Effect of Bronchial Challenge on Breathing Patterns and Arterial Oxygenation in Stable Asthma

I. Casey Stewart, M.D.;† Ann Parker, M.C.S.P.;† James R. Catterall, M.D.;‡ Neil J. Douglas, M.D.;† and David C. Flenley, Ph.D.†

The effect of histamine or methacholine inhalational challenge on breathing patterns and oxygen saturation was investigated in ten stable asthmatic patients. We used the respiratory inductive plethysmograph to record respiratory timing and minute ventilation along with an ear oximeter to measure oxygen saturation (SaO₂). As FEV₁ fell during the challenge procedure, SaO₂ also fell (average 3 percent). Furthermore, with histamine challenge, expiratory time (Te), inspiratory time (Ti), and breath period (Ttot) all increased; minute ventilation probably also fell. These changes in breathing pattern and SaO₂ were reversed by inhalation of a β₂-agonist. However, no such changes in breathing patterns were observed with methacholine challenge despite a similar fall in FEV₁. Bronchial challenge produces hypoxia in stable asthmatic patients, which might result from a combination of hyperventilation with alteration in alveolar ventilation/perfusion relationships. (Chest 1989; 95:65-70)

Te = expiratory time; Ti = inspiratory time; Ttot = total breath time; VT = tidal volume

Hyperreactivity of the airways to inhaled bronchoconstrictor agents is widely used to diagnose asthma, both in clinical practice and in epidemiologic studies, as well as to study the mechanisms of asthma itself. Histamine-induced bronchoconstriction is known to produce mild arterial hypoxemia, but the mechanism of this effect has not been investigated, to our knowledge. Most previous studies on the effect of bronchial challenge on breathing patterns used either masks or mouthpieces, which can affect the breathing pattern. We therefore used the respiratory inductive plethysmograph to measure ventilation and breathing pattern, without mouthpiece, noseclip, or mask, and related these measurements to the arterial hypoxemia observed during bronchial challenge.

**Material and Methods**

**Patients**

We studied ten male asthmatic patients aged 17 to 61 years (mean age, 36 years), all of whom had an increase in FEV₁ of at least 20 percent following the inhalation of a β₂-agonist. All were in a stable clinical state at the time of study, having had no exacerbation of asthma for at least six weeks. Their baseline FEV₁ values before histamine inhalation was 1.1 to 3.8 L (mean, 2.4 L) and before methacholine inhalation 1.4 to 3.6 L (mean, 2.47 L). Five had positive skin reactions to extracts of grass pollens, Dermatophagoides pteronyssinus, and/or cat fur. All were being treated with regular inhaled β₂-agonists, and three patients also received 5 to 10 mg of prednisolone daily by mouth. Three other patients were receiving oral theophylline, but therapy was discontinued for at least 24 h before the study. The β₂-agonists by inhalation were also withheld for at least 8 h before each study. No patient was receiving sodium cromoglycate.

**Bronchial Challenge**

All patients were challenged by inhaling histamine on one day and inhaling methacholine on a subsequent day, using the method described by Cockcroft et al. The FEV₁ was measured using a dry spirometer. After initial FEV₁ measurements were made, the patient inhaled from a Wright nebulizer using a facemask. The nebulizer was driven at a flow rate of 7 L/min, which nebulized 5 ml of a 0.9 percent saline solution over 2 min. The FEV₁ was then measured again 30 and 90 s after the end of this control nebulization. If the FEV₁ remained within 20 percent of the initial value, the patient then inhaled concentrations of either histamine or methacholine over a 2-min period, the dose of both drugs then being doubled every 5 min until a 20 percent fall in FEV₁ occurred. The dose of either histamine or methacholine that induced a fall of 20 percent in FEV₁ (the FCₙ) was then obtained by interpolation. Thereafter, the patient took 2 puffs (200 μg) of salbutamol, (albuterol) from a metered-dose inhaler, and FEV₁ was measured 15 min later.

**Measurements**

Breathing patterns were measured in the seated patients by a respiratory inductive plethysmograph (Respitrace: 15). One band was taped securely around the ribcage at the 2nd to 4th intercostal space anteriorly and the other around the abdomen at the level of the umbilicus. The relative gains of the chest and abdominal bands were arbitrarily fixed to be unity, and the sum of these two signals was then calibrated as the patient gently inflated a 600-ml bag. There was a 4-min adaptation period after calibration, and then breathing patterns were recorded for 4 min before the first bronchial challenge, then from 1½ to 5½ min following the inhalation of the dose of histamine that produced a 20 percent or greater fall in FEV₁. Breathing patterns were again recorded over 15 to 19 min...
Table 1—Bronchial Challenge and Arterial Oxygenation in Stable Asthma (Stewart et al)

Table 1—Ear Oxygen Saturation and Breathing Patterns Following Histamine or Methacholine Bronchial Challenge*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Histamine Challenge</th>
<th>Methacholine Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Histamine</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>2.43±0.25</td>
<td>1.55±0.18*</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>95.0±0.4</td>
<td>91.7±0.8*</td>
</tr>
<tr>
<td>Tl, s</td>
<td>1.62±0.2</td>
<td>2.0±0.2</td>
</tr>
<tr>
<td>Te, s</td>
<td>2.4±0.2</td>
<td>3.1±0.2*</td>
</tr>
<tr>
<td>Ttot, s</td>
<td>4.06±0.29</td>
<td>4.94±0.37§</td>
</tr>
<tr>
<td>VT/Ttot</td>
<td>40±3</td>
<td>41±3</td>
</tr>
<tr>
<td>Vt, (L)</td>
<td>0.40±0.04</td>
<td>0.44±0.03</td>
</tr>
<tr>
<td>Vt/Ttot, /min</td>
<td>6.12±0.53</td>
<td>5.37±0.55§</td>
</tr>
<tr>
<td>Vt/Tl/min</td>
<td>16.7±2.0</td>
<td>15.5±2.2</td>
</tr>
</tbody>
</table>

*FEV₁, forced expiratory volume in 1 s; SaO₂, ear oxygen saturation; Tl, inspiratory time; Te, expiratory time; Ttot, breath period; Vt, tidal volume; Vt/Ttot, minute ventilation. Values as mean ± SE.

†p<0.001; ‡p<0.01; §p<0.05.

after the inhalation of salbutamol (albuterol). All periods of recording the breathing patterns included occasions when the FEV₁ was being measured and 20 s thereafter. The SaO₂ was recorded throughout by the Hewlett-Packard 47201A ear oximeter.18

This Respitrace calibration could be influenced by changes in FRC or by changes in the relative contributions of the chest and abdominal movement. To examine the effect of FRC changes, we simultaneously measured tidal volume by the inductive plethysmograph (as the sum of the abdominal and chest wall signals) and also by a mouthpiece, nose clip, and a water-sealed spirometer in nine normal subjects, breathing both at FRC and at FRC plus 1 L. Analysis of at least 30 breaths at each of these lung volumes showed that increasing the end-tidal lung volume (FRC plus 1 L) did not make a significant difference to the ratio between the summed Respitrace signal and the tidal volume as measured by the water-sealed spirometer. Thus, at FRC plus 1 L this ratio (Respitrace/spirometer volume) was 0.89±0.09 compared with a Respitrace/spirometer volume ratio of 1.00 at FRC (p>0.1).

To investigate the accuracy of the Respitrace after the induction of bronchoconstriction, we compared the sum of the Respitrace signals to the tidal volume as measured by the water-sealed spirometer before and after histamine challenge in four of our patients on a separate occasion. The ratio of the sum of the Respitrace signals (in arbitrary units) to the tidal volume measured by the spirometer fell as bronchoconstriction developed, from 1.0 arbitrary unit/L before histamine challenge to a mean of 0.88 arbitrary unit/L (range, 0.81 to 0.95) after the maximal bronchoconstriction. We made the same comparisons when the Respitrace was calibrated by a multiple linear regression technique.16,17 Again, bronchoconstriction reduced the ratio of the sum of the Respitrace signal/spirometer volume from 1.0 arbitrary unit/L to a mean of 0.92 (range, 0.87 to 1.03 arbitrary unit/L). We conclude that with both calibration techniques, the Respitrace may therefore underestimate tidal volume by some 10 percent following histamine-induced bronchoconstriction.

Data Analysis

We recorded data on-line using a MINC computer (Digital Equipment Company) for subsequent off-line analysis. The significance of differences was assessed by paired t test using the Bonferroni correction for multiple comparisons.18 Values are given as mean ± SEM.

RESULTS

Histamine Challenge

The PC₁₀ to histamine ranged from 0.05 to 3.4 mg/dl (mean, 0.8 mg/dl). On average the FEV₁ fell by

---

Figure 1. Fall in ear oxygen saturation (SaO₂) in ten stable asthmatic patients following inhaled histamine (left) and methacholine (right) administration.
37 ± 11 percent (Table 1), associated with a significant fall in ear oxygen saturation (Fig 1). This hypoxemia was not associated with a significant change in tidal volume (0.1 > p > 0.05), but there was a significant prolongation of Ttot (Fig 2) caused by prolongation of both inspiratory time (Ti; p < 0.04) and of expiratory time (Te; p < 0.02; Fig 3 and 4). The Vr/Ttot fell significantly following histamine inhalation. However, there was no significant change in either Ti/Ttot or Vr/Ti (Table 1). Following inhalation of salbutamol, there was a significant rise in FEV₁ (p < 0.02) associated with a rise in oxygen saturation (p < 0.002). There was also a significant shortening of Te following salbutamol administration (p < 0.02), and Ttot also tended to fall (Table 1).

**Methacholine Challenge**

The PC_{20} to methacholine ranged from 0.04 to 2.5 mg/dl (mean 0.6 mg/dl). The FEV₁ fall after methacholine challenge (an average of 34 ± 11 percent) was similar to that after histamine challenge associated with a significant fall in oxygen saturation (p < 0.02) (Fig 1). However, there were no significant changes in the breathing pattern following the methacholine challenge (Table 1). Salbutamol inhalation again returned FEV₁ to around the control level, and the ear oxygen saturation also rose after salbutamol administration (p < 0.02). However, salbutamol produced no significant change in the breathing pattern following methacholine challenge.

**DISCUSSION**

We confirmed that in stable nonhypoxic asthmatic patients bronchoconstriction induced by both histamine and methacholine produced arterial hypoxemia and that histamine-induced bronchoconstriction was associated with an increase in the Ttot with similar increases in both Ti and Te. These changes were reversed when the bronchoconstriction was relieved by inhaling salbutamol.

Each patient's arterial oxygen saturation fell during both challenge procedures. This hypoxemia was probably not of major clinical significance in these patients, since the average fall in oxygen saturation was only 3 percent, and the lowest oxygen saturation recorded was 86 percent. Nevertheless, this complication of bronchial challenge should be recognized, because a similar degree of bronchoconstriction might induce important hypoxemia in patients who are more hy-
Bronchial Challenge and Arterial Oxygenation in Stable Asthma (Stewart et al)

Figure 3. Increase in expiratory time (Te) in ten patients following histamine challenge (left) and the subsequent decrease in Te after inhalation of the β₂ agonist. In contrast, methacholine inhalation produced no significant change in Te.

Figure 4. Frequency histograms of the distribution of expiratory time (Te) of each breath before (■), at maximal bronchoconstriction ( RESULTS) induced by histamine (upper) or methacholine (lower), and after administration of the β₂ agonist (□) for the same two patients shown in Figure 2.

Comparison of the degree of bronchoconstriction induced in the two studies is difficult, since they recorded only peak flow rate, which showed an average fall of 38 ± 15 percent, whereas we recorded FEV₁, which fell by 37 ± 11 percent, but clearly these changes are broadly similar. Their average reduction in SaO₂
of 1.1 ± 1.8 percent (which was only a third of that observed in this study) may simply reflect their higher level of oxygen saturation (96.6 ± 0.2 percent, compared with a value of 95.0 ± 0.4 percent in our study). The calculated fall in arterial oxygen tension (assuming an arterial pH of 7.40 and a blood P\textsubscript{50} of 26.6 mm Hg) was similar, being on average in our study 12 mm Hg for histamine and 10 mm Hg for methacholine but 9 mm Hg in the study of histamine challenge by Poppius and Stenius.\textsuperscript{7}

The mechanism of the arterial hypoxemia is not clear from these studies. Overall, hypventilation appears to play some role, at least in the hypoxemia produced by histamine inhalation, when we found that minute ventilation fell (p < 0.05). However, in contrast we found no significant change in ventilation to accompany the hypoxia produced by methacholine, with a similar degree of bronchoconstriction, nor did ventilation rise when oxygenation improved following the salbutamol inhalation, after either the histamine or methacholine challenges. The failure to observe a fall in ventilation after methacholine challenge is not likely to result from our use of the Respitrace, since this device tended to underestimate the tidal volume changes following induced bronchoconstriction. It thus seems likely that much of the hypoxemia resulted from changes in the distribution of alveolar ventilation to perfusion ratios within lung alveoli following bronchoconstriction.\textsuperscript{19}

There are conflicting results on the effect of bronchoconstriction on breathing patterns. Minute ventilation has been found to increase\textsuperscript{10,20,22} to be unchanged\textsuperscript{8,11} or decreased\textsuperscript{11} with respiratory frequency either increasing\textsuperscript{9,10} or unchanged.\textsuperscript{9,23} Some of these differences may be due to the use of mouthpieces in many studies\textsuperscript{9,11} which may alter breathing patterns.\textsuperscript{12,14,24,25} Differing severities of bronchoconstriction may also be important, as the effect of moderate and severe bronchoconstriction on breathing pattern may be different.\textsuperscript{21,22} Further, some of these studies were on normal subjects\textsuperscript{8,9,10,19} and some on patients with chronic bronchitis and emphysema,\textsuperscript{11} and these groups may respond differently to bronchoconstriction. The only directly comparable study is that of Tobin et al,\textsuperscript{20} who studied breathing pattern using an inductive technique following methacholine-induced bronchoconstriction in asthmatic patients and found no change in the breathing pattern, which agrees with our result with methacholine but not when a similar degree of bronchoconstriction was induced by histamine inhalation.

The extent of the fall of FE\textsubscript{1} induced by histamine (37 ± 11 percent) and by methacholine (34 ± 11 percent) was similar, and there were also similar falls in oxygen saturation with both agents. The changes in timing were significant following histamine challenge but not following methacholine challenge. This is compatible with the agents' having different types of actions, histamine perhaps stimulating airway afferents, which modulate breathing pattern.

Bronchial challenge can produce hypoxia in stable asthmatic patients. This may result from a combination of hypventilation with alterations in alveolar ventilation/perfusion relationships following bronchoconstriction.

References


2. Makino S. Clinical significance of bronchial sensitivity to acetyl choline and histamine in bronchial asthma. J Allergy 1966;38:127-42


12th Annual Ain Shams Medical Congress

The theme of this 12th annual congress presented by the Chest Medical Department, Ain Shams Faculty of Medicine, is The Lung in Health and Disease. The Congress will be held March 4-9 at the Faculty of Medicine in Cairo, Egypt. For information, contact Prof. Hassan Housny Youssef, General Coordinator, Ain Shams Faculty of Medicine, Ain Shams University, Abbasuya, Cairo, Egypt.

Update in Pulmonary Disease

The Cleveland Clinic Foundation will sponsor this continuing education program March 28-31 at the Grosvenor Resort, Lake Buena Vista, Florida. For information, contact the Department of Continuing Education, Cleveland Clinic Educational Foundation, 9500 Euclid Avenue, Room TT31, Cleveland 44195-5241 (800:762-8172 [outside Ohio]).