Relationship Between Bronchial Hyperresponsiveness and Development of Asthma in Wheezy Infants*

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Study objectives: To evaluate the relationship between bronchial hyperresponsiveness (BHR) in infants with wheezing and the subsequent development of asthma.

Intervention: Bronchial reactivity to inhaled methacholine (BRm) during the infantile period was studied using the transcutaneous partial pressure of oxygen (tcPO2) method. Children were followed long-term for the development of asthma.

Patients: Fourteen children with bronchiolitis (mean age, 0.7 years) and 48 with wheezy bronchitis (mean age, 2.3 years) were enrolled. For comparison, 40 children with asthma (mean age, 4.6 years) and 27 healthy control subjects without chronic respiratory disease (mean age, 2.7 years) were studied.

Measurements: Consecutive doses of methacholine were doubled until a 10% decrease in tcPO2 from baseline was reached. The cumulative dose of methacholine (Dmin) at the inflection point of tcPO2 (Dmin-Po2) was recorded.

Results: During > 10 years of follow-up, seven patients with bronchiolitis developed asthma and all patients in the higher BRm set developed asthma, compared with none in the lower BRm set. In the wheezy bronchitis group, Dmin-Po2 values in the 32 patients who developed asthma were lower than those in patients who had not developed asthma (p < 0.001).

Conclusions: We concluded that there is a tendency for infants with a clinical diagnosis of bronchiolitis or wheezy bronchitis and who show BHR in the infantile period to develop asthma. The presence of increased BHR after infantile respiratory diseases associated with wheezing may be a prelude to the development of childhood asthma. (CHEST 2001; 119:685–690)

Key words: bronchial hyperresponsiveness; bronchiolitis; infants with asthma; methacholine inhalation challenge; transcutaneous oxygen pressure

Abbreviations: BHR = bronchial hyperresponsiveness; BRm = bronchial reactivity to inhaled methacholine; Dmin = minimal dose of methacholine; Dmin-Po2 = minimal dose of methacholine administered at the inflection point where the transcutaneous partial pressure of oxygen decreased linearly; RAST = radioallergosorbent test; RSV = respiratory syncytial virus; tcPO2 = transcutaneous partial pressure of oxygen

Most asthmatic children show bronchial hyperresponsiveness (BHR), which is defined as an exaggerated constrictive response of the airways to a wide variety of stimuli; this phenomenon clearly plays a central role in the pathophysiology of asthma.1,2 Although the association between asthma and BHR has been well-documented, relatively little is known about BHR in wheezing disorders during the infantile period.

Viral bronchiolitis may contribute to the development of subsequent wheezing, and bronchiolitis may be an early marker of genetically determined asthma.3,4 Viral infections exacerbate BHR,5 and it is thought that persistent BHR after a first attack of asthma may be induced or triggered by viral infections.6

Thus, it would be important to evaluate whether infants with BHR more easily succumb to respiratory infections with wheezing, whether BHR is estab-
lished soon after respiratory infections with wheezing, and whether BHR in wheezy infants affects the development of asthma.

To resolve these points, the measurement of BHR in the early stages of life is needed, especially because the first attack of asthma frequently occurs within the first few years of life; 80% of children develop symptoms before the age of 5 years. However, a useful technique for measuring BHR in infants has not been established. The measurement of age-related BHR changes during childhood is associated with problems. There is the need to correct for different body shapes and heights, and the standardized methacholine inhalation challenge cannot be used in younger children because they may be uncooperative during the test. Previously, it has been demonstrated that a technique of evaluating BHR in children by monitoring the transcutaneous partial pressure of oxygen (tcP\textsubscript{o2}) technique of evaluating BHR in children by monitoring may be uncooperative during the test.

To assess the relationship between BHR and the development of asthma in wheezy infants, we performed methacholine inhalation challenges, using tcP\textsubscript{o2} monitoring in infants with bronchiolitis and wheezy bronchitis and followed them long term to see whether they developed asthma.

**Subjects and Methods**

**Study Subjects**

Fourteen infants with bronchiolitis (11 boys and 3 girls; age range, 10 months to 2 years; mean age, 0.7 years) and 48 infants with wheezy bronchitis (25 boys and 23 girls; age range, 10 months to 6 years; mean age, 2.3 years) participated in this study (Table 1). All subjects with bronchiolitis and 44 of the 48 subjects with wheezy bronchitis were atopic. In this report, the clinical diagnosis of atopy was based on a positive family history of allergy or a positive reaction to common environmental allergens administered to the skin and to radioallergosorbent tests (RASTs) (ie, the development of a wheal \( \geq 5 \) mm in a skin prick test and \( > 0.7 \) Phadebus RAST units in the RAST. For comparison, 27 age-matched control subjects (11 boys and 16 girls; age range, 10 months to 6 years; mean age, 2.7 years) and 40 age-matched children with atopic asthma (25 boys and 15 girls; age range, 2 to 6 years; mean age, 4.6 years) also participated. This report includes previously published data on control subjects and asthmatic subjects.

In this study, we have used the conventional, simple clinical diagnoses of bronchiolitis or wheezy bronchitis based on a characteristic history of respiratory symptoms with wheezing and/or dyspnea. The patients with bronchiolitis had respiratory distress characterized by cough, wheeze, and dyspnea triggered by viral infections. In this study, all patients with bronchiolitis displayed a prolonged expiratory phase of breathing and retractions, and needed hospitalization. The patients with wheezy bronchitis had a condition characterized by wheeze, without symptoms of dyspnea, which was triggered by viral infections.

The clinical diagnosis of bronchial asthma was based on a history of recurrent attacks of dyspnea with perceptible wheezing after more than a year of follow-up, plus a positive reaction to causative allergens in skin tests and/or RASTs. Age-matched control subjects had no respiratory or atopic diseases. Asthma was not found in any control subjects during \( > 10 \) years of follow-up.

We measured BHR in infants with wheezing \( > 1 \) month after their respiratory tract infection in order to avoid the influence of transient airway damage by infection. All subjects were free of upper respiratory tract infection for \( > 4 \) weeks before the start of each study; patients received no medication for at least 12 h before testing. Informed parental consent was obtained before each study. After age 16 years, all subjects with bronchiolitis or wheezy bronchitis were assessed for the development of asthma.

**Methacholine Inhalation Challenge**

A tcP\textsubscript{o2} monitoring system was used to measure the results in all subjects. The challenge was performed in subjects during sleep in the supine position after trichloroethyl phosphate monosodium syrup (70 mg/kg) was administered. A mask allowing constant oxygen flow was used.

Each methacholine inhalation challenge was performed using the procedure of Takishima et al. Briefly, methacholine (Daiichi Kagaku Yakuin Co, Tokyo, Japan) was serially diluted with saline solution (from 25 to 50 \( \mu \)g/mL) and was administered via a commercially available delivery system (Astograph; Chest Co, Tokyo, Japan). The system consisted of 12 identical nebulizers.

**Table 1—Profiles of Patients**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients, No.</th>
<th>Sex Male</th>
<th>Female</th>
<th>Development of Asthma No., %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiolitis</td>
<td>14</td>
<td>11</td>
<td>3</td>
<td>7.50</td>
<td>All subjects are atopic</td>
</tr>
<tr>
<td>Wheezy bronchitis</td>
<td>48</td>
<td>25</td>
<td>23</td>
<td>32.67</td>
<td>92% of subjects are atopic</td>
</tr>
<tr>
<td>Asthma</td>
<td>40</td>
<td>25</td>
<td>15</td>
<td>—</td>
<td>All subjects are atopic</td>
</tr>
<tr>
<td>Control subjects</td>
<td>27</td>
<td>11</td>
<td>16</td>
<td>0.0</td>
<td>VSD (8); pKD (4); ASD (3); PDA (3); FM (1); HG (1); siblings (7)</td>
</tr>
</tbody>
</table>

\*VSD = ventricular septal defect; pKD = post-Kawasaki disease; ASD = atrial septal defect; PDA = patent ductus arteriosus; FM = functional murmur; HG = hypoglycemia; siblings = siblings with asthma.

†The clinical diagnosis of atopy was based on a positive family history of allergy or a positive reaction to common environmental allergens administered in skin tests and RASTs.

‡Values in parentheses are the No. of patients.
connected to a main tube and an air compressor that switched from one nebulizer to another automatically at 1-min intervals. Saline solution was used in the first nebulizer as a control. Salbutamol hemisulfate was used in the final nebulizer for the treatment of induced bronchoconstriction.

tc\text{PO}_2 was measured using a monitoring system (Cutaneous PO_2 Monitor 820; Roche; Basel, Switzerland). The sensor temperature was fixed at 45°C and was placed on the anterior part of the forearm of the subjects.

Methacholine doses were doubled until a 10% decrease in tc\text{PO}_2 from baseline was reached. The cumulative minimal dose of methacholine (Dmin) administered at the inflection point where tc\text{PO}_2 decreased linearly (Dmin-P\text{PO}_2) was recorded as the reactivity of tc\text{PO}_2 to methacholine. This was significantly related to the change in Dmin of respiratory resistance obtained from the oscillation method in children.\textsuperscript{9} One Dmin unit was considered to be equal to 1 min of inhaling an aerosolized methacholine solution (1.0 mg/mL) during tidal breathing (Fig 1).

In the present study, the Dmin-P\text{PO}_2 of subjects who could successively inhale the maximum dose of methacholine without a significant decrease in tc\text{PO}_2 was calculated to be 49.952 U, which was the maximum cumulative dose of methacholine.

**Data Analysis**

Nonparametric analysis of variance (Kruskal-Wallis method) was used to assess differences between groups. The Mann-Whitney U test was used to assess differences between paired groups. For convenience, data are expressed as mean ± SD. The logarithmic values (log\text{10 milliunits}) of Dmin-P\text{PO}_2 were used for statistical analysis and illustrations. A p value < 0.05 was considered to be significant.

**RESULTS**

During the methacholine inhalation challenge, the maximum decrease in tc\text{PO}_2 was between 10 and 20 mm Hg in all children. All patients underwent the methacholine inhalation challenge safely. There were no differences in baseline tc\text{PO}_2 values among the bronchiolitis, wheezy bronchitis, asthma, and control groups (p > 0.1).

The mean value of Dmin-P\text{PO}_2 in infants with bronchiolitis (8.1 ± 0.9 U) was significantly lower than that in control subjects (21.0 ± 3.9 U) (p < 0.01) and was significantly higher than that in asthmatic patients (4.35 ± 1.3 U) (p < 0.01) (Fig 2). Similarly, the mean value of Dmin-P\text{PO}_2 in infants with wheezy bronchitis (12.51 ± 2.6 U) was significantly lower than that in control subjects (p < 0.01) and was significantly higher than that in asthmatic patients (p < 0.01) (Fig 2).

Infants with bronchiolitis were divided into two sets based on the values for Dmin-P\text{PO}_2, a higher BHR set (< 7.0 U; n = 7), and a lower BHR (≥ 7.0 U; n = 7). The mean Dmin-P\text{PO}_2 in the lower BHR set (14.2 ± 4.2 U) was significantly less than that in the higher BHR set (2.0 ± 0.4 U) (p < 0.01). During > 10 years of follow-up, seven boys with bronchiolitis, all in the higher BHR set, developed asthma. All of these subjects had reacted positively to allergens in skin tests and/or RASTs and had received diagnoses of atopic-type asthma. The seven subjects with lower BHR in the bronchiolitis group did not develop asthma.

Unfortunately, only eight children with bronchiolitis were assessed for respiratory syncytial virus (RSV). Five of eight children with bronchiolitis were RSV-positive. However, there was no difference in

![Figure 1. Analysis of typical dose-response curves. With the inhalation of an incremental challenge of methacholine, tc\text{PO}_2 decreased curvilinearly. The Dmin-P\text{PO}_2 was taken as the bronchial responsiveness of methacholine, which was significantly related to the change of respiratory resistance obtained from the oscillation method. BD = bronchodilator.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21960/ on 06/26/2017)
Dmin-Po₂ between RSV-positive children (n = 5) and other children with bronchiolitis (n = 9).

In the wheezy bronchitis group, 32 patients (20 boys) have developed asthma. The mean Dmin-Po₂ value in these patients (12.12 ± 0.9 U) was significantly lower than that in the asthma-free group (21.0 ± 3.7 U) (p < 0.001; Fig 2).

The Dmin-Po₂ was the same in girls and boys among patients who developed asthma and among those who did not in both the bronchiolitis group and the wheezy bronchitis group.

**DISCUSSION**

In this study, we showed that the mean Dmin-Po₂ in infants with bronchiolitis or wheezy bronchitis was lower than that in control subjects and was higher than that in asthmatic patients; 50% of children with bronchiolitis and 41% of children with wheezy bronchitis who showed greater BHR subsequently developed asthma.

We previously evaluated BHR in infants with asthma by monitoring tcPo₂. During an acute attack of asthma, tcPo₂ correlates linearly to the severity of the attack. Methacholine-induced airway obstruction results in hypoxemia because the narrowing of the airways changes the local ventilation/perfusion ratio and results in a fall in arterial Po₂. Although this tcPo₂ change reflects the indirect caliber change, we have demonstrated that this method is simple, painless, and effort-independent with high reproducibility and, therefore, is suitable for use with infants. Clarke et al. compared the fall in tcPo₂ during bronchial provocation using histamine with changes in airway function measured by the squeeze technique in healthy infants and those with wheezing disorders. They found that tcPo₂ was a more sensitive indicator than maximum volume of functional residual capacity. In a comparison of forced oscillation, auscultation, and tcPo₂ in children, the tcPo₂ method was the safest and most reliable method of assessing BHR. Van Broekhoven et al. and Wilts...
et al. similarly reported measurement of BHR using the tcPO₂ method in younger children to be convenient and safe. We earlier demonstrated that a tidal breathing technique for evaluating BHR is effortless with high reproducibility and is suitable for measuring BHR in infantile asthma. Using this technique, we found that BHR was detectable in infants with bronchiolitis and wheezy bronchitis, and was more detectable in children who subsequently developed asthma.

It has been reported that BHR is present in very young children and that asymptomatic subjects with BHR subsequently develop asthma. These findings are consistent with the theory that infants either are born with BHR or develop it soon after birth. Our results cast doubt on the speculation that infants with BHR easily succumb to respiratory tract infections with wheezing and that BHR is established soon after respiratory tract infections with wheezing, because only half of our wheezy infants had significant BHR. However, one could speculate that wheezy infants who are born with BHR or have a congenital predisposition to acquiring BHR may evidence wheezing more readily than infants who are born without BHR or any predisposition. The incidence of BHR, which may be persistent in the long-term, in the group of wheezy infants was significantly higher than in the nonasthma group.

It has been suggested that BHR in wheezy infants may be transiently acquired after respiratory tract infections. However, reports have suggested that transient BHR after infection lasts only 1 or 2 weeks. We measured BHR > 1 month after respiratory tract infection; thus the influence of airway damage by respiratory tract infection should not be present in our study.

It is not known whether BHR in wheezy infants affects the development of asthma. Nonspecific BHR has been suggested as a risk factor for accelerated pulmonary function decline during aging and in the development of chronic airflow obstruction. Previous investigations have suggested that subjects with asymptomatic BHR had a greater frequency of asthma symptoms than normoresponsive subjects. Another longitudinal population study showed that BHR was a more important risk factor for the development of asthma than other atopic symptoms.

In our study, surprisingly, all of the patients in the set with higher bronchial reactivity to methacholine (BRm) in the bronchiolitis group developed asthma, compared with none of the patients in the lower BRm set. Similarly, in the wheezy bronchitis group, BRm in patients who developed asthma was significantly higher than in patients who did not. Our data indicate a relationship between BHR in wheezing disorders and the development of asthma in children, but BHR may not be necessary for the onset of wheezing. Although BHR may transiently increase in all patients with airway damage because of respiratory tract infection during the acute phase of bronchiolitis or wheezy bronchitis, we found that persistent BHR has a potent effect on the development of childhood asthma. Bronchiolitis and first attacks of asthma may be confused clinically, but in this study infants without BHR after bronchiolitis did not develop asthma. By measuring BHR in infants with wheezing, we can determine which ones are more likely to develop asthma.

Previously, we showed that BHR in infantile chronic lung disease was higher than in age-matched control subjects. We believe that long-term assisted ventilation and supplemental oxygen may cause irreversible damage to the airway mucosa in neonates whose airway epithelium is immature, resulting in increased reactivity in airway smooth muscle, epithelium, and glands to inhaled methacholine. This may cause ventilation-perfusion disturbances and/or airway obstruction and may be related to acquired BHR. These data support the theory that BHR in children whose airways were damaged as infants is accentuated and persistent. An association between asthma and BHR has been demonstrated, and it has been suggested that airway epithelial damage causes an increase in BHR in asthmatic patients. However, the mechanism that establishes and maintains BHR after respiratory tract infections or infantile chronic lung diseases may be different from that in atopic asthma, just as the course and/or severity of symptoms differ in asthma induced by infantile respiratory disorders vs atopic asthma.

Our results suggest that children with BHR and a history of bronchiolitis or wheezy bronchitis have a significant likelihood of developing asthma, and that it is useful to measure BHR as a predictor of asthma development. Although our patients were divided into bronchiolitis and wheezy bronchitis, based on clinical symptoms, there is likely to be considerable overlap in these two patient groups and, without definitive RSV positivity, it is likely that there is a crossover in the etiology of the wheezing in the children classified as having bronchiolitis or wheezy bronchitis. However, we cannot define the precise mechanisms by which BHR persists in children with asthma induced by infantile respiratory diseases. Further investigation is required.

**References**


CHEST / 119 / 3 / MARCH, 2001
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