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Does the duration of oxygen dependence after birth influence subsequent respiratory morbidity?

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Abstract The relationship of respiratory morbidity at follow up to the development and type of "neonatal" chronic lung disease has been assessed. Three groups, each of ten infants matched for gestational age and gender, were compared. Group A had Type I chronic lung disease and group B bronchopulmonary (BPD), the most severe form of neonatal chronic lung disease (Type II CLD); group C had developed neither Type I or Type II CLD. Group B compared to group A compared to group C required a significantly longer duration of oxygen therapy on the neonatal unit. All three groups were prospectively followed; the occurrence of symptoms was documented in each of the first 3 years of life and lung function was measured using a plethysmographic technique at the end of year 1. In all 3 years a significantly greater proportion of groups A and B were symptomatic compared to group C, but there was no significant difference in the proportion so affected between groups A and B. Airway resistance was higher in both groups A and B compared to C but only reached statistical significance on comparing groups A and C. We conclude oxygen dependency beyond 1 month of age, irrespective of the development of BPD, significantly increases respiratory morbidity at follow up.

Key words Chronic lung disease
Oxygen dependency · Prematurity

Abbreviations *BPD* bronchopulmonary dysplasia · *CLD* chronic lung disease · Raw airways resistance

Introduction

Following premature delivery, sadly, some infants remain chronically oxygen dependent at least until 1 month of age. The majority have Type I chronic lung disease (CLD), but the most severely affected have bronchopulmonary dysplasia (BPD) or type II CLD, diagnosed by its characteristic chest radiograph appearance [6]. Infants with BPD may remain ventilator and oxygen dependent for many months and even need to be discharged on home oxygen therapy [4]. Such infants have lung function abnormalities at follow up [1].

Respiratory symptoms at follow up are common during the 1st year of life amongst infants born prematurely [3] and persist into the 2nd year of life in those who had had a prolonged duration (> 10 days) of oxygen dependency [11]. Thus, it seemed likely that the occurrence of symptoms in the first 3 years of life might be greater in infants with Type II CLD (BPD) than in those who developed Type I CLD and that a greater proportion of both groups would be symptomatic compared to infants who had developed no form of CLD. The aim of this study was to test that hypothesis. In addition, we wished to contrast the respiratory morbidity at follow up of the three groups by comparison of their lung function.

Patients and methods

From a group of infants with birth weights less than 2000 g consecutively admitted to the Neonatal Unit at King's College Hospital and followed prospectively on discharge from hospital, three groups of infants matched for gender and gestational age were identified. Group A consisted of infants who had Type I CLD. They had a continuing oxygen requirement at 1 months of age, but their chest radiograph at that time demonstrated hazy lung fields only, cystic elements were absent. Group B consisted of infants who had been diagnosed by the clinician in charge of the case as having Type II CLD or BPD. The infants had a continuing oxygen requirement at 1 month of age and had cystic elements present on the lung fields on their chest radiographs. Group C infants required no form of respiratory support at 28 days of age.

The median gestational age of all three groups was 28 weeks with a range from 24–30 weeks. Seven males were recruited into each of the three groups. Group C had a significantly higher birth weight than group B ($P< 0.05$) and both groups A and B contained a higher proportion of infants who were growth-retarded. All three groups of infants had been ventilated from birth for respiratory distress syndrome. Both groups A and B were ventilated and in an increased inspired oxygen concentration for significantly longer than group C ($P < 0.01$). In addition, group B required a significantly longer duration of respiratory support than group A ($P < 0.05$) (Table 1).

This study was approved by the King's College Hospital Ethics Committee and parents gave informed consent prior to entry into the study.

Patients were kept under regular clinical review on discharge from hospital when the occurrence of respiratory symptoms was documented over the first 3 years and measurements of lung function were made at 6 monthly intervals over the 1st year of life. Children were defined as being symptomatic in any 1 year if they wheezed and/or coughed for more than 3 days a week over a 4-week period or if they wheezed and/or coughed for at least 3 days following all upper respiratory tract infections.

Lung function measurements were made in the Paediatric Respiratory Laboratory, where a medical history was taken and the infant examined. No child had been symptomatic in the week prior to testing. Height and weight were measured and the infants sedated with oral chloral hydrate (80–100 mg/kg). Airways resistance (Raw) was measured using a whole body plethysmographic technique. The infant breathed through a face mask which was connected to the re-breathing bag via a heated pneumotachograph and was sealed around the infant's nose and mouth using silicone putty to ensure an airtight seal. The infant breathed through a heated, humidified re-breathing system to avoid box pressure changes due to the heating and cooling of respired gas. Raw was measured at two-thirds of maximum inspiratory flow by the classical techniques of Dubois et al. [2] suitably modified for infants. Raw was calculated from at least ten breaths and all measurements were corrected for the resistance of the apparatus (8 $cmH_2O/l/s$, measured at flows between 5 and 15 l/min). Traces were analysed without knowledge of the clinical details of the infants. The reproducibility of Raw was determined in 16 children of similar gestational and postnatal age to the study population. Measurements of Raw were performed before and after infants had been removed and returned to the body plethysmograph. The coefficient of variation of Raw was 9%.

Table 1 Patient characteristics

	Median (range)		
	Group A ($n = 10$)	Group B ($n = 10$)	Group C ($n = 10$)
Birthweight (g)	836 (566–1290)	768 (660–1644)	1312 (450–1778)
Duration of ventilation (days)	9 (3–37)	36 (5–56)	0 (0–19)
Duration of an increased oxygen requirement (days)	56 (40–125)	125 (70–720)	1 (1–24)

Analysis

Differences between the groups in the number of patients who were symptomatic were assessed for statistical significance using Fisher's exact test. Eight of group B were discharged home on oxygen therapy, thus it was not possible to make plethysmographic measurements of lung function at 6 months in all the study population. Thus comparison was made of the lung function results from measurements made at 1 year of age and differences assessed for statistical significance using the Wilcoxon rank sum test.

Trial size

Recruitment of ten infants into each group allowed us to detect with 80% power at the 5% level a difference in the incidence of symptoms of 80% in either groups A or B compared to 20% in Group C. In addition such a trial size would allow us to detect with 80% power at the 5% level a difference in Raw of 15 $cmH_2O/l/s$ between groups.

Results

In all 3 years significantly more patients were symptomatic in both groups A and B than group C ($P < 0.05$), but there was no significant difference in the proportion of symptomatic patients in group A compared to group B (Fig. 1).

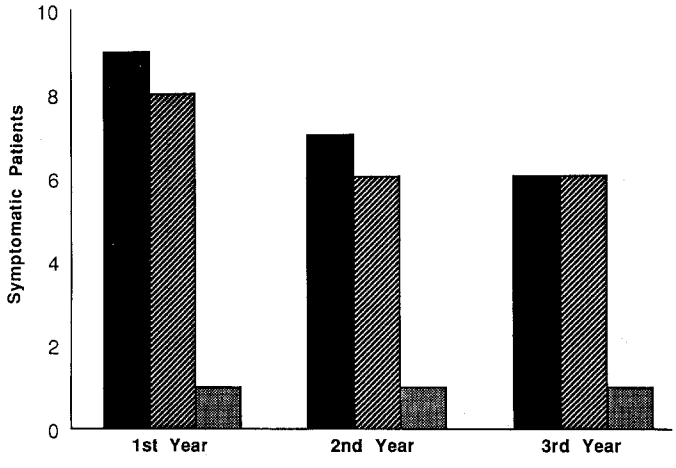

Fig. 1 Number of symptomatic patients in the three groups in the 3 study years. ■ Group A, ▨ Group B, ▩ Group C

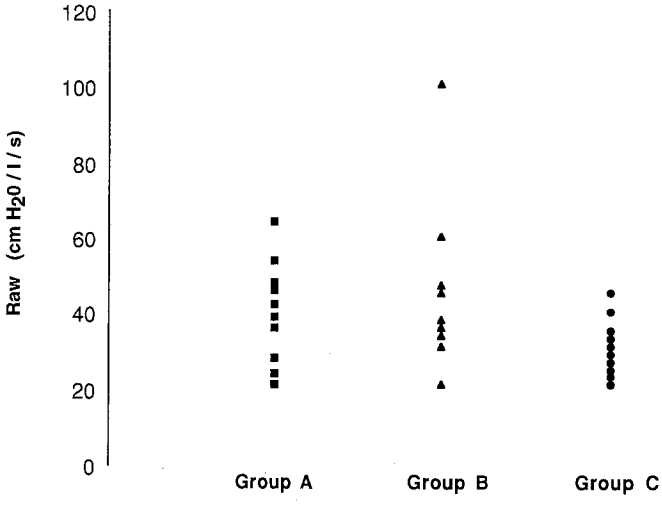

Fig. 2 Airway resistance (Raw) at year 1 in each of the three groups (individual data shown). (In group B two infants had a Raw of 38 $cmH_2O/l/s$ but are demonstrated by one data point). ■ Group A, ▲ Group B, ● Group C

Although, there was no significant difference in Raw between group A (median 39 $cmH_2O/l/s$, range 21–64) and group B (median 38 $cmH_2O/l/s$, range 21–100), group C had a significantly lower Raw (median 28 $cmH_2O/l/s$, range 23–45) than group A ($P < 0.05$). The difference between groups B and C did not reach statistical significance (Fig. 2).

Discussion

Our three groups were matched for gestational age as we [11] and others [8] have found that this influences lung function at follow up. In addition, we matched for gender, as this influences the severity of neonatal respiratory distress and hence is likely to influence lung function at follow up. The lower birth weights of groups A and B compared to C would suggest, as the three groups were gestational age-matched, that the two former groups contained small for dates infants. We have previously reported that growth retardation does not protect against the development of respiratory distress [9], nor does lung function at follow up differ between small for dates and appropriately grown infants [12]. Thus we do no feel differences in birth weight between the three groups influenced our results.

We found significant differences in respiratory morbidity at follow up only between group C compared to the other two groups, buth no significant differences between groups A and B. Relatively few of group C were ventilated (Table 1), whereas all of groups A and B had required that form of respiratory support in the neonatal period. We have previously found that the requirement for ventilation [13], but not its duration [14], is associated with more severe lung function abnormalities at follow up. Thus the present study's results are entirely consistent with those findings. Mallory et al. [7] suggested that lung function is influenced by the severity of BPD. Certain of their patients, however, were very severely affected, as evidenced by a requirement for ventilation for longer than 10 months. In addition, differences in lung function between their groups did not become apparent until after the 1st year of life and we report airways resistance results at 1 year. Our findings are supported by those of Hakulinen et al. [5] who reported that "BPD" (defined as oxygen dependency at 1 month) children had greater respiratory morbidity in the 1st years of life compared to controls.

We found no significant difference in the proportion of symptomatic infants or Raw between groups A and B. Although our trial size would enable us to detect only a relatively large difference in the proportion of symptomatic infants between groups, we were able to detect a small difference in Raw, and certainly of the level likely to be clinically significant. Thus our results might suggest that oxygen dependency persisting to at least 1 month, regardless of its exact duration, is the critical determinant of chronic respiratory morbidity. From our definition of symptomatic infants, however, we cannot exclude that group B compared to group A infants had more severe symptoms, although the similarity of their lung function at follow up would suggest this to be unlikely [10]. We conclude oxygen dependence beyond 1 month of age increases respiratory morbidity at follow up even into the 3rd year of life. Our results, however, would suggest the exact duration of prolonged oxygen dependence may not influence the respiratory outcome.

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