Sleep apnoea in acute bronchiolitis

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SUMMARY Three- to 4-hour polygraphic sleep studies were carried out in 16 infants aged between 1 and 6 months during and after recovery from acute bronchiolitis. During bronchiolitis 35% of total sleep time was active sleep compared with 31% after recovery. Respiration rate was increased during bronchiolitis and was higher in active sleep and quiet sleep irrespective of the stage of the illness. Apnoeic pauses were invariably shorter than 15 seconds, the mean duration for active sleep and quiet sleep being similar during infection and after recovery. Apnoeic episodes were central in type and generally initiated by a sigh or body movements. Preapnoea heart rate was significantly higher than during or after apnoea. Apnoea index (the percentage of time the baby spends apnoeic), apnoea attack rate (the number of episodes of apnoea per unit time), and apnoea percentage (the distribution of episodes of apnoea while in a given sleep state) were increased significantly in quiet sleep during the index illness. Transcutaneous oxygen tension was significantly reduced during the course of infection, but comparable values were obtained in active sleep and quiet sleep during initial and recovery periods. These results show that the main changes in respiration pattern during the course of acute bronchiolitis occur in quiet sleep.

Although apnoea has been studied extensively in preterm infants in the newborn period, there have been few studies in infants beyond 40 weeks gestation. To a large extent these have stemmed from clinical and laboratory observations and suggest an association between prolonged sleep apnoea and the sudden infant death syndrome (SIDS). Breathing irregularities and apnoeic pauses occur during sleep in many apparently healthy infants and may be exaggerated by upper respiratory tract infections, presumably owing to viruses. Prolonged apnoea has also been reported in infants with lower respiratory tract infections caused by respiratory syncytial virus. Moreover, in a study of viral infections in babies dying unexpectedly at home and diagnosed as cot deaths, this virus was the most often detected at necropsy. In the light of these findings and the observation that previous admission to hospital is a significant antecedent of SIDS, we set out to study sleep apnoea and its effect on heart rate and transcutaneous oxygen tension ($TcPO_2$) in infants admitted to hospital with viral respiratory tract infections. We report here our findings in 16 infants with acute bronchiolitis who were investigated during and after recovery from this infection.

Patients and methods

Twenty-two infants were studied during the course of acute bronchiolitis and 16 after clinical recovery. Six of the original 22 were later excluded from the study, 4 because of persisting symptoms at follow-up and 2 because of failure to attend. There were 10 boys and 6 girls of mean gestational age 38.5 (range 32-42) weeks and mean birthweight 3.01 (range 1.56-4.62) kg, whose mean age was 17 (range 7-34) weeks when initial studies were done. The diagnosis of acute bronchiolitis was made on clinical grounds. The infants were studied breathing air, which in many cases restricted the time of studies to a stage of illness when oxygen therapy was no longer considered necessary. The mean duration of illness, from the start of coryzal symptoms, was 7 (range 3-10) days at the first study and the mean interval between studies was 26 (range 18-39) days. Respiratory syncytial virus was isolated in 9 and adenovirus in 1 of the 16 infants. Virological studies were negative in the remaining six. Consent for participation in the study was obtained from parents after giving them a detailed explanation of its purpose and a description of the techniques.
Monitoring procedure. Studies were carried out after the last evening feed, generally between midnight and 0400 hours. For follow-up investigations, infants were readmitted between 1400 and 1500 hours on the preceding afternoon and, if practicable, mothers were admitted too. The infants were monitored in a dimly-lit side room off the main ward, especially equipped for sleep studies. The home environment was imitated as closely as possible. Mean ambient temperature was 23°C (range 22–24). Electrodes were placed in position after a feed when the infant had settled and nasal thermocouples and transcutaneous oxygen electrodes applied during periods of quiet sleep (QS). Each baby was placed lightly clothed and unrestrained in his normal sleeping position. Constant observation was possible throughout and body movements or interventions were recorded on polygraphic paper. A detailed clinical examination was also carried out.

Silver chloride electrodes (81/9 SLE) were used for EEG, EOG, EMG (C50-S Medicotest), and ECG (I–1000 Roche). The electroencephalogram (EEG) was recorded from two electrodes placed sagittally in the frontal and parietal regions (Fz–Pz). The electro-oculogram (EOG) was recorded from two pairs of diagonally arranged electrodes situated adjacent to the outer canthus of each eye, the electromyogram (EMG) from one pair of electrodes in the submental area, and the electrocardiogram (ECG) from electrodes placed on the left and right sides of the chest anteriorly and on the right leg. Airflow at each nostril and the mouth was detected using thermocouples and a summation signal recorded. Movements of the chest and abdomen were recorded from two pairs of magnetometer coils (Cambridge Ltd) attached laterally above and below the costal margins. TcPO2 was monitored with an oxygen electrode placed on the anterior chest wall at an operating temperature of 43°C and the signal recorded on a 2-channel recorder (Draeger Medical Ltd). The electrode was calibrated in air before and after each study, or after a maximum of 4 hours in one position. Mean electrode drift during the study period was +1.5%/hour.

Each of the variables monitored was recorded, after amplification of the electrical signal, on an 8-channel recorder (Mingograf) at a paper speed of 10 mm/second. Sections of recording in each sleep state were studied at a rate of 100 mm/second in order to observe EEG changes more closely. Permanent records were thus available for EEG, EOG, EMG, ECG, airflow at nose and mouth, chest, and abdominal movements, and TcPO2.

Data analysis. Each 30-second period (1 epoch) of the record was analysed visually and coded by one trained observer (V B). The coding criteria were based on the definitions suggested by Anders et al.9 and on those of Rechtschaffen and Kales.10 The age range of the subjects was such that in some infants the transition between perinatal and the 'infantile' sleep pattern11 might not have been completed. Individual proportions of the EEG frequencies and amplitudes during the sleep stages were used rather than absolute limits. Respiration, the variable under study, was omitted from the criteria of the sleep stages.

Awake
EEG irregular mixed pattern or rhythmical components in the theta range. High tonic submental EMG. Blinks and other eye movements. General EMG artefacts suggesting a sustained or repeated motor activity.

Quiet sleep (QS)
EEG high voltage slow pattern or sleep spindles. Tonic submental EMG. No blinks or rapid eye movements (REM). No general motor activity.

Active sleep (AS)
EEG mixed pattern including medium voltage slow or low voltage fast frequencies. No spindles or K complexes. Absent or phasic submental EMG. REM, brief general movements.

Intermediate sleep (IS)
Epochs in which the criteria for awake, QS, or AS are not fulfilled.

The respiration rate and heart rate were counted during the fourth, middle, and last minutes of continuous sleep for QS and AS. If for any reason the respiration rate and heart rate could not be counted at these times, the fifth or adjacent minute was counted instead. Mean respiration rate and heart rate for each sleep state during and after recovery from bronchiolitis were then computed for each patient.

Apnoeic pauses were defined as periods of no airflow at the nostrils or mouth for at least 6 seconds. Episodes of both central and obstructive apnoea were measured from the end of the last breath to the start of the next from thermocouple tracings. Associated body movements were also noted. For each sleep state the mean duration of apnoeic pauses was calculated and the apnoeic episode of longest duration noted.

Indices of apnoea were assessed for apnoeic pauses ≥6 seconds. Apnoea index was defined as the duration of apnoea (seconds) during a given
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sleep state, divided by the total duration of that sleep state, expressed as a percentage. Apnoea attack rate was the number of apnoeic episodes per 100 seconds of a sleep state, and apnoea per cent as the percentage of epochs during which at least one apnoeic pause was initiated. Finally, the percentage of total time in each sleep state was calculated. Each variable was calculated for each sleep phase during and after recovery from infection. The analysis was then repeated for episodes of apnoea >2 seconds.

Heart rate was also computed in relation to episodes of apnoea. The number of complete beats (R-R intervals) within a 6-second period was counted and timed to the nearest 0-1 second for pre- and postapnoea periods and heart rate per minute calculated. The number of complete beats within an apnoeic period and the duration of beats to the nearest 0-1 second were also counted and the heart rate computed. Variability was tested by selecting representative parts of the record and measuring heart rate (as above) over 3 consecutive 6-second periods if there was no apnoea.

\textbf{TeCPO}_2 \textbf{records.} To compare TeCPO\textsubscript{2} during and after recovery from infection, the mean TeCPO\textsubscript{2} during 10 minutes of continuous sleep occurring during the second hour of each study was computed for QS and AS. If there were no 10-minute periods of AS, the longest periods were chosen instead.

We also observed TeCPO\textsubscript{2} in relation to sleep phase in individual subjects. Adjacent pairs of QS and AS periods were identified on each record. These were defined as sleep periods greater than 4 minutes' duration with no intervening ‘awake’ period and between which any indeterminate sleep was less than 3 minutes' duration. Minute by minute TeCPO\textsubscript{2} was noted from the beginning of the fifth minute and mean values computed for each sleep state.

TeCPO\textsubscript{2} changes in relation to episodes of apnoea >10 seconds were assessed by comparing the lowest TeCPO\textsubscript{2} in the 15 seconds before apnoea with the lowest in the 15 seconds after resumption of breathing.

\textbf{Statistical analysis.} Respiration and heart rates were computed in relation to sleep state before and after recovery from bronchiolitis by analysis of variance. The Wilcoxon matched pairs signed rank test was applied to results for the 16 patients before and after bronchiolitis. Each group was further subdivided according to sleep state. The Spearman rank correlation coefficient was used for testing the relationship of the amounts of sleep stages and the age. The paired t test was used to compare TeCPO\textsubscript{2} during AS and QS in individual patients.

\textbf{Results}

Table 1 gives the respiration and heart rates during and after recovery from acute bronchiolitis in both AS and QS. Respiration rate was significantly higher during bronchiolitis in both sleep phases. Respiration was also higher in active than quiet sleep, irrespective of the stage of the illness. Similarly, heart rate was significantly increased during active sleep, but was lower during bronchiolitis than after recovery. During bronchiolitis 35% of total sleep time was AS, compared with 31% after recovery (P<0.05). QS was slightly increased after recovery, but this did not reach statistical significance. There was no significant difference in the percentage of the indeterminate sleep during illness and on recovery. A significant negative correlation was found between the individual percentages of AS and the age of the infants in weeks, both in the first and second recordings (P<0.01). A significant positive correlation was obtained between the individual percentages of QS and the age, both during the illness and after the recovery (P<0.01).

Apnoeic pauses were invariably shorter than 15 seconds. The mean duration of apnoeic pauses was similar for AS and QS when acute and recovery data were compared, with no difference between AS and QS regardless of the stage of illness. Similar results were obtained for the apnoeic episode of longest duration. Table 2 gives the results for apnoea index, apnoea attack rate, and apnoea per cent. These were increased in each sleep phase in bronchiolitis,
the most significant increases being in QS. Comparable results for these variables were obtained when data was reanalysed for apnoea episodes \( \geq 2 \) seconds.

There were 215 apnoea episodes \( \geq 6 \) seconds (central 212, obstructive 2, mixed 1). Central episodes started at end expiration. The onset was spontaneous in 72 (34\%), or followed a sigh in 108 (51\%), or followed body movements in 32 (15\%). The percentage of the apnoea episodes initiated by a sigh or movement was 83\% in QS, 34\% in AS, and 68\% in IS. One hundred and thirty-eight (64\%) apnoea episodes ended spontaneously and 74 (35\%) with associated movement. Preapnoea heart rate was significantly higher than during (P<0.05) or after apnoea (P<0.05) heart rates. Heart rate rarely fell below 80 beats per minute, the lowest recorded value being 71 per minute after an apnoea pause of 6.7 seconds. No difference was observed between heart rates computed over 3 successive 6-second periods which did not include apnoea pauses. Finally, there was no significant relationship between heart rate (pre-, during, or postapnoea) and the total duration of apnoea episodes.

\( \text{TcPO}_2 \) in AS was 61.5±10.6 mmHg during and 77.9±8.9 mmHg after recovery from bronchiolitis (P<0.001). \( \text{TcPO}_2 \) was also significantly reduced in QS during bronchiolitis (P<0.001). Paired comparison of mean \( \text{TcPO}_2 \) for QS and AS in individual patients showed no difference during infections or after recovery. When apnoea episodes of 10–15 seconds’ duration were studied individually, the maximum fall in \( \text{TcPO}_2 \) after apnoea was 4 mmHg. When all 16 such episodes were considered, there was no difference between pre- and post-apnoea \( \text{TcPO}_2 \).

**Discussion**

These results present an opportunity to discuss patterns of breathing during and after recovery from bronchiolitis and to speculate on their importance in relation to SIDS. Our patients were slightly to moderately affected and were studied during the latter days of illness before discharge. Perhaps for this reason we did not encounter prolonged episodes of apnoea such as herald the onset of bronchiolitis in a few infants, especially those of low birthweight.\(^7\) The increases in respiration rate and heart rate in AS compared with QS agrees with the known relationships in normal subjects. The highly significant relationship between the relative amounts of AS and QS and the age of the infants, suggests that the decreased amount of AS found on recovery is primarily related to normal maturation and that other possible factors (such as a regression of the sleep pattern during the illness, or an incomplete adaptation during the second recording) are negligible.

During the course of bronchiolitis apnoea pauses did not exceed 15 seconds, which compares with the findings in normal term infants in the early months of life. When apnoea episodes between 6 and 15 seconds were observed in paired studies, their mean duration and episodes of longest duration were similar. It seems unlikely therefore that hypoxaemia during bronchiolitis had influenced the duration of apnoea, which contrasts with findings\(^15\) in the newborn period where apnoea and periodic breathing have been shown to increase as a result of hypoxaemia.

Several investigators use the terms apnoea index, apnoea attack rate, and apnoea per cent in their analysis of respiratory patterns.\(^1 2 13\) Unfortunately the duration of apnoea upon which calculation of these variables is based varies from one study to another. Normal values vary with age and maturity\(^14\) and the length of sleep studied.\(^2\) Limited sleep studies of <4 hours may underestimate their values compared with 12-hour studies. For these reasons, we did not relate our findings to 'normal' data, but compared the results obtained during bronchiolitis with those after recovery. Apnoea index, apnoea attack rate, and apnoea per cent were all increased significantly in QS but not in AS during the course of infection. It is not known whether the frequency or duration of apnoeic episodes or an increase in the above variables increase the risk of SIDS. It has been suggested that infants susceptible to prolonged sleep apnoea and possibly to SIDS have an increase in respiratory pauses exceeding 6 seconds compared with controls.\(^16\) Studies in 'near miss' for SIDS infants have shown an increase in prolonged...
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Sleep apnoea, obstructive apnoea, and an excessive amount of periodic breathing compared with matched controls.

TcPo₉ was lower during bronchiolitis than after recovery in each case. This is consistent with observations on arterial hypoxaemia in acute bronchiolitis. However, the findings that TcPo₂ was similar in AS and QS both during and after bronchiolitis contrasts with findings in the newborn period when TcPo₂ is lower in AS.

SIDS occurs most often during sleep and there has been speculation concerning the sleep phase during which death might occur. It is not known whether the infant is more vulnerable during AS or QS. The mechanisms underlying respiratory disturbance during sleep are unlikely to be defined without knowledge of the normal behaviour of the respiratory control system during sleep. This has been investigated systematically in dogs where it has been shown that in QS ventilation is regulated by the 'automatic' respiratory control system (chemical inputs and respiratory reflexes), whereas breathing movements during active sleep are fairly insensitive to classical respiratory stimuli with the exception of hypoxaemia. This suggests that the mechanism of apnoeic episodes in QS and AS might be different. In studies of experimental hypoxia in kittens, it has been shown that hypoxia reduces the proportion of AS to QS. It is argued that the kitten is more vulnerable to hypoxia during QS and, by extrapolation, it is suggested that SIDS in infancy is more likely to occur in this phase of sleep. Other investigators have inferred that vulnerability is greatest in AS.

The most significant changes in our patients occurred in QS. It may be that stretch receptor stimulation in the lungs during the course of bronchiolitis had an inhibitory effect on respiration in QS leading to an increase in apnoea. A reflexory component of the apnoea might also explain the fact that the number did not increase during AS. The inflation reflex, like many others, seems to be inhibited during this phase of sleep. An interaction between the metabolic and behavioural control of breathing has been suggested for the origin of periodic breathing often seen in drowsiness and light non-REM sleep. A new adjustment of the breathing control has to be postulated also for transient wakeenings from QS. A higher incidence of apnoeic pauses or other irregularities can be expected on these occasions, particularly at an age when maturation of the mechanism underlying QS has not been completed. In our subjects many apnoeic episodes in QS and IS were initiated by a sigh or movement, behavioural signs suggesting a change of state or possibly a response to a stimulus. In addition, the periods of IS which can be expected to occur during a transition from one stable state to another showed a higher incidence of apnoeic episodes than in either QS or AS.

It seems therefore that bronchiolitis (in the degree studied) increases physiological 'weak-spots' in breathing but is not a major cause of transition from a physiological to pathological apnoea. It is tempting to speculate that in certain infants this causes an increased vulnerability, perhaps during IS or QS, which may be decisive if there is an associated difficulty in ventilatory control as has been suggested in victims of SIDS.

Statistical and computer facilities were made available in the Medical Computing and Statistics Unit of Edinburgh University.

We thank Mrs D Tervit for secretarial assistance.

This study was supported by the Foundation for the Study of Infant Deaths (Grant No 28/HS78) and the Scottish Home and Health Department (Grant No K/MRS/50/C183).

References

The following articles will appear in future issues of this journal:

Fat as an energy supplement for preterm infants
O J Hamner, W T Houlsby, H Thom, I S Ross, D J Lloyd, and G Russell

Early discharge of low birthweight infants
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Causes and management of bronchiolitis with chronic obstructive features
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