Ventilation Response and Drive during Hypoxia in Adult Patients with Asthma*

David W. Hudgel, M.D.; ** Melvin Capehart, M.S.E.E.; and Jerrold E. Hirsch, M.S.

We studied ventilation and inspiratory muscle activity during progressive isocapnic hypoxia in adult asthmatic patients to determine whether the decreased hypoxic ventilatory response previously identified is due to the mechanical abnormalities of the respiratory system or to low respiratory center output. The mouth pressure produced by inspiratory muscle activity, a reflection of respiratory center output, was measured at 100 msec of inspiration against an occluded airway at functional residual capacity. At end-tidal oxygen tension (PETO₂) of 80 mm Hg, inspiratory muscle activity was greater in asthmatic patients than in normal subjects for the same level of ventilation, but at PETO₂ of 40 mm Hg, both inspiratory muscle activity and ventilation were lower in asthmatic patients. Consequently, the changes in inspiratory muscle activity and ventilation per mm Hg change in PETO₂ were lower in the asthmatic patients. To generate the same ventilation during progressive hypoxia, more inspiratory muscle activity was needed by asthmatic patients. We concluded that the decreased hypoxic ventilation in asthmatic patients resulted from both decreased respiratory center output and from mechanical abnormalities of the respiratory system.

Previously we have demonstrated a decreased ventilatory response to hypoxia in a group of adult patients with a history of severe asthma.1 That study did not clarify whether the decreased ventilation was due to diminished respiratory center drive or to an inability of the respiratory system to respond to respiratory center drive because of the mechanical abnormalities of asthma. Recently, Whitelaw et al2 developed a noninvasive technique which quantitates inspiratory muscle activity and indirectly measures the respiratory center stimulus to these muscles. Thus, by measuring both inspiratory muscle activity and ventilation we can differentiate the effects of respiratory center drive and the mechanical abnormalities of the respiratory system present in asthmatic patients.

**Materials and Methods**

Twenty-one adult asthmatic patients and 18 healthy control subjects volunteered for this study. All patients were under good clinical control with a program of regular treatment with methylxanthines and beta adrenergic bronchodilators and, if indicated, inhaled or oral corticosteroids. The asthmatic patients had a duration of illness of 16 ± 4 yrs ( x ± SEM ) (range 1-35 years). Thirteen had a history of acute respiratory failure or obvious cyanosis during acute episodes of asthma. These patients were 28 ± 2 years of age, 171 ± 2 cm in height, and 66 ± 3 kg in weight; normal subjects were 30 ± 1 years, 176 ± 2 cm, and 69 ± 3 kg respectively. The difference in height was significant (P < 0.05), but correction of minute ventilation for this difference did not alter the results.

Asthmatic patients abstained from bronchodilator medicines for at least six hours, and all subjects avoided caffeine beverages for 12 hours prior to testing. Patients had routine spirometric and body plethysmographic pulmonary function tests performed prior to testing for hypoxia.

Progressive hypoxia was induced by rebreathing through a closed circuit attached to a bag-in-box apparatus containing 7 to 10 liters of compressed air. The system had a resistance of 1.3 cm H₂O/L/sec at a flow of 0.5 L/sec. Seated subjects wore noseclips and breathed through a Hans Rudolph valve. End-tidal oxygen tension (PETO₂) and end-tidal carbon dioxide tension (PETCO₂) were monitored by a Perkin-Elmer mass spectrometer (model 1100), and arterial oxygen saturation (SaO₂) was determined by an ear oximeter (Hewlett-Packard, model 47201A) in the majority but not all subjects. End-tidal oxygen tension was allowed to decrease from 80 mm Hg to 40 mm Hg over 5-8 minutes. Resting PETCO₂ was maintained throughout the hypoxic exposure by absorption of CO₂ through a parallel circuit as needed. A Fleisch No. 3 pneumotachograph was attached to a box port of the bag-in-box system. Minute ventilation (Vₕ), tidal volume, and respiratory frequency were recorded by a Nova computer. Running three breath averages of these variables, recorded every ten seconds, were used for calculations. Electrocardiographic monitoring was carried out for safety of the subject. Two tests of hypoxia were done on each subject, separated by a 10-minute rest period.

Inspiratory effort was measured by slight modification of the method of Whitelaw et al. A silent, vibration-free balloon apparatus located in the inspiratory port of the mouth valve was inflated during expiration by a distant solenoid

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294 HUGDEL, CAPEHART, HIRCH

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Table 1—Pulmonary Function Tests in Asthmatic Subjects

<table>
<thead>
<tr>
<th></th>
<th>FEV₁</th>
<th>FEF₂₅-₇₅%</th>
<th>Vtg</th>
<th>Raw Gaw/Vtg</th>
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</thead>
<tbody>
<tr>
<td>Observed</td>
<td>2.63 ± .17</td>
<td>1.88 ± .21</td>
<td>3.64 ± 20</td>
<td>4.75 ± .54</td>
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<tr>
<td>Predicted</td>
<td>3.69 ± .16</td>
<td>4.10 ± .10</td>
<td>3.24 ± .17</td>
<td>&lt; 2.5</td>
</tr>
<tr>
<td>% Predicted</td>
<td>71 ± 5</td>
<td>46 ± 5</td>
<td>112 ± 6</td>
<td>190 ± 50</td>
</tr>
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</table>

FEV₁ = forced expiratory volume in one second (L); FEF 25-75% = forced expiratory flow (L/sec); Vtg = thoracic gas volume (L); Raw, airways resistance (cm H₂O/L/sec); Gaw/Vtg = specific conductance (L/cm H₂O/sec)

Valve to occlude inspiration on a random schedule, approximately every eighth breath. Occlusions lasted approximately 250 msec. The mouth pressure at 100 msec of inspiration, measured against the occluded airway at the beginning of inspiration at functional residual capacity, was termed P₁₀₀.

Ventilation was related to Pₑₒ₂ by the equation Vₑ = Vₑₒ + A/(Pₑₒ₂−32) where Vₑₒ is the asymptote for ventilation at infinitely high Pₑₒ₂ and the constant 32 represents the Pₑₒ₂ at which the slope of the Vₑ−Pₑₒ₂ relationship approaches infinity. The A value describes the shape of the hyperbolic relationship to Pₑₒ₂. The relationship between Vₑ and 1/(Pₑₒ₂−32) is linear and was used for calculations of the Vₑ slope. P₁₀₀ values were plotted against Pₑₒ₂; and their relationship to Pₑₒ₂ is also hyperbolic, P₁₀₀ was plotted against 1/(Pₑₒ₂−32) to obtain a linear relationship, P₁₀₀slope. The Vₑ slope, P₁₀₀ slope, normoxic (Pₑₒ₂ = 80 mm Hg) Vₑ, and hypoxic (Pₑₒ₂ = 40 mm Hg) Vₑ for the two hypoxic exposures were averaged for each subject. There was no statistical difference between the first and second Vₑ and P₁₀₀ slopes in either normal or asthmatic subjects. The variation between the first and second hypoxic exposure for Vₑ slope was 26 ± 5 percent for normal subjects and 39 ± 8 percent for asthmatic patients. The variation of P₁₀₀ slope was 46 ± 13 percent for normal subjects and 55 ± 11 percent for asthmatic patients.

In 16 normal subjects and 14 asthmatic patients, Vₑ and P₁₀₀ were also plotted against SaO₂. The relationship of Vₑ and P₁₀₀ to SaO₂ is linear and results are expressed as the slope.

Independent t test was used to compare variables between normal subjects and asthmatic patients. Data were reported as mean (X) ± standard error of the mean (SEM). To test for a possible relationship of inspiratory muscle activity and ventilation with the extent of bronchoconstriction, product-moment correlation coefficient was used to relate normoxic and hypoxic Vₑ, P₁₀₀, and Vₑ and P₁₀₀ slopes with pulmonary function test variables in the asthmatics. VE slopes were correlated with P₁₀₀ slopes in both subject groups. In addition, slopes calculated from Pₑₒ₂ data were correlated with those derived from SaO₂ data. The level of significance was established at P < 0.05, two tailed.

Results

Pulmonary function test results for the asthmatic group are shown in Table 1. There was a moderate degree of airways obstruction present.

Normoxic (Pₑₒ₂ = 80 mm Hg) P₁₀₀ was greater in asthmatic patients, (1.4 ± 0.1 cm H₂O), than in normal subjects (1.0 ± 0.1 cm H₂O, P < 0.01 Table 2). Normoxic ventilation was 8.4 ± 0.3 L/min for asthmatic patients and 7.6 ± 0.4 L/min for normal subjects (ns). The asthmatic normoxic P₁₀₀ was inversely correlated with FEV₁ and FEF₂₅-₇₅%, r = −0.46 (P < 0.05), and r = −0.47 (P < 0.05) re-

Figure 1. Relationship between inspiratory muscle activity (P₁₀₀) and lung volume (FRC) in normal and asthmatic subjects. Resting normoxic inspiratory effort was not affected by lung volume so no correction of P₁₀₀ for different lung volumes was required.
Table 2—Normoxic and Hypoxic Ventilation and Inspiratory Effort Data in Asthmatic Subjects

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Duration of Asthma (yrs)</th>
<th>Normoxic** $V_E$ (L/min)</th>
<th>Hypoxic** $V_E$ (L/min)</th>
<th>$V_E$ Slope</th>
<th>Normoxic $P_{100}$ (cm H$_2$O)</th>
<th>Hypoxic $P_{100}$ (cm H$_2$O)</th>
<th>$P_{100}$† Slope</th>
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<td>21</td>
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<td>9.3</td>
<td>18.3</td>
<td>89</td>
<td>1.8</td>
<td>2.6</td>
<td>11.8</td>
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</tbody>
</table>

X ± SEM 28 ± 2 16 ± 4 8.4 ± 0.3 14.7 ± 0.7 70 ± 7 1.4 ± 0.1 2.9 ± 0.3 16.4 ± 2.8

Control X ± SEM 30 ± 1 — 7.6 ± 0.4 20.3 ± 2.5 191 ± 28 1.0 ± 0.1 3.6 ± 0.4 31.9 ± 5.0

$P$ ns — ns <0.01 <0.01 <0.01 ns <0.01

*Previous cyanosis or respiratory failure; **Normoxic, $P_{ET\text{O}_2}$ = 80 mm Hg, and hypoxic, $P_{ET\text{O}_2}$ = 40 mm Hg; †VE and P100 slopes, indices of ventilatory and inspiratory muscle activity responses to hypoxia (see text).

respectively, such that the more airflow obstruction present the greater the inspiratory muscle activity produced. In these subjects, normoxic P100 was not related to actual or predicted functional residual capacity, as has been reported by others$^{5,6}$ (Fig 1).

Asthmatic hypoxic ($P_{ET\text{O}_2}$ = 40 mm Hg) P100 was lower than the normal value, but not statistically so (2.9 ± 0.3 cm H$_2$O and 3.6 ± 0.4 cm H$_2$O, respectively). Consequently, hypoxic ventilation was less in asthmatic patients (14.7 ± 0.7 L/min) compared to normal subjects, (20.3 ± 2.5 L/min, $P < 0.01$). The P100 slope was 31.9 ± 5.0 for normal subjects and 16.4 ± 2.8 for asthmatic patients ($P < 0.01$), (Fig 2, Table 2). The lower P100 slopes of asthmatic patients were not due to the relatively high normoxic P100 values since there was no correlation between normoxic P100 and P100 slope; in other words, there was no initial value effect present. Thus, less inspiratory effort was generated throughout progressive hypoxia by asthmatic patients than the normal group. Since hypoxic ventilation was greater in normal subjects, VE slope was greater than for asthmatic patients (191 ± 28 compared to 70 ± 7, $P < 0.01$), (Fig 2).

Results were similar when VE and P100 were plotted against SaO$_2$ in the 16 normal and 14 asthmatic subjects. The VE slope was significantly higher in the normal group (1.12 ± 0.22), compared to the asthmatic subjects (0.48 ± 0.06, $P < 0.02$). The P100 slope was also greater for the normal group (0.21 ± 0.04) compared to 0.12 ± 0.03 for asthmatic
ASTHMATICS

NORMALS

$\frac{1}{(P_{ET}O_2 - 32)}$

$\dot{V}_E$ (L./MIN.)

$P_{100}$ (cm H$_2$O)

Figure 2. Ventilation and inspiratory muscle activity in normal (---) and asthmatic subjects (----). Upper panel, minute ventilation (VE) response to progressive hypoxia. Normal subjects had a significantly greater increase in ventilation as measured by VE slope. Lower panel, pressure developed by inspiratory muscle activity during progressive hypoxia. The increase in inspiratory muscle activity as measured by $P_{100}$ slope was greater in normal subjects.

group, but this difference was not quite statistically significant ($P < 0.06$). There was good agreement between the $P_{100}$ slopes plotted with $P_{ET}O_2$ data and those using $SaO_2$ data in the asthmatic patients; $r = 0.96$ ($P < 0.001$). The $V_E$ slopes were also similar; $r = 0.81$ ($P < 0.001$).

At any level of ventilation during progressive hypoxia, asthmatic patients required more activity of the inspiratory muscle (Fig 2). This was reflected in the $P_{100}/V_E$ ratio which, during normoxia and hypoxia, was greater in the asthmatic group than in the normal group: $0.18 \pm 0.01$ for asthmatic subjects and $0.14 \pm 0.01$ cm H$_2$O/L/min for normals ($P < 0.05$) during normoxia, and $0.21 \pm 0.02$ vs $0.17 \pm 0.01$ cm H$_2$O/L/min ($P < 0.05$), respectively at $P_{ET}O_2 = 40$ mm Hg. The change in $P_{100}/VE$ from normoxia to hypoxia for each group was equivalent; thus, equally more inspiratory muscle activity was expended to move a liter of gas mixture during progressive hypoxia in both normal and asthmatic subjects.

The $V_E$ slope was correlated with the $P_{100}$ slope in asthmatic patients ($r = 0.64; P < 0.01$), and in normal subjects ($r = 0.75; P < 0.001$). Isocapnia was maintained throughout progressive hypoxia. For normal subjects, normoxic $P_{ET}CO_2$ was $34 \pm 0.4$ mm Hg and hypoxic $P_{ET}O_2$ was $34 \pm 0.7$ mm Hg (ns). For asthmatic patients, normoxic $P_{ET}CO_2$ was $34 \pm 0.7$ mm Hg and hypoxic $P_{ET}CO_2$ was $34 \pm 0.7$ mm Hg (ns).

There was no correlation between the normoxic level of pulmonary function as measured by FEV$_1$, FEF$_{25-75}$, airways resistance or specific conductance and $P_{100}$ slopes in the asthmatic group. This may have been due to mechanical changes occurring during hypoxia, as suggested by the increased $P_{100}/V_E$ ratios. There was no relationship between the duration of asthma and the level of hypoxic response. This is illustrated by subjects 6, 9, and 19, who had asthma only a few years but had low responses to hypoxia. Likewise, there was no relationship between a history of cyanosis or acute respiratory failure and the hypoxic response (Table 2).

**Discussion**

The present investigation substantiates our previous findings of a decreased ventilatory response to hypoxia in adult asthmatic patients. There appears to be two causes of this decreased response. The first is a lesser increase in inspiratory muscle activity during progressive hypoxia most likely due to decreased respiratory center output; and the second is the higher inspiratory muscle effort required for each liter of ventilation, probably due to the mechanical effects of asthma.

The measurement of inspiratory muscle activity by the mouth occlusion technique reflects respiratory center output more closely than ventilation measurements in subjects with lung disease. $P_{100}$ is not affected by pulmonary resistance or compliance since during the measurement there is no airflow or change in lung volume. However, there are potential drawbacks to its use in asthmatic patients: 1) the hypoxic $P_{100}$ might be affected by an increase in lung volume occurring during hypoxia, and 2) because of increased time constants, mouth pressure might not equal alveolar pressure at 100 msec of inspiration.

In both our normal and asthmatic subjects, normoxic $P_{100}$ was not related to lung volume (Fig 1). The small increase in asthmatic FRC (12 percent) did not decrease $P_{100}$ compared to normal subjects. In fact, asthmatic normoxic $P_{100}$ was greater than normal $P_{100}$ at the same level of ventilation. This same finding has recently been shown by Burki. This increased $P_{100}$ was at least partially due to the presence of airways obstruction. During hypoxia, a
small increase in lung volume and/or a slight amount of bronchoconstriction might have occurred, as has been noted by Saunders et al.\textsuperscript{8} and Sterling.\textsuperscript{9} Whether these mechanical effects of hypoxia are greater in asthmatic patients than normal subjects is not yet known. In this study, the same increase in inspiratory muscle activity was required per liter of ventilation ($P_{100}/V_e$ ratio) from normoxia to hypoxia in both normal and asthmatic subjects. This would suggest that any increase in lung volume and/or bronchoconstriction that developed during hypoxia was equivalent in each subject group, and therefore, the effects on $P_{100}$ equivalent.

Airway obstruction could potentially delay the equilibration between alveolar and mouth pressures during inspiration against an occluded airway beyond 100 msec. The equilibration of pressures would depend upon the airway resistance and the compliance of the gas within the airways. The amount of decompression and thus change in gas compliance occurring during the measurement would be small. Thus, it would take a large increase in airways resistance to increase the time constant beyond a few milliseconds. The asthmatic subjects’ normoxic airways resistance was about twice the predicted value at 4.75 ± 0.5 cm H$_2$O/L/sec, hardly enough resistance to lengthen the time constant appreciably. If bronchoconstriction occurred during hypoxia, it probably was minimal since no symptoms developed in any asthmatic subject and since the previously reported changes in normal subjects are quite small.\textsuperscript{8,9}

A potential problem with measuring end-tidal $Po_2$ is the possibility of an increased alveolar-arterial oxygen gradient affecting the results in asthmatic patients. Since the results using $SaO_2$ data are quite similar to those using end-tidal data, the alveolar-arterial gradient was not an appreciable factor. $P_{100}$ has been correlated with ventilation and diaphragmatic electromyogram findings during hypoxia.\textsuperscript{10} In our normal and asthmatic subjects there was also a correlation between the ventilation variable, ventilation slope, and the inspiratory effort variable, $P_{100}$ slope, during progressive hypoxia. This would support the validity of using $P_{100}$ as a measure of inspiratory muscle activity, and as an indicator of respiratory center output, in asthmatic patients. Thus, this study suggests that lower respiratory center drive exists during progressive hypoxia in asthmatic patients.

$P_{100}/V_e$ ratio was increased in asthmatic patients during normoxia and hypoxia. Figure 2 shows that for equal levels of $P_{100}$, or respiratory drive, ventilation is less. This suggests that the mechanical abnormalities of asthma cause less ventilation output for the same drive, and appears to be a contributing factor to decreased ventilation during progressive hypoxia.

It is interesting that the asthmatic subjects did not attempt to maintain normal hypoxic ventilation by increasing inspiratory effort to supernormal levels as they did during normoxia. It has been shown that asthmatic patients can increase inspiratory muscle activity to supernormal levels to maintain ventilation with resistive inspiratory loads\textsuperscript{11} or during hypercapnia.\textsuperscript{12} However, there is some evidence to suggest that the response to hypoxia and hypercapnia in asthmatic patients may be different. This difference has been observed in other asthmatic patients studied in this laboratory, where a normal hypercapnic ventilatory response is present along with a low hypoxic ventilatory response.\textsuperscript{1,13}

Little is known about the ventilatory or inspiratory muscle activity responses to a combination of hypoxia and loaded breathing, such as occurs in our asthmatic subjects. All studies addressing this issue have been done only with inspiratory loading so that conclusions may not directly apply to bronchoconstriction where expiratory loading is also present. However, there is a diversity of findings in that some normal subjects increase inspiratory muscle activity and ventilation during hypoxia while others do not.\textsuperscript{14,17} Our data would suggest that asthmatic patients attempt to compensate for mechanical abnormalities during normoxia by increasing inspiratory muscle activity, but fail to do so during hypoxia.

It is not yet clear if a lowered ventilatory response to hypoxia predisposes patients with asthma to acute respiratory failure. Such a relationship exists in some individuals with recurrent respiratory failure.\textsuperscript{13,18,19} In our patient group, those with a past history of cyanosis or acute respiratory failure did not necessarily have low hypoxic responses. Of course, there are many factors, in addition to ventilation during hypoxia, that may influence the occurrence of respiratory failure in asthma; eg, severe idiosyncratic or allergic reactions, concurrent illness such as bronchitis or pneumonia, medication schedule, rapidity with which the patient seeks medical assistance, and the nature and timing of treatment in the acute situation. These factors being equal, an asthmatic patient with a low ventilatory response to hypoxia may not be able to increase ventilation in an attempt to correct hypoxemia during an acute asthma attack and consequently develop hypoxic complications. If hypoventilation is severe, acute respiratory failure may occur.

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CHEST, 76: 3, SEPTEMBER, 1979

VENTILATION RESPONSE AND DRIVE DURING HYPOXIA 299