Bronchial responsiveness and lung function in infants with lower respiratory tract illness over the first six months of life

Jane R Clarke, Amanda Reese, Michael Silverman

Abstract
The aim of this study was to determine whether increased bronchial responsiveness to histamine is associated with lower respiratory tract illness (one or more episodes of wheeze or cough, or both) in infancy.

Fifty four normal newborn infants who had at least one atopic parent were recruited. At a median age of 6-5 months, 45 infants, 23 with a history of lower respiratory tract illness, and 22 without, underwent pulmonary function testing during a symptom free period. The maximum flow at functional residual capacity ($V_{\text{max}}FRC$) was calculated from partial forced expiratory flow volume curves using the squeeze technique. Bronchial responsiveness to increasing doses of histamine was assessed by determining the provoking concentration which caused a 30% decrease in $V_{\text{max}}FRC$ ($PC_{30}$).

The length adjusted $V_{\text{max}}FRC$ was lower for symptomatic infants before the challenge (median 125 ml/s; 95% confidence intervals (CI) 85 to 164 ml/s) compared with control infants (median 215 ml/s; 95% CI 159 to 298 ml/s). There was no significant difference in $PC_{30}$ between symptomatic infants (median 10-3 g/l; 95% CI 2-6 to 23-6 g/l) and control infants (median 16-5 g/l; 95% CI 2-4 to 27-9 g/l).

Bronchial responsiveness to histamine can be shown in most infants early in life and is independent of lower respiratory tract symptoms including wheezing.

(Arch Dis Child 1992;67:1454–8)

LUNG FUNCTION
Partial expiratory flow volume curves were obtained using the squeeze technique by rapidly inflating a snugly fitting, polyethylene thoraco-abdominal jacket (medical engineering department, Royal Postgraduate Medical School, Hammersmith Hospital, London), with the arms enclosed, at the end of tidal inspiration to induce a forced expiration. The jet inflation pressure was measured with a pressure transducer (Validyne MP45). From occlusion tests at the end of inspiration the static pressure transmission to the pleural space with this jacket was 56–80% of the applied pressure. Flow was recorded with a low resistance screen pneumotachograph (medical engineering department, Royal Postgraduate Medical School) and facemask (Rendell-Baker Sourcek, size 1, Ambu International), connected to a pressure transducer (Validyne MP45). A rim of silicone putty (Carters) was applied around the...
Bronchial response in infants with lower respiratory tract illness

mouth and nose and to the facemask to provide an airtight seal. The flow signal was electronically integrated with respect to time to give the volume. All signals were digitised (100 Hz) and stored on a computer (Compaq desktop 386/20e). Partial expiratory flow volume curves were constructed by computer and analysed (RASP Software, Physiologic Ltd) to determine the maximum flow at a lung volume corresponding to the functional residual capacity (VmaxFRC). During baseline measurements the jacket pressure was increased from 25 cm H₂O by increments of 5 cm H₂O until flow limitation had been achieved, as shown by the maximum flow at functional residual capacity, or until the maximum jacket pressure of 80 cm H₂O had been achieved. A mean baseline value of VmaxFRC was derived from eight to 10 baseline measurements made at the optimal jacket pressure. Thereafter the same jacket pressure was used throughout the challenge test procedure.

The shape of the baseline partial expiratory flow volume curves was described qualitatively for each subject, as either concave or convex with respect to the origin.

HISTAMINE CHALLENGE

Aerosols of normal saline, as a control, and doubling concentrations of histamine were administered for 30 seconds each by a Wright nebuliser, with 8 l/min airflow (nebuliser output 0·16 ml/min by weighing, aerosol aerodynamic mass median diameter 1·0–1·5 μm). The facemask, pneumotachograph removed, acted as a chamber into which the aerosol was directed over the mouth and nose of the sleeping infant. Beginning with 0·25 g/l, doubling concentrations of histamine were administered at five minute intervals until either a 30% decrease from baseline VmaxFRC had been observed or the maximum histamine concentration of 32 g/l had been reached. Beginning one minute after completion of each nebulisation, six to 10 squeeze manoeuvres were then carried out. All technically satisfactory curves were analysed to give a mean VmaxFRC for each dose. As a safety measure, oxygen saturation (SaO₂) (Ohmeda Biox 3740 pulse oximeter), transcutaneous oxygen tension (PtcO₂) and carbon dioxide tension (PtcCO₂; Radiometer TCM3, Radiometer) were monitored continuously.

The provoking concentration of histamine producing a 30% decrease in VmaxFRC (PC₃₀) from baseline was obtained by linear interpolation from dose-response plots of VmaxFRC against log histamine concentration for each subject.

ANALYSIS

The lengths, weights, and ages of the infants with and without lower respiratory tract illness were compared using Student's t tests. The gender distribution, ethnic origin, and history of maternal smoking in the two groups were compared using a χ² test with Yates's correction. VmaxFRC was adjusted to a length of 70 cm using regression equations derived from the normal subjects in the cohort. For normal male subjects, VmaxFRC (ml/s)=6·97 (length in cm)−244, and for female subjects VmaxFRC (ml/s)=8·07 (length in cm)−270. For female subjects length adjusted VmaxFRC was further adjusted for gender from the regression equations (by multiplying by 0·822) to group male and female subjects together for comparison. The VmaxFRC jacket pressure, and coefficient of variation data were skewed, and the PC₃₀ data censored, so they were compared using the Mann-Whitney U test. Values were expressed as medians, with 95% confidence intervals (CI) and interquartile ranges. The study design allowed a difference of two doubling concentrations in PC₃₀ (boys and girls grouped together) and a 120 ml/s difference in length adjusted VmaxFRC (boys and girls compared separately) to be detected between the normal and symptomatic groups, with a power of greater than 80% at a significance level of 5%.

Results

There were similar numbers of boys and girls in the study (23/22), but more boys than girls had developed symptoms by 6 months of age (13/10). Of those with lower respiratory tract illness, seven symptomatic boys and six symptomatic girls had coughed without any wheeze. Of the four boys and five girls from the original birth cohort of 54 infants who dropped out of the study, two boys and two girls had developed symptoms by 6 months. The ages and lengths of the infants with lower respiratory tract illness and control infants were similar, but the symptomatic male infants were significantly heavier than the normal boys (p<0·05). There was no significant difference in the numbers of maternal smokers or non-white subjects between the two groups (table 1) or of other family members who smoked. Further analysis into the independent effect of parental smoking on lung function was precluded because of the small number of subjects.

Table 1 Baseline data. Mean (range) or number (%) are given

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Boys LRI* (n=13)</th>
<th>No LRI* (n=10)</th>
<th>p Value</th>
<th>Girls LRI* (n=10)</th>
<th>No LRI* (n=12)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>6·65 (5.5–8.0)</td>
<td>6·45 (6.0–8.0)</td>
<td>0·52</td>
<td>6·60 (6.0–8.0)</td>
<td>6·21 (6.0–7.0)</td>
<td>0·10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>8·51 (6.92–10.0)</td>
<td>7·74 (6.30–8.74)</td>
<td>0·048</td>
<td>7·73 (5.95–10.0)</td>
<td>7·63 (6.6–10.7)</td>
<td>0·80</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>6·93 (66–74)</td>
<td>68·5 (63–72)</td>
<td>0·43</td>
<td>67·8 (65–70)</td>
<td>67·7 (65–73)</td>
<td>0·90</td>
</tr>
<tr>
<td>Maternal smokers</td>
<td>4 (31)</td>
<td>1 (10)</td>
<td>0·49</td>
<td>2 (20)</td>
<td>1 (8)</td>
<td>0·70</td>
</tr>
<tr>
<td>Non-white subjects</td>
<td>3 (23)</td>
<td>1 (10)</td>
<td>0·79</td>
<td>2 (20)</td>
<td>2 (17)</td>
<td>0·83</td>
</tr>
</tbody>
</table>

*LRI=lower respiratory tract illness.

†p Value=significance of difference between subjects with LRI and without LRI (t test or χ² test).
Table 2  Gender and length adjusted VmaxFRC and Pco2

<table>
<thead>
<tr>
<th></th>
<th>LRI*</th>
<th>No LRI*</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VmaxFRC (ml/s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of subjects</td>
<td>23</td>
<td>22</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>125-4</td>
<td>214-9</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>85-0 to 164-2</td>
<td>159-4 to 298-0</td>
<td></td>
</tr>
<tr>
<td>Mean CV (%)</td>
<td>9-9</td>
<td>9-0</td>
<td>0-11</td>
</tr>
<tr>
<td>95% CI</td>
<td>8-2 to 11-3</td>
<td>6-1 to 9-4</td>
<td></td>
</tr>
<tr>
<td>PCo2 (g/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of subjects</td>
<td>19</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Median value</td>
<td>10-3</td>
<td>16-5</td>
<td>0-97</td>
</tr>
<tr>
<td>95% CI</td>
<td>8-2 to 23-82</td>
<td>2-35 to 27-86</td>
<td></td>
</tr>
</tbody>
</table>

* LRI=lower respiratory tract illness; CV=coefficient of variation (within subject).

For both male and female infants the length adjusted VmaxFRC before challenge was significantly lower for the symptomatic group than for the control infants (table 2; fig 1). The median difference in length adjusted VmaxFRC between symptomatic and control infants was 108-0 ml/s for boys (95% CI 45-9 to 251-6 ml/s; p=0-006) and 102-1 ml/s for girls (95% CI 17-8 to 232-2 ml/s; p=0-013). There was no significant difference in repeatability of VmaxFRC expressed as a coefficient of variation between symptomatic and control subjects (table 2).

The median jacket pressure required to produce flow limitation during the squeeze manoeuvre was significantly lower for the group with lower respiratory tract illness than for the control infants (37 ± 46 cm H2O respectively; p<0-05). There was no significant difference between symptomatic subjects and controls in the distribution of the shapes of the partial expiratory flow volume curves (concave:convex = 16:7 for subjects with lower respiratory tract illness and 12:10 for controls; p=0-46).

Five infants awoke before completing the histamine challenge. During baseline measurements, one male infant from the group with lower respiratory tract illness had flow limited flow volume curves during tidal breathing, precluding histamine challenge. For the remaining infants, (nine control and 11 symptomatic boys; 12 control and seven symptomatic girls), there was no significant difference in PCo2 between symptomatic infants and normal infants (table 2; figure 2). There was no correlation between length adjusted VmaxFRC before histamine challenge and PCo2 for the whole study group.

Before histamine challenge, oxygen saturation was greater than 94% for all subjects. During bronchial challenge only four infants desaturated below 90%, the minimum recorded PaO2 being 83%, with spontaneous recovery. The maximum decrease in PtcO2 from prechallenge recordings was 4-2 kPa; in 11 infants PtcO2 decreased by more than 2 kPa during challenge. There was no significant change in PtcCO2 during histamine challenge.

Discussion

In contrast with reports of an association between bronchial responsiveness and wheezing in older children, 1-4 we found no association between bronchial responsiveness to histamine and lower respiratory tract illness in 6 month old infants. Baseline lung function, however, was reduced in symptomatic boys and girls, despite their being free of symptoms at the time of study. Our findings in children of atopic parents are similar to those reported by Stick et al in a random sample of the population, 5 using similar methodology.

The baseline measurements of VmaxFRC for the control subjects were similar to those few reference ranges reported for infants. 6-21 All reference data show a wide scatter of size corrected VmaxFRC between subjects, but the method is repeatable within subjects. Doubt has been cast on the assumption that in healthy infants, flow limitation is achieved by the squeeze technique. 22,23 This study does not determine whether the symptomatic infants had lower VmaxFRC before any respiratory illness (that is, whether small airway calibre might have predisposed them to symptomatic lower respiratory tract illness 24,25), or, alternatively, whether deterioration in previously normal lung function was a consequence of lower respiratory tract illness.

The configuration of the maximum expiratory flow-volume curve is a sensitive index of disturbed pulmonary mechanics, indicating imbalance between peripheral elastic and flow resistive components of the lungs. Minor changes have been interpreted as indicating 'small airway
Bronchial response in infants with lower respiratory tract illness

1547
disease'.27 The similarity in the shape of the partial expiratory flow volume curves in the group with lower respiratory tract illness and control subjects, despite the lower VmaxFRC in those with lower respiratory tract illness, is compatible with a pre-existing developmental pulmonary anomaly, as shown by Martinez and colleagues.25-26 rather than 'lung damage'. The configuration of partial expiratory flow-volume curves in infants are, however, at least partly dependent on the external compression applied. Excessive jacket pressures tend to produce increasingly convex curves and a consequent reduction in, VmaxFRC, sometimes called 'negative pressure dependency of flow'.18 In our study various jacket pressures were used to determine the optimal pressure at which flow limitation was just achieved.

The squeeze technique does not take account of changes in the level at the end of expiration during bronchial challenge. Assessing bronchial responsiveness from changes in VmaxFRC may therefore result in an underestimate of response in infants whose functional residual capacity increases during challenge.28 A difference in the functional residual capacity in response to challenge, between infants with lower respiratory tract illness and controls, could have masked a true difference in PEF.

The levels of bronchial responsiveness to histamine which we found were lower (that is, PC20 was higher) than those reported previously.10-12 Differences between studies in the methodology, especially in the duration of histamine nebulisation and in the type of jet nebuliser used, may be the explanation. The effect of air entrainment on the dose of aerosol delivered to the lungs varies with age,29 but is unlikely to have been a factor as the infants in the group with lower respiratory tract illness and controls were of similar size and age.

Various factors may influence infant lung function and bronchial responsiveness. An Australian study looking at factors influencing bronchial responsiveness in early infancy showed that infants with either a family history of asthma or of parental smoking had increased levels of bronchial responsiveness at around 1 month of age.30 There was no difference in baseline VmaxFRC. In contrast, a more extensive population survey in Boston (USA) showed reduced levels of forced expiratory flow within the first two months of life in infants born to smoking mothers, without a change in the functional residual capacity.31 They did not assess bronchial responsiveness. There were insufficient numbers of maternal smokers in our study to look at the effect of maternal smoking on baseline lung function or bronchial responsiveness. All of our infants had a parental history of atopy, though neither our subjects nor their parents were tested for atopy.

A prospective study in young adults32 showed that enhanced bronchial responsiveness usually precedes the development of clinical asthma and is compatible with a genetic basis for it. Epidemiological studies of 7 and 11 year old children have shown that wheeze is not associated with bronchial hyperresponsiveness in the absence of atopy, but is strongly related to bronchial hyperresponsiveness when atopy is present.33 In a large longitudinal study of 11 year old New Zealand schoolchildren, childhood asthma was shown to be strongly linked to allergy. Bronchial responsiveness correlated significantly with allergy as determined by the serum IgE concentration, even in some children with no clinical features of atopy.

There is reason to believe that the situation may be different in infants and young children, where infantile asthma is essentially a non-atopic illness34 even among the infants of atopic parents.35 At the age of 3 years there was no significant difference in bronchial responsiveness between atopic and non-atopic preschool children, all of whom had a history of severe wheeze.37 It has been suggested that only those wheezy infants who have an atopic predisposition and whose airways become sensitised to aeroallergens will develop asthma in later childhood.35 A prospective study of the relation between bronchial responsiveness and atopic sensitisation by inhaled allergens would further elucidate this hypothesis.

We suggest that at 6 months of age bronchial responsiveness is present in most infants and does not discriminate between those with and without a future history of lower respiratory tract illness. Lower respiratory tract symptoms are associated with reduced airway calibre rather than bronchial responsiveness. Later in childhood bronchial responsiveness may become a more important determinant of wheezing, together with atopy.

This work was supported by Action Research and the National Asthma Campaign. We are indebted to Mr R H Cumberlidge, Physiologic Ltd, for computer software and Mr N Levy and Mr N Sen for technical assistance.


Bronchial responsiveness and lung function in infants with lower respiratory tract illness over the first six months of life.

J R Clarke, A Reese and M Silverman

Arch Dis Child 1992 67: 1454-1458
doi: 10.1136/adc.67.12.1454

Updated information and services can be found at:
http://adc.bmj.com/content/67/12/1454

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/