Sleep apnoea profile in preterm infants recovering from respiratory distress syndrome

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SUMMARY Polygraphic recordings were made on 10 preterm infants recovering from respiratory distress syndrome and 12 healthy preterm control infants at 40, 52, and 64 weeks' conceptual age to study the influence of respiratory distress syndrome on the development of the sleep apnoea profile. Two significant differences were found: infants with respiratory distress syndrome not only had a lower incidence of non-obstructive apnoea and periodic breathing at 40 weeks but also a persistently higher incidence of obstructive and mixed apnoea at 52 and 64 weeks' conceptual age; the latter finding being related to non-rapid eye movement sleep only. While the lower incidence of both types of apnoea at 40 weeks suggests an advanced maturation of respiratory drive, the persistence of obstructive and mixed apnoea related to non-rapid eye movement sleep may reflect the impact of respiratory distress syndrome on airway structures.

Prematurity and low birthweight are known to be associated with an increased incidence of the sudden infant death syndrome (SIDS).¹ When respiratory distress syndrome in preterm infants is complicated by bronchopulmonary dysplasia, the risk of sudden infant death is reported to be further increased,² resulting in a cumulative incidence of up to 3.4%.³ This increased rate of mortality from sudden infant death syndrome in preterm infants recovering from respiratory distress syndrome and bronchopulmonary dysplasia, however, cannot be explained solely on the basis of various lung function abnormalities. These abnormalities, although more pronounced with bronchopulmonary dysplasia, were found in preterm infants with and without evidence of this disorder after respiratory distress syndrome.⁴

Thus, in addition to an impairment of upper and lower airways, disturbed or possibly defective development of the regulatory mechanisms of breathing needs consideration in preterm infants surviving respiratory distress syndrome. It has been suggested that prematurity per se, reflected in a particular and different development of the sleep apnoea profile during the first six months of life is associated with a maturational delay of respiratory drive.⁵ Furthermore, in comparison with preterm infants without apnoea, those with apnoea were found to exhibit not only immature respiratory reflexes but also reduced respiratory centre activity.⁶ To study the influence of respiratory

distress syndrome on the development of respiratory control, which in certain aspects is mirrored by the sleep apnoea profile,⁷ polygraphic recordings were obtained at 40, 52, and 64 weeks' conceptual age in two groups of preterm infants—one group who were healthy and the other recovering from respiratory distress syndrome.

Patients and methods

Infant populations. The study group comprised 10 preterm infants recovering from respiratory distress syndrome, defined by clinical and radiological criteria. A synopsis of these infants' birth characteristics is given in Table 1. The parameters of mechanical ventilation (expressed as mean and

Table 1 *Birth characteristics of healthy preterm infants and those recovering from respiratory distress syndrome (RDS)*

	Preterm with RDS (n=10)	Healthy preterm (n=12)
Gestational age (wks), mean (range)	32 (28-34)	35 (32-36)
Birthweight (kg), mean (range)	1.54 (1.00-2.15)	2.10 (1.73-2.48)
Apgar score at 5 min=6	6	0
Caesarian section	5	4
Twin birth	4	9
Sex, boy:girl	5:5	6:6

(range)) were as follows: total duration of intubation, 16 (3 to 43) days; controlled ventilation, 5.5 (1 to 14) days; intermittent mandatory ventilation and continuous positive airway pressure, 10 (1 to 28) days; and inspiratory oxygen concentration exceeding 0.40, 60 (2 to 336) hours.

Three of the preterm infants were small for gestational age (birthweight below 3rd centile); four presented with clinical and echocardiographic signs of a patent ductus arteriosus, which was ligated in two; seven had received antibiotics because of suspected infection until cultures proved to be negative; seven had recurrent sleep apnoea or bradycardia, or both, for some days after extubation; and two developed bronchopulmonary dysplasia.

At the time of the first recording all of the 10 infants were breathing spontaneously and did not require supplementary oxygen. None had received theophylline or caffeine during the week before the first recording. All infants were free of signs of intracranial haemorrhage and had normal real time ultrasound scans.

The control group comprised 12 healthy preterm infants whose birth characteristics are also shown in Table 1. Except for prematurity none had other peri- or postnatal complications. The study of this control group was also part of a larger project which, in some aspects, has been reported elsewhere.⁵ Four control infants were lost to follow up at 52 weeks (1) and 64 weeks (3), and two infants died from SIDS (both were twins, second in birth order, and had not at that time been under home apnoea surveillance). Informed consent was obtained from the parents of all infants included in the study. Parents were allowed to feed their infants before and occasionally during the recordings.

Methods. All infants underwent polygraphic sleep recordings during at least one complete sleep cycle. A detailed description of our recording techniques has been given in previous reports.^{5 8 9} First recordings were obtained within the week of the expected date of delivery, calculated from the first day of the mother's last menstrual period. While at 40 weeks' conceptual age recordings were made either late in the morning or early in the afternoon; at 52 and 64 weeks' conceptual age all infants were investigated at the same time of day; that is between 8 pm and midnight.

All recordings were analysed visually and the different types of sleep apnoea as well as the episodes of periodic breathing were identified in relation to sleep states according to established criteria described in detail previously.^{5 8-10} Undifferentiated sleep was not evaluated in respect of the

different apnoea variables, since in most instances it was less than 10 minutes of the total sleep time recorded.

Apnoea density was calculated by dividing the total amount of a given type of apnoea by the total time spent in a specific sleep state multiplied by 100. This gave the apnoea density for 100 minutes rapid and non-rapid eye movement sleep separately. In this way the density of periodic breathing related to sleep state was also obtained.

Duration of the different types of apnoea and episodes of periodic breathing were calculated by dividing the total time spent in a specific type of apnoea or in periodic breathing by the time spent in a specific sleep state multiplied by 100.

Mean duration of a given type of apnoea or episodes of periodic breathing was calculated by dividing the total duration of apnoeic episodes during a specific sleep state by the total number of these events. Due to the wide intersubject variation and obviously uneven distribution of the apnoea variables, the median values and the interquartile ranges were calculated for the various apnoea measures at the three age levels studied. For graphical presentation of the median and interquartile range the 'box and whiskers' graphs of Tuckey¹¹ were used. The Mann and Whitney U test¹² was used for statistical comparison between the two groups.

Results

At 40 weeks' conceptual age, preterm infants recovering from respiratory distress syndrome experienced considerably less non-obstructive apnoea than the control group. This difference was observed in terms of both the density and duration of non-obstructive apnoea related to both sleep states, but was more pronounced during non-rapid eye movement sleep (Tables 2 and 3, Fig. 1). The same pattern (with reduced density and duration) was also shown for longer episodes of non-obstructive apnoea (six seconds or more), but this did not, however, reach statistical significance at 40 weeks' conceptual age (Tables 2 and 3). At 40 weeks the density and total and mean duration of periodic breathing were found to be significantly decreased in the study group. Moreover, the number of infants experiencing periodic breathing at 40 weeks' conceptual age was significantly lower in the study group, particularly during non-rapid eye movement sleep. While only 10% of the study group infants showed periodic breathing during non-rapid eye movement sleep this type of breathing was experienced by 50% of the controls (Fig. 2). With regard to rapid eye movement sleep at 40 weeks, this ratio

Table 2 Apnoea density: distribution according to type and sleep state in preterm infants recovering from respiratory distress syndrome (RDS) and healthy preterm controls (values median (interquartile range))

Sleep state	Group	Apnoea, 3-5.9 sec			Apnoea ≥6 sec		
		Non-obstructive	P	Obstructive and mixed	Non-obstructive	P	Obstructive and mixed
Age 40 weeks	REM	RDS		57	3		36.5
		Controls	<0.05	(52.5-59.5)	(0-16)	ns	(24-50)
	Non-REM	RDS		67	15		37
		Controls	<0.05	(52-73)	(6-39)	ns	(34-56)
Age 52 weeks	REM	RDS		6	11		1.5
		Controls	<0.05	(3-12)	(2.5-13.5)	ns	(0-6.5)
	Non-REM	RDS		13	18		6
		Controls	<0.05	(3-19)	(1-39)	ns	(0-14)
Age 64 weeks	REM	RDS		44.5	1.4		14.5
		Controls	ns	(33-60)	(0-3.6)	ns	(11-23.5)
	Non-REM	RDS		38	0		8
		Controls	ns	(11-63)	(0-2)	ns	(3-17)
Age 66 weeks	REM	RDS		3	2.4		0
		Controls	ns	(2.5-3.5)	(0-5.3)	ns	(0-3)
	Non-REM	RDS		0	2		0
		Controls	ns	(0-1)	(0-4)	ns	(0-0)
Age 68 weeks	REM	RDS		21	10		13.5
		Controls	ns	(15-29)	(7-11.5)	ns	(7-19.5)
	Non-REM	RDS		17	8		9
		Controls	ns	(5-26)	(4-10)	ns	(4-12)
Age 70 weeks	REM	RDS		2	4		0
		Controls	ns	(0-4.5)	(3-9)	ns	(0-2)
	Non-REM	RDS		0	4		0
		Controls	ns	(0-0)	(2-8)	ns	(0-0)

REM=rapid eye movement sleep; non-REM=non-rapid eye movement sleep. ns=not significant at the 0.05 level.

Table 3 Apnoea duration: distribution according to type and sleep state in preterm infants recovering from respiratory distress syndrome (RDS) and healthy preterm controls (values, median (interquartile range))

Sleep state	Group	Apnoea, 3-5-9 sec			Apnoea ≥ 6 sec		
		Non-obstructive	P	Obstructive and mixed	Non-obstructive	P	Obstructive and mixed
Age 40 weeks	REM	RDS 2.6 (2.4-3.3)	<0.05	10.5 (6.7-15.3)	0.3 (0-1.7)	ns	9.4 (5.6-14)
		Controls 4.8 (3.3-11.4)		10.5 (7.8-12.3)	1.7 (0.9-4.7)		8.7 (6.5-11.2)
	Non-REM	RDS 1.7 (0.8-2.3)	<0.05	0.6 (0.3-1.2)	1.3 (0.7-1.8)	ns	0.3 (0-0.9)
		Controls 5 (2.4-8.6)		2 (0.3-2.3)	2.3 (1.4-4.2)		1.2 (0-2.3)
Age 52 weeks	REM	RDS 1.1 (0.6-3.1)	ns	4.3 (3-6.7)	0.2 (0-0.6)	ns	2.1 (1.4-4.1)
		Controls 0.8 (0.7-1.9)		3.1 (1.5-5.7)	0 (0-0.2)		1.6 (0.6-2.9)
	Non-REM	RDS 0.6 (0.4-1)	ns	0.2 (0.1-0.7)	0.3 (0-0.7)	ns	0 (0-0.2)
		Controls 0.7 (0.6-1.8)		0 (0-0.2)	0.2 (0-0.5)		0 (0-0)
Age 64 weeks	REM	RDS 3 (2.3-4)	ns	3 (1.6-4.6)	1.2 (0.7-1.7)	ns	2 (1.3-3.5)
		Controls 3 (1.7-4.7)		1.9 (0.8-2.7)	0.8 (0.4-1.9)		1.8 (0.8-1.9)
	Non-REM	RDS 1 (0.6-2)	ns	0.3 (0-0.5)	0.7 (0.4-1.2)	ns	0 (0-0.3)
		Controls 0.8 (0.3-0.9)		0 (0-0)	0.5 (0.2-0.7)		0 (0-0)

Fig. 1 Density of non-obstructive apnoea (≥ 3 seconds) in relation to sleep states and postconceptual age in healthy preterm infants and those recovering from respiratory distress syndrome. Corresponding data for 12 normal term infants included in a former study⁵ are also given for comparison.

The median and interquartile range are shown by the 'box and whisker' graphs of Tuckey.¹¹ S=significant at the 0.05 level.

REM=rapid eye movement; non-REM=non-rapid eye movement.

was 30:70% for the study and control infants respectively. At 52 and 64 weeks, the density and duration of non-obstructive apnoea and periodic breathing were no longer significantly different between the groups (Tables 2 and 3, Fig. 1). Very few infants in either group still experienced periodic breathing during non-rapid eye movement sleep at these ages (Fig. 2).

With regard to obstructive and mixed apnoea, the study group infants exhibited a lower density and duration at 40 weeks' conceptual age than the controls. This difference was only observed during non-rapid eye movement sleep and did not reach statistical significance (Tables 2, 3, and 4). At 52 and 64 weeks, however, infants recovering from respiratory distress syndrome had significantly more and longer episodes of obstructive and mixed apnoea than the controls (Tables 2 and 3, Fig. 3). As shown in Table 4 the mean duration of obstructive and mixed apnoea at 52 and 64 weeks was also significantly longer in the study group. This accounts for

Fig. 2 Number of infants in each group who suffered episodes of periodic breathing in relation to sleep states and postconceptual age. The corresponding data for 12 normal term infants⁵ are given for comparison.

Bars represent the number of infants with periodic breathing given as a percentage of the total number of infants in each group.

Fig. 3 Density of obstructive and mixed apnoea (≥ 3 seconds) in relation to sleep states and postconceptual age in study and control infants and, for comparison, in 12 normal term infants.⁵

The median and interquartile range are shown by the 'box and whisker' graphs of Tuckey.¹¹ S=significant at the 0.05 level.

Table 4 Mean duration of apnoea: distribution according to type and sleep state in preterm infants recovering from respiratory distress syndrome (RDS) and healthy preterm controls (values, median (interquartile range))

Sleep state	Group	Apnoea, 3-5.9 sec			Apnoea ≥6 sec		
		Non-obstructive	P	Obstructive and mixed	Non-obstructive	P	Obstructive and mixed
Age 40 weeks	REM	{ RDS Controls }	ns	11 (8.5-12.5)	6.2 (6-6.6)	ns	13.8 (13-14.5)
				9.1 (8.1-10.8)	6.8 (6.2-7)		11.6 (11-15.4)
	Non-REM	{ RDS Controls }	ns	5.5 (4.7-5)	7.3 (6.9-7.9)	ns	11.7 (9-12)
				9.4 (4-13.1)	7.4 (6.6-7.8)		13.4 (11-14.6)
Age 52 weeks	REM	{ RDS Controls }	ns	5.1 (4.6-6.4)	6.1 (6-7)	ns	9.7 (8.5-12.1)
				5.1 (4.2-6)	6 (6-6)		10.1 (9-10.5)
	Non-REM	{ RDS Controls }	ns	3.5 (3-4.7)	6.8 (6.4-6.9)	ns	9 (8-11)
				0 (0-1.5)	7.5 (6.5-7.9)		6 (6-6)
Age 64 weeks	REM	{ RDS Controls }	ns	7.2 (6.6-10.5)	6.9 (6.5-7.9)	ns	10 (8.8-11.1)
				6.7 (5.5-13)	7.3 (7-8.5)		9 (7.6-13)
	Non-REM	{ RDS Controls }	ns	4 (0-6.9)	8 (7.4-10.2)	ns	9.5 (9-10)
				0 (0-4.8)	7.5 (7-8.6)		7 (7-7)

an even greater number of longer (6 seconds or more) episodes of apnoea in this group. At both 52 and at 64 weeks, differences between density and total and mean duration of obstructive and mixed apnoea were related to non-rapid eye movement sleep only (Tables 2, 3, and 4, Fig. 3).

Discussion

The present study shows two main differences between the sleep apnoea profiles of healthy preterm infants and those recovering from respiratory distress syndrome during the first 6 months after normal term. Firstly, there was a lower incidence (that is a lower density and duration) of non-obstructive apnoea and periodic breathing at 40 weeks and, secondly, a higher incidence of obstructive and mixed apnoea at 52 and 64 weeks' conceptual age in the study group—both findings being closely related to non-rapid eye movement sleep. Thus, an already remarkably lower incidence of apnoea at 40 weeks suggesting an advanced development of respiratory control mechanisms in the study group contrasts with the nearly stable persistence of obstructive and mixed apnoea during non-rapid eye movement sleep in these same infants at 52 and 64 weeks' conceptual age. According to the findings of Curzi-Dascalova *et al.*,¹³ neither the lower mean gestational age and birthweight nor the different number of twins in our study group can account for the differences in the apnoea profile between study and control groups at 40 weeks. On the contrary, the lower mean gestational age and lower number of twins in the study group would more probably have led to an increased rather than a decreased incidence of non-obstructive apnoea at 40 weeks.

In a previous study⁵ we showed that at 40 weeks' conceptual age normal preterm infants compared with term controls experienced significantly more episodes of apnoea, and that at 52 weeks the converse was true. It was suggested that this sleep apnoea profile of healthy preterm infants indicated maturational delay of the respiratory drive at 40 weeks which seemed to be followed by increased respiratory drive, and thus a probably overadaptive maturation of respiratory control, at 52 weeks. In our study, infants who were recovering from respiratory distress syndrome experienced apnoea of both types and periodic breathing to almost as low a degree as that observed in normal term infants (Figs. 1 and 2), particularly during non-rapid eye movement sleep. An advanced maturational process of respiratory drive may therefore be assumed in these infants. Hoppenbrouwers *et al.*,¹⁴ studying the development of sleep state distribution of normal

preterm infants and those suffering episodes of apnoea, found that at 44 weeks' conceptual age infants with apnoea were not different from normal term controls, indicating that 'stress produced by apnoea in the premature infant appeared to accelerate development of sleep state distribution toward normal term patterns'. Although we did not investigate sleep state distribution, different peri- and postnatal conditions producing different amounts of hypoxaemic 'stress' in preterm infants with and without respiratory distress syndrome could have influenced the development of the apnoea profile in the study group towards that of normal term infants at 40 weeks.

Like siblings of SIDS victims who collectively showed not only a reduced incidence of apnoea but also an advanced development of electroencephalographic power spectral patterns suggesting an accelerated central nervous system maturation,¹⁵ preterm infants recovering from respiratory distress syndrome may have experienced considerably more environmental stimulation and episodes of hypoxaemia than healthy preterm controls.

As Quattrochi *et al.* have reported,¹⁶ there is now increasing anatomical evidence supporting our assumption. Takashima and co-workers¹⁷ showed significant differences in the development of axodendritic synaptogenesis of neuronal structures in the medulla oblongata involved in respiratory control in different infant populations. Whereas SIDS victims almost uniformly had a noticeable delay in the development of these respiratory neurons, a group of ventilator dependant preterm infants who died from complications of respiratory distress syndrome showed a developmental status indicating an advanced, but in certain aspects possibly abnormal, maturation in comparison with age matched controls who died from other causes.

The seemingly lower degree of obstructive and mixed apnoea during non-rapid eye movement sleep observed at 40 weeks' conceptual age in the study group is consistent with the significantly lower incidence of non-obstructive apnoea and periodic breathing in these infants, suggesting an advanced maturation of respiratory control. Since a higher degree of obstructive and mixed apnoea during non-rapid eye movement sleep at 40 weeks was the major difference between normal preterm and normal term control infants this was considered to be a marker of developmental delay.⁵ From this point of view the comparably low level of this type of apnoea in the current study group at 40 weeks may be looked at as an indicator of an advanced maturation of respiratory drive. Consequently the persistence of obstructive and mixed apnoea related to non-rapid eye movement sleep can no longer

point to a continuing maturational delay. More probably it reflects structural lesions of the larger and terminal airways as a complication of respiratory distress syndrome and its treatment, factors which are more likely to produce functional abnormalities during non-rapid eye movement sleep since in this sleep state, with a predominantly autonomic control of breathing, healthy preterm infants at 52 and 64 weeks exhibit virtually no obstructive and mixed apnoea. An increased frequency of obstructive and mixed apnoea in preterm infants surviving respiratory distress syndrome was also reported by Fontan *et al.*,¹⁸ whose study group, however, comprised infants of different conceptional ages and whose study results were not related to sleep states. Persistently increased amounts of obstructive and mixed apnoea, known to cause considerable oxygen desaturation,¹⁹ may thus compromise respiration during non-rapid eye movement sleep with its tendency to hypoventilation,²⁰ and challenge preterm infants to overcome the impact of respiratory distress syndrome by breathing at a more mature level. This demand for a more mature level of respiratory drive seems to be indicated by the early reduction in episodes of apnoea and periodic breathing in the study group. Under the additional influence of multiple aggravating intrinsic (developmental changes of sleep state distribution) and environmental factors (that is upper respiratory tract infections, anaemia etc) these infants, whose breathing is already compromised, may suffer an increased risk of SIDS, which has been reported.¹⁻³ As has been pointed out by Hoppenbrouwers and Hodgman,²¹ the challenge for a forced respiratory drive may allow demands to be met for some time and 'initially be adaptive but ultimately cause a depletion of the infant's reserve'.

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