Lung function abnormalities at 6 months of age after neonatal intensive care

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Abstract

Respiratory function was studied in 46 preterm infants (median gestational age 28 weeks) at 6 months of age. Respiratory function was assessed by measurement of thoracic gas volume, airways resistance (from which specific conductance was calculated), and functional residual capacity. To determine the effect of the duration of neonatal intermittent positive pressure ventilation (IPPV) on respiratory function, the infants' results were divided into three groups: group A, no IPPV; group B, IPPV for less than seven days; and group C, IPPV for more than seven days. Measurements of thoracic gas volume and functional residual capacity were similar to published reference ranges and there were no significant differences between the three groups. Measurements of airways resistance and specific conductance were higher than published reference ranges (mean airways resistance of group A, 34 cm H₂O/l/sec; B, 34.1 cm H₂O/l/sec, and C, 30.4 cm H₂O/l/sec) but there was no significant difference between the three groups. The 95% confidence intervals of the difference of the means between groups A and B were -6.94 to 6.73 cm H₂O/l/sec and between groups A and C -3.8 to 11.0 cm H₂O/l/sec. Our results suggest that factors other than neonatal ventilation may be more important in the pathogenesis of chronic lung function abnormalities in preterm infants.

Chronic lung damage is a frequent complication of preterm delivery.^{1 2} Such infants have a high mortality and morbidity, with an increased rehospitalisation rate and risk of respiratory infection.³ Many infants wheeze at follow up,³⁻⁵ and lung function abnormalities may be demonstrated during the first year of life.^{6 7}

Several studies have suggested that positive pressure support is particularly important in the pathogenesis of chronic lung disease.⁸ Before 1969 bronchopulmonary dysplasia, the most severe form of chronic lung disease, was rarely seen, although spontaneously breathing infants were often exposed to 100% oxygen. After 1969, however, bronchopulmonary dysplasia was seen and this coincided with the introduction of continuous positive airways pressure.⁹ Bronchopulmonary dysplasia was also described in ventilated infants who had required an oxygen concentration of less than 60%.¹⁰ The level of peak airway pressure used during mechanical ventilation seemed to be an important determinant of lung damage. Taghizadeh and Reynolds in 1976

reported a highly significant association between the most serious changes of bronchopulmonary dysplasia and use of peak inspiratory pressures in excess of 35 cm H₂O.¹¹ Moreover, the incidence of bronchopulmonary dysplasia was reduced by limiting the peak inspiratory pressure to 35 cm H₂O; this change occurred despite inspired oxygen concentrations during ventilation that were often above 80%. Stocks and Godfrey further incriminated positive pressure support by demonstrating lung function abnormalities at follow up among infants who had received artificial ventilation, but not among those who had been treated with other forms of respiratory support.¹²

The studies implicating positive pressure support in the pathogenesis of chronic lung damage were performed over a decade ago. At that time slow ventilator rates with long inspiratory times were employed during mechanical ventilation. High frequency positive pressure ventilation¹³ and patient triggered ventilation^{14 15} are now more frequently used; both modes of ventilation incorporate short inspiratory times and fast frequencies. A further advance in neonatal ventilation over the 10 year period has been in improvements in the ventilators themselves.¹⁶ Changes in the ventilators and modes of neonatal ventilation may have reduced the damaging effect of positive pressure support.

In this study we have tested the hypothesis that, in 1990, neonatal ventilation is less important in the pathogenesis of chronic lung damage. As an index of chronic lung damage we have measured lung function at 6 months of age. To assess the effect of neonatal ventilation we have compared the lung function results of infants who required no neonatal ventilation with those who were ventilated and also between two groups of preterm infants who required different durations of neonatal ventilation. If our hypothesis is correct then we should expect similar lung function results between infants with and without neonatal ventilation and between infants ventilated for different durations.

Patients and methods

PATIENTS

Forty six preterm low birthweight infants were enrolled into the study and reviewed at 6 months of age (range 23-25 weeks). The infants had a median (range) birth weight of 1210 (506-1900) g and median (range) gestational age of 28 (23-34) weeks. All the infants who had respiratory problems had suffered from respiratory

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distress syndrome. All but four of the infants had required some form of respiratory support either an increase in the inspired oxygen concentration or mechanical ventilation. Infants requiring mechanical ventilation had been ventilated at rates of between 60 and 120 breaths per minute and had an inspiratory to expiratory (I:E) ratio of 1:1.2. Mechanical ventilation was started in the labour suite if the infant made inadequate respiratory efforts or during the course of the infant's illness if either a respiratory acidosis developed ($\text{pH} < 7.25$) or the infant had frequent minor or a major apnoea. Infants with severe bronchopulmonary dysplasia who were still oxygen dependent at 6 months of age were excluded from the study.

Methods

The infants were seen in the paediatric respiratory laboratory at 6 months of age. Their medical history was taken, height and weight measured, and the child examined. Lung mechanics, thoracic gas volume, airways resistance, and functional residual capacity were then measured after sedation. Specific conductance was calculated from thoracic gas volume and airways resistance. The infant was sedated with oral chloral hydrate (100 mg/kg) and lung mechanics measured during quiet sleep in the supine position.

Thoracic gas volume and airways resistance were measured using a whole body plethysmograph. The infant breathed through a face mask, which was connected to the rebreathing 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 rebreathing system to avoid box pressure changes due to the heating and cooling of respired gas. Thoracic gas volume was measured at the end of a normal inspiration and airways resistance at two thirds of maximum inspiratory flow by the classical techniques of Dubois *et al* suitably modified for infants.^{17 18} Thoracic gas volume was calculated from five breaths during occlusion and at least five separate occlusions were made. Airways resistance was calculated from at least 10 breaths. All measurements (thoracic gas volume and airways resistance) were corrected for the apparatus dead space (15 ml) and resistance (8 cm $\text{H}_2\text{O/l/sec}$, measured at flows of between 5 and 15 l/minute). Traces were analysed blind to clinical details.

After completion of the measurements of the thoracic gas volume and airways resistance the infant's face mask was connected to a spirometer (Gould Pulmonet III) for the measurement of functional residual capacity. The spirometer has an internal carbon dioxide absorber and an adjustable oxygen supply and has a total volume of six litres. The water sealed spirometer incorporates a digital display of functional residual capacity, which was recorded on the trace at 15 second intervals. Equilibration was assumed to have occurred when there had been no change in the functional residual capacity readout over a 30 second period; all the traces

were coded and then analysed blind to clinical details. From the trace the equilibration point and expiratory level were determined and functional residual capacity calculated. The results were then converted to body temperature, pressure, and saturation (BTPS) conditions.

The reproducibility of the measurement of thoracic gas volume and airways resistance was determined in 16 children of similar gestational and postnatal age to the study population. Calculation of thoracic gas volume and airways resistance was as described above.

The coefficient of variation calculated from measurements of thoracic gas volume and airways resistance performed before and after infants had been removed and returned to the body plethysmograph was 6% for thoracic gas volume and 9% for airways resistance. To assess the reproducibility of the measurement of functional residual capacity, two separate measurements were made in 20 children of similar gestational and postnatal age to the study population. The coefficient of variation of these measurements was calculated as 7.3%.

STATISTICAL ANALYSIS

To assess the effect of ventilation and the duration of mechanical ventilation (IPPV) on lung function the infants were divided into three groups: no IPPV (group A), IPPV less than seven days (group B), and IPPV greater than seven days (group C). The clinical characteristics of the three groups are shown in table 1. Lung function was then compared between the three groups and differences assessed for significance using the Wilcoxon rank sum test. The confidence intervals were calculated with the appropriate p value from the standard error of the difference between the means of groups A and B and groups A and C.

TRIAL SIZE

We had demonstrated the mean (SD) resistance of a previous group of 20 consecutive preterm infants studied at 6 months of age to be 35 (7.5) cm $\text{H}_2\text{O/l/sec}$. Using these results, 12 patients would be required in each group to detect a difference in resistance of 10 cm $\text{H}_2\text{O/l/sec}$ between groups with 85% power at the 5% level.

Ethical permission for this study was granted by the King's College Hospital ethics committee.

Results

No significant difference in functional residual capacity, thoracic gas volume, specific conductance, or airways resistance was demonstrated

Table 1 Clinical characteristics of the three groups of infants divided according to the duration of ventilation. Results are median (range)

	Birth weight (g)	Gestational age (weeks)
Group A (n=12)	1386 (1100-1800)	29.5 (27-32)
Group B (n=22)	1190 (516-1900)	29 (25-34)
Group C (n=12)	980 (506-1512)	27 (23-32)

Table 2 Lung function data related to the duration of neonatal ventilation. Results are means and mean differences with 95% confidence intervals

	Airways resistance (cm H ₂ O/l/sec)	Functional residual capacity (ml/kg)	Thoracic gas volume (ml/kg)	Specific conductance (sec ⁻¹ /cm H ₂ O)
Group A	34.00	28.82	40.69	0.135
Group B	34.07	27.62	36.23	0.148
Group C	30.43	33.95	37.32	0.167
B-A	+0.07	-1.20	-4.46	+0.013
	(-7.35 to +7.49)	(-5.73 to +3.33)	(-10.55 to +1.62)	(-0.031 to +0.056)
C-A	-3.57	+5.13	-3.38	+0.032
	(-11.48 to +4.35)	(-0.29 to +10.55)	(-8.99 to +2.24)	(-0.020 to +0.083)

Table 3 Results of infants not ventilated in the neonatal period (group A)

Case No	Birth weight (g)	Gestational age (weeks)	Oxygen duration in neonatal period	Weight at time of measurement (kg)	Airways resistance (cm H ₂ O/l/sec)	Functional residual capacity (ml/kg)	Thoracic gas volume (ml/kg)	Specific conductance (sec ⁻¹ /cm H ₂ O)
1	1312	28	0	5.60	22.0	25.5	34.3	0.237
2	1440	28	10 hours	5.40	32.0	24.4	53.7	0.108
3	1426	29	0	6.48	39.0	32.3	40.1	0.099
4	1346	28	1 hour	6.35	39.0	24.3	33.5	0.121
5	1270	30	0	6.42	43.0	41.4	45.2	0.080
6	1780	32	4 hours	7.28	19.0	30.0	33.0	0.219
7	1800	31	2.5 days	6.80	28.0	*	29.7	0.177
8	1640	31	1 day	6.00	42.0	*	42.7	0.107
9	1320	31	1.5 days	6.85	43.0	27.0	34.5	0.099
10	1100	28	5 days	4.20	24.0	35.0	50.0	0.198
11	1210	27	0	6.60	33.0	21.7	51.0	0.089
12	1500	30	0.5 day	6.15	44.0	26.6	40.6	0.091

*Results are not available.

No infant was admitted to hospital during the first six months.

Table 4 Results of infants ventilated for less than seven days (group B)

Case No	Birth weight (g)	Gestational age (weeks)	Oxygen duration after IPPV (days)	Ventilation (days)	No of admissions to hospital (first six months)	Weight at time of measurement (kg)	Airways resistance (cm H ₂ O/l/sec)	Functional residual capacity (ml/kg)	Thoracic gas volume (ml/kg)	Specific conductance (sec ⁻¹ /cm H ₂ O)
13	1900	34	2	5	1 (viral infection)	5.44	42.0	25.5	49.0	0.060
14	1170	29	6	5	—	6.25	49.0	26.0	46.7	0.060
15	1200	28	1	2	—	5.60	50.5	27.3	45.0	0.079
16	1210	28	0.5	1	—	7.30	25.0	24.2	29.9	0.183
17	1180	27	1	3	1 (bronchiolitis)	7.00	23.0	26.0	30.7	0.202
18	876	27	2	5	—	7.50	28.0	26.0	33.6	0.142
19	1274	32	1	4	—	7.05	27.0	25.1	32.4	0.163
20	816	25	0.4	4	—	7.55	23.0	30.6	40.0	0.144
21	1730	32	1.5	3	—	7.03	25.0	28.3	53.0	0.108
22	1778	29	0.1	1.3	—	6.90	40.0	28.0	28.7	0.126
23	516	29	0.1	2	1 (chest infection)	4.99	33.0	37.5	46.9	0.129
24	840	26	1	2	—	4.10	22.0	28.9	39.0	0.284
25	1554	29	0	2	—	6.95	52.0	23.7	25.0	0.111
26	1018	28	2	6	—	6.60	52.0	28.0	28.3	0.104
27	996	29	1.5	2.5	—	5.44	25.0	23.5	25.5	0.288
28	1300	33	2	0.5	—	5.10	45.0	38.5	42.9	0.101
29	1430	31	0.1	0.5	—	6.00	27.1	18.3	34.3	0.202
30	1070	28	0.2	0.5	—	7.46	31.0	20.0	31.5	0.137
31	1279	30	1.5	0.3	—	6.90	31.0	41.0	45.6	0.102
32	720	27	1.5	0.9	—	5.58	28.0	31.5	32.2	0.198
33	1138	27	0.8	0.8	—	5.10	46.0	27.4	27.8	0.153
34	1300	29	0	0.3	—	7.60	25.0	30.4	29.3	0.179

Table 5 Results of infants ventilated for more than seven days (group C)

Case No	Birth weight (g)	Gestational age (weeks)	Oxygen duration after IPPV (days)	Ventilation (days)	No of admissions to hospital (first six months)	Weight at time of measurement (kg)	Airways resistance (cm H ₂ O/l/sec)	Functional residual capacity (ml/kg)	Thoracic gas volume (ml/kg)	Specific conductance (sec ⁻¹ /cm H ₂ O)
35	810	26	6	11	1 (chest infection)	3.80	28.0	37.0	44.5	0.121
36*	886	26	36	42	—	5.40	21.0	34.6	37.6	0.160
37	685	24	6	14	1 (chest infection)	4.73	36.0	34.1	36.6	0.113
38	1074	28	4	11	1 (chest infection)	5.10	23.0	25.5	41.2	0.153
39	1120	27	2	8	—	6.30	26.0	36.0	35.8	0.170
40	1468	32	2	8	—	6.17	30.0	39.2	39.2	0.138
41*	506	23	6	28	1 (chest infection)	3.75	24.0	27.0	41.0	0.271
42*	1444	27	11	20	—	6.27	19.2	22.8	25.3	0.328
43*	1512	29	5	23	—	6.12	27.0	40.8	40.0	0.160
44	1092	30	5	8.5	—	3.94	45.0	41	39.1	0.144
45	682	24	2	10	1 (febrile convulsion)	6.20	35.0	32.1	35.1	0.130
46	836	29	3	9	1 (bronchiolitis)	5.25	51.0	33.5	32.4	0.115

*Oxygen dependent for 28 days or more.

between the three groups of infants regardless of the duration of neonatal ventilation (tables 2, 3, 4, and 5). The 95% confidence intervals of the difference of the means of groups A (34 cm H₂O/l/sec) and B (34.1 cm H₂O/l/sec) are -6.49 to 6.73 cm H₂O/l/sec and between groups A (34 cm H₂O/l/sec) and C (30.4 cm H₂O/l/sec) are -3.8 to 11.0 cm H₂O/l/sec.

Discussion

We report lung function measurements of infants of 6 months of age, rather than those of school age or older, as we thought it important to audit current ventilation practices. Our results could therefore be used, if important abnormalities were demonstrated, to influence that current practice. We investigated very preterm infants and compared our results with those in earlier reports. Our study audits a complete cohort of such preterm infants excluding only those with bronchopulmonary dysplasia who were oxygen dependent at 6 months of age. Our study population were ventilated using modern ventilators by high frequency positive pressure ventilation (IPPV). In this cohort we have been able to report a number of indices of lung function, thoracic gas volume, airways resistance, and functional residual capacity.

Airways resistance measurements in the 46 infants included in the present study showed a slightly greater interindividual variability (SD 9.5 cm H₂O/l/sec) than we had demonstrated in a previous group of 20 consecutive preterm infants, whose data we used to calculate the trial size. As the increase in variability was only small our trial size remained appropriate. Enrolling 12 patients in each group still gave us 75% power at the 5% level to detect a difference in resistance of 10 cm H₂O/l/sec between groups and 85% power at the 5% level to detect a difference of 12 cm H₂O/l/sec.

In the present study we have not included a control group as it was felt unjustifiable to sedate healthy 6 month old infants to perform plethysmographic measurements to establish a normal range. Indeed, one may also query if such infants' results would be appropriate to use as a reference range for comparison with the results of a very preterm population. Many published reference ranges relate only to term infants or a mixture of preterm and term infants.¹⁹ As a consequence functional residual capacity, measured by dilution methods, is reported to vary from 21.5 ml/kg to 37 ml/kg.¹⁹ The mean data of the present study fall within this wide range. For each measurement there was a wide scatter of results. This may reflect differences in our patients regarding their gestation at birth and severity of their respiratory illness.

We have not demonstrated a significant difference in functional residual capacity, thoracic gas volume, or airways resistance in infants ventilated for different lengths of time nor between ventilated and non-ventilated infants. Our measurements of thoracic gas volume are very similar to those of Stocks and Godfrey¹² and previously published reference ranges.^{20 21} Our airways resistance results in all three groups of

infants were similar to Stocks and Godfrey's ventilated infants but higher than their non-ventilated infants and the published reference range.²⁰ Our technique of measurement and its reproducibility was very similar to that used previously,¹² and the number of patients we enrolled was twice that included in the earlier study.¹² We therefore think that we are reporting a true difference in the findings of the two studies. The high airways resistance of all our three groups and the failure to demonstrate a difference in airways resistance between the groups, regardless of the need for neonatal ventilation, may be explained by the immaturity of the patients we examined.¹² Two other recent reports have failed to confirm an association between neonatal ventilation and lung function abnormalities.^{22 23} Both groups reported that poor airway function at school age was independent of neonatal respiratory illness and closely associated with low birth weight.^{22 23} Further evidence to support this association was our finding of abnormal airways resistance in a group of four infants who, although requiring no form of respiratory support in the neonatal period, had been born very preterm between 27 and 30 weeks of gestational age.

Plethysmography cannot be performed on oxygen dependent infants thus, in this study, infants with severe bronchopulmonary dysplasia had to be excluded. Our results cannot therefore represent a complete audit of neonatal ventilation. All five infants with severe bronchopulmonary dysplasia excluded from our study were born before 26 weeks completed gestation and had many complications such as patent ductus arteriosus, infection, and pulmonary air leak. Until a much larger group of these infants can be collected and studied it will not be possible to determine the contribution of a single factor such as neonatal ventilation in the pathogenesis of severe chronic lung damage. All other infants, however, consecutively cared for on our unit, were included in this study. The similarity of results from our non-ventilated and ventilated infants and lack of difference in airways resistance regardless of the duration of ventilation suggests that factors other than neonatal ventilation may be more important in the pathogenesis of chronic lung function abnormalities.

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Hyperactivity

Article number 3861d of the Archivist Transatlantic Guide runs as follows: 'doctors who say "tom-ay-toe" frequently diagnose hyperactivity whilst those who say "tom-ar-toe" rarely do'. This basic rule of medical conduct has never, to my mind, been explained very convincingly on the basis of attitudinal and psychosocial differences between the two nations. Most British paediatricians take in such facts as that 6% of all children in Baltimore County are given stimulant drugs for hyperactivity¹ with more than a touch of incredulity, not to say apprehension. Pathogenesis, too, tends to be viewed differently, more emphasis being given to biological factors in America and to psychosocial determinants in Britain.

Recent work at the National Institutes of Health in Bethesda (Zametkin *et al.*, *New England Journal of Medicine*, 1990; 323:1361-6) will have revived interest in biological mechanisms. Using positron emission tomography cerebral glucose metabolism was studied in 50 normal adults and in 25 adults who had been diagnosed as hyperactive in childhood, still had symptoms, and had hyperactive children. A significant reduction in overall cerebral glucose metabolism was found in the hyperactive subjects and the reduction was greatest in the premotor cortex and the superior prefrontal cortex, areas of the brain known to be concerned with control of attention and motor activity.

A symptom such as hyperactivity is bound to be multifactorial in its origins. People who are still hyperactive as adults and who also have hyperactive children are obviously a select group, but the demonstration of changed cerebral glucose metabolism is of great interest. It is not known whether these changes are primary or secondary or whether they occur in children as well as in adults. Neither is it known whether drug treatment would reverse the changes. Clearly there is much to elucidate but it seems a promising path to follow.

ARCHIVIST

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