

ORIGINAL ARTICLE

Reduced lung function both before bronchiolitis and at 11 years

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Arch Dis Child 2002;87:417-420

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Accepted 21 June 2002

Background and Aims: We have previously shown an association between reduced premorbid lung function (V_{maxFRC}) and bronchiolitis. We hypothesised that individuals with bronchiolitis will go on to have reduced lung function and increased respiratory symptoms in childhood.

Methods: V_{maxFRC} was measured at 1 month of age; individuals with bronchiolitis were prospectively identified. Annual symptom questionnaires were completed from 3 to 6 years. At 11 years of age, children underwent an assessment including questionnaire, lung function, airway response to histamine (AR), and skin prick testing.

Results: Eighteen individuals with bronchiolitis were ascertained from 253 cohort members. Children with bronchiolitis had increased viral induced wheeze at 3 (OR 5.8, 95% CI 1.4 to 25.2; $n = 103$) and 5 years (OR 5.3, 95% CI 1.1 to 25.5; $n = 101$). At 11 years of age, 194 children were assessed including 16 with past bronchiolitis. These 16 individuals had reduced mean z scores for % V_{maxFRC} compared with other children (-0.56 and 0.06 respectively) and mean z scores for % FEF_{25-75} at 11 years (-0.53 and 0.06 respectively). At 11 years, FEV_1 , FVC PEF, AR, atopy, wheeze, and diagnosed asthma were not different between groups.

Conclusions: Reduced lung function is present before and after bronchiolitis; the level of reduction is comparable. The mechanism for wheeze and reduced lung function after bronchiolitis appears to be related to premorbid lung function and not bronchiolitis per se.

Bronchiolitis is a common condition that occurs in the first two years of life¹ and has been associated with increased morbidity in later childhood.² Following bronchiolitis, children have been noted to have increased wheeze,³ cough and asthma,^{4,5} increased airway responsiveness,^{3,6} and reduced lung function.^{3-5,7}

The mechanism for persisting respiratory symptoms and abnormalities in lung function after bronchiolitis is not well understood. From our prospective study of lung function from early life, we noted a trend for reduced maximal flow at functional residual capacity (V_{maxFRC}) before bronchiolitis.⁸ Reduced V_{maxFRC} in infancy has previously been associated with increased wheeze⁹ and reduced FEF_{25-75} in childhood.¹⁰ The associations between bronchiolitis, persisting wheeze, and reduced lung function may therefore be caused by reduced premorbid lung function.

We hypothesised that when compared with other cohort members, infants with bronchiolitis will have reduced lung function and increased respiratory symptoms in childhood.

METHODS

Subjects and study protocol

The antenatal recruitment for this cohort of healthy, term infants has been previously described in detail.⁸ Infant lung function was measured at 1 month of age, before the onset of respiratory symptoms. Using questionnaires that were completed annually, parents identified the presence of cough or wheeze (with or without upper respiratory tract infection) and physician diagnosed bronchiolitis, asthma, eczema, and hay fever up to the age of 6 years. At 11 years of age, children underwent an assessment that included questionnaire, spirometry, airway responsiveness to histamine (AR), and skin prick testing. This study was approved by the Medical Ethics Committee of Princess Margaret Hospital. Consent was obtained from parents and assent from children.

Definitions

Bronchiolitis was defined as physician diagnosed bronchiolitis prior to the second birthday. Children with "confirmed" bronchiolitis were prospectively identified from hospital admission records and questionnaire data. At 11 years of age, there was an additional group of children whose parents recalled an episode of physician diagnosed bronchiolitis before the child's second birthday; this group was defined as having "probable" bronchiolitis. The "control" group consisted of all remaining children seen at 11 years of age. At 6 and 11 years old, wheeze was defined as at least one episode of wheezing in the previous year. Parental asthma was defined as at least one parent with a history of asthma at enrolment; atopy was defined as at least one positive skin test.

Infant lung function testing

This has been described previously⁸; V_{maxFRC} was determined from the rapid thoracoabdominal compression technique during tidal breathing. AR was determined from the response of V_{maxFRC} to doubling concentrations of nebulised histamine solutions from 0.125 to 8 mg/ml.

Assessment of childhood pulmonary function, airway responsiveness, and atopy

Pulmonary function was performed using a portable spirometer (Pneumocheck Spirometer 6100; Welch-Allyn, Skaneateles Falls, NY). AR was determined using the rapid technique¹¹; briefly a hand held dosimeter was used to administer increasing doses of inhaled histamine in a stepwise manner. The change in FEV_1 after the final dose was expressed as a dose response slope (DRS).¹² Sensitisation to 10 common

Abbreviations: AR, airway responsiveness to histamine; DRS, dose response slope; FRC, functional residual capacity; RSV, respiratory syncytial virus; URTI, upper respiratory tract infection

Table 1 Group details at 11 years of age

	Control (n=170)	Confirmed bronchiolitis (n=16)	Probable bronchiolitis (n=8)
Male	95 (56%)	7 (44%)	6 (75%)
% V _{max} FRC at 1 month (SD)	103 (51)	72† (33)	79 (21)
No. * maternal smoking during pregnancy	41 (24%)	3 (19%)	1 (13%)
No. with parental asthma	48 (28%)	5 (31%)	5‡ (63%)
No. atopic at 11 years	81 (47%)	8 (50%)	4 (50%)
No. with asthma ever at 11 years	43 (25%)	7 (44%)	3 (38%)
No. with current asthma at 11 years	24 (14%)	2 (13%)	3 (38%)
No. ever wheezed at 11 years	41 (24%)	10¶ (63%)	3 (38%)
No. with wheeze at 11 years	27 (16%)	3 (19%)	2 (25%)

*No.=number of subjects, †p=0.02 compared with control group, ‡p=0.06 compared with control group, ¶p=0.004 compared with control group.

allergens was determined using the skin prick test. A positive reaction was defined as a weal >2 mm in any dimension.

Statistics

V_{max} FRC was expressed as percent of predicted (%) after adjustment for gender, age, length, weight, and maternal smoking in pregnancy.¹³ General linear models were created to determine sex and height regression coefficients for FEV₁, FVC, FEF₂₅₋₇₅, and PEF; this allowed % lung function to be obtained. Z scores for % of infant and childhood lung function were obtained using this calculation: (% lung function – 100)/standard deviation. Student's *t* test was used to compare differences in % and z scores of lung function between groups aged 1 month and 11 years. A linear regression model was created to determine the relation between AR and previous bronchiolitis, adjusting for atopy and any reduction in lung function. χ^2 or Fisher's exact test were used to compare dichotomous outcomes between groups. The Mann-Whitney U test was used to compare number of positive skin tests between groups. Normal distribution of data was assumed if the skewness statistic was less than plus or minus one. Analyses were performed using a standard statistical software package (SPSS release 9.0.1, SPSS, Chicago, IL).

RESULTS

Subjects

A total of 253 infants were initially recruited; 18 individuals with confirmed bronchiolitis were ascertained from hospital

records (n = 3, two positive for respiratory syncytial virus) or parental questionnaires (n = 15). Eleven were diagnosed before their first birthday. At 3 years of age, questionnaire data were available for 121 cohort members (nine with previous confirmed bronchiolitis); at 4, 5, and 6 years respective figures were 133 (9), 113 (7), and 123 (11). At 11 (SD 1.0) years old, 194 (77%) cohort members were assessed, including 16 with previous confirmed bronchiolitis. Compared with the original cohort, data were available for a smaller proportion of children at 4, 6, and 11 years of age whose mothers had smoked during pregnancy (27 versus 19%, 20%, and 23% respectively, p < 0.02 for all analyses). At 11 years of age, eight children had previous probable bronchiolitis, mean age at diagnosis 12 months (range 3–18). None of these eight individuals were admitted to hospital for bronchiolitis and five had incomplete questionnaires. Table 1 shows the details for the three groups seen at 11 years of age.

Infant lung function for those assessed at 11 years

Lung function was measured in 243 individuals at 1 month of age; 185 of these were assessed at 11 years of age, including 16 with previous confirmed bronchiolitis and eight with probable bronchiolitis. Mean % V_{max}FRC at 1 month for the previous confirmed bronchiolitis group was 72% (SD 33%) compared with 103% (SD 51%) for controls (p = 0.02); mean z scores for these groups were –0.56 and 0.06 respectively (p = 0.02; fig 1). The mean % V_{max}FRC at 1 month for individuals with previous probable bronchiolitis was 79% (SD 21%; p > 0.2

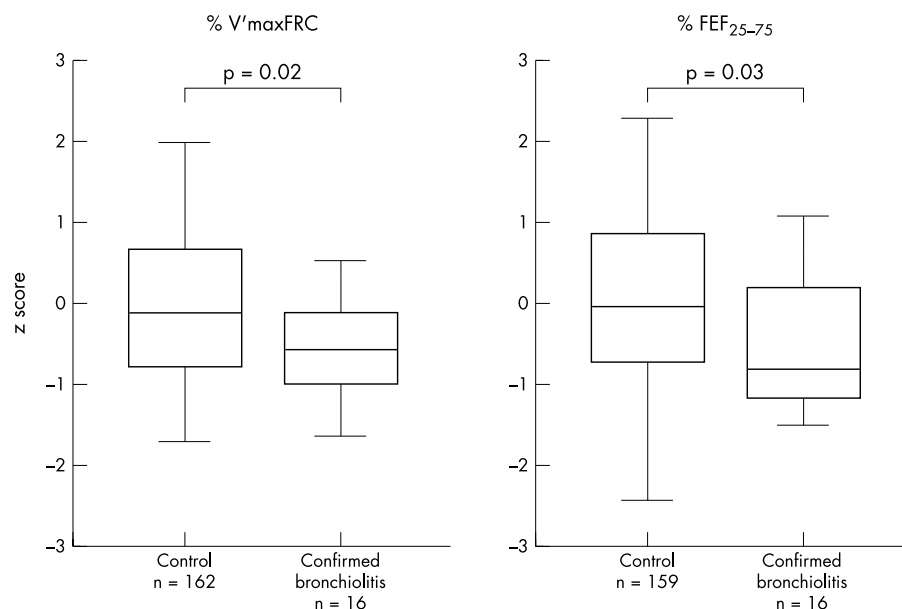


Figure 1 Box and whisker plot for z scores for % V_{max}FRC at 1 month and % FEF₂₅₋₇₅ at 11 years. Plots for five children with z scores for % V_{max}FRC over 2.5 are not displayed (values 2.5, 2.8, 3.1, 3.3, 3.9).

compared with controls). At one month, AR was not different between groups.

Respiratory symptoms

Compared with controls, those with previous confirmed bronchiolitis were more likely to wheeze with upper respiratory tract infection (URTI) at 3 (OR 5.8, 95% CI 1.4 to 25.2; $p = 0.02$) and 5 years of age (OR 5.3, 95% CI 1.1 to 25.5; $p < 0.05$); there was a similar trend at 4 years (OR 3.3, 95% CI 0.8, 13.5; $p = 0.08$). At 11 years of age, children with previous confirmed bronchiolitis were more likely to have ever wheezed compared with controls (OR 4.4, 95% CI 2.4 to 8.0; $p = 0.015$). Children with previous confirmed bronchiolitis were at no greater risk of diagnosed asthma at any age. Compared with controls, individuals with previous probable bronchiolitis were more likely to wheeze with URTI at 5 years of age (OR 11.8, 95% CI 1.2 to 120.3; $p = 0.03$) and have physician diagnosed asthma at age 6 years (OR 8.0, 95% CI 1.4 to 46.8; $p = 0.02$) but not 11 years. When the incidence of all wheeze (that is, with and without URTI) was compared between groups, there were no significant differences at any age. There were no differences between groups in terms of cough, eczema, or hay fever.

Lung function, AR, and atopy at 11 years

Lung function was obtained from all individuals at 11 years of age except for 10 controls. Mean % FEF₂₅₋₇₅ for children with previous confirmed bronchiolitis was 91% (SD 16%) compared with 101% (SD 19%) for controls ($p = 0.03$); mean z scores between these groups were -0.53 and 0.06 respectively ($p = 0.03$; fig 1). Mean % FEF₂₅₋₇₅ was also lower for individuals with previous probable bronchiolitis compared with controls, although the difference was not significant (96% (SD 30%) versus 101% (SD 19%), respectively, $p > 0.4$). There were no differences between any groups in terms of FEV₁, FVC, PEF, atopy, number of positive skin tests, or AR.

DISCUSSION

This is the first longitudinal study where lung function was known before and after bronchiolitis. In keeping with many other studies, the results showed that individuals with bronchiolitis had reduced lung function and increased wheeze in later childhood. Previously, our group has reported that there was a trend for reduced V_{max}FRC at 1 month in individuals who subsequently developed bronchiolitis⁸; however, with appropriate adjustment for factors known to affect infant lung function,¹³ this trend became significant. Importantly, with the use of z scores this study showed that the level of reduced lung function at 1 month was maintained at 11 years of age in subjects with bronchiolitis compared with the remainder of the cohort. This suggests that reduced lung function predisposes to bronchiolitis and that the respiratory infection does not influence the natural history of lung function in childhood.

No other study has measured lung function in healthy children before bronchiolitis, but reduced V_{max}FRC has been shown during acute bronchiolitis¹⁴ and between 4 and 10 months afterwards.¹⁵ Five months after respiratory syncytial virus (RSV) bronchiolitis, Renzi and coworkers showed reduced V_{max}FRC only in those who went on to wheeze at 2 years of age.¹⁵ This suggests that acute bronchiolitis causes a reversible reduction in V_{max}FRC over and above premorbid levels; reduced premorbid V_{max}FRC has previously been associated with increased wheeze.⁹

Some studies have shown increased AR following bronchiolitis^{5,6}; others,^{3,4} including the current study, have been unable to confirm this. In our cohort AR was not raised before bronchiolitis⁸; Peat and coworkers¹⁶ have reported that viral lower respiratory infection in early childhood is a risk for increased AR in childhood. These data suggest that increased

AR is acquired as a consequence of bronchiolitis. Saga and coworkers¹⁷ have followed a cohort with RSV bronchiolitis; only those with raised AR at diagnosis had asthma 10 years later, suggesting that only certain individuals are prone to develop increased AR as a consequence of bronchiolitis. Renzi and colleagues¹⁵ have described increased AR five months after bronchiolitis as a risk factor for persisting wheeze at 2 years, suggesting that increased AR after bronchiolitis is preserved in some individuals. The influence of bronchiolitis on increased AR remains uncertain, although those studies that have found a negative relation have studied older children, suggesting that the increase in AR after bronchiolitis may be transient.

In children with bronchiolitis, the results showed an increased risk of wheeze with URTI between 3 and 5 years, but at 11 years there was not an increase in current wheeze, or asthma or atopy. This suggests that the mechanism for post-bronchiolitic wheeze is not usually related to asthma or atopy; evidence from bronchoalveolar lavage fluid strongly suggests that the mechanism for viral induced wheeze is different to asthma.¹⁸ Wheeze following bronchiolitis may be in part related to abnormalities in lung function present from very early life, as increased wheeze has been shown in young children with airways of reduced calibre⁹ or altered compliance.¹⁹

The confirmed and probable groups with bronchiolitis were very similar in terms of symptoms and lung function. We considered that combination of these groups would be inappropriate because of the major differences in ascertainment. In the probable bronchiolitis group, case identification relied on parental recall of events many years previously; this was poor in the confirmed bronchiolitis group where for only six (38%) children could parents recall the diagnosis.

One important aspect of our study was that the cases were recruited from the community and not from hospital admissions. Cases in this study were therefore likely to have had milder forms of bronchiolitis and been older at diagnosis compared with other studies where recruitment was of infants admitted to hospital. Follow up studies of infants admitted with bronchiolitis have shown abnormalities of lung function^{4,5,7} and wheeze in early but not later childhood.⁷ These data are consistent with ours, although some follow up studies after bronchiolitis have also shown increased airway responsiveness,^{3,7} asthma,^{4,5,20} and atopy^{6,20} many years after bronchiolitis. Heterogeneities of populations, definitions of asthma, and study inclusion criteria may explain differing outcomes.

A second important aspect of our study was that we have only identified the virus causing bronchiolitis in two RSV positive cases admitted to hospital.⁸ RSV status may be important in the outcome of bronchiolitis, there are data to suggest that there is a different immune response in RSV bronchiolitis compared with non-RSV bronchiolitis²¹ and that RSV induced wheeze is associated with decreased asthma three years later.²² However, studies where up to 50% of cases had non-RSV bronchiolitis⁶ have reported reduced lung function and increased wheeze many years afterwards, suggesting that these outcomes may not be specific to RSV.

Follow up of the cohort has introduced the potential bias of fewer cases being studied whose mothers smoked while pregnant. Reduced V_{max}FRC in early life is associated with both in utero tobacco smoke exposure¹³ and wheeze in early childhood⁹; however, V_{max}FRC was adjusted to account for the influence of maternal smoking during pregnancy. We therefore believe that the follow up of fewer individuals exposed to in utero tobacco has not influenced our results.

In summary, we have found that a reduction in lung function was present both before bronchiolitis and at 11 years of age; importantly the level of reduction was consistent. The mechanism for post-bronchiolitic wheeze and reduced lung function may be related to premorbid lung function and not

bronchiolitis per se. Interventions aimed at producing normal lung function after bronchiolitis would be futile as lung function is reduced long before diagnosis and cannot be "normalised".

ACKNOWLEDGEMENTS

The authors are very grateful to the children and parents who have participated in this study. We are also grateful for the valuable contributions to this study made by colleagues over the past 14 years.

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REFERENCES

- 1 Wood RE. In: Nelson WE, ed. *Textbook of pediatrics*, 14th edn. Pennsylvania: WB Saunders, 1992:1075.
- 2 Sigurs N. Epidemiologic and clinical evidence of a respiratory syncytial virus-reactive airway disease link. *Am J Respir Crit Care Med* 2001; **163**(3 pt 2):S2–6.
- 3 Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999; **354**:541–5.
- 4 Noble V, Murray M, Webb MS, et al. Respiratory status and allergy nine to 10 years after acute bronchiolitis. *Arch Dis Child* 1997; **76**:315–19.
- 5 Mok JY, Simpson H. Outcome of acute lower respiratory tract infection in infants: preliminary report of seven-year follow-up study. *BMJ Clin Res Ed* 1982; **285**:333–7.
- 6 Murray M, Webb MS, O'Callaghan C, et al. Respiratory status and allergy after bronchiolitis. *Arch Dis Child* 1992; **67**:482–7.
- 7 Pullan CR, Hey EN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *BMJ Clin Res Ed* 1982; **284**:1665–9.
- 8 Young S, O'Keefe PT, Arnott J, et al. Lung function, airway responsiveness, and respiratory symptoms before and after bronchiolitis. *Arch Dis Child* 1995; **72**:16–24.
- 9 Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995; **332**:133–8.
- 10 Le Souëf PN, Turner SW, Rye P, et al. Pulmonary function at 4 weeks correlates with pulmonary function at 6 and 12 years. *Am J Respir Crit Care Med* 2001; **163**:A541.
- 11 Yan K, Salome C, Woolcock AJ. Rapid method for measurement of bronchial responsiveness. *Thorax* 1983; **38**:760–5.
- 12 O'Connor G, Sparrow D, Taylor D, et al. Analysis of dose-response curves to methacholine. An approach suitable for population studies. *Am Rev Respir Dis* 1987; **136**:1412–17.
- 13 Young S, Sherrill DL, Arnott J, et al. Parental factors affecting respiratory function during the first year of life. *Pediatr Pulmonol* 2000; **29**:331–40.
- 14 Seidenberg J, Masters IB, Hudson I, et al. Disturbance in respiratory mechanics in infants with bronchiolitis. *Thorax* 1989; **44**:660–7.
- 15 Renzi PM, Turgeon JP, Marcotte JE, et al. Reduced interferon-gamma production in infants with bronchiolitis and asthma. *Am J Respir Crit Care Med* 1999; **159**(5 pt 1):1417–22.
- 16 Peat JK, Salome CM, Woolcock AJ. Factors associated with bronchial hyperresponsiveness in Australian adults and children. *Eur Respir J* 1992; **5**:921–9.
- 17 Saga R, Mochizuki H, Tokuyama K, et al. Relationship between bronchial hyperresponsiveness and development of asthma in wheezy infants. *Chest* 2001; **119**:685–90.
- 18 Stevenson EC, Turner G, Heaney LG, et al. Bronchoalveolar lavage findings suggest two different forms of childhood asthma. *Clin Exp Allergy* 1997; **27**:1027–35.
- 19 Frey U, Makkonen K, Wellman T, et al. Alterations in airway wall properties in infants with a history of wheezing disorders. *Am J Respir Crit Care Med* 2000; **161**:1825–9.
- 20 Sigurs N, Bjarnason R, Sigurbergsson F, et al. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000; **161**:1501–7.
- 21 Oymar K, Elsayed S, Bjerknes R. Serum eosinophil cationic protein and interleukin-5 in children with bronchial asthma and acute bronchiolitis. *Pediatr Allergy Immunol* 1996; **7**:180–6.
- 22 Reijonen TM, Kotaniemi-Syrjänen A, Korhonen K, et al. Predictors of asthma three years after hospital admission for wheezing in infancy. *Pediatrics* 2000; **106**:1406–12.

ARCHIVIST

Heart disease in Williams syndrome

Williams syndrome is caused by a microdeletion in the chromosomal region 7q11.23. The deleted genes included the elastin gene. The typical vasculopathy consists of progressive supravalvular aortic stenosis and nonprogressive or improving pulmonary artery stenosis. Other lesions may include aortic arch obstructions and involvement of innominate or carotid arteries, localised coarctation, and abnormalities of mitral and aortic valves. The diagnosis can be confirmed by demonstrating hemizygosity for the elastin gene by fluorescence in situ hybridisation (FISH). The cardiovascular manifestations have been described in a large retrospective follow up study in Finland (M Eronen and colleagues. *J Med Genet* 2002; **39**:382–6).

The study included 75 patients aged 0.3–76 years (median 22.7 years) with Williams syndrome confirmed clinically and by FISH. Neonatal manifestations recorded in hospital records consisted of a heart murmur in 28 patients, heart failure in four, cyanosis in two, and absent femoral pulses in one. Twenty-seven of these 35 neonates had structural cardiovascular disease. Altogether 44 of the 75 patients had structural cardiovascular disease demonstrated at some time.

Cardiovascular disease was diagnosed in infancy in 23 patients. Twenty-one of these infants had supravalvular aortic stenosis (6), pulmonary artery stenosis (4), or both (11), and five with both also had coarctation, hypoplastic aortic arch, and hypertrophic cardiomyopathy. One infant had cardiomyopathy alone and one had the tetralogy of Fallot. Fourteen of these infants needed heart surgery or balloon dilatation either in infancy or later. Two died.

Fourteen children had a cardiovascular diagnosis made between the ages of 1 and 15 years. Eleven of these had supravalvular aortic stenosis alone, two had pulmonary artery stenosis alone, and one had a mitral valve defect. Three of the patients with supravalvular aortic stenosis had surgery at ages 8, 11, and 45 years. None of these 14 children died during follow up.

Seven patients were older than 15 years when a cardiovascular diagnosis was made. The diagnoses were supravalvular aortic stenosis alone (3), aortic valve defect (2), mitral valve defect (1), and both supravalvular aortic stenosis and mitral valve defect (1). None of these patients had a cardiac intervention but three died. Two of the three cases of supravalvular aortic stenosis alone were diagnosed only at autopsy. Twenty-three of 42 patients over the age of 15 years were hypertensive and 14 of these were treated with antihypertensive drugs.

Cardiovascular disease associated with Williams syndrome may be diagnosed at any age but most commonly in infancy. Surgery or other procedures are often necessary. Hypertension is common in adults with the syndrome.