Respiration during the First Six Months of Life in Normal Infants. III. Computer Identification of Breathing Pauses

TOKE HOPPENBROUWERS,¹⁽⁷⁾ JOAN E. HODGMAN, KAZUKO ARAKAWA, RONALD HARPER, AND M. B. STERMAN

Newborn Division of the Los Angeles County/University of Southern California Medical Center; Department of Pediatrics, University of Southern California School of Medicine; Sepulveda Veterans Hospital; Departments of Anatomy, Psychiatry, and the Brain Research Institute, University of California, Los Angeles, USA

Summary

The first objective of this study was to quantify computer-identified breathing pauses in excess of two sec duration in relation to sleep states. The second objective was to examine which respiratory variables at one wk and one month of age predicted total apnea at 2 and 3 months of age.

Short apnea (2 to 5 sec) were abundant in recordings of normal infants during the first one-half year of life. Apnea between 6 and 9 sec should be considered normal, whereas apnea in excess of 9 sec occurred most frequently in the first wk of life and declined sharply thereafter. Recording duration substantially affected apnea counts. Apnea at later ages could not be reliably predicted from recordings during the first wk of life.

Speculation

Short breathing pauses in QS during the age span under investigation are probably inversely related to breathing rate and caused by the same mechanism responsible for the decline in rate. The change in breathing pauses over age in AS can probably be accounted for by two sources of variance, first, the decline in rate and second, rate-independent developmental changes in control of ventilation during AS.

An estimated 7000 to 8000 infants die each year in the United States of sudden infant death syndrome (SIDS) (1). Whereas apnea and short breathing pauses have been implicated in the etiology of SIDS (3, 10, 12), the significance of these respiratory phenomena is still a matter of conjecture. The vast majority of infants succumbing to SIDS are healthy term infants who die suddenly without any prodromal symptoms. Moreover, the prevalence of short apnea in normal infants has generally not been appreciated.

Steinschneider (11) is exploring the utilization of a composite laboratory risk score to identify neonates at increased risk to subsequently die of SIDS. This score incorporates a number of sleep variables and a count of apneic pauses ≥ 2 sec, based on a 1- to 3-hr recording. A previous report in normal infants (7) was restricted to central apnea ≥ 6 sec identified through visual analysis of 12-hr recordings. In the present study, we report the density of breathing pauses in excess of 2 sec duration identified by computer. This study also examines the question whether or not apnea in the newborn period predict counts at later ages, whether quiet sleep (QS) apnea densities predict active sleep (AS) apnea densities, and whether the incidence of short pauses are correlated with the incidence of longer breathing pauses.

MATERIAL AND METHODS

MATERIAL AND MONITORING PROCEDURES

Twenty-five neurologically normal infants participated in this study. The mean and standard deviation of gestational age, Apgar scores, birth weights, and age at the time of monitoring are provided in Table 1. Infants were full term, and weights were appropriate for gestational age according to the intrauterine growth curve of Usher and McLean (14). Participants in all groups were volunteers, and informed consent was obtained.

Each infant was admitted at 5:00 PM to the sleep laboratory for 12-hr all night monitoring sessions during the first wk of life and at 1, 2, 3, 4, and 6 months of age. The infants were fed during preparation for monitoring and application of electrodes. A demand feeding schedule was followed, and in several instances, the infants were breast fed. Arm restraints were applied before the initiation of recording. Monitoring was carried out in a darkened room adjacent to the room containing recording equipment. Room temperatures ranged between 22 and 30°C. The infants were placed in a supine or side-lying position and observed continuously with the use of a low illumination television camera and monitor. Behaviors such as closing or opening of eyes, startles, crying, and nursing interventions were charted on the polygraph paper.

RECORDING METHOD

The sleep variables recorded included two electroencephalogram derivations, a chin electromyogram, and eye movements. Thoracic or abdominal excursions were monitored by impedance pneumography. In addition, a Beckman pCO₂ monitor sampled expired gas through a miniature cannula taped under the infant's nostrils. To adjust for the time lag inherent to this instrument, the phase of respiration was simultaneously detected with a thermistor placed into one arm of the cannula. The electrocardiogram was recorded with two disposable electrodes placed symmetrically beneath the clavicles. A ground electrode was applied above the umbilicus. Additionally, a skin temperature probe was applied to the abdomen below the right costal margin. Electrodes on the mattress surface under the crib sheet registered the infant's gross body movements (5). Data were recorded on a 16-channel Honeywell analog tape recorder together with an IRIG E time code.

DATA ANALYSIS

The 12-hr recordings were coded by trained observers according to established state criteria (6). Each min of the record was classified as either awake, QS, AS, or indeterminate state (IN).

Data on the analog tapes were processed by a PDP-12 computer (4). The respiratory signal was digitized at eight samples per sec and stored on industry-compatible magnetic tape together with digitized values of other physiologic measures. The $p\text{CO}_2$ signal was used for this analysis because movements of the infant did not affect the signal quality. Peaks and troughs of breaths were measured by a peak-sensing program developed by Mason *et al.* (9). A computer package was developed to identify breathing pauses equal to or longer than 2 sec duration in each sleep state. Measurements were made from the peaks of the CO_2 tracing, and breathing intervals were therefore measured differently from those identified visually. Figure 1 provides three respiratory tracings, an estimate of the length of a breathing pause based upon criteria used for visual identification of apnea (7), and the computer-derived breathing pause. The latter technique, although reliable, tends to overestimate the duration of a pause by 1 sec compared to visual inspection (7). The minimum interval of 3 sec was selected so as to be comparable to an estimate of a 2-sec breathing pause measured visually. Duration categories will be arbitrarily adjusted to visual criteria: short, 2, 3, 4 and 5 sec duration; medium, between 5 and 9 sec duration; and long, equal to or in excess of 10 sec. Inasmuch as the $p\text{CO}_2$ signal was used, this computer strategy did not differentiate between but included central, mixed, and obstructive pauses. The absolute number of breathing pauses per state was integrated with the total number of minutes spent in each state, and a density score was calculated with the aid of an IBM 360. Data from the first 19 infants were submitted to an analysis of variance to examine developmental trends. A Tukey test (15) was used to examine differences between means.

Table 1. Characteristics of the Study Group

Maternal race	
White	20
Black	1
Asian American	2
Mexican American	2
Maternal age	26.10 $\pm$ 3.64 ¹
Gravida	2.84 $\pm$ 1.43
Parity	2.48 $\pm$ 1.19
Birth wt (g)	3575 $\pm$ 465
Gestational age	40.78 $\pm$ 1.64
Apgar at 1 min	8.52 $\pm$ 1.64
Apgar at 5 min	9.28 $\pm$ 0.54
Age in days at time of monitoring	
1 wk	4.88 $\pm$ 2.15
1 mo.	30.88 $\pm$ 6.02
2 mos.	60.08 $\pm$ 6.56
3 mos.	88.92 $\pm$ 7.94
4 mos.	118.40 $\pm$ 8.72
6 mos.	170.88 $\pm$ 8.70

¹ Mean $\pm$ S.D.

A previous study demonstrated the variability among infants in incidence of breathing pauses (7). We therefore selected the Spearman rank order correlation to examine in data from all infants whether breathing pauses at one age or in one state predicted those at other ages and in other states. To answer the question of which variable(s) best predicted the density of total breathing pauses at 2 and 3 months of age, we submitted the data, supplemented with both the median and interquartile range of state-related respiratory rates for each infant, to a multiple regression program. Variables considered as potential predictors were QS, AS, IN, and awake apnea densities, median respiratory rates, and respiratory variability as measured by the interquartile range. Breathing pause duration categories entered as independent variables were between 2 and 5 sec, ≥ 6 sec duration, and ≥ 10 sec duration. Dependent variables were total apnea ≥ 2 sec, ≥ 7 sec, and ≥ 10 sec. When appropriate, a square root transformation was performed to normalize the data. Finally, paired *t* tests were used to compare mean densities of breathing pauses during sleep states and comparison of pauses of short, medium, and long durations.

RESULTS

DENSITY OF BREATHING PAUSES

Two to 5 Sec Duration. Pauses of this length were extremely common during the first 6 months of life (Fig. 2). During the newborn period, a density score of 100 was observed in QS, indicating that on the average each min of the recording had one breath-to-breath interval of this length. Between 3 and 6 months of age, each min of the recording contained 2 to 3 breathing pauses of this duration. In spite of the apparent differences in the figure, due to considerable variability among infants, QS density scores obtained during the first 4 months of life could not be

Fig. 2. Density of breathing pauses between 2 and 5 sec (ordinate) in QS, AS, and IN, between 1 wk and 6 months of age (abscissa). Profound increase of such pauses at 3 months of age, especially in QS.

MEASUREMENT OF BREATHING PAUSES

Fig. 1. In a previous study (6), apneas were identified through visual inspection of three respiratory tracings. The intervals a-b in the $p\text{CO}_2$ tracing and c-d in the impedance tracing had to be equal to or exceed 6 sec. Computer identification of breathing pauses involved measurement between points e and f. The latter interval is approximately 1 sec longer than the former. The interval g-h reflects the lag time between the respiratory signal based on a nasal thermistor and the $p\text{CO}_2$ signal.

differentiated, but the score obtained at 6 months of age was significantly elevated compared to the first 2 months of life.

The AS density score was 200 in the newborn period and changed less than did the QS score during subsequent ages. The age trend was identical to that observed during QS, with only the 6 months score being significantly elevated compared to the score obtained at the remaining ages. Densities of breathing pauses in IN were most comparable to those seen in QS.

Six to 9 Sec Duration. A plot of density scores is provided in Figure 3. The number of the ordinate is reduced by a factor of ten. In the newborn period, an average of 15% of QS min contained a breathing pause of this length, which is equivalent to approximately once every sixth QS min. Again, variability among infants was large, and none of the differences between the means at the various ages studied was significant.

The AS density score was 25% in the newborn period, indicating that on the average every fourth min of AS contained a breathing pause of this duration. This density score is significantly higher than those seen at 2 and 6 months of age. The IN score resembled that of QS in the newborn period, but that of AS at subsequent ages.

Equal to or Longer than 10 Sec. Apnea of this duration were more common during the first wk of life than at subsequent ages, as previously reported (6). In the newborn period, they were observed in approximately 4% of the QS min, 8% of AS min, and 5% of IN min (Fig. 4). A significant age trend was restricted to AS where the newborn density score was significantly elevated compared to all other ages.

SLEEP STATE COMPARISONS

Short breathing pauses (2 to 5 sec) during QS were less common than during AS for the first 2 months of life; thereafter, the density scores in these sleep states could not be differentiated. Breathing pauses between 6 and 10 sec were significantly more common in

Fig. 3. Density of breathing pauses between 6 and 9 seconds (ordinate), as a function of age (abscissa). Only the AS density at one wk of age was significantly elevated compared to later ages.

Fig. 4. Density of breathing pauses equal to or longer than 10 sec. Elevated number of these apnea characterized the first wk of life.

AS at every age examined. Finally, no sleep state-related differences were observed in long apnea (≥ 10 sec).

A high-density score in short respiratory pauses during QS was correlated with a high score in AS at every age except one month. QS and IN density scores were significantly correlated throughout the entire age span, as were AS and IN density scores. Significant correlation coefficients were found in pauses equal to or longer than 6 sec obtained in every sleep state at every age. Finally, short and longer apnea were significantly correlated in every sleep state and at every age ($P < 0.01$).

THE RELATIONSHIP BETWEEN APNEA IN THE NEWBORN PERIOD AND SUBSEQUENT AGES

Results of multiple regression analysis indicated that none of the variables recorded during the first wk of life proved to be useful in predicting total apnea density of any duration category between the ages of 1 and 3 months. In one instance, the value of R was in excess of 0.65, with R^2 being 0.48, a value of questionable significance (Table 2).

In contrast, from the recordings at 1 month, it became possible to predict total breathing pauses at 2 and 3 months of age. Only those instances in which a variable explained more than 60% of the variance were included, and in one case, only one variable was responsible for this percentage. All breathing pauses at 2 months of age were best predicted by one month AS breathing pauses in excess of 6 sec duration, and at 3 months of age, they were predicted by 1 month AS breathing pauses in excess of 6 and 9 sec duration (Table 2). In other words, comparatively long AS breathing pauses predicted total densities at 2 months of age, whereas short and long IN pauses predicted those at 3 months of age. The pauses in excess of 6 and 10 sec duration in the 1, 2, and 3 months recordings could not be forecast. Furthermore, respiratory rates and variability never entered as significant variables.

COMPARISON WITH PREVIOUS STUDIES

To compare the data presented here with studies reported by others based on 1 or 2 hr of recording, density scores at 3 months of age were recomputed based on the first 2 hr of monitoring (Table 3). Most striking is the discrepancy between scores based on length of recording. In AS, twice as many pauses were counted when densities were based on 12 hr of monitoring compared to 2 hr. In QS, that discrepancy rose to six times.

DISCUSSION

A previous study showed that central apnea between 6 and 15 sec are an integral part of normal respiratory development (7). The data presented in this study amplify this message and show in addition that shorter apnea are abundant in recordings of

Table 2. Prediction of apnea at subsequent ages; results of multiple regression analysis

<i>R</i>	<i>R</i> ²	Independent variable	Dependent variable: total density of breathing pauses ≥2 sec
At 1 wk			
0.426	0.182	Awake pauses ≥6 sec	At 3 mos.
0.561	0.314	QS pauses 2-5 sec	
0.694	0.481	IN pauses ≥6 sec	
At 1 mo.			
0.782	0.611	AS pauses ≥6 sec	At 2 mos.
At 1 mo.			
0.851	0.724	IN pauses 2-5 sec	At 3 mos.
0.890	0.792	IN pauses ≥10 sec	

Table 3. Apnea density scores at 3 months of age comparison with previous studies

Studies (Total apnea)	2-4 sec		≥5 sec	
	AS	QS	AS	QS
Present study: computer identified				
2 hr	99.7	27.9	10.3	4.8
12 hr	190.8	182.8	24.8	11.7
Gould <i>et al.</i> (2): visually identified				
2-3 hr	70.2	3.9	10.4	2.5

normal infants during the first one-half year of life. Mean QS respiratory rates at 3 months of age, between 10:00 PM and 4:00 AM, were found to be 25 breaths per min (8), indicating an interbreath interval of 2.4 sec. At 3 months of age, a sudden increase in apnea between 2 and 5 sec therefore represents the developmental slowing of respiratory rates (6).

The impressive differences in apnea counts based on short and long recordings can be explained by two physiologic factors. The early portion of the recording, as is true of recording during a nap, is affected by events preceding monitoring, such as feeding and activity which reduce apnea density. Secondly, beyond the newborn period, slowing of autonomic function occurs during the early morning hr, resulting in longer breathing intervals (8). After adjustment for length of recordings, a significant difference remains in figures reported from different laboratories. This variance can be explained by technical factors such as differences in measurement techniques and analysis strategies.

Because apnea counts varied widely among infants, significant age trends were restricted to differences between the recordings at the youngest and oldest ages, a finding in agreement with those of Thoman *et al.* (13), who failed to observe significant age trends in infants between birth and 5 wk of age. Significant correlations in all sleep states between short and long apnea counts reported here were also found by the same investigators (13).

The stepwise discriminate analysis showed that apnea counts during the newborn period could not reliably identify infants with large numbers of apnea at subsequent ages. At 1 and 2 months of age, the predictive power of apnea counts increased significantly.

In light of the abundance of short breathing pauses and the variability among normal infants recorded under similar conditions, attaching pathologic significance to breathing pauses must be done with caution. The length of recording now must be considered as an additional source of variance.

CONCLUSION

Short respiratory pauses between 2 and 5 sec were abundant, whereas apnea between 6 and 9 sec must be considered normal.

Apnea in excess of 10 sec were common during the first wk of life, especially during AS, but became infrequent at later ages. Three additional features deserve mention. First, during early infancy, there was considerable variability in apnea densities among infants. Second, recording duration substantially affected the results. Finally, apnea at later ages could not be reliably predicted from recordings during the first wk of life.

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17. Requests for reprints should be addressed to: Toke Hoppenbrouwers, Ph.D., Director, Sudden Infant Death Syndrome (SIDS) Research Project, Room 4L40B, Women's Hospital, LAC/USC Medical Center, 1240 North Mission Road, Los Angeles, CA 90033 (USA).
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