The Effect of Isoproterenol Sulfate Aerosol on the Small Airways in Asymptomatic Asthmatic Patients*  

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In 19 asymptomatic asthmatic patients the effect of isoproterenol sulfate aerosol on small airways was assessed. All patients were symptom-free for at least three days before the investigation. On the day of examination, before inhalation of isoproterenol, the total lung resistance (Rt) was normal, while the frequency dependence of lung compliance (Crs) was increased, indicating an obstruction of airways with an inner diameter of less than 2 to 3 mm. After inhalation of 400 micrograms of isoproterenol, no statistically significant change in Crs occurred up to one hour. From our results we assume that in the early stage of recovery from an acute asthmatic attack, isoproterenol aerosol has no effect on the obstruction of peripheral airways.

During recent years, isoproterenol sulfate aerosol in pressurized form has been widely used to alleviate bronchospasm in asthmatic patients. While the potent bronchodilator action of this drug on the large airways is well known, it is surprising how meager, and in part controversial are the reports regarding the effect of this drug on the peripheral airways.1-3

Since the important role of peripheral airways in the pathogenesis of chronic obstructive lung disease (COLD) is now well established,1,4 and since it is assumed that the site of obstruction is in the airways with an inner diameter of less than 2 to 3 mm,2,5,6,8 it seemed to us important to investigate more thoroughly the effect of this drug on the small airways in patients with asymptomatic bronchial asthma.

In the present study, the changes in the smooth muscle tone of the small airways following inhalation of isoproterenol were determined by the changes in frequency dependent lung compliance.

**Material and Methods**

Nineteen inpatients, (13 men and 6 women), with bronchial asthma in full remission were included in the study. The diagnosis was made according to the criteria of the American Thoracic Society.9 The average age of the patients was 43 years and ranged from 13 to 64 years. The control group was composed of five normal subjects, four men and one woman. Their age ranged from 16 to 30 years and all were nonsmokers.

All the patients were free of symptoms for at least three days before the investigation, and on the day of investigation did not receive any bronchodilator drugs. All performed ventilatory studies, at least three to six days before the investigation. These included: (1) Lung volumes determined on a Godart Pulmonet. The best of three values was chosen and converted to body temperature and pressure saturated with water vapor (BTPS). The determined volumes were expressed as the percentage of the predicted values. The functional residual capacity (FRC) was measured by the closed helium dilution method.11 (2) Mechanics of breathing, which included measurement of forced expiratory flow (FEF 200 to 1200), forced expiratory volume in first second (FEV1), and percentage forced expiratory volume expired in first second (FEV1/FVC), before and after inhalation of 400 µg of isoproterenol sulfate aerosol.

On the day of investigation, total lung resistance (Rt), static lung compliance (Cstat) and dynamic lung compliance (Cdyn) were measured by the method of Mead and Wittenberger.12 The Cdyn was measured at frequencies of 60 and 90 breaths per minute respectively. The subject breathed at a constant tidal volume and was asked not to deviate from his resting and expiratory level, which was displayed before him on an X-Y oscilloscope. Only patients with a Rt less than 3 cm H2O/L/sec were included in the study. The parameters of Cstat and Cdyn were measured before and after administration of 400 µg of isoproterenol sulfate aerosol. The measurement was repeated 5, 30 and 60 minutes after inhalation of the drug.

The results of Cdyn before and after inhalation of isoproterenol sulfate aerosol, as well as the possible influence of age and FRC on the results, were statistically analyzed on a computer.13

In order to eliminate the initial value of Cstat, the percentage of decline of Cdyn was examined according to the formula:

$$100 \times \left( 1 - \frac{C_{dyn \text{post}}}{C_{stat}} \right)$$ and $$100 \times \left( 1 - \frac{C_{ dyn \text{post}}}{C_{stat}} \right)$$

The statistical analysis and the calculations were suggested and supervised by a biostatistician.

**Results**

Table 1 summarizes the results of ventilatory functions three to six days before the investigation. As can be seen, there is a decrease in FEV1/FVC and FEF 200-1200 and an increase in FRC. After inhalation of 400 µg of isoproterenol sulfate aero-
Table 1—Mean Values of Lung Volumes* and Mechanics of Breathing in 19 Asthmatic Patients, before and after Inhalation of Isoproterenol Aerosol.

<table>
<thead>
<tr>
<th></th>
<th>VC** L</th>
<th>FRC† L</th>
<th>FEV†† L</th>
<th>FEV1/VC x 100</th>
<th>FEF 200-1200§ (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Isoproterenol</td>
<td>3.60(101)</td>
<td></td>
<td>3.33(147)</td>
<td>2.26(80.5)</td>
<td>63</td>
</tr>
<tr>
<td>After Isoproterenol</td>
<td>3.95(111.5)</td>
<td>2.74(96.3)</td>
<td>75</td>
<td>228</td>
<td></td>
</tr>
</tbody>
</table>

*Lung volumes, corrected to body temperature and pressure saturated with water vapor (BTPS).

**Vital capacity.

††Functional residual capacity.

§§Forced expiratory volume in one second.

$Forced expiratory flow.

||Numbers in parentheses indicate percent of predicted value.

Table 2 summarizes the mean values of $R_t$, $C_{stat}$ and $C_{dyn}$ before and after inhalation of 400 mcg isoproterenol sulfate aerosol. As can be seen, the $R_t$ and $C_{stat}$ were within normal limits in the five normal subjects, as well as in the 19 patients. On the other hand, while in the five normal subjects there was no decrease in $C_{dyn}$ as compared to $C_{stat}$, a statistically significant decrease in $C_{dyn}$ occurred before isoproterenol in all 19 patients at a rate of 60 and 90 breaths per minute respectively ($P<0.05$) indicating the presence of small airways obstruction. After inhalation of 400 μg isoproterenol sulfate aerosol, the statistically significant decrease in $C_{dyn}$ before isoproterenol occurred also 5, 30 and 60 minutes after isoproterenol and indicated no appreciable change in peripheral airways obstruction (Table 2).

The results of $C_{dyn}$ were also analyzed in relation to age and FRC. Six out of 19 patients were under the age of 20 years, and in 7 out of 19 patients the FRC was below 140 percent of the predicted value. No statistically significant difference in $C_{dyn}$ as compared to $C_{stat}$ was detected with this size sample before and after inhalation of isoproterenol sulfate aerosol in the younger age group when compared to the older one, except after 60 minutes at $C_{dyn} 90$ ($P<0.05$). A similar finding in $C_{dyn}$ was encountered in the group of patients with normal FRC as compared to the group with an elevated FRC.

**DISCUSSION**

The important role of small airways in the pathogenesis of COLD is well known. In asthmatic patients during clinical remission, in spite of normal ventilatory studies and normal airway resistance, an obstruction in peripheral airways may persist. This obstruction can be demonstrated by measuring the frequency dependence of lung compliance, or by measurement of "closing volume." In asthmatic patients isoproterenol sulfate aerosol in pressurized form is widely used. While the potent bronchodilator action of this drug on large bronchi is well known, the effect on the small airways is controver-

Table 2—Mean Values of Total Airway Resistance, Static Lung Compliance and Dynamic Lung Compliance at Respiratory Frequencies of 60 and 90 Breaths per Minute before and after Inhalation of Isoproterenol Aerosol in Five Normal Subjects and 19 Asthmatic patients.

<table>
<thead>
<tr>
<th></th>
<th>$C_{stat}$* (L/cm H2O)</th>
<th>$C_{dyn60}$** (L/cm H2O)</th>
<th>$C_{dyn90}$†† (L/cm H2O)</th>
<th>$R_L$‡‡ (cm H2O/L/second)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Controls</td>
<td>0.286††</td>
<td>0.283</td>
<td>0.276</td>
<td>1.74</td>
</tr>
<tr>
<td>Before Isoproterenol</td>
<td>0.235</td>
<td>0.187‡§</td>
<td>0.150‡§</td>
<td>2.9</td>
</tr>
<tr>
<td>After Isoproterenol</td>
<td>0.247</td>
<td>0.205‡§</td>
<td>0.165‡§</td>
<td>2.5</td>
</tr>
<tr>
<td>5 min.</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>30 min.</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>60 min.</td>
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$C_{stat}$* Static lung compliance.

$C_{dyn60}$** Dynamic lung compliance at respiratory frequency of 60 breaths per minute.

$C_{dyn90}$†† Dynamic lung compliance at respiratory frequency of 90 breaths per minute.

$R_L$‡‡ Total lung resistance.

§§Indicates $P<0.05$.

||Mean values in 12 patients.
sial. Woolcock and co-workers reported that in bronchial asthma isoproterenol sulfate aerosol caused a partial relief of the obstruction in small airways as measured by an increase in $C_{dyn}$, while in patients with chronic bronchitis no change occurred. However, they measured the effect of isoproterenol in three asthmatic patients and only in one significant improvement in $C_{dyn}$ was recorded. Hill and associates measured changes in $C_{dyn}$ in 15 adolescent asymptomatic asthmatic patients. In eight patients frequency dependence of compliance was found indicating small airways obstruction. Of five of these eight patients, isoproterenol abolished the frequency dependence of compliance. On the other hand McFadden and colleagues in ten asthmatic patients measured the distribution of ventilation and $C_{dyn}$ during an asthmatic attack and during the immediate recovery period while the patients were treated with isoproterenol. In all these patients in spite of isoproterenol treatment and in the presence of normal airway resistance, uneven ventilation and frequency dependence of compliance persisted and indicated that the drug had no effect on the small airways.

Our results in 19 asthmatic patients who were asymptomatic for at least three days after the attack are similar to those reported by McFadden and Lyons, ie isoproterenol had no effect on the frequency dependence of compliance. Since our group of 19 asthmatic patients is composed of different age groups, we analyzed our results in relation to age as well. In seven patients under the age of 20, no statistically significant change was found after inhalation of isoproterenol as compared to the patients over the age of 30 years, except after 60 minutes and at $C_{dyn}$. We assume that in our group of patients, age is most probably not a factor in the irreversibility of the small airways obstruction following isoproterenol.

The question therefore arises as to the cause of the irreversible obstruction of the small airways in our group of patients. Several factors in addition to bronchospsasm may be responsible for it: (1) the presence of mucosal edema in the small airways; (2) mucus secretion in these airways; and (3) overdistension of the lung which may cause a nonhomogeneous loss of elastic recoil.

Our patients were clinically asymptomatic for only three to six days after the relief of an asthmatic attack. Therefore, it is conceivable that edema of the mucosa and mucus secretion in the small bronchi were still present, thus preventing the bronchodilator effect of isoproterenol on these airways. Variations in the delivery of the aerosol drug to different areas of the bronchial tree, and especially to the small airways due to bronchial secretions have to be taken into account as an additional possible cause for the bronchodilator failure of isoproterenol in our patients.

Regarding overdistention of the lung, although the mean FRC was 149 percent of the predicted value, no statistically significant difference in $C_{dyn}$ was found when the group of seven patients with normal FRC was compared to the 12 patients with increased FRC. We assume that an increase of FRC of this magnitude has no effect on the changes in $C_{dyn}$.

We conclude, therefore, that in patients with asymptomatic asthma in the early stages of recovery from an asthmatic attack, isoproterenol in doses sufficient to cause a bronchodilatation in the large airways has no effect on the small airways. The most probable cause for it is the presence of mucosal edema and mucus secretion in these airways.

REFERENCES