Peripheral Airways Function and Nonspecific Airways Reactivity in Cigarette Smokers*

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Increasing concentrations of inhaled aerosolized histamine acid phosphate were administered to 31 heavy cigarette smokers from a smoking cessation clinic. Nineteen of 31 smokers (mean age ± 1SD: 39.6±11.5 yrs; pack years 22.5±13.5) failed to reduce forced expired volume in one second (FEV1) while inhaling histamine and were labelled nonresponders. In 12 of 31 smokers (age 38.4±9.4 yrs; pack years 23.0±10.5), extrapolated provocation concentration of inhaled histamine required to reduce forced expired volume in one second (FEV1) by 10 percent (PC10) could be determined and these smokers were labelled responders. We also measured maximum expiratory flow volume curves with air and also a mixture of 90 percent helium and 20 percent oxygen (HeO2) to determine the percentage of increase in maximal flow at 50 percent vital capacity breathing HeO2 as compared to air (ΔVmax50), and the slope of phase III of the single breath oxygen test (ΔN2/L). In the responders, PC10 ranged from 1.4 mg/ml to 10.2 mg/ml (mean 5.5±3.3 mg/ml) and ΔVmax50 ranged from 7.1 percent to 68.4 percent (mean 30.6±18.3 percent). There was a significant positive correlation between PC10 and ΔVmax50 (r = 0.77, p<0.01), and a significant negative correlation between PC10 and ΔN2/L (r = −.61, p<0.01). There was no difference between responders and nonresponders in mean values for lung function tests, allergy skin tests, or symptoms. These results suggest that there may be two fundamentally different groups of smokers with peripheral airways dysfunction: one group in which dysfunction is associated with, or related to, airways reactivity, and one group in which dysfunction is related to other factors.

Previously, it has been observed that patients with chronic obstructive pulmonary disease (COPD) appear to have increased nonspecific bronchial reactivity to intravenous or inhaled histamine or methacholine.14 As altered airways tone could be one of the factors contributing to the development of COPD in some cigarette smokers, we previously determined the concentration of inhaled nebulized histamine required to produce a fall of 35 percent in specific conductance (PC10) in a group of symptomatic cigarette smokers with normal lung function.5 We demonstrated increased nonspecific bronchial reactivity in these smokers,5 a finding confirmed on a subsequent study on another smoking population.4 Brown et al6 exposed a group of asymptomatic smokers to inhaled histamine and demonstrated a predominantly large airways response in smokers as compared to nonsmokers. In the study reported herein, we have extended the observations of Gerrard et al7 and Brown et al7 by studying a group of heavy cigarette smokers with the objective of determining if those smokers with evidence of peripheral airways dysfunction as gauged by flow-volume curves with air and helium, and also by the single breath oxygen test, might also have airways that are more sensitive to histamine. The results, which have been presented in part elsewhere,8 suggest a relationship between peripheral airways obstruction and histamine sensitivity in cigarette smokers.

METHODS

We evaluated a group of 31 heavy cigarette smokers recruited from a smoking cessation clinic and studied them following informed consent. All smokers had the following studies carried out: an American Thoracic Society Standardized Respiratory Questionnaire,3 three acceptable forced expired maneuvers from total lung capacity to residual volume to obtain forced vital capacity (FVC), forced expired volume in one second (FEV1), and maximum midexpiratory flow rate (MMFR), expressed both in absolute values and as percent predicted values according to Morris et al9 flow-volume curves with air and also with 80 percent helium-20 percent oxygen (HeO2) to determine maximum expiratory flow at 50 percent FVC (Vmax50) and at 25 percent VC (Vmax25) with air, as well as the percentage of increase in Vmax50 breathing HeO2 as compared to air (ΔVmax50), according to the method of Dosman et al10 and three acceptable single breath oxygen tests according to the method of Buist and Ross11 to determine the slope of phase III (ΔN2/L) expressed as percent predicted according to the regression equations of Dosman et al12 Pulmonary function tests were performed with the subject seated at rest with a noseclip in place. After an initial period of instruction, subjects performed as many as six forced expiratory maneuvers from total lung capacity (TLC) to residual volume breathing air. In each subject, we obtained three forced expiratory maneuvers such that the FVC in each was within 5 percent of the maximal FVC value. We measured flow with a heated pneumotachograph (Fleisch No. 4) and obtained volume by digital integration of flow. The pneumotachograph was calibrated separately for both air and a gas mixture containing HeO2. The expiratory resistance in both air and HeO2 maneuvers was limited to the resistance of the pneumotachograph. Spiromograms and flow-volume

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Table 1—Anthropomorphic Data, Pulmonary Function Test Variables, Skin Test Results, and Symptoms in Nonresponders and Responders to Inhaled Histamine

<table>
<thead>
<tr>
<th></th>
<th>Nonresponders</th>
<th>Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Age (Yrs)</td>
<td>39.6 ± 11.5</td>
<td>38.4 ± 9.4</td>
</tr>
<tr>
<td>Male:Female</td>
<td>10:9</td>
<td>3:9</td>
</tr>
<tr>
<td>Pack years</td>
<td>25.5 ± 13.5</td>
<td>23.0 ± 10.5</td>
</tr>
<tr>
<td>$V_{max}$ (L/s)</td>
<td>3.99 ± 1.58 (105.7 ± 48.1)</td>
<td>3.62 ± 1.05 (91.5 ± 25.0)</td>
</tr>
<tr>
<td>$V_{max}$ (L/s)</td>
<td>1.27 ± 0.76 (38.7 ± 33.2)</td>
<td>1.19 ± 0.79 (65.6 ± 40.8)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>4.30 ± 0.92 (106.1 ± 21.5)</td>
<td>4.29 ± 0.89 (105.6 ± 13.7)</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>3.40 ± 0.76 (106.4 ± 21.9)</td>
<td>3.33 ± 0.72 (105.6 ± 14.8)</td>
</tr>
<tr>
<td>$\Delta V_{max}$ (%)</td>
<td>45.54 ± 34.47 (96.3 ± 72.9)</td>
<td>39.6 ± 15.3 (83.8 ± 38.6)</td>
</tr>
<tr>
<td>$\Delta N/L$ (%)</td>
<td>1.31 ± 0.62 (137.7 ± 48.6)</td>
<td>1.15 ± 0.50 (126.5 ± 45.02)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No.</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>No./Subject</td>
<td>1.42</td>
<td>2.00</td>
</tr>
<tr>
<td>$PC_{10}$ (mg/ml)</td>
<td></td>
<td>5.54 ± 3.26</td>
</tr>
</tbody>
</table>

*Values are mean ± 1 SD. Numbers in brackets are percent predicted values. There were no differences between Responders and Nonresponders for any of the variables listed, except for $PC_{10}$ which was not measurable in the Nonresponders.

maneuvers were simultaneously obtained on paper with an X-Y recorder and digitally recorded with an on-line computer. The computer analyzed the data and stored the results on magnetic tape. From each forced expiratory maneuver we measured the FEV₁, $V_{max}50$ and $V_{max}25$.

The smokers also had histamine inhalation challenge tests carried out, modified from the method of Cockcroft et al.* using doubling concentrations of aerosolized histamine acid phosphate from 0.025 mg/ml to 8 mg/ml inhaled during two minutes of tidal breathing with five-minute intervals between each doubling concentration. Saline comprised the diluent for histamine and a series of saline inhalations were given to act as the control or baseline. Histamine was nebulized using compressed air at a flow rate of 7.5 L/min through a Wright nebulizer which gave an output of 0.135 ml/min and produced a particle size of approximately 1μ mass median diameter. The FEV₁ was measured at 30 and 90 seconds after each two minute period of histamine inhalation, and the percentage of fall was calculated from the lowest postsaline value to the lowest posthistamine value. The extrapolated concentration of histamine required to produce a 10 percent fall in FEV₁ was labelled "provocation concentration 10 percent" or $PC_{10}$. Skin sensitivities to a battery of common allergic agents were determined on each subject. Statistical analysis was carried out using standard techniques.²³

RESULTS

Of the 31 smokers challenged with inhaled histamine, 19 did not alter FEV₁ significantly at the highest concentration of histamine inhaled and were labelled nonresponders. Those in whom $PC_{10}$ could be measured were labelled responders. The anthropomorphic data, pulmonary function test variables, allergy skin test results, and symptom data for the nonresponders and the responders are detailed in Table 1. There was no significant difference between nonresponders and responders in regard to age, pack years of smoking, expired flow rates, the tests of peripheral airways function ($\Delta V_{max}50$ and $\Delta N/L$), or allergy skin tests.

As shown in Figure 1, there was a significant correlation between $\Delta V_{max}50$ and $PC_{10}$ in the 12 smokers who responded to histamine ($r = 0.77$, $p < 0.01$) suggesting that smokers with evidence of functional impairment of peripheral airways also had

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21502/ on 06/24/2017)

**Figure 1.** Relationship between nonspecific bronchial reactivity as measured by the concentration of inhaled histamine that reduced forced expired volume in one second by 10 percent ($PC_{10}$) and the percentage of increase in maximum expiratory flow at 50 percent vital capacity breathing a mixture of helium and oxygen as compared to air ($\Delta V_{max}50$). $\Delta V_{max}50$ is on the vertical axis and $PC_{10}$ is on the horizontal axis. There is a significant correlation between the two variables ($r = 0.77$, $p < 0.01$).

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21502/ on 06/24/2017)

**Figure 2.** Relationship between the slope of phase III of the single breath oxygen test ($\Delta N/L$) (vertical axis) and $PC_{10}$ (horizontal axis). There is a significant correlation between the two variables ($r = -0.61$, $p < 0.05$).
more sensitive airways as measured by the response to inhaled histamine. That smokers with more sensitive airways tended to demonstrate more functional impairment is supported by the data shown in Figure 2 which demonstrates a significant negative correlation between $\Delta N_p/L$ and $PC_{10}$ ($r = -0.61$, $p<0.05$). There was no significant relationship when $PC_{10}$ was plotted against baseline FEV$_1$ (Fig 3) or smoking pack years (Fig 4).

**Discussion**

We have previously demonstrated that smokers had greater airway sensitivity to inhaled histamine than did a matched group of lifetime nonsmokers, raising the possibility that one mechanism in the development of COPD could be altered airways reactivity in cigarette smokers. The foregoing idea was supported by the work of Brown et al. The results of our current study would appear to indicate that among the generally symptomatic smokers that were studied, smokers appear to separate into a group that does not respond to histamine and a group that does. There was no apparent difference between the nonresponders and the responders on the basis of age, smoking pack years, tests of lung function, allergy skin tests, or symptoms. In the smokers who responded to histamine, the relationship between the response to inhaled histamine and tests of peripheral airways function was present both with evaluation by helium flow-volume curves and by the single breath nitrogen test. It is thus possible that increase in airways reactivity and peripheral airways dysfunction go hand-in-hand in a susceptible group of smokers.

What are the pitfalls? In order to evaluate the possibility that the smokers who responded to histamine might have lower FEV$_1$ values, and therefore, might respond to inhaled histamine on the basis of baseline airways caliber, we plotted baseline FEV$_1$ against $PC_{10}$ (Fig 3). No significant relationship between FEV$_1$ and $PC_{10}$ was found. We were also careful to evaluate symptoms, and particularly allergy skin tests, but there was no relationship between numbers of symptoms per smoker and $PC_{10}$, or between numbers of skin tests positive and $PC_{10}$, helping to rule out the possibility that the smokers that we described with lower $PC_{10}$ might also be more atopic.

One factor that might lead to the appearance of increased airways reactivity in histamine sensitive smokers would be differential site of histamine deposition in smokers with peripheral airways obstruction. The work of Dolovich et al. suggests that inhaled radioactively tagged aerosols appear to be deposited in central, larger airways in smokers as compared to normal subjects, but no tests of peripheral airways function were carried out. If subjects with peripheral airways obstruction distribute inhaled aerosols more centrally than do subjects without peripheral airways obstruction, the altered site of deposition could affect the response to inhaled histamine, as measured by forced expiratory flow rates, in the direction observed in our subjects. The data of Brown et al. could suggest a more central deposition of histamine in smokers with peripheral airways obstruction. However, the recent work of Trajan et al. suggests that lung regions with mild airflow obstruction have an absolute increase in aerosol deposition. Thus, if aerosol mixtures are retained in lung units with longer time constants, as is considered the case in patients with suspected peripheral airways dysfunction as demonstrated by tests such as $\Delta V_{max}50$ and $\Delta N_p/L$, the argument for reduction in expired flow rates following histamine inhalation, on the basis of central deposition of the histamine, would be less strong.

The possible mechanisms whereby smokers might develop increased nonspecific bronchial reactivity as measured by inhaled histamine have been recently reviewed and include the possible acute effects of cigarette smoking, epithelial injury as is likely to occur in acute respiratory viral infections and after breathing ozone which might lead to increased permeability, allowing greater chemical exposure to the subendothelial irritant receptors. This line of reasoning has

![Figure 3](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21502/)  
**Figure 3.** Relationship between forced expired volume in one second (FEV$_1$) (vertical axis) and $PC_{10}$ (horizontal axis). There was no significant relationship between the two variables.

![Figure 4](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21502/)  
**Figure 4.** Relationship between pack years of smoking (vertical axis) and $PC_{10}$ (horizontal axis). There was no significant relationship between the two variables.
some merit in that Cosio et al. have demonstrated a convincing relationship between small airways inflammation and alterations in tests of peripheral airways obstruction, particularly ΔN/L, in cigarette smokers. That cigarette smoke itself might lead to increased permeability is suggested by the work of Simani et al. who demonstrated increased penetration of the electron microscopic tracer, horseradish peroxidase, through guinea pig respiratory epithelium following acute exposure to cigarette smoke. 

These findings raise the possibility that in some smokers, a common defect, such as mucosal inflammation, could lead to both airways obstruction and altered reactivity. However, the possibility might also be considered that, in some smokers, increased nonspecific bronchial reactivity could predispose to the development of peripheral airways obstruction. The latter possibility is an interesting one to consider in view of the fact that, at least in these smokers tested in this manner, one group responds to histamine inhalation and one does not. Yet the frequency distributions for ΔVmax50 and ΔN/L are similar in those who responded to histamine and those who did not. This leads to an interesting speculation about these groups: it is possible that smokers with peripheral airways dysfunction who demonstrate increases in nonspecific bronchial reactivity, as gauged by inhaled histamine, could be smokers who are destined to go on to develop airways obstruction of the chronic bronchiitis variety. On the other hand, smokers with evidence of peripheral lung dysfunction who are not histamine sensitive might have peripheral airways dysfunction on the basis of another mechanism, such as loss of the elastic recoil properties of the lung. This group of smokers could conceivably include those who might be prone to develop future chronic lung disease in which parenchymal destruction predominates.

Of course, the foregoing idea is speculative, and while being compatible with the data presented here, remains a suggestion for structuring future investigation into the relationship between nonspecific airways reactivity and lung dysfunction in cigarette smokers.

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Airways Function and Reactivity in Cigarette Smokers (Dosman et al)