Respiratory Center Output and Ventilatory Timing in Patients with Acute Airway (Asthma) and Alveolar (Pneumonia) Disease*

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To investigate the mechanism for hyperventilation in two common but dissimilar conditions, asthma (A) and lobar pneumonia (P), we examined the ventilatory pattern in 17 A and six P subjects. When acutely ill, hyperventilation (PaCO₂) was similar in the two groups. Minute ventilation (VE) however, was slightly greater in group A than in P. In A patients, measurements of occlusion pressure (dP/dT) and inspiratory flow rate (VT/t₁) during quiet breathing showed enhancement of respiratory center output. By contrast, in P patients, dP/dT and VT/t₁ were not elevated. Tidal volume (VT) was 0.59 ± 0.19 L in A; 0.45 ± 0.09 in P. Respiratory rate was increased in both groups. With supplementary oxygen therapy, neither VE nor PaCO₂ changed in either group. The mechanism for the increased ventilatory drive in group A is unclear. Most likely, reflexes initiated by either bronchospasm or by the sudden increase of end-expiratory lung volume (EELV), not operative in P, account for the increased respiratory center output seen in A. To examine the latter possibility, we studied the ventilatory pattern at both normal and increased EELV in six nonasthmatic subjects. Both dP/dT and VT/t₁ were increased in all subjects after elevation of EELV. Thus, changes in EELV may be important for the regulation of ventilation during bronchospasm.

Hyperventilation occurs in many acute pulmonary diseases. Current concepts indicate that minute ventilation (VE) represents the product of two components, respiratory timing and medullary respiratory center output. Either of two mechanisms, change in the timing component or increase of ventilatory drive, may cause hypcapnea. Respiratory frequency (f) and inspiratory time (t₁), both easily measured in acutely ill patients, are indices of respiratory timing. The occlusion pressure (that subatmospheric mouth pressure developed by isometric contraction of respiratory muscles 100 milliseconds after the onset of an inspiratory effort against an occluded airway) is a noninvasive index of respiratory center output well suited for quantification of ventilatory drive in the acutely ill patient. Tidal volume (VT) and mean inspiratory flow rate (VT/t₁) are other easily measured indices of ventilatory drive.

In this study, we investigated first the role of each of these two mechanisms in the genesis of hyperventilation during acute illness, and second, the possibility that supplementary oxygen will attenuate either respiratory center output or the timing mechanism.

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We studied patients with reversible airway (asthma) and alveolar (pneumonia) diseases. Patients were assessed by conventional clinical criteria and results of pulmonary function tests. We recorded occlusion pressure, VE and its components (VT, VT/t₁, t₁, and f) in these subjects before therapy, with supplementary oxygen as the only therapy, and, last, after specific bronchodilator or antibiotic therapy. Since this study required that the subject breathe through a mouthpiece, we examined the effect of mouthpiece breathing on both ventilatory drive and the time mechanism. Finally, to examine the possibility that the increased respiratory center output in the asthmatic patient might be caused by changes in functional residual capacity during bronchospasm, we studied ventilatory drive and timing in nonasthmatic subjects at increased end-expiratory lung volume.

Materials and Methods

Subjects

Seventeen asthmatic patients, six subjects with acute bacterial pneumonia, and 17 normal volunteers were studied. All signed informed consent. Asthmatic subjects were well known to the pulmonary service. Their studies were performed at the onset of an acute illness when each met the following criteria: (1) acute onset of dyspnea; (2) wheezing; (3) past history of bronchospasm; and (4) no ventilatory impairment between asthmatic attacks, judged by both clinical and functional observations.
Pneumonia patients, selected from the College Hospital in-patient population, met the following criteria: (1) fever, chills, and productive cough of recent onset; (2) neutrophils and microorganisms demonstrable on sputum Gram stain; and (3) roentgenographic infiltrates on examination. Patients with clinical evidence for either heart disease or chronic lung disease (e.g., chronic respiratory symptoms, evidence for airway obstruction, or roentgenographic abnormality other than the infiltrate) were excluded.

Control subjects volunteered from the medical and para-medical staffs.

All 17 asthmatic subjects performed pulmonary function and ventilatory control studies prior to therapy, and 16 repeated ventilatory control studies after inspiring oxygen, 4 L/min, for ten minutes. To demonstrate that the decrease in occlusion pressure often observed during O₂ inhalation did not represent psychologic adaptation to the laboratory setting, we again repeated ventilatory control testing in five patients ten minutes after discontinuation of O₂.

In 12 subjects, both pulmonary function and ventilatory control testing were repeated after bronchodilator therapy. Eight had been treated as outpatients; four were reexamined after a brief hospitalization.

The pneumonia patients were studied within 18 hours of hospital admission. All had received an initial dose of antibiotic therapy by this time. Some had received non narcotic analgesic. Testing was repeated prior to discharge. Criteria for discharge were appreciable resolution of the infiltrate and white blood cell count and body temperature within normal limits.

Procedures

Pulmonary function tests were performed with a 9-L Collins spirometer. Functional residual capacity and airway resistance were measured in a pressure-variable body plethysmograph by the DuBois method. Lung volumes were expressed as a percentage of a predicted value. For studies of ventilatory control, the subjects, seated and wearing nose clips, breathed from a mouthpiece into a low-resistance, one-way valve. To record airway pressure, an occluding valve was opened promptly; occlusions never persisted for more than 400 milliseconds after the onset of inspiration against the closed valve. We reported dP/dT as the slope of the mouth pressure vs time tracing measured between 0.05 and 0.1 second and expressed as cm H₂O in one second. To validate the use of dP/dT in the presence of increased functional residual capacity, we measured both dP/dT and Vₐ/ti in nonasthmatic subjects at both normal and increased end-expiratory lung volume.

The dP/dT measurements represented the average of three or more determinations. Other measurements calculated from the oscilloscope tracing were: tidal volume (Vₚ); inspiratory time (ti); mean inspiratory flow (Vₚ/ti); minute ventilation (VE); and the ratio of inspiration to total duration of the respiratory cycle (tᵢ/ttot).

Preliminary observations revealed that administration of oxygen or bronchodilator therapy lessened the occlusion pressure but had little effect on minute ventilation. Other authors previously indicated that in normal subjects, tidal volume during mouthpiece breathing, and therefore minute ventilation, exceeds that measured during natural respiration without a mouthpiece. We reasoned that this mouthpiece effect on tidal volume might be diminished during bronchospasm. The reappearance of this mouthpiece artifact after bronchodilation may conceal changes in the ventilatory pattern after treatment from the observer. Therefore, we

![Figure 1. Simultaneous trace of mouth pressure measured from a mouthpiece and chest wall circumference during unobstructed tidal breathing. Mouthpiece effect on inspiration quantified as ratio of chest wall excursion with subject breathing on a mouthpiece (B) to that without mouthpiece (A).](image-url)
examined the effect of a mouthpiece on the ventilatory pattern of our subjects before and after bronchodilatation.

To evaluate the mouthpiece effect, we compared ribcage and abdominal excursions from pneumogram belt tracings during natural respiration and mouthpiece breathing. We reasoned that changes in the amplitude of chest wall excursion during a respiratory cycle must reflect changes in tidal volume as long as no paradoxical or expiratory abdominal motion could be observed during inspiration.

Accordingly, during the study, pneumograms were placed at the xyphoid process and umbilicus in four subjects. None of these subjects demonstrated paradoxical chest wall and abdominal movements during resting ventilation. As shown in Figure 1, we quantified the mouthpiece effect as the ratio of chest wall excursion during tidal breathing with and without the mouthpiece.

**End-Expiratory Lung Volume Elevation (EELV) in Nonasthmatic Subjects**

We hypothesized that changes in respiratory center output and timing seen in asthma may result from increased EELV. To test this hypothesis, we measured dp/dt, Vr, t1, and Vr/t1 in six normal subjects both at normal and at elevated EELV. To increase EELV, tubing from the expiratory port of the breathing valve was immersed under water, from 6 to 8 cm depth. Subjects were instructed to relax during expiration so that EELV might be determined by the recoil of the relaxed respiratory system alone. Measurements of tidal breathing were made from three or more breaths beginning 30 seconds or ten breaths after immersion of the expiratory tubing. At this time, Vr appeared to be stable. Changes in EELV were measured with respiratory magnetometers (obtained from Norman H. Peterson, Boston). Because the subjects were making a conscious effort to relax during expiration, we did not compute Vf or frequency, both of which depend, in part, on expiratory time.

**Table 1—Pulmonary Function Testing**

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Age, yr</th>
<th>n (M/F)</th>
<th>VC, %</th>
<th>FEV1, VC, %</th>
<th>FRC, %</th>
<th>Raw</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Without therapy</td>
<td>44 ± 13</td>
<td>17 (8/9)</td>
<td>58 ± 19</td>
<td>46 ± 12</td>
<td>163 ± 39</td>
<td>7.6 ± 3.4</td>
</tr>
<tr>
<td>After therapy</td>
<td>73 ± 19</td>
<td>55 ± 14</td>
<td>137 ± 20</td>
<td>2.9 ± 1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Without therapy</td>
<td>40 ± 9</td>
<td>6 (4/2)</td>
<td>66 ± 13</td>
<td>75 ± 6</td>
<td>109 ± 6</td>
<td></td>
</tr>
<tr>
<td>After therapy</td>
<td>77 ± 14</td>
<td>77 ± 7</td>
<td>99 ± 22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subject</td>
<td>31 ± 7</td>
<td>11 (9/2)</td>
<td>91 ± 9</td>
<td>80 ± 8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: VC, % = vital capacity, % predicted; FEV1/VC, % = forced expiratory volume in one second as % of VC; FRC, % = functional residual capacity, % predicted; Raw = airway resistance as cm H2O L-1 sec-1; (±) = SD; n (M/F) = number of subjects (male/female).

**Statistical Analysis**

To test for differences in age and pulmonary function in the control, asthma, and pneumonia groups, we used the one-way analysis of variance. To examine the individual effect of oxygen and specific therapy on dp/dt, we used the Friedman rank-sums test. Differences between two groups were examined with Student's paired and unpaired t tests. Correlations between airway resistance and measurements of ventilatory control were examined by regression analysis.

**RESULTS**

Pulmonary function data appear in Table 1. Normal control subjects were younger than patients (F = 4.45; P < 0.025). By standard criteria, vital capacity (VC) was moderately decreased in asthmatic subjects (58 ± 19 percent) on entry into the study, while functional residual capacity (FRC) was increased (163 ± 39 percent). Airway obstruction was documented by a decreased FEV1 (46 ± 12 percent of VC) and an increased airway resistance (7.8 ± 3.4). After bronchodilatation, airway resistance decreased (2.9 ± 1.5). FEV1/VC (percent) increased after therapy (paired t = 2.73; P < 0.05). Nevertheless, persistent airflow obstruction was documented by the FEV1 (55 ± 14 percent of VC). Similarly, FRC decreased with therapy (paired t = 2.80; P < 0.02) but remained abnormal (137 ± 20 percent).

Prior to therapy, VC was minimally decreased in the pneumonia group (66 ± 13 percent). After antibiotic and respiratory physical therapy, VC in the pneumonia patients (77 ± 14 percent) demonstrated functional improvement (paired t = 3.33; P < 0.025). Of note, pulmonary function improved after therapy in both patient groups. Nevertheless, functional abnormality persisted at the end of the treatment period in both asthma and pneumonia patients.

Arterial blood gas analyses appear in Table 2. All pH determinations were compatible with acute respiratory alkalosis. All patients had hypoxemia and hypocarbia. As anticipated, P02 increased with oxygen administration in both groups. In those five asthmatic subjects who repeated their control
ventilatory studies after withdrawal of supplementary oxygen, $P_{O_2}$ at the time of the second control study ($62 \pm 16$) was different from the initial $P_{O_2}$ for the entire group ($65 \pm 15$). Although $P_{CO_2}$ in asthmatic subjects was lower after therapy ($28 \pm 5$) than the initial study ($31 \pm 3$), this change was not statistically significant. With therapy, $P_{O_2}$ increased slightly ($71 \pm 17$) in asthmatic subjects. In the pneumonia patients, $P_{CO_2}$ decreased from $33 \pm 5$ to $28 \pm 4$ with oxygen ($P < 0.05$); this decrease persisted after antibiotic and respiratory physical therapy.

### Occlusion Pressure Measurements

The $dP/dT$ values for asthmatic subjects appear in Figure 2 and Table 3. In this group, $dP/dT$ measured before therapy, during oxygen supplementation, and repeated without therapy after discontinuation of oxygen was greater than the mean for normal subjects. Measurements of $dP/dT$ at the time of presentation to the emergency service, after oxygen, and again after bronchodilation were available for 12 asthmatic subjects. The rank sums test indicated that both oxygen and bronchodilator treatments attenuated $dP/dT$ ($\chi^2 = 10.17$; $P = 0.005$). By this analysis, the tendency of bronchodilator to reduce $dP/dT$ from control was no greater than that for supplementary oxygen alone. This finding was confirmed by paired $t$ test analysis between $dP/dT$ measurements with oxygen and bronchodilator therapies, respectively. The $dP/dT$ was less after bronchodilation than with oxygen administration in seven subjects; however, it was no different or slightly greater after bronchodilation, compared with oxygen, in five. In 16 subjects $dP/dT$ measurements were available both before and after oxygen therapy. The decrease in $dP/dT$ observed with oxygen was statistically significant by the paired $t$ test ($P < 0.05$). Furthermore, $dP/dT$ returned to or was above the preoxygen value in three of five subjects who repeated these measurements after discontinuation of oxygen.

Finally, before-therapy $dP/dT$ varied from 0.99 to 4.66 cm H$_2$O in the 17 asthmatic subjects. The $dP/dT$ measured prior to therapy did not correlate with either $P_{O_2}$ or airway resistance measured at the same time. These data demonstrate great individual variability in the intensity of respiratory drive provoked by bronchospasm. The $dP/dT$ data for pneumonia patients appear in Figure 3 and

![Figure 2. Occlusion pressure ($dP/dT$) measurements in asthmatic subjects. During quiet breathing $dp/dt$ was greater in asthmatic patients both before treatment (Acute: Room Air) and after oxygen therapy (Acute: $4 L/min O_2$); than in normal subjects. Rank sum testing indicated that $dP/dT$ decreased from Acute: Room Air with both oxygen therapy and bronchodilator therapy (After Therapy), however.](image)

### Table 3—Ventilation and Ventilatory Pattern Before and After Therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>$dP/dT$</th>
<th>$V_E$</th>
<th>$V_T$</th>
<th>$t_i$</th>
<th>$V_T/t_i$</th>
<th>$f$</th>
<th>$t_i/t_{tot}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No therapy</td>
<td>2.13 ± 1.03†</td>
<td>13.4 ± 4.4†</td>
<td>0.59 ± 0.19</td>
<td>1.05 ± 0.18†</td>
<td>0.58 ± 0.20†</td>
<td>22 ± 4†</td>
<td>0.38 ± 0.08†</td>
</tr>
<tr>
<td>Nasal ($O_2$)</td>
<td>1.67 ± 1.03†</td>
<td>11.9 ± 2.6</td>
<td>0.58 ± 0.15</td>
<td>1.14 ± 0.20†</td>
<td>0.53 ± 0.14</td>
<td>22 ± 6†</td>
<td>0.38 ± 0.07</td>
</tr>
<tr>
<td>$O_2$ Discontinued</td>
<td>3.17 ± 1.78†</td>
<td>11.2 ± 1.3</td>
<td>0.57 ± 0.16</td>
<td>1.07 ± 0.24†</td>
<td>0.53 ± 0.07</td>
<td>21 ± 7†</td>
<td>0.35 ± 0.01</td>
</tr>
<tr>
<td>Bronchodilator therapy</td>
<td>1.12 ± 0.46</td>
<td>12.9 ± 5.5</td>
<td>0.57 ± 0.16</td>
<td>1.20 ± 0.31†</td>
<td>0.51 ± 0.25</td>
<td>22 ± 5†</td>
<td>0.43 ± 0.05</td>
</tr>
<tr>
<td><strong>Pneumonia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No therapy</td>
<td>1.06 ± 0.50</td>
<td>9.2 ± 2.4</td>
<td>0.45 ± 0.09</td>
<td>1.34 ± 0.35</td>
<td>0.35 ± 0.10</td>
<td>20 ± 4</td>
<td>0.44 ± 0.06</td>
</tr>
<tr>
<td>Specific therapy</td>
<td>1.02 ± 0.53</td>
<td>9.7 ± 2.0</td>
<td>0.58 ± 0.30</td>
<td>1.64 ± 0.86</td>
<td>0.36 ± 0.07</td>
<td>19 ± 6</td>
<td>0.45 ± 0.04</td>
</tr>
<tr>
<td>Normal subjects</td>
<td>0.73 ± 0.46</td>
<td>9.1 ± 4.5</td>
<td>0.65 ± 0.27</td>
<td>2.05 ± 0.80</td>
<td>0.34 ± 0.16</td>
<td>15 ± 6</td>
<td>0.44 ± 0.06</td>
</tr>
</tbody>
</table>

* Abbreviations: $dP/dT$ = occlusion pressure, cm H$_2$O/S; $V_E$ = minute ventilation, L/min; $V_T$ = tidal volume, L; $t_i$ = inspiratory time, seconds; $V_T/t_i$ = L/sec; $f$ = breaths per minute; $t_{tot}$ = duration of one breath, seconds; $\pm$ = SD.†$P < 0.05$.
The breathing pattern in the pneumonia subjects prior to therapy was unlike that of the asthmatic group. The VE for pneumonia patients (9.2 ± 2.4) was no greater than that for control (9.1 ± 4.5). Normalization of VE by the predicted VC indicated that this finding could be explained in part by differences in the anthropometric characteristics between pneumonia and control subjects. VE divided by predicted VC was 2.26 ± 0.54 in pneumonia patients and 1.90 ± 0.96 in normal controls. Moreover, normalization by measured VC emphasized the difference in the ventilatory pattern between these groups. The VE/measured VC was 3.60 ± 1.17 in pneumonia patients and 2.05 ± 0.90 in control subjects (unpaired t = 3.04; P < 0.01). In pneumonia patients Vt/ti (0.35 ± 0.10) was normal and ti decreased (1.34 ± 0.35). Therefore, Vt was diminished (0.45 ± 0.09). Supplementary oxygen did not alter this ventilatory pattern: Vt, on oxygen, was 0.41 ± 0.12; VE, 8.6 ± 3.3. After considerable resolution of the pneumonia, Vt increased (0.58 ± 0.30), whereas little change occurred in either inspiratory flow rate or ventilatory timing.

**Mouthpiece Effect**

Measurements of mouthpiece effect (ME) in three asthmatic subjects appear in Table 4. Airway resistance and dP/dT measurements before and after bronchodilator therapy in these three subjects are similar to those of the 17 subjects shown in Table 1 and 3. These data indicate that ME may cause an exaggeration of chest cage expansion during resting breathing when ventilation is measured after bronchodilation. ME was negligible.
Asthma, pretreatment frequency either before or after therapy. Further-
minimally elevated (3.1) prior to therapy and
ence was significant at the P
measured after therapy
occlusion during tidal breathing with mouthpiece to
that without mouthpiece; \( f_{ME} \) =mouthpiece effect on
breathing frequency (ratio of frequency on mouthpiece to
that without mouthpiece). Data appear as mean ± SD.

prior to therapy (1.1 ± 0.1) but substantial when
measured after therapy (1.9 ± 0.2). This
difference was significant at the P < 0.025 level. In
contrast, the mouthpiece did not alter breathing
frequency either before or after therapy. Further-
more, we studied a fourth patient whose Raw was
minimally elevated (3.1) prior to therapy and
did not change with administration of isoproterenol
and theophylline. ME also did not change (1.4
prior to therapy and 1.6 after). This observation
supported further our conclusion that the lack of
ME during bronchoconstriction and its presence
after therapy is related to normalization of airway
function.

End-Expiratory Lung Volume Elevation (EELV)

Data in Table 5 represent the average of two
trials in all but one subject. In subject 5, a trial
was discarded during which \( dP/dT \) increased
during expiratory loading; paradoxic inward inspira-
tory abdominal motion occurred, however, and
both \( V_r \) and \( V_r/t_i \) decreased. End-expiratory
airway pressure measured during the one-minute
periods of increased EELV was, on the average,
5.8 ± 1.2 cm H\(_2\)O. Airway resistance measured
1.78 ± 0.17 in these subjects. For all subjects, \( dP/dT \) and \( V_r/t_i \) increased with elevation of FRC.
Inspiratory time decreased and \( V_r \) was thus un-
changed.

**Discussion**

We found in the asthmatic subjects evidence for
both increased inspiratory drive (\( dP/dT \) and \( V_r/t_i \))
and altered respiratory timing (\( f, t_i \)). With
bronchodilation, inspiratory drive decreased, while
the alteration of respiratory timing persisted; hypox-
capnia persisted as well. Possibly, the artifactual
effect of breathing through a mouthpiece may have
influenced \( V_r/t_i \) (and thus \( V_r \)) while persistent
obstruction of small airways may have affected the
timing mechanism to account for hyperventilation
after the treatment period. In contrast, only the
respiratory timing was altered in the pneumonia
group.

While many studies have examined simultaneous
occlusion pressure and ventilation responses to
chemical stimuli in patients with lung disease, few
have measured the occlusion pressure during sponta-
neous breathing in these subjects.\(^5\) The occlusion
pressure measurement during CO\(_2\) stimulation,
while a specific test of respiratory center chemosensitiv-
ity, requires increasing rates of inspiratory
muscle contraction during the rebreathing period.
The achievement of such rates of contraction may
be difficult for the asthmatic patients whose inspi-
ryatory muscles function at a poor mechanical
advantage because of increased thoracic gas vol-
ume at end-expiration. The observation that the
occlusion pressure in asthmatic patients is greater
than in normal controls early during carbon dioxide
rebreathing while the rise of occlusion pressure

<table>
<thead>
<tr>
<th>Subject</th>
<th>FRC, L (%(_i))</th>
<th>( \Delta )FRC, L (%(_i))</th>
<th>( dP/dT )</th>
<th>( V_r )</th>
<th>( t_i )</th>
<th>( V_r/t_i )</th>
</tr>
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<tbody>
<tr>
<td>C</td>
<td>L</td>
<td>C</td>
<td>L</td>
<td>C</td>
<td>L</td>
<td>C</td>
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<tr>
<td>1</td>
<td>2.85 (76)</td>
<td>1.46 (151)</td>
<td>0.98</td>
<td>6.09</td>
<td>0.59</td>
<td>0.42</td>
</tr>
<tr>
<td>2</td>
<td>2.90 (73)</td>
<td>0.40 (114)</td>
<td>1.12</td>
<td>2.69</td>
<td>0.77</td>
<td>1.82</td>
</tr>
<tr>
<td>3</td>
<td>3.50 (112)</td>
<td>1.49 (128)</td>
<td>1.21</td>
<td>3.12</td>
<td>0.93</td>
<td>0.83</td>
</tr>
<tr>
<td>4</td>
<td>3.30 (88)</td>
<td>0.40 (113)</td>
<td>1.09</td>
<td>1.83</td>
<td>0.46</td>
<td>0.51</td>
</tr>
<tr>
<td>5</td>
<td>3.42 (92)</td>
<td>0.94 (127)</td>
<td>0.97</td>
<td>2.38</td>
<td>0.41</td>
<td>0.41</td>
</tr>
<tr>
<td>6</td>
<td>3.60 (96)</td>
<td>0.41 (111)</td>
<td>0.83</td>
<td>4.66</td>
<td>0.70</td>
<td>0.78</td>
</tr>
<tr>
<td>Mean</td>
<td>3.56 (90)</td>
<td>0.85 (124)</td>
<td>1.03</td>
<td>3.46(†)</td>
<td>0.64</td>
<td>0.80</td>
</tr>
<tr>
<td>SD</td>
<td>±0.90 (14)</td>
<td>0.53 (15)</td>
<td>0.13</td>
<td>1.61</td>
<td>0.20</td>
<td>0.53</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: \( \Delta \)FRC =change in FRC in liters, with expiratory loading; \( \%\(_i\) =FRC with expiratory load/FRC (\times 100); C =control; L =after expiratory loading. Other definitions as in Tables 1 and 3.
†Different from control group, P < 0.02.
with increasing PaCO₂ is less supports the hypothesis that the blunted response to hypercapnia may reflect respiratory muscle dysfunction in asthma. Therefore, dP/dT as measured in this study, while not a specific index of ventilatory response to chemical stimuli, may be an appropriate index of inspiratory drive in asthma.

Mann et al⁵ have measured spontaneous ventilation, occlusion pressure, and airway resistance in normal subjects both before and after methacholine inhalation. A relationship was found between the increase in airway resistance and increase of occlusion pressure, but no systematic change in tidal volume or inspiratory flow ensued. This result was not unexpected, because chest wall reflexes, lung reflexes, or conscious mechanisms as well as respiratory center output may affect the tidal breath. In this study, dP/dT was greatly increased in patients with asthma but not pneumonia. Possibly, a difference in the degree of hypoxia or level of anxiety could account for this difference in dp/dt between groups. More likely a mechanical factor present only in asthma may account for this difference in ventilatory drive between groups. Conceivably the increased respiratory center output in asthma represents a reflex, or neuromechanical, response to an added resistive load. Both external inspiratory resistive loading and bronchoconstriction (with methacholine) bring about an immediate increase in occlusion pressure and inspiratory flow in asthmatic subjects.¹⁷ Hypocapnia ensues. In that study, changes in ventilatory drive were greater after bronchoconstriction than after external loading.

An alternative possibility is that the increased inspiratory drive in asthma results from a neuromechanical reflex originating in muscle or joint receptors stimulated by the increased end-expiratory lung volume. There is some evidence for this hypothesis in the literature. Kelsen et al¹⁸ speculate that the increased occlusion pressure seen in normal persons confronted by an external resistive load originates from chest wall mechanical receptors. Matthews and Howell¹⁹ and Green et al¹⁹ have provided further support for this possibility. They demonstrated (with occlusion pressure and diaphragmatic EMG techniques) that normal persons whose functional residual capacity is raised by either positive airway pressure or negative pressure outside of the thorax defend tidal volume by increasing ventilatory drive.

Data from Table 5 demonstrate that increasing end-expiratory lung volume induces changes in the ventilatory drive of normal subjects similar to those seen in asthma. In two subjects (1 and 3) the increase in EELV appeared out of proportion to the expiratory airway pressure. Most likely, these subjects failed to relax inspiratory muscles during expiration. The dP/dT was greatly increased in these subjects. Tonic inspiratory muscle activity during expiration occurs in asthma.²⁰ These observations raise the possibility that, while dP/dT is an index of medullary respiratory center output, the increased occlusion pressure during bronchospasm may represent presynaptic facilitation of tonically contracting inspiratory muscles as well.²¹

Because the occlusion pressure is increased in patients with chronic interstitial lung disease, we anticipated an increased dP/dT in the pneumonia group.²² In contrast to the patients in that group with chronic interstitial lung disease, the pneumonia patients in this study demonstrated normal FRC. Out patients maintained a normal VT/t, with only minimal augmentation of dP/dT. Their breathing load was therefore not substantially increased over the tidal breath. These observations taken together might indicate that patients with interstitial or alveolar filling disease increase inspiratory center output only to maintain VT/t. The dP/dT may increase above normal only when lung distensibility is decreased over the tidal volume range.

Finally, increased ventilatory drive (as defined by hypocarbia) persisted in our treated asthmatic patients in spite of a normal dP/dT. To some degree, posttherapy measurements may be influenced by mouthpiece artifact. We have demonstrated that mouthpiece breathing enhances tidal volume (probably by increasing inspiratory flow rate) in stable subjects but not in those with severe airway obstruction.

**Oxygen Administration**

The elevated dP/dT was attenuated by oxygen in our asthmatic subjects but returned to pretreatment values when oxygen was discontinued. Only slight changes in minute ventilation and PaCO₂ accompanied this reduction of respiratory center output, however. Others have suggested that hypoxic drive may not be important to maintain ventilation in asthma.²³ Both the lack of correlation of dP/dT in the untreated asthmatic patients with simultaneously measured PaO₂ and failure of oxygen to abolish hyperventilation indicate that hypoxemia was not a major determinant of respiratory center output in our asthmatic patients.

Possibly, oxygen may have affected dP/dT in our subjects indirectly, by bronchodilation, rather than directly by reduction of stimulation to peripheral chemoreceptors. This appears unlikely, however, because bronchoconstriction caused by alveolar hypoxia occurs only when hypoxemia is more severe.
than in our subjects and hemoglobin desaturation is apparent. Finally, it should be noted that the hypoxemia was not severe in either the pneumonia or asthma patient group. That oxygen administration does not alter the ventilatory pattern in the pneumonia patient is well known.

**Ventilatory Timing**

Current concepts indicate that in both asthma and pneumonia, the respiratory rate is modified by vagal inflation-inhibition reflexes. This reflex, which brings about a slightly decreased inspiratory time, increased frequency, and, often, increased minute ventilation, accounts for hyperventilation in pneumonia patients. Although trends toward normalization of ventilatory timing (increased \( t_i \) and \( V_T \); decreased \( f \)) occurred with treatment in both patient groups, the differences in these indices before and after therapy were not statistically significant. We identify three explanations for the inconsistency of these data: (1) the increased ventilatory drive with bronchospasm that protected the tidal volume despite of the increased frequency; (2) mouthpiece artifact; and (3) persistent functional abnormality, as defined by moderate airway obstruction (\( FEV_1/VC \)) in asthmatic subjects, and minimal restrictive disease (VC) in the pneumonia patients.

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**References**