Airway Response to a Bronchodilator in Healthy Parents of Infants With Bronchiolitis*

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In order to assess the role of genetic factors and environmental influences in bronchial responsiveness, we studied the airway response to an inhaled bronchodilator in 66 nonasthmatic parents (age, 30.9 ± 5.9 years) of infants with bronchiolitis (group 1). It was a placebo-controlled double-blind study. A control group (group 2) of healthy parents of infants who did not have bronchiolitis also were investigated with the test of bronchodilator response. All subjects showed normal expiratory airflow and lung volumes (forced vital capacity [FVC], forced expiratory volume in 1 s [FEV1], and mean forced expiratory flow during the middle half of FVC [FEF25-75%]) > 80 percent of predicted) at baseline forced expiratory maneuver. In 16 (24.2 percent) subjects of group 1, there was significant increase in at least one parameter after salbutamol administration, but not after placebo inhalation, with respect to baseline levels. Furthermore, no significant changes in FVC, FEV1, or FEF25-75% values were found in group 2. In conclusion, this study confirms that parents of infants with bronchiolitis have an enhanced airway responsiveness, greater than control parents. Further studies are needed to assess whether one may infer the outcome of infants with bronchiolitis from this characteristic in their parents. (Chest 1994; 105:706-09)

Bronchiolitis is a viral disease of the lower respiratory tract resulting from inflammatory obstruction of the small airways. It occurs under 2 years of age and is characterized by the acute onset of serous nasal discharge, wheezing, cough, and dyspnea with obstructive pulmonary hyperinflation as seen on a chest roentgenogram.1

A significant proportion of infants affected by bronchiolitis have clinical manifestations of asthma later on in childhood.1,4 Thus, even if there is no definite link between wheezing in infancy and asthma in childhood, about 30 percent of infants with bronchiolitis are expected to develop asthma.1

Respiratory viral infections may be a pivotal component in the pathogenesis of airway hyperresponsiveness and asthma.5

Recently, however, some investigators6,7 have shown that pre-illness lung function is predictive of subsequent wheezing diseases. Hence, infants who have lower lung function very early in life, before any lower respiratory tract illness, are at higher risk for developing subsequent wheezing illnesses.

It also has been suggested that there may be a genetic predisposition to develop bronchiolitis and that such infants have hyperresponsive airways even before they become infected.8,10 In this regard, Gurwitz and associates3 reported a high incidence of bronchial hyperreactivity, as defined by methacholine challenge, in the first-degree relatives of children who had contracted bronchiolitis.

Also, the responsiveness to a bronchodilator drug may be a useful guide to the presence of bronchial reactivity in epidemiologic studies of obstructive airway disease.11,12 This test is safe, is relatively inexpensive, and is in widespread use.13 Indeed, the airway responsiveness to a bronchodilator is tested several times daily in most clinical respiratory function laboratories to assist in the diagnosis of asthma.14 In addition, recently it has been reported that a significant increase in expiratory airflow following inhalation of a β2-agonist is suggestive of nonspecific airway hyperreactivity in children with normal baseline lung function tests.15

Hence, in order to assess the role of genetic factors and environmental influences related to development or persistence of bronchial responsiveness, we have studied the bronchodilator response in healthy parents of infants with bronchiolitis compared with the response in healthy parents of infants who did not have bronchiolitis.

Materials and Methods

From January through March 1992, we have studied 132 adults (66 males and 66 females) in good past and present health at least 4 weeks after any upper respiratory tract infection. Informed consent was obtained before participation in the study. In particular, these adults should have had a negative health history for chronic bronchitis, asthma, and allergy. None used inhaled bronchodilators. None had skeletal deformities such as kyphoscoliosis. All came from the same geographic area, with similar exposure to environmental pollution. Socioeconomic conditions and level of education also were similar in the two groups. All subjects had normal values for expiratory airflow.
and lung volume (FVC), FEV₁, and mean forced expiratory flow during the middle half of FVC (FEF25-75%) >80 percent of predicted) at baseline forced expiratory maneuver. We used the prediction equations of Knudson and coworkers.¹⁶

There were 66 parents (two by two) of 35 children (2 pairs of twins) affected by bronchiolitis (age, 30.9 ± 5.9 years; height, 167.1 ± 8.6 cm). Only 20 (30.3 percent) (13 males and 7 females) were smokers (>10 cigarettes a day). The second group was composed by 66 parents of children without bronchiolitis (33 males and 33 females) who were almost the same age (30.4 ± 3.9 years), height (169.5 ± 10.3 cm), and percentage of smokers (28.7 percent); 9 were male and 10 female.

Subjects were tested with an automated instrument (pneumotachograph Multispiro-PC, Burke & Burke, Wurzburg, Germany). The lung function protocol is based on American Thoracic Society recommendations.¹⁷ In particular, each subject performed baseline forced expiratory maneuvers from maximal inspiration until 3 technically acceptable tests were obtained; of these, 2 comparable flow volume loops should have FEV₁ and FVC values that did not differ more than 5 percent.¹⁷ The maximum FVC and the maximum FEV₁ were chosen among each set of spirometry values. The FEF25-75 percent was recorded from the spirometry with the maximum sum of FVC and FEV₁.

Parents of infants with bronchiolitis performed pulmonary function tests before and after 15 min inhalation, using a metered-dose inhaler, either of salbutamol (200 μg) or of a placebo, within 2 subsequent days (double-blind). Parents of infants without bronchiolitis performed pulmonary function tests only before and after 15 min of inhalation of salbutamol. Use of the inhaler with an open mouth technique was demonstrated by an investigator.¹⁸

The change from baseline after placebo or salbutamol in selected spirometric measurements was expressed as a percentage of variation from the initial value.¹⁹ Consistently with the recommendations of most authorities,¹⁹,²¹ we have used at least a 12 percent increase in FEV₁ from the baseline value in order to obtain a meaningful response. Recommended criteria for response to a bronchodilator in adults are as follows: Intermountain Thoracic Society²⁻⁻⁻—FVC, 15 percent; FEV₁, 12 percent; FEF25-75% 45 percent; American Thoracic Society²⁻⁻⁻—FVC, 12 percent, FEV₁, 12 percent. When the postbronchodilator FVC value did not change, a significant improvement in FEF25-75% also (>45 percent) was taken into account.

Two-tailed paired and unpaired Student's t tests were used for group comparisons where appropriate. Statistical significance was chosen at a probability level of less than 0.05.

### Table 1 — Characteristics of Study Groups

<table>
<thead>
<tr>
<th>Clinical Data</th>
<th>Parents of Bronchialotic Infants</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Females</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Age, yr</td>
<td>30.9 ± 5.9</td>
<td>30.4 ± 3.9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167.1 ± 5.6</td>
<td>169.5 ± 10.3</td>
</tr>
<tr>
<td>Smokers</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>Family history of atopy</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Baseline lung function parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>101.1 ± 14.8</td>
<td>107.6 ± 15.2</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>102.1 ± 13.5</td>
<td>105.8 ± 11.6</td>
</tr>
<tr>
<td>FEF25-75% (% predicted)</td>
<td>108.8 ± 28.4</td>
<td>118.1 ± 31.8</td>
</tr>
</tbody>
</table>

### Table 2 — Mean Changes in Spirometric Indexes After Salbutamol or Placebo Inhalation (in Percent of Baseline)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Salbutamol</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>1.5 ± 6.3</td>
<td>2.3 ± 4.9</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁</td>
<td>1.0 ± 5.1</td>
<td>5.4 ± 6.0</td>
<td>0.001</td>
</tr>
<tr>
<td>FEF25-75%</td>
<td>-0.6 ± 11.4</td>
<td>15.7 ± 16.6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Results

Main characteristics of the investigated subjects are reported in Table 1. There was no significant difference for anthropometric parameters nor for smoking habit between the two groups.

As stated in the Materials and Methods section, both groups had normal mean values of baseline lung function values: control subjects had slightly higher figures than parents of infants with bronchiolitis, but not significantly higher values.

Furthermore, no significant increase in FVC, FEV₁, and FEF25-75% values was observed after placebo administration in group 1. Conversely, after the inhalation of salbutamol, all parameters showed an increase, expressed as percentage of variation from the baseline value. In addition, the changes of FEV₁ and FEF25-75% values, but not of FVC, after salbutamol administration in the parents of infants with bronchiolitis were significantly different from the values measured after placebo inhalation (Table 2). On the contrary, in the control subjects, no significant increase was observed in the spirometric parameters after salbutamol administration with respect to baseline values (Table 2).

Finally, the changes in FVC, FEV₁, and FEF25-75% values in the parents of infants with bronchiolitis were significantly different from those of the control subjects after salbutamol administration (Table 2).

Indeed, using the criteria mentioned previously, 16 (24.2 percent) subjects of group 1 had a significant increase in at least one of the measurements (FVC, FEV₁, and FEF25-75%) [Table 3]; con-

### Table 3 — Number (Percent) of Subjects With a Significant Response to Salbutamol

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC &gt;15%</td>
<td>3 (4.5%)</td>
<td>0</td>
</tr>
<tr>
<td>FEV₁ &gt;12%</td>
<td>14 (21.2%)</td>
<td>0</td>
</tr>
<tr>
<td>FEF25-75% &gt;45%</td>
<td>5 (7.6%)</td>
<td>0</td>
</tr>
<tr>
<td>At least 1 index</td>
<td>16 (24.2%)</td>
<td>0</td>
</tr>
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versely, no change resulted in the values for the control group.

**Discussion**

Our study shows that healthy parents of infants with bronchiolitis have a high prevalence of bronchial hyperresponsiveness as defined by the bronchodilator response. The number of parents (24.2 percent) with a positive bronchodilator response suggests that there may be a genetic predisposition to the development of bronchiolitis and airway hyperresponsiveness.

The design of our study included two subsequent steps. First, we showed an increased airway response to an inhaled bronchodilator in the parents of infants with bronchiolitis, compared with the response after placebo administration. Second, we observed that the former response was absent in a control group.

Our results cannot be influenced by the design of the study, since the spirometric maneuvers were always well performed at the baseline evaluation: at this step, there was no difference between patients and control subjects. Moreover, the study of parents of infants with bronchiolitis was double-blind, and it was performed on two subsequent days.

Our evaluation agrees with the results obtained by Gurwitz and associates.3 In their study, 33 percent of healthy relatives of children with a history of bronchiolitis and a bronchial hyperreactivity had a positive methacholine response. Also Konig and Godfrey,22 studying healthy relatives of children with wheezy bronchiolitis, found an increased occurrence of exercise-induced bronchial lability, which was very similar to that observed in relatives of children with asthma.

Indeed, a bronchial hyperactivity was observed by some investigators23-25 in surveys carried out on healthy individuals or parents belonging to families of asthmatic patients. These and other observations2,4,28,31 would suggest either a heritability component in bronchial hyperresponsiveness or an interrelationship between infections, in particular bronchiolitis, and bronchial lability. Thus, there may be a subgroup of infants with bronchiolitis who develop respiratory problems in response to a number of triggers besides viral infections.

Our interpretation should, however, be viewed with caution. In fact, there is epidemiologic evidence that airway hyperresponsiveness may be present in normal subjects and may be absent in asthmatic subjects.32 Moreover, our study design has not been able to establish a relationship between the airway responsiveness of the parents and the outcome of the infants with bronchiolitis during later childhood.

Hence, further studies are necessary to explain fully the importance of the increased bronchodilator response in parents of children with a history of bronchiolitis. Such surveys should include investigation of respiratory characteristics of a large number of parents, together with long-term follow-up of their infants with bronchiolitis. Indeed, only these studies might elucidate whether it is possible to predict the outcome of the infants with bronchiolitis from the enhanced response to an inhaled bronchodilator in their parents.

**References**

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