Diminished lung function, RSV infection and respiratory morbidity in prematurely born infants

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Abstract

Objective: Diminished lung function appears to be a risk factor for RSV infection/bronchiolitis in term born infants. We aimed to determine if diminished lung function prior to neonatal unit discharge was associated with subsequent symptomatic RSV lower respiratory tract infection (LRTI) and respiratory morbidity in prematurely born infants.

Design: Prospective observational study.

Setting: Tertiary neonatal intensive care unit

Patients: Thirty nine infants, median gestational age 28 (range 23-31) weeks, 20 had bronchopulmonary dysplasia.

Interventions: Lung function (compliance and resistance of the respiratory system (Crs and Rrs) and functional residual capacity (FRC)) was measured on the neonatal unit at 36 weeks post menstrual age (PMA). Following neonatal unit discharge, nasopharyngeal aspirates were obtained on every occasion, at home or in hospital, an infant had a LRTI. RSV was identified by immunofluorescence and/or culture.

Main outcome measures: RSV positive LRTI and respiratory morbidity (cough and wheeze at follow up)

Results: The 15 infants who suffered a symptomatic RSV LRTI had a higher mean Rrs (p=0.01) and suffered more wheeze (p=0.04) at follow up than the rest of the cohort. Regression analysis demonstrated that a high Rrs was significantly associated with a symptomatic RSV LRTI (p=0.037) and significant factors for cough were a high Rs (p=0.002) and a symptomatic RSV LRTI (p<0.001) and for wheeze were a high Rs (p<0.001).

Conclusion: Prematurely born infants, who suffered a symptomatic RSV LRTI and/or respiratory morbidity at follow up, had worse lung function prior to neonatal unit discharge.
Introduction

Respiratory syncytial virus (RSV) is the most important respiratory pathogen in childhood. RSV lower respiratory tract infection (LRTI) causes acute morbidity and, in the United States, it has been estimated that RSV LRTI is responsible for approximately 400,000 hospital inpatient days every year in children less than five years of age.[1] In previously healthy term born infants, it also increases the risk of asthma at follow up.[2][3] Diminished lung function, in particular small airways, may predispose to symptomatic RSV LRTI in infants born at term.[4] Infants who subsequently developed bronchiolitis had a lower maximal flow at functional residual capacity ($V_{\text{max}}$FRC) at five weeks of age.[4] In addition, in the Tucson Children’s Respiratory Study, children who had at least one wheezing LRTI, (44% of which were due to RSV infection) in the first three years after birth had a lower $V_{\text{max}}$FRC prior to the LRTI.[5][6] It is not known whether abnormal lung function predisposes prematurely born infants to symptomatic RSV LRTI, yet prematurely born infants can suffer chronic respiratory morbidity following RSV infection [7][8], and also are at high risk of lung abnormalities as a result of perinatal insults.[9] The aim of our study, therefore, was to determine if prematurely born infants who subsequently developed a symptomatic RSV LRTI and/or respiratory morbidity at follow up had impaired lung function at 36 weeks PMA.

Methods

Infants born prior to 32 weeks of gestational age in a single centre were eligible for entry into the study, if they delivered prior to the onset of the RSV season (thus all recruited infants would be exposed to a complete RSV season on neonatal unit discharge). The RSV season was defined as October 1st to March 31st, consistent with UK experience.[10] Consecutive infants, whose parent gave informed written consent, were recruited. The Research Ethics Committee of King’s College NHS Trust approved this study. The infants underwent lung function measurements at 36 weeks PMA and were followed prospectively until a corrected age of one year.

Lung function measurements

The infants were studied while supine and asleep, they were not sedated and none were ventilated at the time of study. Lung volume was assessed by measurement of functional residual capacity (FRC), using a commercially available helium gas dilution system (EBS 2615, Equilibrated Bio Systems, New York, USA). The FRC system contained a 500 ml re-breathing bag, the system reservoir, enclosed in an airtight cylinder and a helium analyser, with a real time digital display. A facemask (Rendell Baker, Laerdal, facemask size 0 or 1) was held snuggly over the infant’s nose and mouth; silicone putty was used around the mask to achieve an airtight seal. The facemask was connected to the rebreathing bag via a three-way valve. The three-way valve was switched at the end of expiration, so that the infant subsequently breathed from the rebreathing bag. Digital display of the helium dilution curve allowed precise determination of when gas equilibration occurred. During the measurement, if there was no change in the helium concentration over a 15 second period, equilibration was deemed to have occurred. The initial and equilibration helium concentrations were used to calculate FRC, which was corrected for oxygen consumption (7 ml/kg/minute) [11] and converted to body temperature and water vapour saturated conditions. FRC was measured at least twice in each infant to obtain two results which were within ten per cent of each other. The paired FRC results were then meaned. The mean intrasubject coefficient of variability of the measurement of the FRC was 7%.
Compliance ($C_{rs}$) and resistance ($R_{rs}$) of the respiratory system were measured using the single breath occlusion technique. A facemask was placed over the infant’s nose and mouth; silicone putty was used around the face mask to ensure an airtight seal.

A pneumotachograph (Mercury F10L; GM Engineering, Kilwinning, UK) connected to a differential pressure transducer (range: $\pm 2$ cm H$_2$O, MP 45, Validyne engineering, Northridge, California USA) was inserted into the facemask. The flow signal from the pneumotachograph was integrated to give volume (Validyne CD280: Validyne engineering, Northridge, California, USA). From a sideport on the pneumotachograph mouth pressure was measured using a differential pressure transducer (range: $\pm 100$ cm H$_2$O, MP 45, Validyne engineering, Northridge, California USA). The signals were amplified (Validyne CD280: Validyne engineering, Northridge, California, USA) and displayed in real time on a computer (Dell inspiron) running Labview software (version 4.0, National Instruments, Austin, Texas, USA), with 100 Hz analogue to digital sampling (DAQ 16XE-50; National Instruments, Austin, Texas, USA). Occlusions were made at end inspiration, which was identified from the flow signal. The distal end of the pneumotachograph was briefly occluded and only occlusions during which there was no flow, there was a mouth pressure plateau of at least 100 milliseconds in duration and a linear flow-volume plot after the occlusion were considered acceptable. $C_{rs}$ was calculated from the inspiratory volume and the pressure plateau and related to body weight. The time constant of the respiratory system was calculated from the linear part of the flow volume plot and $R_{rs}$ given by the time constant divided by the $C_{rs}$. The mean $C_{rs}$ and $R_{rs}$ were calculated from at least five technically acceptable occlusions and the results were then meaned. The mean intrasubject coefficient of variability of the $C_{rs}$ and $R_{rs}$ measurements were 8% and 13% respectively.

Following neonatal unit discharge, the parent(s) were asked to contact the research team during the RSV season when their infant was symptomatic and had signs consistent with a lower respiratory tract infection (LRTI), that is cough, wheeze and/or shortness of breath.[12] In addition, the parent(s) were telephoned every two weeks by one of the researchers to ascertain whether the infant had been or was symptomatic. A researcher visited the home on every occasion that an infant had a LRTI and a nasopharyngeal aspirate (NPA) was obtained; NPAs were also obtained from all infants admitted to hospital with a LRTI. Immunofluorescence and culture for RSV were performed on the NPAs. Respiratory morbidity at follow up was documented by asking parents to complete diary cards for a month when their infants reached eleven months of age. They recorded on a daily basis whether their infant had cough or wheeze.

Patients

Sixty infants were eligible for inclusion into the study. Ten parent(s) did not consent for their infant to take part in the study, a further five initially consented but then defaulted from follow up, three infants died before discharge from the neonatal unit and unsatisfactory lung function recordings were obtained from a further three infants. The remaining 39 infants had a median gestational age of 28 (range 23-31) weeks and a birthweight of 1000g (610-1930g); neither their gestational age, birthweight nor BPD status differed significantly from those who did not take part (data not shown). The study population consisted of 23 males (59%), 14 of the mothers (36%) had had an antenatal infection (maternal positive blood culture, histologically proven chorioamnionitis or maternal temperature with a positive culture from a high vaginal swab and rupture of membranes of duration greater than 24 hours [13]) and 31 (79%) had received antenatal steroids. Twenty seven of the infants (69%) had received surfactant and 20 (51%) developed bronchopulmonary dysplasia (BPD, oxygen dependence beyond 36 weeks postmenstrual age (PMA)). Nineteen (49%) had a postnatal infection (positive blood culture or suspected clinical infection with a raised C-reactive protein, increased or decreased neutrophil count and/or decreased platelet count [14], but none had had a nosocomial viral infection. During the study period, only infants with BPD who had required supplementary oxygen at least until one week before NICU discharge and were being discharged.
during the RSV season were given Palivizumab. As a consequence, six infants received Palivizumab; two of the Palivizumab group subsequently suffered a symptomatic RSV positive LRTI, but did not require hospital admission.

Analysis
The outcomes RSV infection and respiratory morbidity (cough or wheeze) at follow up were related to potential explanatory variables, which included infant, parental and family characteristics. We chose potential explanatory variables which had been previously identified as factors which might influence RSV infection and/or respiratory morbidity in prematurely born infants.[15][16][17][18] Antenatal variables recorded were antenatal infection (maternal positive blood culture, histologically proven chorioamnionitis, maternal urinary tract infection or maternal temperature with a positive culture from a high vaginal swab and rupture of membranes of duration greater than 24 hours [13]), maternal smoking and antenatal corticosteroid administration. Postnatal variables were sex, gestational age, birthweight, use of surfactant, postnatal infection, the number of days of mechanical ventilation, BPD, discharge from the neonatal unit between September and December and whether the infant was bottle fed. Family variables were a family history of atopy (asthma or hay fever in a parent or sibling), the number of siblings, attendance at day-care and postnatal parental smoking. In addition the FRC, Crs and Rrs results were considered as possible explanatory variables. All data were assessed for normality using the Shapiro-Wilk test for normality; those that were normally distributed continuous variables were tested for significance using the one way ANOVA significance test (all lung function data, birthweight, gestational age and duration of ventilation). Multiple comparisons were performed using a one way ANOVA significance test with a post-hoc Bonferroni test for multiple comparisons. Non normally distributed were tested for statistical significance using the Mann Whitney or Chi Squared test as appropriate. Any variable which was significant at \( p \leq 0.10 \) level was entered into regression analysis. Binary logistic regression was used to further explore the differences between the symptomatic RSV LRTI group and the rest of the cohort controls. The controls consisted of infants who had an RSV negative symptomatic LRTI (RSV negative symptomatic LRTI) and infants who had had no symptomatic LRTI (no LRTI symptoms group). Multiple regression analysis was used to explore the relationships to outcomes of cough and wheeze. Analysis was performed using SPSS version 12.0, SPSS Inc, Chicago, Illinois 60606, USA.

Results
Fifteen infants suffered at least one symptomatic RSV positive LRTI (symptomatic RSV LRTI group), six of whom required admission to hospital. The symptomatic RSV LRTI group were compared to 24 infant controls who had either a non RSV LRTI (RSV negative symptomatic LRTI group (n=15)) or no LRTI symptoms (no LRTI symptoms group (n=9)). There were no significant differences in the demographics of the symptomatic RSV LRTI group and the controls (table 1). The two groups had similar mean FRC and Crs (table 2a and 2b), but the symptomatic RSV LRTI group had a significantly higher mean Rrs at 36 weeks PMA than the controls (figure 1). Subanalysis demonstrated that the symptomatic RSV LRTI group tended to have a higher resistance than the no LRTI symptoms group (126.1 vs 80.41 cm H20/l/s) (\( p=0.06 \)), but not than the RSV negative symptomatic LRTI group (126.1 vs 94.4 cm H20/l/s) (\( p=0.17 \)).

Results of the diary card analysis demonstrated that the RSV symptomatic LRTI group had more days of wheeze (median 5 (range 0-22) days) than the control group (median 0 (range 0-7) days) (\( p=0.040 \)) and tended to have more days of cough (median 7 (range 0-31) versus median 3 (range 0-14) days (\( p=0.056 \)). Subanalysis demonstrated the symptomatic RSV LRTI group did not
significantly have more wheeze than the no LRTI symptoms group (median 0 (range 0-5) days) (p=0.084), or the RSV negative symptomatic LRTI group (median 0 (range 0-7) days) (p=0.125).

Regression analysis demonstrated that the only factor significantly related to symptomatic RSV LRTI was a high $R_n$ at 36 weeks PMA (p=0.037) (odds ratio 1.30 (1.10 – 1.50)). Factors related to the number of days of cough were a symptomatic RSV LRTI (p<0.001) and a high $R_n$ (p=0.002) and to the number of days of wheeze were a high $R_n$ (p<0.001) and RSV LRTI (p=0.09).

Table 1. Demographics of the symptomatic RSV LRTI group and the controls. Data are demonstrated as median (range) or n (%).

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic RSV LRTI Group</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>15</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Gestational age (wks)</td>
<td>28 (24-31)</td>
<td>28 (24-31)</td>
<td>0.30</td>
</tr>
<tr>
<td>Birthweight (kg)</td>
<td>1.08 (0.38)</td>
<td>1.09 (0.38)</td>
<td>0.94</td>
</tr>
<tr>
<td>Males</td>
<td>10 (66%)</td>
<td>13 (54%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Antenatal smoking</td>
<td>2 (13%)</td>
<td>3 (12%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>12 (80%)</td>
<td>18 (69%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Surfactant</td>
<td>10 (66%)</td>
<td>17 (71%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Duration of ventilation (days)</td>
<td>6 (0-30)</td>
<td>6 (0-79)</td>
<td>0.96</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>10 (67%)</td>
<td>14 (58%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Parental atopy</td>
<td>5 (33%)</td>
<td>10 (41%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Postnatal smoking</td>
<td>2 (13%)</td>
<td>4 (16%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Daycare</td>
<td>5 (33%)</td>
<td>4 (16%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Number of siblings</td>
<td>1 (0-3)</td>
<td>1 (0-4)</td>
<td>0.67</td>
</tr>
<tr>
<td>Palivizumab</td>
<td>2 (13%)</td>
<td>4 (17%)</td>
<td>0.92</td>
</tr>
</tbody>
</table>
**Table 2a.** Lung function results and respiratory morbidity.
Data are shown as mean (standard deviation), or median (range).

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RSV LRTI group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>15</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td><strong>Lung function:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenstrual age (wks)</td>
<td>35.8 (0.6)</td>
<td>35.9 (0.5)</td>
<td>0.89</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>2.13 (0.38)</td>
<td>2.38 (0.46)</td>
<td>0.17</td>
</tr>
<tr>
<td>FRC (ml/kg)</td>
<td>21.9 (4.2)</td>
<td>21.6 (3.4)</td>
<td>0.94</td>
</tr>
<tr>
<td>$C_r$ (ml/cm H$_2$O/kg)</td>
<td>0.98 (0.47)</td>
<td>0.99 (0.52)</td>
<td>0.82</td>
</tr>
<tr>
<td>$R_{rs}$ (cm H$_2$O/l/s)</td>
<td>126.1 (62.1)</td>
<td>89.1 (27.8)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Respiratory morbidity at one year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough (days/month)</td>
<td>7 (0-31)</td>
<td>3 (0-14)</td>
<td>0.06</td>
</tr>
<tr>
<td>Wheeze (days/month)</td>
<td>5 (0-22)</td>
<td>0 (0-7)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Table 2b. Lung function and respiratory morbidity by RSV and LRTI status.

<table>
<thead>
<tr>
<th></th>
<th>RSV symptomatic LRTI group (1)</th>
<th>RSV negative symptomatic LRTI group (2)</th>
<th>No LRTI symptoms group (3)</th>
<th>p 1 vs 2</th>
<th>p 1 vs 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>15</td>
<td>9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Lung function:**

- Postmenstrual age (wks) 35.8 (0.6) 36.0 (0.7) 35.8 (0.9) 1.000 1.000
- Weight (kg) 2.13 (0.38) 2.30 (0.44) 2.54 (0.49) 0.900 0.091
- FRC (ml/kg) 21.9 (4.2) 19.7 (1.9) 23.1 (3.5) 1.000 1.000
- $C_{rs}$ (ml/cm H$_2$O/kg) 0.98 (0.47) 0.75 (0.33) 1.2 (0.51) 1.000 0.959
- $R_{rs}$ (cm H$_2$O/l/s) 126.1 (62.1) 100.6 (28.9) 80.4 (19.9) 0.173 0.058

**Respiratory morbidity at one year**

- Cough (days) 7 (0-31) 4 (0-14) 0 (0-5) 0.292 0.072
- Wheeze (days) 5 (0-22) 0 (0-7) 0 (0-5) 0.125 0.084
Discussion

We have demonstrated that prematurely born infants who suffer a symptomatic RSV LRTI and/or had more cough and wheeze at follow up, had significantly higher resistance of the respiratory system prior to NICU discharge. There were, however, no significant differences in the lung volumes or the results of compliance of the respiratory system results of the two groups. The reproducibilities of the three types of measurements were similar and thus we do not feel the lack of significant differences in the lung volumes and compliance results reflects a type II error. Indeed, our results of a higher mean resistance in the infants who subsequently developed symptomatic RSV LRTI and respiratory morbidity are in keeping with the results found in term born infants. The high $R_{rs}$ we now demonstrate and the low $V_{max}$ FRC previously demonstrated [4] suggest that abnormal airway function predisposes to symptomatic RSV LRTI. Our subanalysis suggests this effect may not be specific to RSV LRTI, as the resistance results at 36 weeks PMA of the RSV LRTI and the non RSV LRTI groups were similar (p=0.17). It should, however, be emphasised that the numbers included in each subanalysis were relatively small and the observation needs further testing in a larger study.

The lung function results we report are similar to those published previously. We had reported results from 20 prematurely born infants (10 with BPD), their lung volumes measured by helium gas dilution were between 13 and 35 ml/kg, $C_{rs}$ between 0.4 and 1.5 ml cm H$_2$O/kg and $R_{rs}$ between 87 and 194 cm H$_2$O/l/s.[19] In addition, Hjalmarson et al [9] reported 32 prematurely born infants (none with BPD) at 40 weeks PMA had a mean (SD) $R_{rs}$ of 97.4 (SD 30.4) cm H$_2$O/l/s. The similarity of the lung function results would suggest our findings are generalisable to other populations of prematurely born infants.

We were unable to follow twenty one of the eligible infants. Those not followed, however, did not differ significantly from the study population with regard to their birthweight, gestational age or BPD status, all factors known to affect the severity of RSV infection.[17] Thus, it seems unlikely that our results were biased by loss to follow up. A small number of infants received Palivizumab, but it is not known whether Palivizumab prevents RSV LRTI and, as similar proportions in each group received Palivizumab, we do not feel this biased our results. Our sample was relatively small, nevertheless we identified significant differences in those who developed RSV infection and chronic respiratory morbidity.

Parents were requested to contact the research team on each occasion that their infant had a symptomatic LRTI. It is possible some parents failed to do so, but to minimise the risk of missing infants with LRTIs we also contacted the parents at two weekly intervals. The proportion (38%) of our cohort who tested positive for RSV infection, is similar to that found (31.8%) in a community based study of term born infants.[20] In that study [20] parents were requested to contact the research team within 24 hours of their infant developing nasal stuffiness, runny nose, cough, fever or noisy breathing and the infant was then visited and an NPA obtained. We only obtained NPAs from infants when they had signs of a LRTI and thus we cannot comment on risk factors for asymptomatic RSV infection. We, however, were keen as in studies in term born infants [15] [17][18] to identify risk factors for symptomatic infection.

In conclusion, our results suggest that abnormal airway function is associated with subsequent symptomatic RSV LRTI and cough and wheeze at follow up in prematurely born infants. The relative importance of the RSV LRTI and the premorbid diminished airway function on subsequent respiratory morbidity merits investigation.
Sponsors
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Competing interests
There are no competing interests.

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What is already known on this topic
Abnormal premorbid lung function, consistent with smaller airway size, appears to predispose otherwise healthy term born infants to a symptomatic RSV lower respiratory tract infection (LRTI).

What this study adds
We now demonstrate that prematurely born infants who suffered a symptomatic RSV LRTI and/or had respiratory morbidity at follow up, had significantly higher respiratory resistance at 36 weeks PMA than infants who had neither adverse outcome.

Figure legends

Figure 1
Scatter plot of Rrs in the symptomatic RSV LRTI group and the controls. The solid line shows the mean value.
References

Figure 1. Scatter plot of $R_s$ in the symptomatic RSV LRTI group and the controls. The solid line shows the mean value.
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