Ventilatory Response to Continuous Incremental Changes in Respiratory Resistance in Patients With Mild Asthma*

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**Background:** Conflicting results from previous studies on the effect of bronchial challenge on ventilatory patterns in asthmatics may be due to airflow obstruction present before induction of bronchospasm onset, as well as the different degrees of bronchoconstriction induced.

**Purpose and methods:** We examined the ventilatory response to stepwise increments in respiratory resistance (Rrs) induced by continuous methacholine inhalation in eight patients with mild stable asthma without airway obstruction and eight normal subjects. Methacholine was inhaled continuously during tidal breathing until a nearly two-fold increase in Rrs was observed. Respiratory parameters, including tidal volume (Vt), respiratory frequency (f), inspiratory ventilation (Vi), mean inspiratory flow (Vi/Ti), and duty ratio (Ti/Tt), were measured simultaneously by respiratory inductive plethysmograph (RIP). Arterial oxygen saturation (SaO2) was examined by pulse oximetry. The end-tidal CO2 fraction (FETCO2) was measured with a rapid-response infrared analyzer at the mouthpiece.

**Results:** Rrs, SaO2, FETCO2, and respiratory parameters, measured after saline solution inhalation, were not different between the two groups. Inhaled methacholine first decreased and then increased Vt in both groups. However, changes in Vt occurred earlier and to a greater extent in asthmatics than in normal subjects. At 200% Rrs (percent control), %Vi was greater in asthmatics than in normal subjects (p<0.005) because of significant differences in %Vt and %Vi/Ti between the two groups. **Conclusion:** For a given degree of bronchoconstriction, the ventilatory response was more rapid and greater in patients with mild stable asthma without airway obstruction than in normal subjects. The different response to bronchial challenge between the two groups may be due to different increases in drive due to irritant receptor stimulation.

*(CHEST 1996; 109:1525-31)*

**Key words:** bronchial asthma; bronchoconstriction; control of breathing; vagal reflex; ventilatory response

**Abbreviations:** f=respiratory frequency; FETCO2=end-tidal CO2 fraction; Grs=the reciprocal of respiratory resistance; PC02=Gr=intravenous saline solution dose at 35% decrease in Grs from initial control value; RIP=respiratory inductive plethysmograph; Rrs=respiratory resistance; SAS=slowly adapting stretch receptors; SaO2=arterial oxygen saturation; Ti=inspiratory time; Vt=duration of a single breathing cycle; Ti/Tt=duty ratio; VC=vital capacity; Vi=inspiratory ventilation; Vt=tidal volume; Vi/Ti=mean inspiratory flow

Methacholine inhalation constricts the airways and alters pulmonary mechanics. Methacholine-induced bronchoconstriction affects central respiratory output, inspiratory motor activity, and breathing patterns. Previous studies on the effect of bronchial challenge on breathing patterns in asthmatics have yielded conflicting results. Kelsen and coworkers increased specific airway resistance up to 371% with aerosolized methacholine in asthmatics, and found a rise in both mean inspiratory flow (Vi/Ti) and respiratory frequency (f). In contrast, Scano and coworkers have reported that increased airway resistance did not affect Vi/Ti or f in asthmatics.

One possible reason for these discrepancies is that the baseline pulmonary function in the asthmatics studied was different. In Kelsen et al.,1 FEV1 (percent predicted) in asthmatics was 80.7%, while it was 75.7% in those with moderate asthma studied by Scano and coworkers.5 Burdon and coworkers6 have reported that there is less respiratory distress in asthmatic patients in whom airflow obstruction is present at the onset of pharmacologically induced bronchospasm. Therefore, the presence of airflow obstruction may affect ventilatory responses during methacholine-induced bronchoconstriction.

A second possible reason involves differences in the
degree of bronchoconstriction induced. Kelsen et al.\textsuperscript{1} 
induced moderate-to-severe bronchoconstriction in asthmatics, and Scano and 
coworkers\textsuperscript{5} produced mild bronchoconstriction.

The purpose of this study was to measure respiratory 
parameters during stepwise increments in respiratory 
resistance (Rrs) induced by continuous methacholine 
inhalation in patients with mild stable asthma without 
airway obstruction and in normal subjects.

**Materials and Methods**

**Subjects**

We studied eight naive subjects (six men and two women; mean 
age, 29 years) and eight patients with mild stable 
aortic asthma without airway obstruction (four men and four 
women; mean age, 24 years). All were nonsmokers. Bronchial asthma was diagnosed by 
a history of episodic dyspnea with wheezing and by reversible 
increases in FEV\textsubscript{1} of more than 20\%, either spontaneously or after 
medication. No subject with bronchial asthma had had any attacks 
during the 6-week period prior to the study. In addition, no subject 
had a history of respiratory tract infection for 6 weeks prior to 
the study. Patients avoided all medication for at least 12 h before 
the study. At the time of the study, all subjects had spirometric 
values within the normal range. Written informed consent was obtained 
from each subject before the start of the study, which was approved 
by the institute’s committee on human research.

**Measurement of Respiratory Parameters**

Respiratory parameters were measured with a respiratory induc¬
tive plethysmograph (RIP) (Respiritrace; Ambulatory Monitoring 
Inc; Ardsley, NY). One band was taped securely around the rib cage at 
the second to fourth intercostal space anteriorly and the other 
around the abdomen at the level of the umbilicus. Volume calibra¬
tion of the RIP was obtained using the simultaneous equation 
method by having the subject breathe through a mouthpiece attached to a spirometer.\textsuperscript{7} 
The sum of the rib cage and abdominal signals correlated well with 
the tidal volume (VT) measured with the spirometer. Similarly, there was good correlation between the RIP 
and spirometer signals for individual timing parameters. From the 
RIP signal, the amplitude and inspiratory and expiratory time for 
each breath were measured as follows: VT, liters; inspiratory time 
(Ti), seconds; and the duration of a single breathing cycle (Tt), 
seconds. From these values we calculated the following ventilatory 
parameters: respiratory frequency (f), breaths/min; inspiratory 
ventilation (Vi), L/min; VT/Ti, L/s; and duty ratio (Ti/Tt). Arterial 
\textsuperscript{8}
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Pulmonary function test results of normal subjects and asthmatics are shown in 
Table 1. Sex, age, body height, body weight, %VC (%) 

| Table 1—Characteristics and Baseline Pulmonary Function Test Results and Bronchial Sensitivity (PC\textsubscript{25}Grs) and Reactivity (Slope)* |
|-----------------|---|---|---|---|---|---|---|
| **Subject** | **Sex** | **Age, yr** | **Height, cm** | **Weight, kg** | **VC, %pred** | **FEV\textsubscript{1}, %pred** | **PC\textsubscript{25}Grs, log µg Methacholine** | **Slope, ΔGrs/Δt** |
| Normal subjects | 6:2 | 29±8 | 166±14 | 60±9 | 120±11 | 100±6 | 4.3±0.7 | 0.075±0.022 |
| Asthmatic subjects | 4:4 | 24±5 | 168±9 | 59±12 | 117±11 | 95±9 | 1.9±0.9 | 0.061±0.015 |

*Slope—the linear slope of the Grs decrease; VC, FEV\textsubscript{1}, and Rrs were determined before methacholine challenge. VC and FEV\textsubscript{1} are percent 

\textsuperscript{p}<0.005, significantly different between two groups.
Table 2—Comparative Results of Rrs, Breathing Pattern, SaO2, and FETCO2 During Saline Solution Inhalation Between Two Groups*

<table>
<thead>
<tr>
<th></th>
<th>Asthmatics (n=8)</th>
<th>Normal Subjects (n=8)</th>
<th>Statistical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rrs, cm H2O/L/s</td>
<td>3.4±0.6</td>
<td>3.3±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Vt, L/min</td>
<td>8.31±3.13</td>
<td>7.95±0.81</td>
<td>NS</td>
</tr>
<tr>
<td>Vt, L</td>
<td>0.69±0.27</td>
<td>0.69±0.22</td>
<td>NS</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>12.5±2.4</td>
<td>12.6±4.1</td>
<td>NS</td>
</tr>
<tr>
<td>Vt/Ti, L/sec</td>
<td>0.36±0.12</td>
<td>0.33±0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Ti/Tt</td>
<td>0.39±0.05</td>
<td>0.40±0.04</td>
<td>NS</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>97.1±0.64</td>
<td>96.6±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>FETCO2, %</td>
<td>4.9±0.4</td>
<td>5.1±0.5</td>
<td>NS</td>
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</table>

*Values are means±SD. NS=not significant.

predicted), and %FEV1 were not significantly different between the two groups.

We defined bronchial sensitivity as the methacholine concentration that produced a 35% decrease in reciprocal Rrs (Grs) from the initial control value (PC35Grs). \(^{10}\) \(\log(\text{PC35Grs})\) was significantly lower in asthmatics (1.9±0.9) than in normal subjects (4.3±0.7) (p<0.005). However, the slopes of the dose-response curves for methacholine were not significantly different between the two groups. Control Rrs, SaO2, FETCO2, and respiratory parameters were not different between the two groups (Table 2).

Figure 1 shows the changes in Rrs, Vt, and SaO2 in a representative normal and asthmatic subject. Inhaled methacholine first decreased, and then normalized Vt in normal subject 2. In contrast, ventilation in asthmatic subject 2 decreased initially, and then increased at the same degree of bronchoconstriction. Therefore, the change in Vt was more rapid and greater in an asthmatic subject than in a normal subject. We calculated the %Vt, %Vt, %f, %Vt/Ti, and %Ti/Tt (all as percent control) at 125%, 150%, 175%, and 200% Rrs (% control) in both asthmatics and normal subjects. The relationship between %Rrs and %Vt, %Vt, %f, %Vt/Ti, and %Ti/Tt during methacholine provocation in normal and asthmatic subjects is shown in Figures

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21733/ on 04/01/2017)

**Figure 1.** A representative recording of Vt and Rrs obtained from a normal (left) and asthmatic subject (right). The upper recording indicates Vt, the middle Rrs, the lower SaO2. The ventilatory response in normal subject 2 decreased initially and then normalized during inhaled methacholine. The respiratory response of asthmatic subject 2 exhibited a greater ventilatory response at the same degree of bronchoconstriction. The SaO2 decreased in both groups, but the degree of hypoxemia was mild.
2 through 4. %Vt decreased in both groups at 125% Rrs. In normal subjects, %Vt increased at 150% Rrs, increased at 175%, and reached a plateau at 200% Rrs. However, in asthmatics, %Vt increased continuously from 150 to 200% Rrs. Therefore, at 150%, 175%, and 200% Rrs, %Vt was greater in asthmatics than in normal subjects (p<0.01, p<0.01, p<0.005, respectively) (Fig 2). The change in %Vt/Ti was similar to that for %Vt (Fig 3). Thus, at 200% Rrs, %Vt and %Vt/Ti were greater in asthmatics than in normal subjects (Figs 3

![Figure 2](image)

**Figure 2.** The relationship between %Vi and %Rrs in terms of control values during a provocative test in normal subjects (open circles) and asthmatics (closed circles). Mean values ± SD of %Vi obtained from 8 normal subjects and 8 asthmatics are shown at 125%, 150%, 175%, and 200% Rrs. Asterisks indicate a significant difference between the two groups (two asterisks, p<0.01; three asterisks, p<0.005). The %Vi of asthmatics significantly exceeded that of normal subjects at a given degree of bronchoconstriction (150%, 175%, and 200% Rrs).

![Figure 3](image)

**Figure 3.** The relationship between %Rrs and %Vt (upper) and %f (lower) in terms of control values during a provocative test in normal subjects (open circles) and asthmatics (closed circles). Mean values ± SD of %Vt and %f are shown at 125%, 150%, 175%, and 200% Rrs. Asterisks indicate a significant difference between the two groups (asterisk, p<0.05; three asterisks, p<0.005). Asthmatics exhibited a greater %Vt at 150%, 175%, and 200% Rrs. The %f increased significantly at 200% Rrs in both groups, but was not different between the two groups.

![Figure 4](image)

**Figure 4.** The relationship between %Rrs and %Vt/Ti (upper) and %Ti/Tt (lower) in terms of control values during a provocative test in normal subjects (open circles) and asthmatics (closed circles). Mean values ± SD for %Vt/Ti and %Ti/Tt are shown at 125%, 150%, 175%, and 200% Rrs. Asterisks indicate a significant difference between the two groups (two asterisks, p<0.01). The %Vt/Ti of asthmatics significantly exceeded that of normal subjects at 200% Rrs. The %Ti/Tt was not significantly different between the two groups.
and 4). The %f in both groups increased significantly with increasing Rrs, but was not significantly different between the two groups (Fig 3). The %Vt/Ti in both groups did not change significantly (Fig 4). The SaO₂ decreased significantly in both groups, but the degree of hypoxemia was mild (from approximately 97% during control saline solution inhalation to 94% after provocation). FETCO₂ also decreased in the two groups. Although SaO₂ was not significantly different between the two groups, FETCO₂ in asthmatics was significantly lower than in normal subjects at 175% and 200% Rrs (p<0.05, p<0.05, respectively). Similarly, at 200% Rrs, %Vi was significantly greater in asthmatics than in normal subjects because of the significant differences in %Vt and %Vt/Ti between the two groups (Table 3).

**Discussion**

This study showed that inhaled methacholine first decreases Vi and then increases it in both normal subjects and asthmatics. However, the change in Vi was more rapid and greater in asthmatics than in normal individuals.

There are conflicting reports on the effect of bronchoconstriction on respiratory patterns in asthmatics. One possible reason for these differences may be the presence of preexisting airflow obstruction in the study population. FEV₁ (percent predicted) in our asthmatics (95%) was within normal limits and was higher than in the report of Kelsen et al¹ (80.7%) and in the study of Scano et al⁵ (91% and 75.7% in patients with mild and moderate asthma, respectively). It is well known that differences in baseline airway function are associated with differences in bronchial reactivity.¹¹,¹² If baseline airway function is different, pulmonary receptor activity and respiratory center output may also be changed. Patients with chronic airway obstruction have impaired perception of resistive loads and, unlike individuals with normal lung function, do not increase respiratory efferent activity when a ventilatory load is added during inspiration.¹³ Therefore, in this study, we selected individuals with mild stable asthma without airway obstruction as subjects.

A second possible reason for differences in study results is the differing severity of bronchoconstriction induced. In the study by Scano et al⁵ mild bronchoconstriction (3.5% decrease in FEV₁) did not affect f, Vt/Ti, and Vi in patients with mild asthma. Conversely, Kelsen and coworkers¹ reported that moderate-to-severe bronchoconstriction (an increase of 371% in specific airway resistance) increased f, Vt/Ti, and Vi. It seems likely that mild bronchoconstriction does not affect ventilation and that moderate-to-severe bronchoconstriction causes increased ventilation in asthmatics as indicated by changes in f and Vt/Ti. Our study showed that increments in respiratory resistance induced by continuous methacholine inhalation, first decrease Vi in asthmatics, followed by a plateau phase, with a final increase Vi at higher Rrs because of the increase in Vt, f, and Vt/Ti. Therefore, our results are consistent with the two studies previously cited.

The respiratory pattern induced by methacholine may be mediated by reflexes arising from pulmonary receptors such as slowly adapting stretch receptors (SAS), irritant receptors, and C fibers. Since SAS are arranged in series with smooth muscle fibers and their electrical activity is proportional to the tension produced by these fibers, they are in a position to be stimulated by bronchoconstriction. On the other hand, irritant receptors may also be stimulated indirectly in response to bronchoconstriction. Since pulmonary C fibers are insensitive to histamine, they are unlikely to be affected by methacholine inhalation.¹⁴,¹⁵ There have been reports that methacholine-induced augmentation of respiratory output is elicited by the activation of irritant receptors.¹⁶,¹⁷ An increase in irritant receptor activity in the present study is consistent with our finding that methacholine inhalation increased f in both normal and asthmatic subjects. Therefore, in our study, methacholine mostly stimulated irritant recep-

**Table 3—Comparative Results of Rrs, Breathing Pattern, SaO₂, and FETCO₂ at %Rrs=200% Between Two Groups**

<table>
<thead>
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<th>Asthmatics (n=8)</th>
<th>Normal Subjects (n=8)</th>
<th>Statistical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rrs, cm H₂O/L/s</td>
<td>6.7±1.3</td>
<td>6.6±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>%Vi</td>
<td>125.7±11.8</td>
<td>87.7±18.1</td>
<td>p&lt;0.005</td>
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<tr>
<td>%Vt</td>
<td>114.3±15.9</td>
<td>74.9±21.3</td>
<td>p&lt;0.005</td>
</tr>
<tr>
<td>%f</td>
<td>111.3±11.9</td>
<td>110.5±10.9</td>
<td>NS</td>
</tr>
<tr>
<td>%Vt/Ti</td>
<td>126.5±21.4</td>
<td>91.3±19.8</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>%f/Ti</td>
<td>99.5±17.5</td>
<td>98.0±15.0</td>
<td>NS</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>94.9±1.6</td>
<td>94.2±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>FETCO₂, %</td>
<td>4.6±0.3</td>
<td>4.6±0.3</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

*Values are means±SD. NS=not significant.

¹p<0.01, significantly different from control values (saline solution inhalation), by paired Wilcoxon rank sum test.

¹p<0.05, significantly different from control values (saline solution inhalation), by paired Wilcoxon rank sum test.
tors in the conducting airways, inducing a ventilatory response.

To our knowledge, there is no previous study comparing ventilatory responses between asthmatics and normal subjects for a given degree of bronchoconstriction. The results of the present study show that there was a significant difference in Vt between the two groups at the same level of respiratory resistance because of differences in Vr and Vt/Ti.

Two mechanisms could be responsible for our results. First, vagal afferent input, activated by irritant receptors for respiratory center output and response, may be more sensitive in asthmatics than in normal subjects. This explanation is supported by our observation of a greater ventilatory response in asthmatics than normal subjects for the same respiratory resistance. Second, the respiratory center response may be more rapid and more pronounced at the same level of vagal afferent activity and respiratory resistance in asthmatics than in normal subjects.

Nadel proposed a mechanism for the irritant-bronchoconstrictor reflex in asthmatics. This hypothesis suggests that stimulation of irritant receptors in airway epithelium causes significant reflex bronchoconstriction via the vagal pathway, and this reflex may be exaggerated in asthma. The first mechanism described above would suggest that Nadel's irritant-bronchoconstrictor reflex influences the respiratory response during bronchoconstriction. However, %Vt, %Vr, and %Vt/Ti, which represent respiratory center output, were greater in asthmatics than in normal subjects at 200\% Rs. Thus, in asthmatics, the respiratory centers or higher centers would respond earlier and to a greater extent to bronchial challenge at the same level of respiratory resistance than in normal subjects. It is difficult to draw definitive conclusions regarding the mechanism underlying our results. However, our results are consistent with the first mechanism, that of an exaggerated irritant-bronchoconstrictor reflex in asthmatics.

In this study, we used RIP to measure alterations in respiratory parameters. RIP is a noninvasive technique for monitoring the volume and time components of ventilatory patterns. Abraham and coworkers have used RIP in sheep before and during bronchospasm induced with aerosolized carbachol, and suggested that it is possible to use RIP to determine tidal volumes with a good degree of accuracy even with high degrees of airflow obstruction. Chadha and coworkers have also described a high accuracy for RIP in clinical applications in asthmatics. We have also investigated the accuracy of RIP after the induction of bronchoconstriction. We compared the sum of RIP signals with the Vt measured by spirometry before and after a methacholine challenge that induced a mean Rs of 205\% (range, 190 to 210\%) in six of our normal subjects and two of our asthmatic subjects. The ratio of the sum of RIP signals to the Vt measured by spirometry fell as bronchoconstriction developed from 1.01 before the challenge to a mean of 0.97 after bronchoconstriction. Therefore, RIP slightly, but not significantly, underestimated Vt changes following induced bronchoconstriction in our experiments.

In this study, there was no effect from methacholine-induced hypoxemia. While there was a decrease in arterial oxygenation during methacholine inhalation, SaO2 was never low enough to increase the ventilatory drive. Furthermore, FETCO2 decreased during our experiments, so that changes in respiratory response could not be ascribed to changes in chemical drive.

In summary, our results show that the ventilatory response to a given degree of bronchoconstriction occurs earlier and to a greater extent in patients with mild stable asthma without airway obstruction than in normal subjects. This may be due to different increases in drive due to irritant receptor stimulation.

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