A comparative study was made of ventilatory and airway occlusion pressure ($P_{o,1}$; a parameter reflecting respiratory center output) responses to carbon dioxide between 11 patients with bronchial asthma and 10 chronic obstructive lung disease (COLD). Increments in ventilatory volume ($V_E$) produced by a rise in end-tidal CO$_2$ pressure ($P_{ETCO_2}$), i.e. $\Delta V_E/\text{BSA}/\Delta P_{ETCO_2}$, were smaller in 4 patients with hypercapnic COLD than in 6 normal subjects. On the other hand, increments in $P_{o,1}$ produced by an elevation of $P_{ETCO_2}$ (i.e. $\Delta P_{o,1}/\Delta P_{ETCO_2}$) tended to be diminished in patients with hypercapnic COLD. Higher values for both $V_E/\text{BSA}$ and $P_{o,1}$ were observed in 6 patients with normocapnic COLD, but the differences from corresponding control values failed to achieve statistical significance due to a large variance. In 11 patients with bronchial asthma without attack, $V_E/\text{BSA}$ elevated significantly at $P_{ETCO_2}$ levels of 50 and 60 torr, but values of $\Delta V_E/\text{BSA}/\Delta P_{ETCO_2}$ were virtually same as those in normal subjects.

Key Words: Control of breathing, Occlusion pressure, COLD, Bronchial asthma

Of primary importance in the respiratory control system are the chemical regulatory mechanisms which depend for their operation upon the central and peripheral chemoreceptors. In these regulatory mechanisms of respiration a predominant role is played by the influence of changes in CO$_2$ and O$_2$, especially the former, in blood and cerebrospinal fluid upon the respiratory center$^1$. Previous studies$^2,3$ have shown that the response of ventilation to CO$_2$ is diminished in chronic obstructive lung disease patients with CO$_2$ retention. It has also been demonstrated that in this group of patients there occur lesser changes than normal in the mouth occlusion pressure (an index of neural drive to respiratory muscles) during CO$_2$ rebreathing. On the other hand, ventilatory responses to CO$_2$ in asthmatics have been studied by several authors. The CO$_2$ response curve in stable asthmatics was shift to the left, but parallel to that of normal subjects$^9$. Zackon et al$^5$ measured ventilatory responses to CO$_2$ and occlusion pressure ($P_{o,1}$) in asthmatics without CO$_2$ retention and showed that ventilation at high end-tidal CO$_2$ ($P_{ETCO_2}$) increased and $P_{o,1}$ were distinctly higher than normal subjects. The purpose of the present study is two-fold: 1) to contribute to the elucidation of the pathogenetic mechanism of CO$_2$ retention in COLD, 2) to measure ventilatory response to CO$_2$ and $P_{o,1}$ in asthmatic patients and compare the results with those in COLD patients.

MATERIALS AND METHODS

The subjects used in this study were 7 normal subjects, 10 patients with chronic obstructive lung disease (6 normocapnic, PaCO$_2$ $\leq$ 48 torr and 4 hypercapnic, PaCO$_2$ $>$ 48 torr) and 11 patients with bronchial asthma.

The subjects were connected to an apparatus which was developed by Read$^6$ and Whitelaw$^7$ as illustrated in figure 1. A 2-way valve separated the inspiratory from expiratory line, allowing

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**CO₂ Response in COLD**

Fig. 1. Schematic representation of the method used for measuring mouth occlusion pressure and CO₂ response curve.

occlusion of the inspiratory line at end-expiration by turning the occluding valve during the antecedent expiratory phase. By appropriately turning the valve A₁, the subject could either breathe room air or rebreathe from the bag in box system containing 7 percent CO₂, 50 percent O₂ and balance N₂. End-tidal CO₂ (PETO₂) was measured by a mass spectrometer (Parkin Elmer, MGA 1100 B) and it was assumed to be equal to alveolar PCCO₂. Pressure at the airway opening was assumed with a differential pressure transducer (Validyne, Model MP45-1) and tidal volume (VT) was measured by a box type spirometer (Chest, Spilor 81) connected to the bag in box system. All parameters were recorded on a multi-channel recorder (Watanabe, Multi-corder MC 6601). The mouth occlusion pressure was recorded on 3-channel recorder (Nihon Kohden, Recticoder RJG-4124) using a paper speed of 100 mm/sec during airway occlusion.

Our subjects were comfortably seated and were given a time to adjust to the breathing apparatus. While breathing room air, several airway occlusions were performed randomly. The subjects were switched to the CO₂ rebreathing circuit and occlusion maneuvers were performed randomly every 20 seconds during rebreathing. Mouth occlusion pressure measurements were made 0.1 sec after the onset of the inspiratory phase and were denoted P₀.₁. Ventilation per minute (Vₑ) was determined from each Vₜ measurements obtained during the time of 20 seconds preceding each occlusion. All volume measurements were corrected to BTPS. Plots of Vₑ versus PETCO₂ and P₀.₁ versus PETCO₂ were subjected to linear least square regression analysis. In addition, statistical analysis between control and patients values were done with the unpaired t test.

**RESULTS**

Ventilatory responses and drives to hypercapnia in the normal group and individual disease

![Fig. 2. Ventilatory response to hypercapnia in normal subjects. (n = 7)](image)

![Fig. 3. Ventilatory response to hypercapnia in patients with normocapnic COLD. (n = 6)](image)

Shaded areas represent the mean ± SD in normal subjects.

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groups are indicated in Table 1. As shown in Fig. 2, 7 normal subjects exhibited a modest increase in both $\dot{V}_E/\text{BSA}$ and $P_{0.1}$ at elevated $P_{\text{ETCO}_2}$ levels of 50 and 60 torr. Parenthetically, all values of $\dot{V}_E$ divided by body surface area (BSA) because $\dot{V}_E$ varies depending upon BSA. Six patients with normocapnic COLD had a higher value for both $\dot{V}_E/\text{BSA}$ and $P_{0.1}$, but the differences from corresponding control values failed to achieve statistical significance due to a large variance (Fig. 3). Nevertheless, these patients undoubtedly tended to show an increased ventilatory response and drive to CO$_2$. As is obvious from Table 1, values of $\Delta \dot{V}_E/\text{BSA}/\Delta P_{\text{ETCO}_2}$ and $\Delta P_{0.1}/\Delta P_{\text{ETCO}_2}$ for these patients were virtually same as those from normal subjects.

In contrast, patients with hypercapnic COLD, as can be seen in Fig. 4, showed a definite decrease in $\dot{V}_E/\text{BSA}$ with a marked reduction in reactivity to rising $P_{\text{ETCO}_2}$ (i.e. $\Delta \dot{V}_E/\text{BSA}$/

![Figure 4](image)

Fig. 4. Ventilatory response to hypercapnia in patients with hypercapnic COLD ($n=4$)
Shaded areas represent the mean ± SD in normal subjects.

Table 1. Ventilatory, occlusion pressure responses to hypercapnia in four groups and normal subjects.

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects ($N=7$)</th>
<th>Normocapnic COLD ($N=6$)</th>
<th>Hypercapnic COLD ($N=4$)</th>
<th>Bronchial asthma ($N=11$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\dot{V}<em>E/\text{BSA}, \text{L/min/M}^2$ at $P</em>{\text{ETCO}_2}=50$ torr</td>
<td>7.46 ±3.26</td>
<td>15.7 ± 8.7</td>
<td>15.6 ±4.26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&quot; 55 torr</td>
<td>13.5 ±4.42</td>
<td>22.8 ±13.16</td>
<td>22.5 ±6.82</td>
</tr>
<tr>
<td></td>
<td>&quot; 60 torr</td>
<td>7.60 ±0.78</td>
<td>7.76 ±1.48</td>
<td></td>
</tr>
<tr>
<td>$\Delta \dot{V}<em>E/\text{BSA}/\Delta P</em>{\text{ETCO}_2}$</td>
<td>0.607±0.125</td>
<td>0.576± 0.17</td>
<td>0.211±0.052</td>
<td>0.681±0.61</td>
</tr>
<tr>
<td>$P_{0.1} \text{cmH}<em>2\text{O}$ at $P</em>{\text{ETCO}_2}=50$ torr</td>
<td>2.14 ±0.82</td>
<td>8.28 ± 6.88</td>
<td>6.90 ±4.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&quot; 55 torr</td>
<td>4.02 ±1.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&quot; 60 torr</td>
<td>5.6 ±2.63</td>
<td>5.05 ±1.59</td>
<td>15.67 ±8.87</td>
</tr>
<tr>
<td>$\Delta P_{0.1}/\Delta P_{\text{ETCO}_2}$, cmH$_2$O/torr</td>
<td>0.33 ±0.17</td>
<td>0.662±0.412</td>
<td>0.145±0.086</td>
<td>0.867±0.612</td>
</tr>
</tbody>
</table>

*+significantly different ($P < 0.05$) from value of normal subjects
++significantly different ($P < 0.01$) from value of normal subjects

Abbreviations: COLD= chronic obstructive lung disease; $\dot{V}_E/\text{BSA}$= Ventilation per minute per body surface area; $\Delta \dot{V}_E/\text{BSA}/\Delta P_{\text{ETCO}_2}$ = slope of ventilatory response to end-tidal carbon dioxide tension; $\Delta P_{0.1}/\Delta P_{\text{ETCO}_2}$ = slope of occlusion pressure response to end-tidal CO$_2$ tension.

Values are mean ± SD.
CO2 Response in COLD

$\Delta$PETCO2) (Table 1) even though $P_{O.1}$ levels were within the normal range.

In 11 patients with bronchial asthma without attack $\dot{V}_E/BSA$ was found significantly increased at $P_{ETCO2}$ levels of 50 and 60 torr and $P_{O.1}$ also tended to be elevated (Fig. 5). This group of patients gave no significantly different values of $\Delta\dot{V}_E/BSA/\Delta$PETCO2 and $\Delta$P0.1/$\Delta$PETCO2 as compared with normal subjects (Table 1).

![Fig. 5. Ventilatory response to hypercapnia in patients with bronchial asthma. (n = 11)](image)

Shaded areas represent the mean ± SD in normal subjects.

DISCUSSION

In many cases of chronic obstructive lung disease effort ventilation is required owing to dyspnea. There are instances in which CO2 retention ensues from a failure to maintain a sufficient ventilatory volume to effect adequate alveolar gas exchange, presumably as a result of decreased ventilatory drive of the respiratory center. According to our study, hyperventilation results from airway obstruction or increased inspiratory flow resistive loading in many cases of normocapnic COLD. Ventilatory responses to CO2 in such patients are nearly identical with those elicited in normal individuals. Thus, airway obstruction appears to increase ventilatory drive without chemical stimuli. The mechanism of this responses is not certain, nor is it clear how it interacts with other factors which control ventilatory effort. Although the movement of chest wall is passive element of the respiratory control system, this play important role in determining the effects of mechanical ventilatory loading. However it is not clear whether lung disease activates mechano-receptors in lung and chest wall by sensitizing them or by providing large amounts of normal stimuli. Situations are different in hypercapnic COLD; thus, hyperventilation does not take place despite the presence of airway obstruction and ventilatory drive of the respiratory center remains within the normal limits. According to Gelb, Althose and Dossman, this is due to decreased response to an increase in inspiratory flow resistive loading. In hypercapnic COLD CO2 response is so weak that chemical CO2 drive of the respiratory center could not be effected to any desired extent.

In bronchial asthma, hyperventilation occurs during as attack, while during attack-free periods ventilation usually is normal so long as the disease is not severe. According to the results of our study, however, patients with bronchial asthma were in a state of relative hyperventilation during attack-free periods when compared with normal subjects. This is probably because such patients have a slight degree of airway obstruction even during attack-free periods. There was no significant difference between asthmatic patients and normal individuals in CO2 response, however. Airway obstruction entails increased ventilatory work, which in turn gives rise to hyperventilation and an increase in CO2 drive of the respiratory center. Nevertheless, CO2 response was normal in this group of patients. The ventilatory and mouth occlusion pressure responses to CO2 observed in COLD and BA groups were in good agreement with previous reports.

REFERENCES


