

Pulmonary sequelae of neonatal respiratory distress in very low birthweight infants: a clinical and physiological study

Y C WONG, C S BEARDSMORE, AND M SILVERMAN

Department of Paediatrics and Neonatal Medicine, Institute of Child Health, Hammersmith Hospital, London

SUMMARY Twenty infants, mechanically ventilated in the neonatal period for respiratory distress syndrome, were compared with 15 healthy controls, matched for birthweight (less than 1501 g) but greater in mean gestational age. Clinical features and lung mechanics (by whole body plethysmography) were recorded at 6-monthly intervals until about one year. The neonatal course of the mechanically ventilated infants was commonly complicated by tracheobronchial hypersecretion and the later course by a fairly high incidence of lower respiratory tract illness. In this group, thoracic gas volume, dynamic compliance, pulmonary and airways conductance were all abnormal during the middle 4 months of the first year and reverted towards normal towards the end of the first year. The control group had normal lung mechanics. Early lung function tests were of limited value in predicting later lower respiratory tract illness, which was more common in boys, after neonatal mechanical ventilation for longer than 24 hours or raised ambient oxygen for longer than 5 days. There were few predictive physical signs. In this group of very low birthweight infants, respiratory distress syndrome of sufficient severity to require mechanical ventilation led to significant physiological and clinical disturbances of lung function which lasted into the second 6 months of life and which were particularly severe in those who had recurrent lower respiratory tract illness.

Recent advances in ventilatory support have improved survival for preterm infants suffering from respiratory distress syndrome (RDS).¹⁻⁴ However, it has become clear that some survivors may develop pulmonary sequelae. Thus bronchopulmonary dysplasia is not rare in infants of low birthweight who are treated with intermittent positive pressure ventilation (IPPV).⁵⁻¹⁰ Chest infections during the first year of life are a common sequel. Several studies of pulmonary mechanics have shown that impaired lung function is not uncommon after IPPV.^{5 11 12} Such effects as these might be expected to be more severe in very low birthweight infants, who form an increasing proportion of newborn infants requiring respiratory intensive care.

This report represents the results of a prospective study of a cohort of infants with birthweight <1501 g admitted to the Premature Baby Unit of Hammersmith Hospital who survived the neonatal period. Pulmonary sequelae were studied clinically, together with investigations of lung mechanics during the first year of life. The aim was to describe

the sequelae and to determine possible aetiological factors.

Patients and clinical management

Patients were drawn from a cohort of 86 infants with birthweight <1501 g admitted to the Premature Baby Unit at Hammersmith Hospital between December 1978 and November 1979. Forty of the 59 surviving infants took part in the study after informed parental consent had been obtained; 19 survivors were not enrolled since it was thought that regular follow-up was unlikely.

For the analysis of lung function tests, the 40 infants followed up were divided into three groups according to diagnosis and early respiratory support. Fifteen of the infants (the control group) had no significant neonatal respiratory disease and required <48 hours of oxygen therapy, although 2 were briefly subjected to IPPV, one for no clear reason at a referring hospital¹³ and the other for 24 hours postoperatively after a laparotomy for intestinal

obstruction. Twenty of the infants (the IPPV group) had neonatal RDS requiring IPPV. The other small group of 5 infants had a variety of respiratory disorders and treatments and, because of this, have not been included in the analysis of the lung function data. Ten of the 15 control infants and 17 of the 20 infants in the IPPV group followed up for longer than 8 months provided most of the follow-up data.

For the retrospective analysis of perinatal factors and later clinical features in the prediction of subsequent lower respiratory tract illness (LRTI), the data from all 40 infants were used.

Infants were managed according to well established principles,¹⁴ with the exceptions that continuous positive airways pressure (CPAP) was not used to treat RDS before proceeding to mechanical ventilation and that a high ambient oxygen concentration ($F_{I}O_2$) was used in preference to early IPPV, if this provided adequate oxygenation. Mechanical ventilation was carried out, without muscle paralysis, according to the principles of Reynolds.¹⁵

The equipment used included pressure-limited, time-cycled ventilators (Vickers Neovent 90) and humidifiers (Vickers). Size 2.5 to 3.0 mm shouldered oro-tracheal tubes (Portex) were used if endotracheal intubation was needed. Regular tracheal toilet (after instillation of 1 ml physiological saline when necessary) was performed at 1–2 hourly intervals.

Methods

The perinatal course of these infants was documented at the time of the inpatient treatment, and their subsequent clinical course assessed at about 6-monthly intervals to about one year of age. At each follow-up visit a history was taken and the examination was carried out by one of us (Y C W) who knew the background of the infant.

Gestational age was based on the mother's dates and gestational assessment.¹⁶ Diagnoses of transient tachypnoea of the newborn and RDS were made using clinical and radiological criteria.¹⁷ LRTI was documented if an infant was readmitted to hospital with chest x-ray evidence of acute pulmonary changes.

Lung mechanics were measured at each follow-up attendance. The first study was performed just before discharge from the premature baby unit or the referring hospital. With one exception, only patients who no longer required raised ambient oxygen were studied. All measurements were performed 30–60 minutes post-prandially. Infants over age one week were sedated with trichlorol 100 mg/kg unless specifically contraindicated. The infant was

placed in the right lateral position inside a plethysmograph. Once the infant was sleeping quietly, an oesophageal balloon catheter was inserted orally into the stomach. Watching the oscilloscopic display of oesophageal pressure (Poes), the catheter was withdrawn slowly until the pressure signal became inverted, indicating that the balloon was then in the oesophagus. The rebreathing apparatus with its built-in pneumotachograph¹⁸ was then carefully manipulated into place, and the face mask sealed around the mouth and nose with silicone putty, taking care to avoid pressure on the nose and ensure a tight fit. The oesophageal balloon was then inflated bringing it into its working range.¹⁹ Pulmonary conductance (Gp) and dynamic compliance (C_{dyn}) were calculated from at least 10 breaths of reasonable regularity.²⁰

Thoracic gas volume (TGV) and airways conductance (GAW) were measured by an adaptation of a plethysmographic technique²¹ in which the infant rebreathed heated humidified gas, using a rebreathing apparatus containing occluding valves.¹⁸ The characteristics of the catheter/transducer systems (Valedyne MP45-1 for oesophageal pressure, box pressure, and flow; SE Labs 1150 for mask pressure) and the amplifiers/UV chart recorder (Emma, SE Labs) have previously been described.¹⁹ TGV was calculated from at least 3 separate airway occlusions. Calculation of GAW was based on changes in gas flow and alveolar (box) pressure between points of mid-iso-lung volume.

The statistical tests used were the two-tailed χ^2 test with Yates's correction, or the Student's *t* test.

Results

Perinatal features. The perinatal data for the control and IPPV groups are presented in Table 1. As the mean gestational age of these weight-matched groups differed, so too did the incidence of lightness-for-dates.

In the control group, only one infant received high ambient oxygen (>60%) and 2 were briefly mechanically ventilated (see methods). In the IPPV group, 15 infants received high ambient oxygen concentrations (median duration 258 hours) and 5 required peak inspiratory ventilator pressures >25 cmH₂O (median duration of IPPV 108 hours). Twelve required subsequent prolonged CPAP (>24 hours). There were some differences in the incidence of cardiorespiratory complications between the groups (Table 1). No patient in either group had lobar emphysema, pulmonary haemorrhage, meconium aspiration, or cystic fibrosis.

No significant differences were found between the control and IPPV groups in the incidence of parental

Table 1 Perinatal data (mean or median values \pm range or SD)

	Control group	IPPV group
Number of infants	15	20
Gestational age (weeks)	31.6 \pm 2.0*	29.1 \pm 1.6
Birthweight (g)	1229 \pm 204 (800–1450)	1167 \pm 208 (840–1500)
Light-for-dates†	10 *	1
Outborn	4	11
Boys	7	14
Prolonged rupture of membranes		
>24 hours	3	5
Maternal steroid	7	10
Apgar score		
At 1 min	5.7 \pm 2.5	4.7 \pm 3.4
At 5 min	8.6 \pm 1.3	7.5 \pm 2.5
Air leak syndrome	0	6
Pulmonary collapse/consolidation	0	6
Tracheobronchial hypersecretion‡	0	8
Patent ductus arteriosus, diagnosed clinically	3	10
Stridor	0	3

* $P < 0.05$, † birthweight < 10 centile,^{33,34} ‡ excessive airways secretion requiring bronchial lavage.³⁵

smoking, fetal wastage, steroid administration to mother in labour, antepartum haemorrhage, amniocentesis, chronic amniotic fluid loss, or prolonged rupture of membranes.

Lower respiratory tract illness in infancy. The clinical features at follow-up examinations in the 6 infants who required hospital readmission for LRTI were compared with those in the 34 infants who did not. These two groups were similar for gestational age and birthweight.

The 6 infants in the LRTI group were severely compromised by the LRTI (one died with radiological evidence of bronchopulmonary dysplasia, while 2 others were admitted moribund but survived). The features which distinguished the LRTI group from the others were gender (all 6 were boys), the need for CPAP > 24 hours (4/6: 0/34), and IPPV > 24 hours (6/6: 15/34), and oxygen therapy > 5 days (6/6: 12/34). By choosing CPAP > 24 hours,

the intention was to eliminate the few who had CPAP very briefly during weaning from IPPV. By setting the 24-hour minimum time limit for IPPV, it was intended to exclude those who were ventilated very briefly, generally just before and during transfer from referring hospitals.

The interval symptoms which were significantly more common in those who required readmission for LRTI were a weak cry and shortness of breath as reported by mothers. Other symptoms—such as snoring, nasal discharge, cough, wheeze, feeding difficulties due to shortness of breath, and frequency of upper respiratory tract infection—were similar in prevalence in the two groups. Signs which were appreciably more common in those who required readmission for LRTI were the presence of stridor, abnormal cry, and abnormal chest movements.

Lung mechanics. Because of the changes in lung

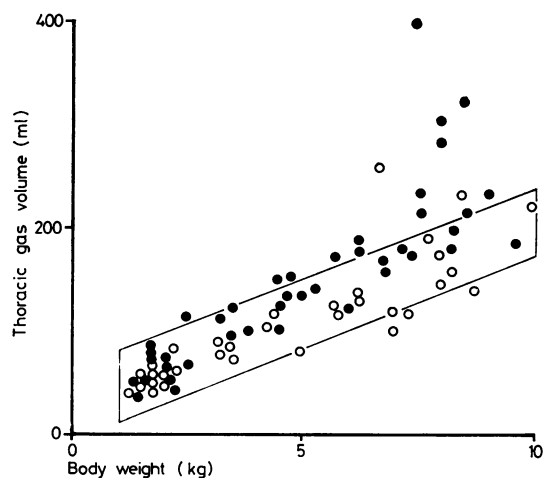


Fig. 1 Relationship of thoracic gas volume and body weight. ○ = controls, ● = IPPV group; the box indicates mean \pm 1 SD for control group.

Table 2 Lung mechanics (mean values \pm 1 SD)

	0–4 months		5–8 months		9–12 months	
	Control	IPPV	Control	IPPV	Control	IPPV
Body weight (kg)	2.1	2.1	5.1	5.0	7.7	8.1
TGV/body weight (ml/kg)	30.9 \pm 5.5 (n = 15)	31.7 \pm 8.2 (n = 16)	21.3 \pm 4.3 (n = 7)	27.1 \pm 6.8 (n = 15)	21.9 \pm 6.05 (n = 12)	26.3 \pm 7.4 (n = 20)
Cdyn/TGV (ml/cm H ₂ O per ml)	0.053 \pm 0.019 (n = 6)	0.038 \pm 0.011 (n = 15)	0.078 \pm 0.013* (n = 5)	0.053 \pm 0.026 (n = 13)	0.076 \pm 0.023 (n = 7)	0.069 \pm 0.025 (n = 15)
Gp/TGV (per second/cm H ₂ O)	0.22 \pm 0.10 (n = 8)	0.17 \pm 0.08 (n = 15)	0.21 \pm 0.04 (n = 5)	0.11 \pm 0.02 (n = 13)	0.16 \pm 0.14 (n = 8)	0.10 \pm 0.07 (n = 15)
GAW/TGV (per second/cm H ₂ O)	0.29 \pm 0.15 (n = 14)	0.21 \pm 0.10 (n = 15)	0.20 \pm 0.05 (n = 6)	0.12 \pm 0.04 (n = 14)	0.13 \pm 0.08 (n = 12)	0.12 \pm 0.08 (n = 20)

TGV = thoracic gas volume; Cdyn = dynamic compliance; Gp = pulmonary conductance; GAW = airways conductance; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; n number of observations.

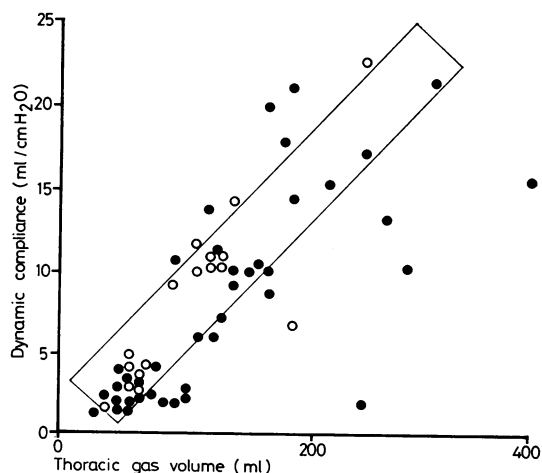


Fig. 2 Relationship of dynamic lung compliance and thoracic gas volume (key as Fig. 1).

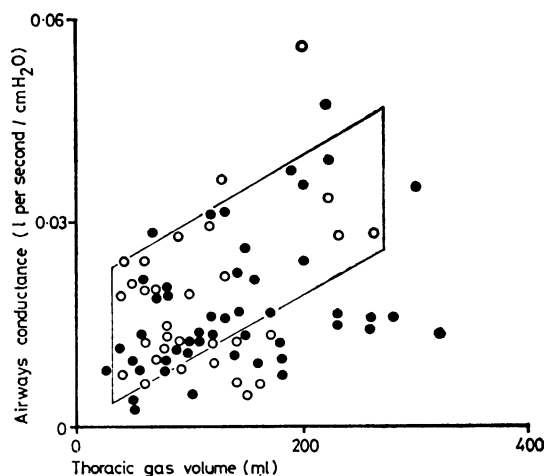


Fig. 4 Relationship of airways conductance and thoracic gas volume (key as Fig. 1).

function which occur during the first year of life, the first year was divided into three 4-month periods before comparing the control and IPPV groups. Mean data are presented in Table 2 and graphically in Figs 1 to 4.

During the first 4 months, apart from a suggestion of low compliance in the IPPV group, there were no demonstrable differences. However, there was a significant difference in lung mechanics between the two groups during the middle 4 months of the first year; TGV was higher, while both dynamic compliance and flow conductance were lower in the IPPV group. The differences in resistance and com-

pliance were present whether normalised for body weight or TGV. There was no difference between the light-for-dates infants and those who were appropriate for dates, within the control group. No differences were discernible during the last 4 months of the first year. Within each age-band the mean body weights of the two groups were similar at the time of testing.

The subgroup of 6 infants (all from the IPPV group) who were readmitted to hospital after the neonatal period with LRTI, had particularly poor lung function compared with the 14 other patients in the IPPV group or with the control infants. Those suffering recurrent LRTI had very significant hyperinflation (mean TGV 37 ml/kg) as well as a reduction in mean specific airways conductance (0.06 per cmH₂O/second) at age 9–12 months, indicating continuing severe airways disease.

Discussion

Perinatal factors. This prospective study was designed to investigate the pulmonary sequelae in survivors of very low birthweight, and was not intended to be an epidemiological study. The selection of admissions to the Hammersmith Hospital Premature Baby Unit was dependent on many factors apart from strictly clinical decisions. Some inborn babies were preselected by early antenatal referral for high-risk pregnancy, while others were *in-utero* transfers of babies with mothers in labour from local hospitals. Infants transferred postnatally from other premature baby units were also preselected by many factors at the referring hospital, apart from the condition of the infant.

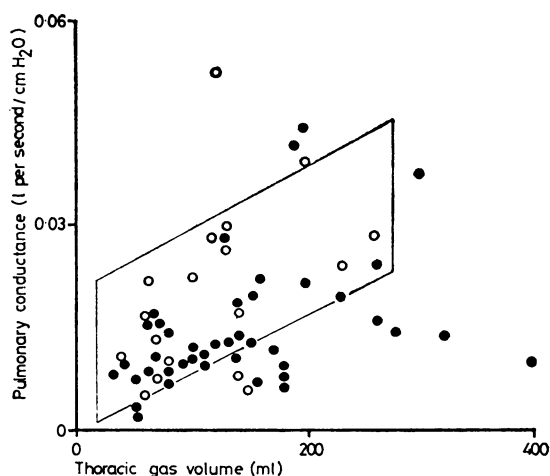


Fig. 3 Relationship of pulmonary conductance and thoracic gas volume (key as Fig. 1).

The selection of a matched control group is clearly important. It would have been inappropriate to use clinical data on the incidence of chest infections from a historically, geographically, or socially different population to compare with that of the present study. Furthermore, normal values of lung mechanics vary considerably between studies, so that comparison with other data could be misleading. Defining the control group as those who required <48 hours' oxygen therapy in practice excluded all those with RDS, although the group did include 2 infants who were briefly mechanically ventilated.

The higher mean gestational age of infants in the control group and the higher proportion of light-for-dates infants, probably accounted for the fairly uneventful respiratory course. The severity of the respiratory failure in the IPPV group can be deduced from the duration of IPPV (median 108 hours) and oxygen therapy (median 258 hours). Although the two groups were matched for birthweight, the higher proportion of light-for-dates infants in the control group could have made it difficult to ascribe differences in sequelae to the effects of RDS or IPPV alone. However, within the control group, there was no difference in normalised lung function between normal and light-for-dates infants.

The incidence of the various complications of pregnancy or labour was not different between the control and IPPV groups. It would appear that premature labour was the common end result of several perinatal factors. No individual factor could be identified specifically as the cause of prematurity or as a possible predisposing factor in chronic respiratory disease in this small group of infants. There were insufficient infants with RDS alone (not requiring IPPV) to be able to distinguish the effects of RDS (or oxygen therapy) from those of IPPV and its complications.

The IPPV group not surprisingly exhibited a higher incidence of nearly all pulmonary complications during the intensive care period and, significantly, tracheobronchial hypersecretion.

Clinical follow-up. The use of the strict criteria for the diagnosis of LRTI (readmission to hospital for lower respiratory tract illness with chest x-ray evidence of acute changes) was necessary to prevent two possible sources of confusion: mild LRTI diagnosed and managed at home, or hospital admission for minor LRTI, causing concern to anxious parents or physicians.

Criteria have been less rigid in many earlier studies, most of which are therefore not directly comparable with this one.^{7 22-26} However, Bryan *et al.*⁵ reported a significantly higher incidence of LRTI in the ventilated survivors of RDS compared with the

non-ventilated, normal preterm group, a finding which matched the present study. The appreciably higher incidence of LRTI in the IPPV group does not however tell us whether RDS was responsible or its treatment.

Among the many symptoms one would normally seek during the course of a routine follow-up, only a weak cry and shortness of breath were particularly noted by the parents of the LRTI group. An abnormal cry, stridor, and abnormal chest movements were the only physical signs significantly present. These results show that many of the symptoms and signs routinely sought at follow-up clinics are probably irrelevant (for example the number of upper respiratory tract infections) while only a few clinical features may be relevant to the identification of those at risk of serious respiratory tract illness during the first year.

Even though there were only 6 infants in the LRTI group, there was a statistically significant association with the male sex, CPAP >24 hours, increased $F_{I_{O_2}}$ >5 days, and IPPV >24 hours. This may suggest that boys are more susceptible to LRTI, but could be a result of their increased susceptibility to RDS and its complications.

Physiological studies. Thoracic gas volume per unit body weight was significantly higher during the middle 4 months of the first year in the IPPV than the control group. This suggests that gas trapping may be a common phenomenon in this group of survivors. There are no directly comparable published data. Stocks *et al.*²⁷ demonstrated no significant difference in TGV between normal preterm infants whether or not ventilated. However, her population of preterm infants had a mean birthweight nearly 1 kg greater than the infants in this study. It is not conceivable that infants of very low birthweight (<1501 g) may suffer more severe lung damage than larger low birthweight infants. Our finding of increased lung volume during the middle 4 months of the first year suggests the presence of continued lung disease, with resolution towards the end of the first year.

The increased lung volume in the IPPV group was presumably secondary to airways disease, as suggested by the significantly low airways and pulmonary conductance during the middle 4 months of the year. Whether these measurements of conductance were corrected for differences in TGV or body weight made no difference to the conclusion. This pattern of changes in lung mechanics persisted into the last 4 months of the year, although the two groups were no longer statistically significantly different. The findings are similar to those of Stocks and Godfrey,¹² applied to larger preterm infants.

Small airways damage may be at least partly responsible, fibroplastic proliferation obstructing small airways having been demonstrated in fatal chronic lung disease.²⁵ The localisation of airways damage to large or small airways awaits the development of more sensitive tests of airways function.

Even during the first 4 postnatal months, C_{dyn} was significantly lower in the IPPV group than in the controls, and the difference persisted into the middle third of the first year. There was no demonstrable difference between the two groups in the last 4 months of the first year, a finding similar to that of other workers.^{5 27-29} Whether the abnormal C_{dyn} was due to a true increase in lung stiffness or was a reflection of uneven regional time-constants remains uncertain in the absence of a satisfactory method for measuring the static pressure/volume curve of the infant lung.

The physiological consequence of disturbed lung mechanics is that ventilated RDS survivors exert more effort for the same effective ventilation than do their normal counterparts. The clinical consequence of disturbed lung function appears to be an increased incidence of severe LRTI in infancy. Indeed, as a group, those children who did suffer significant LRTI during the first year of life had the worst lung function. This group presumably has the greatest risk of long-term sequelae.

Conclusions

For infants <1501 g at birth, the pulmonary prognosis seemed to be good during the first year of life if there was no significant neonatal respiratory illness. Prognosis for those who were ventilated for RDS was less favourable with a significantly higher incidence of LRTI in infancy, and abnormalities of lung mechanics during the middle 4 months of the first year, with a return towards normality by the end of the first year of life for most infants. The only infants with persistently abnormal lung function were those who, having survived severe RDS, had recurrent LRTI in infancy. Their long-term prognosis may be poor.

Early lung mechanics were of limited value in predicting later LRTI. However, neonatal requirement of CPAP for over 24 hours, raised ambient oxygen for longer than 5 days, and IPPV for more than 24 hours, symptoms of shortness of breath and weak cry, and signs of dyspnoea and abnormal cry may be interpreted as warning signs, alerting the attending physician to the increased risk of LRTI in infancy.

We can only speculate on the long-term pulmonary outcome in the absence of any large, controlled prospective study. Certainly radiological changes

may persist for several years,³⁰ while even in the absence of symptoms, subtle functional abnormalities can be detected late into childhood in survivors of severe RDS.³¹ On an even greater time scale, there is evidence to suggest that pulmonary disorders of infancy may have life-long consequences.³²

We thank Action Research—the National Fund for Research into Crippling Diseases, the Sir William Coxen Trust, and the Medical Research Council for financial support.

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Correspondence to Dr M Silverman, Department of Paediatrics, Hammersmith Hospital, Du Cane Road, London W12 OHS.

Received 14 December 1981