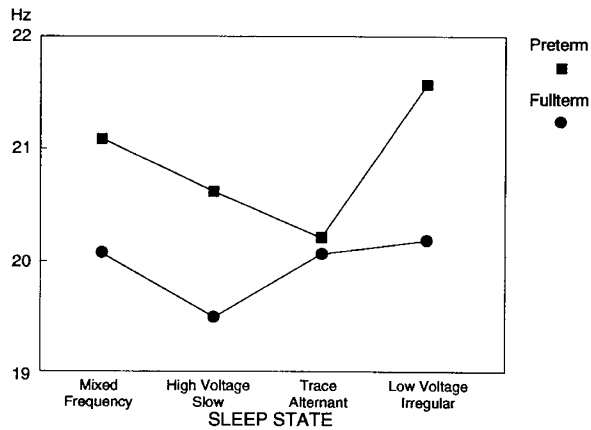


Figure 5. Heart rate bandwidth spectral calculation for study infants, with lower values for term infants during mixed frequency and low-voltage irregular active sleep segments.

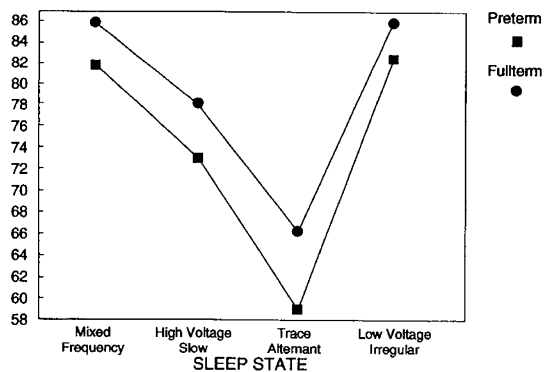


Figure 6. Ratio of harmonics spectral calculation for respiratory rate, with lower values for preterm infants most notable during tracé alternant quiet sleep.

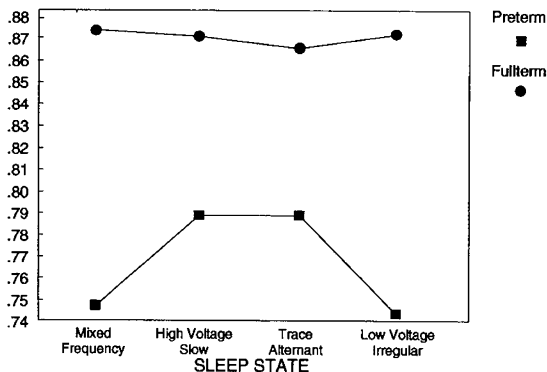


Figure 7. Mean frequency spectral calculation for respiratory rate for study infants, with lower values for preterm infants most notable during active sleep segments.

nervous system as the healthy infant matures (23, 24), but also these measures can help identify differences in cardiac function during sleep in infants at risk for SIDS.

Studies of cardiac rate and variation in infants who later died of SIDS have noted higher rates in all states (25) and diminished heart rate variation while awake (24). SIDS victims show reduced dispersion of interbeat intervals across all sleep-waking states with smaller beat-to-beat changes in heart rate relative to controls (26).

Assessment of cardiac parameters must control for sleep state, time of day, relationships with circadian

Table 4. Multivariate analysis of variance results (*p* values) for differences among sleep states for cardiorespiratory measures

	All four states	Active vs quiet
ECG frequency	0.0008	0.0020
ECG bandwidth	0.0009	0.0002
Heart ratio	0.0001	0.0001
Heart average	0.0252	0.0060
Respiration frequency		
Respiration spectral edge	0.0072	
Respiration ratio	0.0001	0.0001
Log of respiration variance	0.0001	0.0001

Table 5. Multivariate analysis of variance results (*p* values) for differences between full-term and premature neonates for cardiorespiratory measures

	All four states	Mixed frequency	High voltage	Tracé alternant	Low voltage
ECG frequency					
ECG bandwidth					0.0161
Heart ratio	0.0398		0.0234	0.0039	
Heart average	0.0001	0.0001	0.0001	0.0001	0.0001
Respiratory frequency	0.0174	0.0026			0.0052
Respiratory spectral edge		0.0058			0.0049
Respiratory ratio	0.0005	0.0001		0.0030	0.0008
Log of respiratory variance					

Table 6. Multivariate analysis of variance results (*p* values) for interactions between sleep state and full-term or premature infants

	All four states	Active vs quiet
ECG frequency		
ECG bandwidth	0.0021	0.0260
Heart ratio	0.0003	0.0001
Heart average		
Respiration frequency		
Respiration spectral edge		
Respiration ratio		
Log of respiration variance		

influences on biologic rhythms, and relationships with respiratory parameters (27–30). Digital filtering techniques help identify frequency- and time-dependent relationships among other physiologic signals, such as respirations. One particular measure, respiratory sinus arrhythmia (23), has been used by a number of researchers to demonstrate important changes in cardiorespiratory behavior as the neonate matures during infancy. These studies not only contribute to our understanding of the ontogeny of state-specific cardiorespiratory behavior in normal infants under different state conditions and ages, but also focus on dysfunction of autonomic control in SIDS victims.

The establishment of normative cardiorespiratory behavior in healthy asymptomatic preterm infants as they mature to postconceptional term ages provides useful information regarding alterations in brain maturation in a population at increased risk for SIDS (31). Given the higher mean heart rates and less-organized cardiorespi-

ratory behavior during quiet sleep in preterm infants, we speculate that preterm neonates at postconceptional term ages may have autonomic behavior similar to that noted for SIDS victims (26), with altered brain function, which potentially affects other vital functions such as cardiorespiration regulation.

We recognize that the minute-by-minute averages of nonspectral and spectral values for cardiorespiratory behavior reported in our study are gross measures of physiologic function and do not delineate dynamic changes in variability that continuously occur (23, 24, 26). Differences in cardiorespiratory behavior between sleep states as well as between neonatal study groups nonetheless have been demonstrated. These preliminary findings can serve as a basis for comparison with these more sophisticated computer algorithms.

We therefore conclude that specific measures of cardiorespiratory behavior detect sleep-state-specific differences, as well as differences between preterm and full-term infants at similar postconceptional term ages. How long these differences will persist with maturation during infancy needs to be explored in future analyses.

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