Bronchial Reactivity to Methacholine in HIV-Infected Individuals Without AIDS*

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To evaluate bronchial reactivity to methacholine in human immunodeficiency virus (HIV) infection, we submitted 25 HIV-seropositive subjects without full-blown AIDS and 25 HIV-seronegative subjects, all inmates in a drug rehabilitation center for previous intravenous drug abuse, to interview and to bronchial challenge with methacholine. Four (16 percent) HIV-seropositive and three (12 percent) HIV-seronegative subjects noted bronchospastic symptoms. Baseline FEV₁ and MEF₅₀ percent were within the normal range in every patient. Bronchial hyperreactivity to methacholine (PD₂₀FEV₁ < 1,400 µg) was found in two (8 percent) HIV-seropositive and in four (16 percent) HIV-seronegative subjects, with no significant difference in the frequency between the two groups. We conclude that HIV infection without AIDS in intravenous drug users does not appear to be associated with an increased frequency of bronchospastic disorders and to bronchial hyperreactivity to methacholine.

I ndividuals with human immunodeficiency virus (HIV) infection are subject to a wide spectrum of respiratory complications. Bronchospastic disorders have been described in a proportion of patients with full-blown AIDS and CD8 lymphocyte counts.

AIDS1-2 and also in HIV-seropositive subjects without full-blown AIDS.3 The recognition of an asthma-like syndrome in HIV infection is important since it could be confused with other conditions such as opportunistic infection and could lead to inappropriate diagnostic evaluation and therapy.2

Asthma is characterized by airway inflammation, airways obstruction with spontaneous and pharmacologic reversibility, and increased bronchial reactivity to exogenous and endogenous stimuli.4 To our knowledge, bronchial reactivity in HIV-infected individuals has not been investigated previously. We designed the present study to evaluate bronchial reactivity to methacholine in a group of HIV-infected individuals without overt AIDS.

MATERIALS AND METHODS

Study Design

This was a 1-day study. A group of HIV-seropositive subjects (HIV+, group A) and a control group of HIV-seronegative subjects (HIV−, group B) were submitted to interview, clinical examination, spirometry, methacholine challenge, and blood withdrawal for CD4 and CD8 lymphocyte counts.

Subjects

Twenty-five HIV-seropositive subjects (HIV+, group A) and a control group of 25 HIV-seronegative subjects (HIV−, group B or control) (Table 1), all inmates in a drug rehabilitation center (DRC) for former intravenous drug abusers (IVDUs), gave their informed consent to participate in the study. According to clinical features, seropositives were classified following the Centers for Disease Control (CDC) rules: 11 subjects were symptom free (CDC group 2); 8 subjects had systemic lymphadenopathy (persistent generalized lymphadenopathy [PGL], CDC group 3); 6 subjects had AIDS-related complex (ARC, CDC group 4 A).

Each subject underwent clinical interview to record personal and familial history of atopy and pertinent data about drug abuse history, smoking habits, respiratory symptoms and infections, and stay in the DRC. A detailed history was collected about previous smoking habits. The average number of cigarettes smoked per day, the number of years of smoking, and the number of pack-years were then calculated for each subject. On these data, subjects were classified as follows: mild smokers were subjects who had smoked less than 10 pack-years; moderate smokers were subjects who had smoked between 11 and 30 pack-years; and heavy smokers were subjects who had smoked more than 30 pack-years.

Table 1—Clinical and Functional Features of Study Subjects*

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Male, No.</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>Female, No.</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Age, yr†</td>
<td>27.9 ± 0.6</td>
<td>25.3 ± 0.6</td>
</tr>
<tr>
<td>Smoking habits, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 pack-years</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>11-30 pack-years</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>&gt;30 pack-years</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>CD4 mm³†</td>
<td>398.0 ± 49.5</td>
<td></td>
</tr>
<tr>
<td>FEV₁, L†</td>
<td>3.97 ± 0.1</td>
<td>3.28 ± 0.3</td>
</tr>
<tr>
<td>FEV₁, %†</td>
<td>97.7 ± 2.1</td>
<td>94.9 ± 1.7</td>
</tr>
<tr>
<td>MEF50% (% predicted)†</td>
<td>111.6 ± 5.0</td>
<td>97.3 ± 0.2</td>
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*See text for explanation of groups.
†Mean and SE.
Spirometry was performed by means of a dry turbine spirometer (Printer, Markos). Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁) were taken as the best of three satisfactory respiratory tracings. Maximum expired flow rate at 50 percent (MEF50 percent) was calculated. FEV₁ and MEF50 percent values were referred to the predicted values reported by Quanjer.

**Inhalation Challenge With Methacholine**

At the time of the study, all subjects had to be free from clinical symptomatic viral respiratory infections for at least 8 weeks and from use of any drug that might alter airway responsiveness. Moreover, the patients had to abstain from smoking for at least 12 h before undergoing the challenge.

Methacholine (Lofarma Allergeni, Milan, Italy) was delivered by a nebulizer (Mefar, Brescia, Italy) connected to a dosimeter driven by compressed air (MK1, Mefar, Brescia, Italy), equipped with a control device that allowed us to program the nebulization data, that is, the duration of each nebulization, the minimum interval between two subsequent nebulizations, and the total number of nebulizations to be delivered. With 20-psi inlet pressure and 1.5-s-long nebulization, an output of 10 SD 1 μl was measured by weighing the nebulizer before and after one discharge. Each subject wore a noseclip and was instructed to breathe via a mouthpiece from functional residual capacity. The nebulizer was filled with 2 ml of methacholine solution (either 0.2 percent or 1 percent) or diluent control, following its passage through a 0.2μ polymer (Millipore) filter. Five inhalations were taken for phosphate-buffered saline solution and for each increasing, doubling dose of methacholine, administered at 2-min intervals, from 30 to 4,750 μg maximal cumulative dose until a fall in FEV₁ ≥20 percent from the highest post-saline solution control level was observed or until the maximal 4,750-μg dose was reached. Two minutes after each series of inhalations, FEV₁ was measured as described above.

**Expression and Analysis of Data**

The methacholine dose capable of causing a 20 percent fall in FEV₁ (PD20FEV₁) was calculated by interpolating on a semilogarithmic dose-response curve plot the point corresponding to the dose causing the FEV₁ fall just below 20 percent with the point corresponding to the dose causing the FEV₁ fall just above it. In the challenges in which FEV₁ decreased less than 20 percent, the maximal 4,750-μg dose was considered for calculating the mean PD20.

A subject was considered hyperreactive when the PD20FEV₁ was equal to or lower than 1,400 μg."}

Statistical analysis was performed by means of the Kruskal-Wallis, Fisher Exact, and χ² tests corrected for continuity, when appropriate, at a 95 percent or greater significance level.

**RESULTS**

No subject had a personal history of previous asthma or of clinically relevant pulmonary infection. From the beginning of their residence in the DRC (mean 13.3 months [SE 1.8] for group A; 12.5 months [SE 1.5] for group B), all subjects had been smoking 5 cigarettes a day; previous smoking habits were comparable in the two groups (Table 1). Occasional respiratory symptoms (dyspnea, cough, sputum production, wheezing, chest tightness) were referred to by nine (36 percent) HIV+ subjects and by four (16 percent) HIV− subjects. The difference almost reached a statistical significance (p<.07, Fisher's exact test). In particular, bronchospastic symptoms (dyspnea, wheezing, dry cough, chest tightness) were referred to by four (16 percent) HIV+ subjects and three (12 percent) HIV− subjects. One subject of group A suffered from seasonal rhinitis. At the time of the study, all subjects were symptom free.

No difference was found between HIV-seropositive subjects (group A) and HIV-seronegative subjects for sex, age, drug abuse and DRC stay length, and baseline FEV₁ values (Table 1). Baseline FEV₁ percent and MEF50 percent were in the normal range in every patient. Bronchial hyperreactivity to methacholine was found in two subjects in group A (PD20FEV₁ range, 125 to 340 μg) and in four subjects in group B (PD20FEV₁ range, 215 to 1,100 μg) with an overall frequency of 8 percent in HIV-seropositive subjects and of 16 percent in HIV-seronegative subjects (χ² test: NS). Nine subjects in group A and 10 in group B reached the PD20FEV₁. The mean PD20FEV₁ did not differ between HIV-seropositive subjects (3,092.4 μg).
mu, SEM 115.8) and HIV-seronegative subjects (2,765.5 mu, SEM 120), (Fig 1).

None of the four HIV-seropositive subjects but two HIV-seronegative subjects with symptoms of bronchospasm had bronchial hyperreactivity to methacholine. No difference was found in mean PD20FEV1, baseline FEV1, and MEF50 percent values considering the three classes of previous smoking habits.

**Discussion**

Our data show that bronchial hyperreactivity to methacholine is not a common feature in HIV-infected IVDUs without overt AIDS at different stages of infection and does not differ in frequency from a control group of HIV-seronegative IVDUs.

To the best of our knowledge, bronchial reactivity in HIV-infected individuals has not been investigated yet, despite asthma-like respiratory disorders and/or abnormal airway function that have been frequently described in infected subjects with AIDS1,2,9 or without full-blown AIDS. Stover et al.10 reported a 3 percent prevalence rate of bronchospastic disorders in 130 subjects with AIDS. O'Donnell et al.11 found that 44 percent of 99 subjects with AIDS had either abnormally low forced expiratory flow rates or a significant response to inhaled bronchodilator. In that study, abnormal airway function was significantly associated with clinical signs and symptoms and the recognition of an asthmalike syndrome led to bronchodilator therapy with clinical improvement. Furthermore, in HIV-infected individuals without AIDS belonging to different risk groups, Wallace et al.12 found a high prevalence of bronchitis, asthma, and respiratory symptoms, particularly among IVDUs. In the present study, we evaluated a sample of HIV-seropositive and HIV-seronegative subjects, previous IVDUs who were all inmates in a DRC. HIV-seropositive individuals were at different stages of infection, but without overt AIDS. Thirty-six percent of HIV-seropositive individuals, without differences in the stage of infection, and 16 percent of HIV-seronegative patients referred occasional various respiratory symptoms. This frequency, although lower than that reported by Wallace et al.12 in a comparable population (found to be between 56 and 84 percent) in HIV-positive subjects and between 19 and 83 percent in HIV-negative subjects, whatever symptom is considered) may reflect previous disproportionate tobacco smoking habits. However, in our data, HIV-seropositive subjects tended to have a higher frequency of overall respiratory symptoms than HIV-seronegative subjects. The difference between the two groups almost reached statistical significance. By contrast, the frequency of bronchospastic symptoms was similar for the two groups (16 percent in HIV+ and 12 percent in HIV− subjects). The tendency to have a higher frequency of respiratory symptoms in HIV-seropositive subjects may possibly reflect subclinical respiratory infections that HIV-infected individuals may experience even at initial stages of their disease. An early respiratory involvement in HIV infection is suggested by several findings, in particularly by Shaw et al.13 who found abnormalities in diffusion capacity in patients with ARC and in patients with AIDS but without other evidence of pulmonary disease and, quite recently, by Backer et al.14 who have shown in a prospective study that HIV-infected individuals with impaired immune function have in the absence of pulmonary symptoms a slow but steady decrease in specific diffusion capacity. These authors suggest an early diffuse "nonspecific" interstitial damage in HIV infection that may be caused by HIV itself, which has been isolated from lung tissue and alveolar macrophages in patients with AIDS11,12 or may be related to opportunistic or nonopportunistic subclinical infections.10

In the present study, we found no abnormality in baseline expiratory flow rates, FEV1, and MEF50 percent being within the normal range in every subject. These findings are consistent with those of Shaw et al.13 who found FEV1, peak expiratory flow, and MEF50 percent values within the normal predicted range in HIV-infected subjects without overt AIDS (HIV positive, PGL, ARC) and in subjects with nonpulmonary AIDS, and with those of Backer et al.14 who reported no change in ventilatory capacity over a 9-month observation period in HIV-infected patients without pulmonary symptoms. All these findings seem to suggest a lack of involvement of bronchial airways in the early stages of HIV infection.

In our cases, the history of bronchospastic symptoms was associated with a moderate bronchial hyperreactivity to methacholine in only two seronegative subjects but in none of the seropositive subjects. The overall frequency of bronchial hyperreactivity found both in group A (8 percent) and in group B (16 percent) is similar to that reported in the general population.15

Tobacco smoking did not seem to have affected airway function or bronchial reactivity to methacholine, whereas, as discussed above, it could be taken as the most likely explanation for the observed frequency of respiratory symptoms reported in both groups. The relation between cigarette smoking and bronchial reactivity to methacholine is under debate.14 The bulk of studies performed to date comparing smokers with nonsmokers have produced conflicting results, which may reflect differences in population sample sizes and in characteristics of subjects such as respiratory symptoms and baseline function values.15 Our findings are not pertinent in evaluating the role of tobacco smoking on bronchial reactivity in HIV infection since both HIV-seropositive subjects and HIV-seronegative control subjects were smokers and had similar previous data.
and current smoking habits. Studies comparing smoking and nonsmoking HIV-infected individuals are required to elucidate this point.

The subjects we studied were all previous IVDUs. To date we are unaware of studies on bronchial reactivity in this category; therefore, it is not clear if this condition has in some way affected our results.

In conclusion, from our data, HIV infection in the risk group of previous IVDUs does not appear to be associated with an increased frequency of bronchospastic disorders nor to bronchial hyperreactivity to methacholine. The pathophysiology of bronchospastic disorders reported in HIV-infected individuals requires further studies.

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