Eur J Pediatr (1998) 157: 336–339

PNEUMOLOGY

V. Kavvadia · A. Greenough · G. Dimitriou · Y. Itakura

Lung volume measurements in infants with and without chronic lung disease

Received: 5 May 1997 / Accepted in revised form: 29 September 1997

Abstract Infants born prematurely who develop chronic lung disease (CLD) have airways obstruction and hence may have low lung volume. The aim of this study was to test that hypothesis and ascertain whether the nature of the comparison control group influenced the results. Sixteen infants who were oxygen dependent for more than 28 days (CLD) and eight infants without CLD had measurements of functional residual capacity (FRC) at 14 and 28 days. The 16 CLD infants consisted of eight less than 27 weeks gestational age (group A) and eight greater than 26 weeks gestational age (group B). The eight infants without CLD (group C) were each matched for gestational age and gender to infants in group B. Group A compared to group C had lower FRCs both at 14 days (median 18 ml/kg vs 27 ml/kg, $P < 0.01$) and 28 days (median 20 ml/kg vs 26 ml/kg, $P < 0.05$), but group A differed from group C with respect to both gestational age ($P < 0.01$) and birth weight ($P < 0.01$). The FRC results of group B were lower than those of their matched controls (group C) only at 28 days (median 22 vs 26 ml/kg, $P < 0.05$). Overall, the FRC results at 14 and 28 days correlated significantly with the duration of oxygen and ventilator dependence and weakly with gestational age.

Conclusion These results support the hypothesis that FRC results are lower in infants with CLD compared to those without CLD when measured in the neonatal period and emphasize the importance of an appropriate control group. Measurement of lung volume may facilitate assessment of the response to therapies for CLD.

Key words Prematurity · Functional residual capacity · Chronic lung disease

Abbreviations *CLD* chronic lung disease · *FRC* functional residual capacity · *RDS* respiratory distress syndrome

Introduction

Neonatal chronic lung disease (CLD) is an important problem; affected babies have a prolonged NICU stay [13] then after discharge suffering troublesome respiratory symptoms [1, 19, 21] and even requiring re-admission for chest related problems [16]. A number of potential therapies are available and a method of measurement which would quantitatively assess the infant's response to such treatments would be extremely useful, as it could give an early indication of benefit as well as perhaps facilitating elucidation of the mechanism of the response. In respiratory distress syndrome (RDS), a disease associated with atelectatic low lung volume, assessment of functional residual capacity (FRC) has demonstrated both the speed and magnitude of response to different types of surfactant [6, 12]. Infants with CLD as a result of airways obstruction, may also have a low

V. Kavvadia · A. Greenough · G. Dimitriou · A. Greenough (✉)
Dept of Child Health,
King's College Hospital,
London SE5 9RS, UK,
Tel.: +44 171 346 3037,
Fax: +44 171 924 9365

lung volume. Affected infants, however, differ in many respects to similarly aged infants without CLD, for example regarding gestational age [5]. The aim of this study was to determine whether infants with compared to those without CLD have lower FRCs during the neonatal period and if the nature of the control group influenced the results.

Patients and methods

Methods

Infants with birth weight less than 2.0 kg were prospectively recruited. Infants were selected if their parents were local residents, as this meant they would remain on the NICU until discharge home and hence their long-term respiratory outcome would be known. Measurements of FRC (see below) were made at 14 and 28 days.

Lung volume was assessed by measurement of FRC using a helium gas dilution technique [7]. Infants were measured in the supine position. A specially designed infant circuit with a circuit volume of 95 ml was used [11]; the measurement technique has been previously described in detail [23]. In brief, the FRC system contained a rebreathing bag, the system reservoir, enclosed in an airtight cylinder. During the measurement, spontaneously breathing infants breathed through a face mask which was connected to the rebreathing bag via a three-way valve. For ventilated infants, the endotracheal tube was connected to the rebreathing bag via the three-way valve; the ventilator was also connected to the three-way valve and, via a connection from the valve, to a side port on the cylinder. Thus it was possible for the infant to be ventilated directly or, once the position of the three-way valve was changed, to breathe from the rebreathing bag whilst receiving positive pressure support by changes in pressure within the cylinder resulting in compression of the rebreathing bag. The helium analyser (Equilibrated Biosystems Inc, Series 7700, Melville, NY) had a digital display which was recorded prior to and at 15 s intervals during the measurement. Equilibration was assumed when there was similar helium concentration over a 30 s interval. The initial and equilibration helium concentrations were used in the calculation of FRC. FRC results were corrected for oxygen consumption (assumed to be 7 ml/kg/min [15]) and to body temperature under pressure saturated conditions. FRC was estimated twice in each infant on each occasion, with an interval of 10 min between measurements. The FRC was expressed as the mean of the paired measurements and related to body weight. The coefficient of repeatability of the measurement had previously been determined to be 5.7 ml/kg [8], the coefficient of repeatability was calculated according to the method of Bland and Altman [3] and is greater than 95% of the differences between the paired measurements [4].

Analysis

Three groups were retrospectively identified:

1. Group A: consecutive infants less than 27 weeks of gestational age who developed CLD.
2. Group B: infants of at least 27 weeks gestational age who developed CLD and could be matched for gestational age and gender with infants who did not develop CLD (i.e. group C).
3. Group C: infants who did not develop CLD (non-CLD).

Differences between groups were assessed for statistical significance using the Kruskall Wallis, Mann Whitney or chi-square test, as appropriate. The relationships of FRC results at 14 and 28 days to the duration of ventilator and oxygen dependency and gestational age were assessed by calculation of Spearman's correlation coefficients.

Patients

Twenty-four infants were studied (Table 1). All mothers and babies followed the routine policies of the antenatal clinic and NICU. In particular, mothers received antenatal steroids if delivery was anticipated prior to 33 weeks of gestation and there was no evidence of systemic infection. Surfactant replacement therapy was given if the infant was fully ventilated in an increased inspired oxygen concentration and had a chest radiograph appearance compatible with RDS; the first dose usually being given within 12 h of birth and the second 12 h later. During mechanical ventilation infants received a maximum of 3 cm H_2O PEEP and were ventilated through shouldered endotracheal tubes. Infants received postnatal dexamethasone only if they remained oxygen dependent beyond 1 week of age without improvement in their respiratory status over the previous 48 h; infection, patent ductus arteriosus and gastro-oesophageal reflux having been excluded. Diuretics were only given if infants were found to be fluid overloaded or had evidence of heart failure.

Group A differed significantly with respect to gestational age and birth weight to groups B ($P < 0.01$, $P < 0.02$ respectively) and C ($P < 0.01$, $P < 0.01$, respectively). The use of antenatal steroids did not differ significantly between the three groups, but more of group B compared to group A received surfactant ($P < 0.01$). A significantly greater proportion of group A had received postnatal steroids than group C ($P < 0.01$), but not group B. The duration of ventilation was significantly longer in group A than groups B ($P < 0.05$) and C ($P < 0.01$), and in group B compared to group C ($P < 0.05$). The duration of oxygen dependency was longer in group A than group B (non-significant) and group C ($P < 0.01$) and in group B compared to group C ($P < 0.01$). The proportion of infants oxygen dependent beyond 36 weeks postconceptional age differed significantly only between groups A and C ($P < 0.01$).

Serial FRC measurements were approved by the Kings College Hospital Ethics Committee.

Table 1 Comparison of infant characteristics and FRC results in the three groups. Data expressed as median (range) or *n* (%)

	CLD <27 weeks Group A	CLD ≥27 weeks Group B	non-CLD Group C
n	8	8	8
Gestational age (weeks)	25 (24–26)	28 (27–30)	28 (27–30)
Birth weight (g)	724 (584–900)	1010 (716–1218)	1115 (824–1558)
Antenatal steroids	7 (87.5)	4 (50)	7 (87.5)
Postnatal surfactant	3 (37.5)	8 (100)	3 (37.5)
Diuretics	4 (50)	2 (25)	0
Steroids	7 (87.5)	6 (75)	0
Duration of intermittent positive pressure ventilation (days)	25 (9–51)	8 (6–43)	4 (1–11)
Duration of O_2 dependence (days)	72 (47–150)	43 (30–250)	12 (2–17)
O_2 dependence at 36 weeks postconceptional age	6 (75)	3 (37.5)	0

Results

The FRC results at days 14 and 28 were significantly lower in group A compared to group C (median 18 ml/kg, range 14–28 vs 27 ml/kg, range 20–34, $P < 0.01$; median 20 ml/kg, range 10–28 vs median 26 ml/kg, range 22–36, $P < 0.05$) respectively but in group B compared to group C only at 28 days (median 22 ml/kg, range 10–34, $P < 0.05$) and not at 14 days (25 ml/kg, range 13–30, non-significant) (Fig. 1).

In the study population overall, the FRC results at 14 days had a significant inverse correlation both with the duration of ventilation (intermittent positive pressure ventilation) ($r = -0.67$, $P < 0.01$) and oxygen dependency ($r = -0.65$, $P < 0.01$). Similarly at 28 days, FRC inversely correlated both with ventilator ($r = -0.56$, $P < 0.01$) and oxygen dependency ($r = -0.49$, $P < 0.02$). There was a relatively weak correlation between gestational age at birth and the FRC results both at 14 days ($r = 0.49$, $P < 0.05$) and 28 days ($r = 0.27$, non-significant).

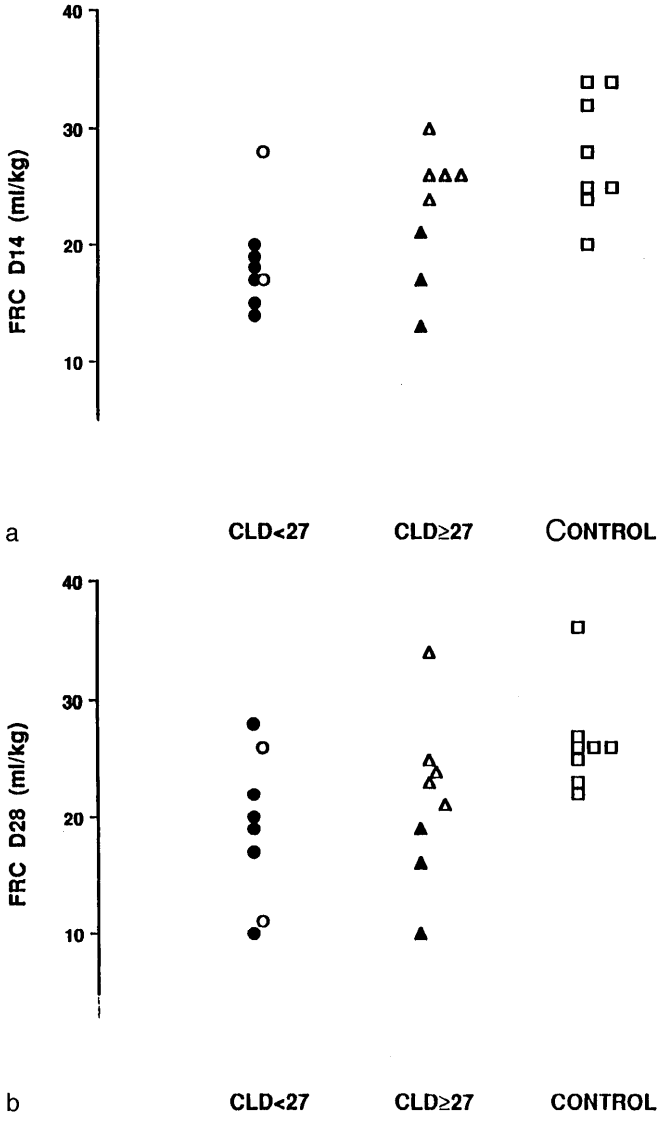

Fig. 1 Comparison of FRC results at 14 and 28 days in infants. □ no CLD, △ ○ oxygen dependent at 28 days, ▲ ● oxygen dependent at 36 weeks PCA

Discussion

These results support the hypothesis that infants with CLD, defined as oxygen dependency beyond 28 days, tended to have lower lung volumes. Similar trends occurred even when the more stringent definition of CLD was used [22], that is oxygen dependency beyond 36 weeks postconceptional age (Fig. 1). There are a number of possible explanations for the results. We assessed lung volume by measurement of FRC using a helium gas dilution technique. Particularly at 28 days, a larger proportion of groups B and C tended to be non-ventilated than group A. In the intubated infants the anatomical dead space is "by-passed", but as this is approximately 3 ml/kg [20] this would account for only a proportion of the difference in lung volume we document between groups A and C. During mechanical ventilation all patients were supported additionally by PEEP which may have lessened any differences we saw between ventilated and non-ventilated infants and hence groups A and C. Similarly leaks around the endotracheal tube could have led us to over-estimate lung volume in the ventilated infants. We feel confident, however, that the likelihood of error from such a source was minimal as previous measurements of tidal volume using shouldered endotracheal tubes have shown little evidence of leak [17]. In addition, equilibration of the helium was assumed only when there was a similar concentration of helium over a 30 s interval. A gas dilution technique measures only the functional lung volume that is only the parts of the lung which are in contact with the inhaled gas and in which gas mixing can occur. Infants with CLD have been demonstrated to have a high airway resistance in the first weeks of life [14], which would impair gas mixing and hence a low lung volume would be recorded. That hypothesis is supported by the finding that the infants most severely affected, that is those who remained oxygen dependent beyond 36 weeks post conceptional age, tended to have the lowest lung volumes (Fig. 1). An alternative explanation is that the reduced alveolar and small airway space consequent upon disseminated atelectasis and alveolar influx of fluid found in RDS [10] may persist in infants with CLD.

Interestingly, the median FRC of all of the infants with CLD only differed significantly from the controls at 28 days, whereas at 14 days significant differences only existed between the more immature infants and the controls. This suggests factors other than CLD affect FRC. We demonstrated that FRC had an inverse correlation with the duration of ventilation and oxygen dependence, but also directly correlated with gestational age. Our results thus emphasize the importance of using

gestational age matched controls if the results of lung volume measurements are to be appropriately interpreted in a prematurely born population. Relatively few of the very immature group had received surfactant therapy, which may reflect uncertainly regarding its efficacy in such a population. Surfactant replacement therapy has been shown to improve lung function even after the perinatal period [2], thus differences in surfactant usage may explain the higher FRC at 14 days in the "mature" compared to the "immature" infants with CLD.

Postnatal steroid use was restricted exclusively to the infants who developed CLD. Data from animal studies [18] have highlighted postnatal arrest of lung growth after administration of corticosteroids. Our results could be interpreted as demonstrating an association between lower lung volume and postnatal steroid use, but it should be emphasized that the results are not from a randomized trial. Nevertheless we would suggest this merits further investigation particularly as systemic rather than inhaled therapy appears more effective [9].

Infants who are chronically oxygen dependent, by definition, remain hypoxic in air. The present data suggest a mechanism for this abnormality, that is affected infants have a low functional lung volume or at least impaired gas mixing probably due to an increased airways resistance. Our results indicate that measurement of FRC might facilitate assessment of the response of therapies directed at neonatal CLD.

Acknowledgements Dr Kavvadia is and Dr G. Dimitriou was supported by a grant from the South Thames Regional Health Authority. Dr Itakura, from the Department of Paediatrics, Saitama Medical Centre, Saitama, Japan, was supported on the King's College Fellowship Programme by a grant from SLE Ltd, Croydon. We are most grateful for Professor N. Beratis' support and to Ms S. Williams for secretarial assistance. Equipment for this study was funded by a grant from the Royal Society.

References

1. Abbasi S, Sivieri E, Bowen FR, et al (1989) Pulmonary outcome of infants with respiratory distress and bronchopulmonary dysplasia. Pediatr Res 25:1781(A)
2. Bhutani VK, Abbasi S, Long WA, Gerdes JS (1992) Pulmonary mechanics and energetics in preterm infants who had RDS treated with synthetic surfactant. J Pediatr 120:518–524
3. Bland JM, Altman DG (1986) Statistical methods for assessing agreement between two methods of clinical measurement. Lancet:i307–310
4. British Standards Institution (1979) Precision of test methods. 1. Guide for the determination and reproducibility of a standard method (BS 5497, part 1). British Standards Institution, London
5. Corcoran JD, Patterson CC, Thomas PS, Halliday HL (1993) Reduction in the risk of bronchopulmonary dysplasia from 1980–1990: results of a multivariate logistic regression analysis. Eur J Pediatr 152:677–681
6. Cotton RB, Olsson T, Law AB, et al (1993) The physiological effects of surfactant treatment on gas exchange in newborn premature infants with hyaline membrane disease. Pediatr Res 34:495–501
7. Dimitriou G, Greenough A (1995) Early measurement of functional residual capacity – a useful discriminator of neonatal respiratory disease severity. Physiol Meas 40:1–6
8. Dimitriou G, Greenough A (1995) Measurement of lung volume and optimization of oxygen during high frequency oscillation. Arch Dis Child 72:F180–F183
9. Dimitriou G, Greenough A, Giffin FJ, Kavvadia V (1997) Inhaled versus systemic steroids in chronic oxygen dependency in preterm inants. Eur J Pediatr 156:51–55
10. Edberg KE, Sandberg K, Silberberg A, Ekström-Jodal B, Hjalmarson O (1991) Lung volume, gas mixing and mechanics of breathing in mechanically ventilated very low birthweight infants with idiopathic respiratory distress syndrome. Pediatr Res 30:496–500
11. Fox WW, Schwartz JG, Shaffer TH (1979) Effects of endotracheal tube leaks on functional residual capacity determination in intubated neonates. Pediatr Res 13:60–64
12. Goldsmith LS, Greenspan JS, Rubenstein D, Wolfson MR, Shaffer TH (1991) Immediate improvement in lung volume after exogenous surfactant: alveolar recruitment after distension. J Pediatr 119:424–428
13. Greenough A, Hird MF, Gamsu HR (1991) Home oxygen therapy following neonatal intensive care. Early Hum Dev 26:29–35
14. Greenspan JS, Abbasi S, Bhutani VK (1988) Sequential changes in pulmonary mechanics in the very low birthweight (< 1000 g) infants. J Pediatr 113:732–737
15. Hey EN (1969) The relation between environmental temperature and oxygen consumption in the newborn baby. J Physiol 200:589–603
16. HiFi Study Group (1990) High frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants: assessment of pulmonary function at 9 months of corrected age. J Pediatr 116:933–941
17. Hird MF, Greenough A, Gamsu HR (1990) Gas trapping during high frequency positive pressure ventilation using conventional ventilators. Early Hum Dev 22:51–56
18. Massaro D, Teich N, Maxwell S, et al (1985) Postnatal development of alveoli: regulation and evidence for a critical period in rats. J Clin Invest 76:1297–1305
19. Mayes L, Perkett E, Stahlman MT (1983) Severe bronchopulmonary dysplasia: a retrospective review. Acta Paediatr Scand 72:725–733
20. Numa AH, Newth CJ (1996) Anatomic dead space in infants and children. J Appl Physiol 80:1485–1489
21. Sauve RS, Singhal N (1985) Long term morbidity of infants with bronchopulmonary dysplasia. Pediatrics 76:725–733
22. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM (1988) Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 82:527–532
23. Yüksel B, Greenough A, Chan V, Ross-Russell RI (1993) Comparison of helium dilution and nitrogen washout measurements of functional residual capacity in premature infants. Pediatr Pulmonal 16:197–200