

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 (\dot{V}_{maxFRC}) 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 \dot{V}_{maxFRC} (PC_{30}).

The length adjusted \dot{V}_{maxFRC} 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 2.8 to 23.8 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.

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In groups of schoolchildren and adults there is an association between increased bronchial responsiveness and asthma,¹⁻⁴ though in individual subjects variations in bronchial responsiveness correlate poorly with the clinical manifestations of asthma⁵⁻⁷ and with airway calibre at the time of testing.^{8,9} Bronchial responsiveness has been shown in infancy in recurrently wheezy subjects^{10,11} and in small groups of normal infants.¹²⁻¹⁴

Until recently little was known about the relation of bronchial responsiveness to wheezing in infancy. In one small study of recurrently wheezy infants it was shown that, in contrast with older subjects, bronchial responsiveness in infancy is independent of wheezing, but may be dependent on airway calibre.¹⁵

The aim of this study was to determine whether the airways of infants with lower respiratory tract illness (one or more episodes of wheeze or cough, or both) were more responsive

to histamine than those of asymptomatic control subjects.

Subjects and methods

SUBJECTS

All 45 infants in this study were recruited in the neonatal period from Hammersmith Hospital or Queen Charlotte's and Chelsea Hospital, and were followed up as part of a cohort study. Of the 54 subjects who had originally been recruited, two had moved away from the area by the age of 6 months and seven no longer wished to take part in lung function tests. All members of the cohort had at least one atopic parent, but had otherwise been normal healthy term infants. Infants were classified according to the presence or absence of one or more episodes of cough or wheezing, or both (henceforth referred to as lower respiratory tract illness). Parents were interviewed and details of any recurrent cough or wheezing, or both, since birth were recorded, in addition to a detailed family history including smoking.

At the time of study at the age of 6 months, all infants had been free of respiratory symptoms for at least two weeks. None was receiving any drugs known to affect bronchial responsiveness. Infants were studied after sedation with chloral hydrate (100 mg/kg) or the equivalent dose of triclofos sodium (167 mg/kg). The study was approved by the hospital's ethics committee and parental consent was always obtained. Parents generally stayed in the laboratory during studies.

LUNG FUNCTION

Partial expiratory flow volume curves were obtained using the squeeze technique by rapidly inflating a snugly fitting, polythene 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.^{16,17} The jacket 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 is 56-80% of the applied pressure.¹⁸ Flow was recorded with a low resistance screen pneumotachograph (medical engineering department, Royal Postgraduate Medical School) and facemask (Rendell-Baker Soucek, size 1, Ambu International), connected to a pressure transducer (Validyne MP45). A rim of silicone putty (Carters) was applied around the

Department of Paediatrics and Neonatal Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN
J R Clarke
A Reese
M Silverman

Correspondence to:
Dr Silverman.

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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 deskpro 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 (\dot{V}_{maxFRC}).¹⁹ 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 \dot{V}_{maxFRC} 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^{20}). 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 \dot{V}_{maxFRC} 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 \dot{V}_{maxFRC} for each dose. As a safety measure, oxygen saturation (Sao_2) (Ohmeda Biox 3740 pulse oximeter), transcutaneous oxygen tension (PtcO_2) and carbon dioxide tension (PtcCO_2 ; Radiometer TCM3, Radiometer) were monitored continuously.

The provoking concentration of histamine producing a 30% decrease in \dot{V}_{maxFRC} (PC_{30}) from baseline was obtained by linear interpolation from dose-response plots of \dot{V}_{maxFRC}

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 χ^2 test with Yates's correction. \dot{V}_{maxFRC} was adjusted to a length of 70 cm using regression equations derived from the normal subjects in the cohort. For normal male subjects, \dot{V}_{maxFRC} (ml/s) = 6.97 (length in cm) – 244, and for female subjects \dot{V}_{maxFRC} (ml/s) = 8.07 (length in cm) – 270. For female subjects length adjusted \dot{V}_{maxFRC} was further adjusted for gender from the regression equations (by multiplying by 0.822) to group male and female subjects together for comparison. The \dot{V}_{maxFRC} jacket pressure, and coefficient of variation data were skewed, and the PC_{30} 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 PC_{30} (boys and girls grouped together) and a 120 ml/s difference in length adjusted \dot{V}_{maxFRC} (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

Characteristic	Boys			Girls		
	LRI* (n=13)	No LRI* (n=10)	p Value†	LRI* (n=10)	No LRI* (n=12)	p Value†
Age (months)	6.65 (5.5–8.0)	6.45 (6.0–8.0)	0.52	6.60 (6.0–8.0)	6.21 (6.0–7.0)	0.10
Weight (kg)	8.51 (6.92–10.0)	7.74 (6.30–8.74)	0.048	7.73 (5.59–10.0)	7.61 (6.6–10.7)	0.80
Length (cm)	69.3 (66–74)	68.5 (63–72)	0.43	67.8 (63–70)	67.7 (65–73)	0.90
Maternal smokers	4 (31)	1 (10)	0.49	2 (20)	1 (8)	0.70
Non-white subjects	3 (23)	1 (10)	0.79	2 (20)	2 (17)	0.83

*LRI=lower respiratory tract illness.

†p Value=significance of difference between subjects with LRI and without LRI (*t* test or χ^2 test).

Table 2 Gender and length adjusted $\dot{V}_{\max}\text{FRC}$ and PC_{30}

	LRI*	No LRI*	p Value
$\dot{V}_{\max}\text{FRC}$ (ml/s)			
No of subjects	23	22	
Median	125.4	214.9	0.0001
95% CI	85.0 to 164.2	159.4 to 298.0	
Mean CV (%)	9.9	9.0	0.11
95% CI	8.2 to 11.3	6.1 to 9.4	
PC_{30} (g/l)			
No of subjects	19	20	
Median value	10.3	16.5	0.97
95% CI	2.82 to 23.82	2.35 to 27.86	

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

For both male and female infants the length adjusted $\dot{V}_{\max}\text{FRC}$ before challenge was significantly lower for the symptomatic group than for the control infants (table 2; fig 1). The median difference in length adjusted $\dot{V}_{\max}\text{FRC}$ 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 $\dot{V}_{\max}\text{FRC}$ 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 v 46 cm H_2O 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 PC_{30} between symptomatic infants and normal infants (table 2; figure 2). There was no correlation

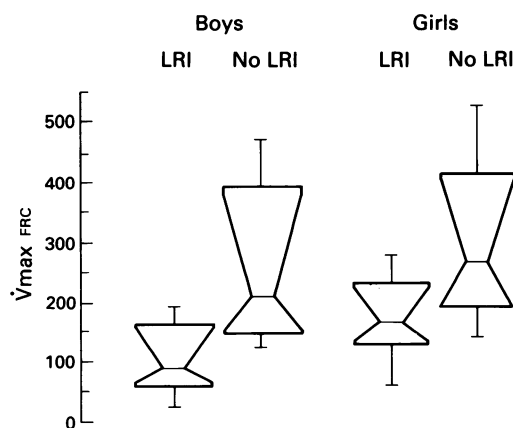


Figure 1 Maximum flow at functional residual capacity ($\dot{V}_{\max}\text{FRC}$, ml/s), adjusted for length, for boys and girls with and without lower respiratory tract illness (LRI). The box, notches, and bars indicate median with interquartile range, 95% CI, and range respectively.

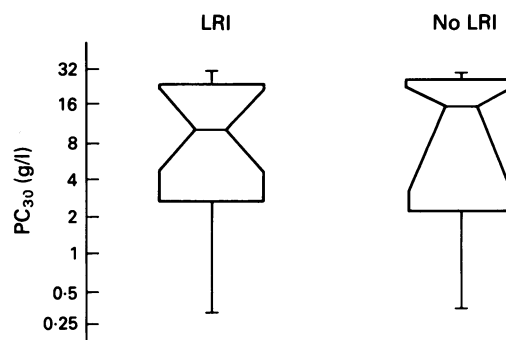


Figure 2 Concentration of histamine which caused a 30% decrease in maximum flow at functional residual capacity (PC_{30}) (g/l) for infants with and without lower respiratory tract illness (LRI). The box, notches, and bars indicate median with interquartile range, 95% CI, and range respectively.

between length adjusted $\dot{V}_{\max}\text{FRC}$ before histamine challenge and PC_{30} 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 SaO_2 being 83%, with spontaneous recovery. The maximum decrease in P_{tCO_2} from pre-challenge recordings was 4.2 kPa; in 11 infants P_{tCO_2} decreased by more than 2 kPa during challenge. There was no significant change in P_{tCO_2} during histamine challenge.

Discussion

In contrast with reports of an association between bronchial responsiveness and wheezing in older subjects,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,¹⁵ using similar methodology.

The baseline measurements of $\dot{V}_{\max}\text{FRC}$ for the control subjects were similar to those few reference ranges reported for infants.^{21 22} All reference data show a wide scatter of size corrected $\dot{V}_{\max}\text{FRC}$ 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.^{23 24} This study does not determine whether the symptomatic infants had lower $\dot{V}_{\max}\text{FRC}$ before any respiratory illness (that is, whether small airway calibre might have predisposed them to symptomatic lower respiratory tract illness^{25 26}), 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

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 $\dot{V}_{max}FRC$ 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 $\dot{V}_{max}FRC$, 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 $\dot{V}_{max}FRC$ 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 PC_{30} .

The levels of bronchial responsiveness to histamine which we found were lower (that is, PC_{30} 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 $\dot{V}_{max}FRC$. 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,³⁴ 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 illness³⁵ even among the infants of atopic parents.³⁶ 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 aero-allergens 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 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.

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