Pulmonary Gas Exchange During Histamine-induced Bronchoconstriction in Asthmatic Subjects*

Thomas V. Burke, M.D.; Markus König, M.D.; and Nausherwan K. Burki, M.D., F.C.C.P.

Bronchial provocation for testing airway hyperreactivity is now well-established. However, the effects of histamine-induced bronchoconstriction on pulmonary gas exchange in man have not been systematically studied. We empirically noted marked decreases in PaO₂ in some asthmatic subjects following induced bronchoconstriction. Nine subjects with mild, stable asthma were studied, each on two separate days. The first determined the dose of inhaled histamine necessary to decrease FEV₁ by 20 percent and the relationship to lung volume and to pulmonary resistance by the interrupter technique (Rint). On the second day arterial blood gases, ventilation, Rint, and the anatomic (V̇ano) and physiologic (V̇ophys) dead spaces were measured simultaneously. There was a significant (p<0.05), profound fall in pulmonary gas exchange in response to histamine inhalation.

At the initial study, spirometric evaluation was performed at baseline and at 5-min intervals for 30 min following histamine inhalation. A rolling seal spirometer (Ohio Medical Products, model 840) and X-Y plotter (Hewlett-Packard, model 7041M) were used to perform spirometry by standard techniques. Immediately following each spirometric measurement, pulmonary resistance (Rint) was measured by the interrupter technique (see below). The lung volume at FRC was measured at baseline and at time intervals similar to the FEV₁, following histamine inhalation. FRC was measured in a constant volume body plethysmograph (Collins, Inc) by the technique of Dubois et al. Following baseline measurements, histamine in graded concentrations was inhaled by the subject; the technique has been described in detail previously. The total dose of histamine required to achieve an approximately 20 percent decrease in FEV₁, and the corresponding change in Rint in each subject, was noted. In the majority of subjects, the FEV₁ returned to baseline at 25 min following histamine inhalation.

Each subject returned on a separate day for the subsequent study. An arterial catheter was inserted into the radial artery of the nondominant arm using an aseptic technique. Spirometric measurements including FRC were measured as described above. In addition, measurements of Rint, minute ventilation (V̇e), tidal volume (V̇t), respiratory frequency (f), and the anatomic and physiologic dead spaces (V̇ano and V̇ophys, respectively) were made while the subject breathed through a one-way valve (Hans-Rudolph, model 1400; dead space 18 ml) on the apparatus shown in Figure 1. Measurements were not made until the subject was judged to be comfortable on the mouthpiece, adjusted to the apparatus, and breathing in a stable state; this usually required 3 to 5 min.

For ventilatory measurements, the flow signal from the pneumotachograph/differential pressure transducer assembly (Hans-Rudolph, Inc, model 3800, and Validyne Corp, model MP45, respectively) on the inspiratory side of the valve was electronically integrated to volume and recorded on a four-channel direct pen writing recorder (Gould, Inc, model 2400) at a paper speed of 5
mm/s. From the recording, the minute ventilation (\(V_{e}\)), tidal volume (\(V_t\)), and frequency (\(f\)) were measured.

Measurements of pulmonary resistance (\(R_{int}\)) were made by the interrupter technique: during inspiration, inspiratory flow was completely occluded by means of the electronically operated shutter at a flow rate of approximately 0.5 L/s; pressure at the mouth was measured via a pressure transducer (Validyne Corp., model MP45), and the mouth pressure and inspiratory flow signals were recorded at a paper speed of 50 mm/s. From the record, \(R_{int}\) was measured as described by Jackson et al.\(^{18}\) On each occasion, at least seven measurements of \(R_{int}\) were obtained.

The anatomic dead space was measured by a technique described in detail previously.\(^{19}\) Simultaneous recordings of the expired gas volume and expired CO\(_2\) concentration were made at paper speed of 25 mm/s. These were digitized (Summagraphics Corp., Digitizer model ID-1-20) using a computer (Zenith Data Systems Corp., model Z-150), and the resultant CO\(_2\) concentration-volume relationship was displayed on an X-Y plotter (Houston Instruments, Inc). The instrument and sampling delay for CO\(_2\) was measured before each experiment as described previously.\(^{19}\) From the CO\(_2\)/volume plot, another computer digitizer routine was used to measure the anatomic dead space. On each occasion, at least five tidal volume breaths were analyzed for measurement of V\(_{oa}\).

The physiologic dead space (V\(_{phys}\)) was measured by the Enghoff modification of the Bohr technique.\(^{18}\) Mixed expired P\(_{CO_2}\) (P\(_{ECO_2}\)) was measured, from the distal end of a mixing chamber (Fig 1), simultaneously with the withdrawal of blood from the arterial catheter over a 90-s period. The blood sample was placed on ice and analyzed for P\(_{O_2}\), P\(_{CO_2}\), and pH in duplicate, within 20 min of sampling, using a calibrated blood gas analyzer (IL, Lexington, MA, model Micro 13). From these data the V\(_{phys}\) was calculated.\(^{14}\) The measurements of V\(_{oa}\) and V\(_{phys}\) were made simultaneously.

The sequence of measurements consisted of baseline measurements of spirometry and FRC, after which the subject breathed on the apparatus, and the resting ventilation and \(R_{int}\) were measured, followed by measurements of resting V\(_{oa}\) and V\(_{phys}\). The subject was then given the predetermined dose of histamine by inhalation and the measurements were repeated at 5, 10, and 20 min following the histamine inhalation.

Statistical analysis of the data was made by one-way analysis of variance by Newman-Keuls pairwise comparison.\(^{15}\)

**RESULTS**

Mean baseline values (Table 1) for \(R_{int}\) were moderately increased, the upper limit for \(R_{int}\) in normal subjects in our laboratory being 2.5 cm H\(_2\)O/L/s. Minute ventilation and arterial blood gas values were within normal limits, although the subjects displayed a mild degree of hyperventilation.

Following histamine inhalation, all of the subjects noticed a tightness in the chest and developed a mild wheeze. There were significant (\(p<0.05\)) increases in \(R_{int}\) and FRC; however, minute ventilation did not alter significantly, although respiratory frequency increased significantly and tidal volume decreased significantly, immediately following the histamine inha-

### Table 1—Effects of Histamine-induced Bronchoconstriction on Pulmonary Function Test Values (n=9)*

<table>
<thead>
<tr>
<th>Time</th>
<th>Rint, cm H(_2)O/L/s</th>
<th>V(_{L}), L</th>
<th>V(_{E}), L/min</th>
<th>f, min⁻¹</th>
<th>V(_{T}), L</th>
<th>PaO(_2), mm Hg</th>
<th>PaCO(_2), mm Hg</th>
<th>pH</th>
<th>P(A-a)O(_2), mm Hg</th>
<th>V(_{phys}), L</th>
<th>V(_{oa}), L</th>
<th>V(<em>{phys})/V(</em>{t})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.94 ± 0.80</td>
<td>2.70 ± 0.55</td>
<td>11.5 ± 3.6</td>
<td>12.8 ± 3.6</td>
<td>0.93 ± 0.35</td>
<td>98.2 ± 4.7</td>
<td>32.8 ± 0.042</td>
<td>7.456 ± 6.6</td>
<td>±0.11 ± 0.07 ± 0.11</td>
<td>0.34 ± 0.22 ± 0.38</td>
<td>0.34 ± 0.22 ± 0.38</td>
<td></td>
</tr>
<tr>
<td>5 min</td>
<td>4.67 ± 0.84</td>
<td>3.94 ± 0.73</td>
<td>10.7 ± 3.8</td>
<td>17.9 ± 3.6</td>
<td>0.65 ± 0.28</td>
<td>99.9 ± 2.8</td>
<td>±0.003 ± 9.4</td>
<td>±0.12 ± 0.07 ± 0.10</td>
<td>0.67 ± 0.32 ± 0.18 ± 0.42</td>
<td>0.67 ± 0.32 ± 0.18 ± 0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>4.18 ± 1.28</td>
<td>3.60 ± 0.77</td>
<td>9.2 ± 3.6</td>
<td>12.2 ± 3.6</td>
<td>0.83 ± 0.35</td>
<td>87.8 ± 3.4</td>
<td>±0.040 ± 7.0</td>
<td>±0.13 ± 0.09 ± 0.11</td>
<td>0.68 ± 0.32 ± 0.20 ± 0.41</td>
<td>0.68 ± 0.32 ± 0.20 ± 0.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 min</td>
<td>3.72 ± 1.00</td>
<td>2.95 ± 0.75</td>
<td>11.1 ± 4.9</td>
<td>14.4 ± 5.6</td>
<td>0.78 ± 0.16</td>
<td>90.4 ± 10.7</td>
<td>±0.043 ± 6.7</td>
<td>±0.10 ± 0.10 ± 0.10</td>
<td>0.78 ± 0.16 ± 0.10 ± 0.10</td>
<td>0.78 ± 0.16 ± 0.10 ± 0.10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mean ± SD. Rint = pulmonary resistance by interrupter technique; V\(_{L}\) = lung volume at FRC; V\(_{E}\) = expired minute ventilation; f = respiratory frequency; V\(_{T}\) = tidal volume; PaO\(_2\), PaCO\(_2\) = arterial PaO\(_2\) and PaCO\(_2\), respectively; P(A-a)O\(_2\) = alveolararterial PaO\(_2\) difference; V\(_{phys}\), V\(_{oa}\), physiologic and anatomic dead space, respectively. Statistical analysis by Newman-Keuls one-way analysis of variance.\(^{15}\)

†Significantly different (\(p<0.05\)) from baseline.

‡Significantly different (\(p<0.05\)) from 5-min values.
lulation. There was a significant (p<0.01) decrease in PaO₂ (mean decrease 21.8 mm Hg) and a significant increase in the alveolo-arterial PO₂ difference P(\(A-a\))O₂, associated with a significant increase in the ratio of Vd/phys/VT; however, alveolar ventilation fell with a rise in PaCO₂, although this was not statistically significant.

**DISCUSSION**

The present study indicates that, even in mild asthmatic patients with a normal resting PaO₂, histamine inhalation sufficient to cause a 20 percent decrease in FEV₁ results in a profound fall in PaO₂. This is not related to significant changes in minute ventilation or alveolar ventilation, but to marked alterations in ventilation (V)/perfusion (Q) matching.

It is well recognized that during spontaneous attacks of asthma, as well as in chronic asthma, marked abnormalities of V/Q occur. Thus, previous studies during acute asthma have documented V/Q abnormalities as the primary cause of the hypoxemia that is an invariable accompaniment. There is a marked broadening of the V/Q relationship; on the other hand, no absolute pulmonary shunt (pulmonary blood flow through areas of totally nonventilated lung) occurs, although in extreme prolonged status asthmaticus, some shunt may be present.

However, while studies of the acute effects of bronchodilation on arterial blood gases and V/Q relationships in asthma have been reported, there are, to our knowledge, no published reports specifically examining the effects of histamine-induced bronchoconstriction on V/Q relationships. In a study primarily concerned with the pulmonary vasodilator actions of nifedipine, Ballester et al found a smaller decrease in PaO₂ (mean decrease 11.5 mm Hg) following methacholine-induced bronchoconstriction in mild asthma. The difference in magnitude can probably be accounted for by differences in the study population. Poppius and Stenius reported only a small decrease (mean -1.1 percent) in arterial O₂ saturation (SaO₂), measured with an ear oximeter, during histamine inhalation; changes in SaO₂ and peak expiratory flow rate were only monitored for 90 s, before bronchoconstriction was reversed with isoproterenol inhalation. This may explain the difference in the magnitude of the induced hypoxemia between their report and the present study; in addition, small inaccuracies in SaO₂ measurement in the range of PaO₂ in these subjects could mask relatively large changes in PaO₂, and, finally, the degrees of induced bronchoconstriction between the two studies were probably not comparable. Other studies have examined the effects of bronchoconstriction on radioisotope-measured V/Q matching; these studies report that major changes occurred in ventilation distribution after histamine.

In the present study, we utilized measurements of arterial blood gases and dead space to define V/Q abnormalities. While newer techniques of assessing V/Q relationships utilizing inert gases have been described, these are very complex and require steady state conditions, which would have been difficult to achieve during histamine inhalation. The concept of dead space ventilation, originally described over a century ago, remains valid for analyzing V/Q relationships. Since unclear definitions in the past have bedeviled discussions of respiratory dead space, in the present study we have adhered to currently accepted definitions; thus, the anatomic dead space (VDan), as measured from the expired CO₂ concentration-volume trace, is synonymous with the series or airways dead space and extends from the lips to the interface between inspired and alveolar gas, in the respiratory bronchioles. The physiologic dead space, as measured in the present study, consists of the sum of VDan and the alveolar (VDA) or parallel dead space.

The present study shows that bronchoconstriction in these mildly asthmatic subjects resulted in a significant increase in P(\(A-a\))O₂ and the Vd/phys/VT ratio which, in the absence of an increase in overall ventilation, resulted in a marked fall in PaO₂. An increase in the Vd/phys/VT relationship, as derived in the present study by the Enghoff modification of the Bohr technique, can be due to one of three mechanisms: an increase in right-to-left shunt, a decrease in O₂ saturation, or an increase in ventilation to areas with low blood flow. Increased right-to-left shunt, by elevating the PaCO₂, may increase Vd/phys/VT. However, absolute shunts do not occur in asthma and have not been noted with pulmonary radioisotope perfusion scans following induced bronchoconstriction. A decrease in O₂ saturation of the blood, by reducing the release of CO₂ from the blood (Haldane effect) into the alveoli would tend to increase Vd/phys/VT; however, this would not explain the fall in PaO₂. The most likely mechanism for the increase in Vd/phys/VT and decrease in PaO₂ is an increase in ventilation to regions with low blood flow; associated with little change in minute ventilation, this would result in the observed fall in PaO₂ and slight rise in PaCO₂. This explanation would conform to the findings following exercise-induced asthma in children and in adults, in whom areas of increased Va/Q developed. These findings contrast with those of Wagner et al, who demonstrated no areas of increased Va/Q in patients with asymptomatic asthma. It is possible that these changes in Va/Q only become manifest during acute exacerbations; alternatively, histamine and exercise challenge may result in different V/Q abnormalities compared with asymptomatic asthma. A further point, not examined in the present or previous studies, to our
knowledge, in man, is the effect of bronchoconstriction on pulmonary blood flow; induced bronchoconstriction in dogs results in increased cardiac output,

probably due to increases in intrathoracic pressure swings.

The effects of the increased pulmonary blood flow would be to attenuate the fall in PaO₂ which would occur for any given V/Q mismatch.

In theory, there could be several possible effects of induced bronchoconstriction on the dead space. Firstly, narrowing of the airways could be predicted to decrease airway volume and hence, the anatomic dead space. The present results show that this does not occur: absolute VDan did not alter significantly (Table 1). The reason for this may lie in the fact that there was a significant elevation in FRC following bronchoconstriction, which would act to increase VDan. It is probable that the opposing effects on VDan of bronchoconstriction and increase in lung volume canceled each other and resulted in a net absence of significant change in VDan. These results are in accord with a previous study on chronic asthma subjects in whom the VDan was within predicted normal values.

Similarly, it would be predicted that VdpHys would increase with an increase in FRC; however, VdpHys actually decreased following bronchoconstriction, and this was associated with a decrease in Vt, which is known to reduce VdpHys. It is likely, therefore, that had Vt not changed, the VdpHys would have increased. Thus, the change in ventilatory pattern following histamine inhalation limited the increases in VDan and VdpHys that would otherwise have occurred.

It could be argued that a different breathing pattern, with large tidal volumes and the same or lower respiratory frequency, would be more advantageous, since, in normal subjects, while the absolute values of VDan and VdpHys increase with this pattern, the ratio Vd/VT greatly decreases, resulting in higher PaO₂ and lower PaCO₂. However, there may be two reasons why this pattern may be disadvantageous during induced bronchoconstriction in asthmatic subjects: first, the associated increase in FRC may, by increasing VdpHys to an even greater extent, result in no decrease in Vd/VT. Second, the increase in work of breathing associated with the increase in ventilation inherent in this ventilatory pattern could be more dyspneogenic as well as increasing the oxygen uptake of the respiratory muscles. Thus, the ventilatory pattern adopted by these asthmatic subjects in response to bronchoconstriction is probably optimal under the circumstances.

The ventilatory pattern response to inhaled histamine is believed to be neurally mediated via airway irritant receptors; hypoxemia itself increases respiratory frequency but usually without any decrease in Vt. The ventilatory pattern changes observed after bronchoconstriction in the present study were similar to those seen in chronic stable asthma.

A curious feature of the present study is the finding that alveolar ventilation did not increase in these asthmatic subjects with induced bronchoconstriction. In this regard, these subjects responded in a similar manner to patients with chronic bronchitis and emphysema, who respond to methacholine-induced bronchoconstriction with alveolar hypoventilation, which is in contrast to the hyperventilation occurring with spontaneous bronchoconstriction in asthmatics.

This could be a function of the degree of bronchoconstriction, the length of time over which it occurred, or of the bronchoconstrictor stimulus itself. Further work is necessary to elucidate this.

The present study indicates that there may be a profound decrease in arterial Po₂ following histamine challenge even in very mild, stable asthma. The clinical implications of the present study are that bronchoconstrictor challenge should be undertaken with caution in patients with decreased resting PaO₂ and that the arterial Po₂ or oxygen saturation should probably be monitored in these subjects; it may be necessary to give supplemental oxygen in some patients during a bronchoconstrictor challenge. The results of the present study indicate that the decrease in PaO₂ is primarily due to an increase in the physiologic dead space, which is also influenced by a marked change in ventilatory pattern.

REFERENCES

1 Subcommittee on Bronchial Inhalation Challenges, Assembly of Allergy and Clinical Immunology. ATS News. 1980, Spring, 11-19
4 Mayfield JD, Faen FN, Nicholson DP. Static and dynamic lung volumes and ventilation-perfusion abnormality in adult asthma. Thorax 1971; 26:591-96
12 Jackson AC, Milhorn HT, Norman JR. A reevaluation of the interrupter technique for airway resistance measurement. J Appl Physiol 1974; 36:204-68
13 Baker RW, Burki NK. Alterations in ventilatory pattern and ratio of dead-space to tidal volume. Chest 1987; 92:1013-17
19 Munkner T, Bundgaard A. Regional V/Q changes in asthmatics after antigen inhalation. Eur J Respir Dis 1986; 68(suppl 143):44-47
27 Burki NK. The dead space to tidal volume ratio in the diagnosis of pulmonary embolism. Am Rev Respir Dis 1986; 133:679-85
33 Shepherd RH, Campbell EJM, Martin HB, Enns T. Factors affecting the pulmonary dead space as determined by single breath analysis. J Appl Physiol 1957; 11:241-44
37 Burki NK. Effects of acute exposure to high altitude on ventilatory drive and respiratory pattern. J Appl Physiol 1984; 56:1027-31
38 Burki NK. Resting ventilatory pattern, mouth occlusion pressure, and the effects of aminophylline in asthma and chronic airways obstruction. Chest 1979; 76:629-35